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Mathematical Modeling of Complex Biological Systems

A Kinetic Theory Approach

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Preface

Contents and Scientific Aims

The scientific community is aware that the great scientific revolution of this century will be the mathematical formalization, by methods of applied mathematics, of complex biological systems. A fascinating prospect is that biological sciences will finally be supported by rigorous investigation methods and tools, similar to what happened in the past two centuries in the case of mechanical and physical sciences.

It is not an easy task, considering that new mathematical methods may be needed to deal with the inner complexity of biological systems which exhibit features and behaviors very different from those of inert matter.

Microscopic entities in biology, say cells in a multicellular system, are characterized by biological functions and the ability to organize their dynamics and interactions with other cells. Indeed, cells organize their dynamics according to the above functions, while classical particles follow deterministic laws of Newtonian mechanics. Cells have a life according to a cell cycle which ends up with a programmed death. The dialogue among cells can modify their behavior. The activity of cells includes proliferation and/or destructive events which may, in some cases, result in dangerously reproductive events. Finally, a cellular system may move far from equilibrium in physical situations where classical particles generally show a tendency toward equilibrium.

An additional source of complexity is that biological systems always need a multiscale approach. Specifically, the dynamics of a cell, including its life, are ruled by sub-cellular entities, while most of the phenomena can be effectively observed only at the macroscopic scale.

This book deals with the modelling of complex multicellular systems by a mathematical approach which is related to mathematical kinetic theory. Applications refer to the mathematical description of the immune competition with special attention to the interactions between tumor and immune cells.

The contents of this book are described in the last section of the first chapter; they are related to some prospective ideas concerning the

mathematical formalization of complex biological systems.

Complex biological systems cannot be described by simple mathematical equations traditionally motivated by the need to allow an effective dialogue between biologists and mathematicians. On the other hand, the mathematical formalization may need new mathematical methods and tools.

Chapter 2 deals with the derivation of a general mathematical framework suitable for describing the evolution of multicomponent cellular systems. The mathematical framework is defined by a system of integro-differential equations which describe the evolution in time and space of the distribution function over the microscopic state of cells of each population.

Indeed it can be regarded as a new mathematical approach which develops methods of mathematical kinetic theory to deal with active particles (cells) rather than with classical particles. The microscopic state includes biological functions in addition to geometrical and mechanical variables.

The modelling of microscopic interactions also refers to the organized, somehow intelligent, behavior and ability of cells to interact and communicate with other cells. Moreover, proliferating and destructive (even self-destructive) ability is included in the mathematical description.

Mathematical models cannot be designed on the basis of a purely heuristic approach. They should be referred to well-defined mathematical structures, which may act as a mathematical theory.

Chapter 3 develops a mathematical model precisely related to the mathematical structures proposed in Chapter 2. The model describes the competition between immune and progressing cells. It should be regarded as a reference model to be enlarged to include additional phenomenological descriptions, such as modelling therapeutic actions, or space dynamics, while the model is proposed in the spatially homogeneous case. Microscopic interactions are described by simple phenomenological models which relate the output of the interactions to the biological state of the interaction pairs.

A mathematical model is never a copy of physical reality; it can only approximate real behaviors. On the other hand a model can visualize, at least at a qualitative level, phenomena which are not experimentally observed.

Chapters 4 and 5 develop a qualitative analysis of the initial value problem related to the application of the model proposed in Chapter 3. The rigorous information delivered by the qualitative analysis is integrated with simulations which complete the description delivered by the model. Special attention is devoted to the analysis of the asymptotic behavior of the solutions, which may show either the destruction of the cells carrying a pathology (the authors call them abnormal cells) due to the action of the immune system, or conversely, their blowup due to the progressive inhibition of immune cells.

The analysis shows how the above behaviors can be related to parameters which have a well-defined biological meaning. This means pointing

out the role of microscopic biological functions in the overall evolution of the system. This analysis contributes to the modelling and analysis of therapeutic actions according to models such as those reported in Chapter 7.

Biological systems are characterized by a multiscale structure corresponding, for instance, to the scales of subcellular, cellular, and aggregate matter. Mathematical models should possess the ability to deal with the passage from one scale to the other.

Chapter 6 deals with multiscale problems, showing how macroscopic equations can be obtained from the microscopic descriptions given by the underlying mathematical kinetic theory for multicellular systems. The analysis is applied to the mathematical model proposed in Chapter 3; first in the case of models with conservative interactions only, and then to models in the case of production or destruction of mass. The methodological approach is valid for a variety of models, so that the interested reader can develop it to analyze technically different models. The structure of macroscopic equations essentially depends on the rates of interactions, biological with respect to mechanical, while the analysis provides a rigorous framework for the heuristic approach generally applied when reaction-diffusion equations are derived by conservation equations closed by material models which are justified only by means of phenomenological interpretations.

Looking Forward

This book aims on one hand to offer mathematical tools to deal with the modelling of complex multicellular systems, and on the other hand to deal with a variety of research perspectives. Indeed, mathematical methods reported in this book can be developed to study various problems related to the immune competition and, more generally, to the dynamical behavior of multicellular systems. Only a part of the above problems are dealt with, while several suggestions and research perspectives are proposed and critically analyzed in the last chapter of this book.

Finally, is worth remarking that the application of the various models proposed in this book to the analysis of phenomena of interest in biological sciences generates a variety of challenging mathematical problems. This means not only the qualitative analysis of the solutions to mathematical problems, but also additional problems such as the development of the asymptotic theory from the microscopic to macroscopic description, and the computational treatment of cellular motion driven by cell signalling. Possibly, the analysis of both of the above problems may lead to a deeper understanding of several biological phenomena. Therefore applied mathematicians will find in this book interesting hints not only towards modelling,

but also to several analytic problems. In conclusion, I cannot avoid mentioning that I feel pleased that the authors of this book have transferred into a mathematical framework various ideas proposed in my scientific collaboration with the immunologist Guido Forni.

Nicola Bellomo

1

On the Modelling of Complex Biological Systems

I have deeply regretted that I did not proceed far enough at least to understanding something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense.

— Charles Darwin

1.1 Introduction

Systems of the real world can be observed to reach an understanding of their inner structure and behavior. The collection of experimental data may be organized into a mathematical model to obtain a formal description of the behavior of the observed system.

Generally, the systems of the real world consist of a large number of interacting elements, where their state is described by a set of microscopic variables. The modelling of the overall system is defined by evolution equations corresponding to the dynamics of all their elements. Moreover, the evolution equations are linked together because of the interactions among the above entities.

The first conceptual step in using this approach is the choice of the representation scale of the observed phenomena. Mathematical models can be derived at the microscopic scale when the evolution of each element is individually described, and at the macroscopic scale when the model refers to the evolution of quantities obtained by local averages of the microscopic state.

A typical example is a fluid of several interacting particles. Theoretically, it is possible to describe the above systems through microscopic-type

models related to the dynamics of each element interacting with the others; however this kind of approach generates complexity problems which cannot be properly dealt with. This approach leads to a large number of equations because of the enormous number of particles involved in the system, while their numerical solution needs a very large computational time, making the approach too cumbersome and expensive.

The above modelling approach can be replaced by a macroscopic description, typical of continuum mechanics, which reduces the complexity by dealing with quantities which are averaged locally in space. The application of this modelling method is possible when the number of elements is so large that a given small volume still contains a sufficiently large (in mathematical terms to be specified) number of elements. However, it is easy to see that this approach will not always work. For instance, in the case of a diluted fluid in a container the mean distance between particles is large with respect to their dimension and may even become of the same order of the container, making the macroscopic description impossible.

Methods of mathematical kinetic theory represent an alternative to the above approaches. Kinetic theory looks for evolution equations for the statistical distribution of the state of each element: gross quantities (those delivered by macroscopic models) are obtained as suitable moments of the above statistical distribution. Modelling in kinetic theory means deriving suitable evolution equations for the above distribution function.

The fundamental model of mathematical kinetic theory is the Boltzmann equation (see Cercignani, Illner, and Pulvirenti 1994), which describes the evolution of the first distribution function over the microscopic state of a system of equal particles modelled as point masses. If such a distribution is known, then macroscopic quantities can be computed, as we shall see, by moments averaged by the above distribution. A large literature is devoted to this fundamental model, as documented among others in the books by Cercignani (1998) and the review papers by Villani (2002) and by Perthame (2004), which deal with foundations, analytic problems, and applications to fluid dynamics.

Models of mathematical kinetic theory describe the evolution of the one-particle distribution function over the physical state characterizing a large population of interacting subjects, and refer to the classical models of kinetic theory, the Boltzmann equation and the Vlasov equation. The Boltzmann and Vlasov equations are the fundamental models of nonequilibrium statistical mechanics and represent not only the conceptual framework for generalizing the methods of kinetic theory to various fields of applied sciences, but also a way of understanding phenomena of nonequilibrium statistical mechanics which are not described by the traditional macroscopic approach.

In this book we will focus on models referred to the Boltzmann equation, calling them ***generalized kinetic Boltzmann models***. Our attention will

be focused on dynamics of populations of several interacting active particles. The evolution equations may be called ***kinetic population models***. The interested reader may refer to the books edited by Bellomo and Pulvirenti (2000) for information on mathematical foundations and applications related to the above class of equations. Additional information can be found in the recent book by Schweitzer (2003), which deals with the modelling of several large systems in applied sciences such as biology and sociology by stochastic dynamical systems derived by methods of statistical mechanics.

The modelling of biological systems implies the need for representing and solving complex problems generated by the fundamental characteristic of living matter: biological systems are generally constituted by a large number of interacting entities, whose dynamics follow rules of mechanics and rules generated by their ability to organize movement and biological functions.

This new modelling approach is motivated not only by applied mathematicians, but also by researchers in the field of biological sciences. For instance, Hartwell, et al. (1999) suggest that one looks at suitable developments in statistical mechanics. This enlightening paper will be regarded as a relevant source of motivations and guide for the contents of this book. An important hint on the use of methods of kinetic theory and nonequilibrium statistical mechanics is given in the paper by Bellomo and Forni (2006), which offers various motivations for the development of the mathematical approach proposed in this book, as well as some of the reasoning about future perspectives reported in the last chapter.

The use of methods of statistical mechanics and kinetic theory to model complex biological systems is capturing the attention of applied mathematicians, as documented in the book by Deutsch and Dormann (2004), which uses methods of kinetic theory somewhat complementary to the ones proposed in our book. General aspects on the modelling of biological equations are dealt with in various books, such as Alt, Deutsch, and Dunn (1997); Murray (2004); and Jones and Sleeman (2003).

1.2 Motivations and Aims

This book deals with the modelling and simulation of complex biological systems, specifically multicellular systems, by a mathematical approach obtained as an extension of the methods of kinetic theory. It is not a straightforward generalization, as dealing with living matter rather than inert matter generates a variety of complexity problems which have to be

carefully dealt with, and which generally need new tools and new mathematical approaches.

The modelling of biological systems requires a preliminary reflection on the objects dealt with, and consideration must be given to the approximations and simplifications that might be introduced.

In the above-mentioned paper, Hartwell, et al. propose a conceptual framework for the mathematical approach to biological systems:

> " Biological systems are very different from the physical or chemical systems analyzed by statistical mechanics or hydrodynamics. Statistical mechanics typically deals with systems containing many copies of a few interacting components, whereas cells contain from millions to a few copies of each of thousands of different components, each with very specific interactions.
>
> ... In addition, the components of physical systems are often simple entities, whereas in biology each of the components is often a microscopic device in itself, able to transduce energy and work far from equilibrium."

The microscopic description of a biological system is far more complex than that of a physical system of inert matter, and it is necessary to move to a higher level of analysis to deal with such complexity. At the same time, a biological system cannot simply be observed and interpreted at a macroscopic level, where it shows only the output of the cooperative and organized behaviors which may not be apparent at the cellular scale.

In order to properly describe a biological phenomenon, Hartwell and coworkers introduce the concept of ***function*** as the main difference between the objects of biology and physics: the functions of a biological object, which is mainly devoted to survival and reproduction, are developed by suitable ***functional modules***, which are discrete biological entities with cellular functions separable from those of other modules. The functions, which arise from interactions between the components of the module (proteins, DNA, molecules...) and from interactions between several modules, cannot easily be predicted by studying the properties of the isolated components. The functions of a single module may be activated, regulated, suppressed, or switched between different functions by signals from other modules; moreover, high-level functions can be built by connecting several modules together.

It does not really matter whether the modules are real or not, although several lines of evidence suggest they are quite real. Indeed, it is worth stressing that, by this approach, a biological phenomenon can be described as the evolution of the dynamics of several interacting modules; moreover, such a description naturally links biology to mathematics, thus emphasizing the necessity of integrating experimental data with conceptual frameworks and modelling.

The above reasoning refers to general aspects of modelling complex biological systems. Additional hints may be found referring to specific biological systems. For instance, Gatenby and Maini (2003) note the necessity of developing a new science, which they call ***mathematical oncology***, to provide oncologists and tumor biologists with a modelling framework to understand and organize experimental data: as an example, they suggest the development of models for the evolution of invasive cancer based on "... a sequence of competing populations subject to random mutations while seeking optimal proliferative strategies in a changing adaptive landscape."

They observe that, although not entirely correct, mathematical models represent the next step beyond simple verbal reasoning, and conclude their considerations affirming that "... as in physics, understanding the complex, non-linear systems in cancer biology will require ongoing interdisciplinary research, in which mathematical models guide experimental design and interpretation."

A relatively more precise suggestion for the use of kinetic theory and nonequilibrium statistical mechanics is given, as already mentioned, in the paper by Bellomo and Forni (1994), who propose a mathematical model to describe the competition between tumor and immune cells. A recent paper by the same authors (2006) analyzes an interesting topic: the development of mathematical models toward the challenging objective of designing a mathematical theory of biological sciences, with a structure analogous to the mathematical theory of physical systems. As the authors say, "...the heuristic experimental approach which is the traditional investigation method in biological sciences should be gradually linked by new methods and paradigms generated by a deep interaction with mathematical sciences."

A particularly interesting field of application is mathematical immunology. For instance, given the spread of an illness, it is possible to derive a class of models which are not limited to the description of the evolution of the numbers of healthy individuals and the number of individuals who are carriers of pathology, but may also take into account the evolution of the statistical properties of a certain pathology. Specifically, models should describe the evolution of the statistical distribution of the level of pathological states characterizing each individual.

Generally, research in immunology may benefit from interaction with mathematics; applied mathematicians can contribute to a research program in modelling and simulating particular aspects of the immune system. Considering that in immunology it is necessary to develop experiments *in vivo*, one has to make every effort to reduce the number of experiments; in fact, simulating the behavior of the system can consistently reduce the experimental effort.

The interplay between mathematics and immunology is already documented in a large literature. Specifically, regarding tumor and immune

system interactions, the reader can refer to the collection of surveys by Adam and Bellomo (1996) and by Preziosi (2003), in order to find useful information on the state of the art in the field.

1.3 Mathematical Background

The Boltzmann equation offers the mathematical background for this book. Indeed, it is the reference model for a class of evolution equations which will be derived, in Chapter 2, for a large system of interacting entities whose microscopic state is identified not only by geometrical and mechanical variables, but also by an additional biological variable which may assume different meanings corresponding to the specific system which is the object of the modelling process.

The interacting entities are occasionally called ***active particles*** to indicate that their microscopic state includes characteristic activities (biological functions) which are typical of the living matter.

Of course, the Boltzmann equation cannot be used, as it is, to model the complex systems we deal with. Indeed, microscopic interactions between active particles are very different from those between classical particles. The main difficulty arises from the fact that mechanical interactions are somehow affected by biological functions and vice versa. Moreover, interactions are not mass-preserving, as in the case of the classical Boltzmann equation, but may include source or sink terms related to proliferation and destruction events.

Still the Boltzmann equation is an essential reference. Therefore, the Appendix provides a concise introduction to this fundamental model of kinetic theory and provides a preliminary analysis of its fundamental properties. It is only a brief introduction, and the interested reader can find additional information in the book by Cercignani, Illner, and Pulvirenti (1994), mainly devoted to the derivation and the mathematical properties, while more recent mathematical approaches are dealt with in the survey by Villani (2002).

1.4 Contents

This book is motivated by the idea that methods of mathematical kinetic theory can be developed to describe the evolution of several biological systems of interest in applied sciences. Specific fields of applications are,

among others, collective social behaviors, immunology, epidemiology, and the dynamics of swarms. Specifically, this book deals with modelling and simulations of biological systems constituted by large populations of interacting cells. The modelling is then focused on the analysis of the competition between cells of an aggressive host and cells of the immune system.

The line which is followed is the classical one of the mathematical sciences when applied to modelling real systems. This line links the phenomenological observation of the system to be described within a mathematical framework to modelling and simulations. Between these two steps, a qualitative analysis has to be inserted not only to define the background for the application of computational algorithms, but also to precisely identify the prediction ability of the model.

Bearing the above reasoning in mind, the contents of the chapters which follow the above introduction can be given:

Chapter 2 deals with methodological aspects, namely with the derivation of a generalized Boltzmann equation for large systems of interacting entities, whose microscopic state is identified not only by position and velocities, but also by a microscopic additional variable corresponding to their biological functions. The mathematical framework is obtained starting from a detailed description of microscopic interactions which include not only modifications of the microscopic state, but also proliferation and destruction of cells. Therefore this chapter provides various mathematical tools which will be used to derive various models proposed in the chapters which follow. It is a general framework which can hopefully also be used to model other biological systems different from those specifically dealt with in this book.

Chapter 3 deals with the derivation of various mathematical models concerning the immune competition. A specific application is the competition between tumor and immune cells. The mathematical framework is the one proposed in Chapter 2, while specific models are obtained by a detailed mathematical description of cellular interactions. As we shall see, interactions not only may modify the ability of cells to apply their specific functions, but may also generate destruction or proliferation phenomena which are typical of the immune competition. For instance, destruction of the cells of the aggressive guest due to the action of the immune cells, which may proliferate to fight against it. Of course, the opposite situation may occur: proliferation of the cells of the guest which may not be sufficiently contained by the immune system.

Chapter 4 develops a quantitative analysis of the models proposed in Chapter 3. Well-posedness of the initial value problem is analyzed. Special attention is paid to studying the asymptotic behavior of the solutions. The qualitative analysis is developed with the aim of recovering, out of the description of the model, suitable information on the output of the competition and, in particular, on the role of the parameters of the model in

the asymptotic behavior of the solutions. The final aim consists of analyzing the conditions which may generate blowup of cells of the aggressive guest with inhibition of the immune system and vice versa. Classically, the above qualitative analysis defines the mathematical background useful in the application of algorithms for the computational analysis developed in Chapter 5.

Chapter 5 deals with a computational analysis of the models proposed in Chapter 3. The mathematical problem is the analysis of the initial value problem for systems of integro-differential equations. Simulations visualize the behavior of the models, with a detailed quantitative analysis of the role of parameters and of the initial conditions. Suitable biological interpretations relate the above parameters and conditions to real biological states or conceivable actions including the development of therapies.

Chapter 6 deals with the introduction to models with space dynamics. The mathematical background is still the one of Chapter 2, however the microscopic state of models dealt with in this chapter includes the space variable, while models dealt with in Chapters 3 to 5 were limited to the description of spatially homogeneous phenomena. The greatest part of this chapter is devoted to the derivation of macroscopic models by suitable asymptotic theories out of the microscopic description given by the kinetic theory approach. This derivation can be regarded as a relatively more rigorous alternative to the purely phenomenological derivation offered by classical methods of continuum mechanics. Indeed, phenomenological continuum models are derived on the basis of conservation equations closed by models of the behavior of the matter, which generally do not take into account the fundamental role of biological functions at the cellular level. The analysis developed in this chapter shows how these functions, and in particular the rates of mechanical and biological interactions, play a relevant role in the derivation of macroscopic equations. Specifically different evolution equations and descriptions of diffusion phenomena are obtained with different rates of the above-mentioned interactions.

Chapter 7 develops a critical analysis of the contents of preceding chapters in view of further generalizations and developments of the modelling approach proposed in this book. Specifically, the following two topics, selected among several ones, are dealt with. The first one refers to generalizations of the mathematical approach in view of modelling additional phenomena, with special attention to therapeutical actions. The second topic refers to derivation of mathematical frameworks technically different from those used in this book.

Finally, this chapter also analyzes, with reference to a recent paper by Bellomo and Forni (2006), an interesting issue related to the mathematical treatment of living matter: how mathematical models of biological systems can be properly developed into a biological–mathematical theory. Indeed, it is a fascinating perspective which already involves the intellectual energy

of various applied mathematicians. Within this framework a challenging subject is the derivation of biological–mathematical theory as a natural development of specific mathematical models.

It is worth stressing that, although the applications dealt with in Chapters 3 to 5 essentially refer to various aspects of immune competition, the mathematical methods proposed in this book may act as a new paradigm for a variety of applications. This aspect is analyzed in Chapter 6 and 7, which look at further research perspectives.

An Appendix and a short Glossary complete the overall contents of the book. The Appendix provides a brief description of the Boltzmann equation, its derivation, and some of its properties. This Appendix also deals with a concise account of the so-called discrete Boltzmann equation, a mathematical model of kinetic theory corresponding to a gas of particles which can attain only a finite (discrete) number of velocities. The Glossary provides a short description of the biological terms used in the systems dealt with in this book.

2

Mathematical Frameworks of the Generalized Kinetic (Boltzmann) Theory

... the importance of integrating experimental approaches with modelling and conceptual frameworks ...

— Hartwell, et al.

2.1 Introduction

One of the most interesting and challenging research perspectives for applied mathematicians is the description of the collective behavior of large populations of interacting entities whose microscopic state is described not only by mechanical variables, typically position and velocity, but also by a biological state related to an organized, and maybe even intelligent, behavior.

This chapter deals with the development of a new approach based on the methods of kinetic theory. In this approach we derive mathematical equations suitable for describing the evolution of the interacting population, taking into account the above microscopic state.

It is an ambitious goal motivated by papers delivered by scientists active in the field of biology, for instance by Hartwell, et al. (1999), who deeply analyze the conceptual differences between inert and living matter. The motivations and reasoning behind this type of mathematical modelling of biological systems are the guiding principles of this book and have already been outlined in Section 1.2.

Some mathematical structures have already been proposed in the literature, in some cases with reference to specific applications. Specifically some generalizations of the classical Boltzmann equation, which is briefly reviewed in the Appendix, have been proposed in the paper by Bellouquid and Delitala (2005), while mathematical aspects are dealt with in the book by Arlotti, Bellomo, De Angelis, and Lachowicz (2003) dealing with the well-posedness of the initial value problem and the development of asymptotic theory toward the derivation of equations of continuum mechanics.

The above-mentioned class of equations applies to the evolution of the probability distribution over the microscopic state of the interacting entities. The derivation of the evolution equations is based upon conservation equations in the space of the microscopic state. The net flow in the elementary volume in the state space is determined by short-range microscopic interactions. This means that the derivation method is analogous to that of the Boltzmann equation.

Specific applications have been proposed, among others, in mathematical biology, e.g., Arlotti, Lachowicz, and Gamba (2002); Bellouquid and Delitala (2004); as documented in the review papers by Delitala (2002) and by Bellomo, Bellouquid, and Delitala (2004); in social dynamics, Bertotti and Delitala (2004); and in modelling the spread of epidemics, Delitala (2004). The above recent papers have been to some extent inspired by the pioneer papers by Jager and Segel (1992) on the biological behavior of insects and by Bellomo and Forni (1994) on the competition between tumor and immune cells.

It is possible to show that some models already available in the literature can be related to the mathematical framework of generalized kinetic theory, and that new models can be designed referring to the structure. The interest in this type of mathematical approach toward the modelling of complex systems in applied sciences is documented in the collection of surveys in the book edited by Bellomo and Pulvirenti (2000). In this book we focus on mathematical biology, and specifically on complex multicellular systems.

This chapter is organized as follows:

Section 2.2 provides some preliminary definitions concerning the microscopic state of the interacting entities and their statistical representation. Moreover, it also shows how macroscopic quantities of interest in biological sciences can be technically recovered from the above statistical distribution.

Section 2.3 deals with the modelling of microscopic interactions between pairs of cells. As in mathematical kinetic theory, short-range interactions are dealt with.

Section 2.4 deals with the derivation of the evolution equations for the one-particle distribution function corresponding to the above models of microscopic interactions.

Section 2.5 deals with some technical simplifications: the particularization of the evolution equations in the spatially homogeneous case with

dominant biological interactions, or with dominant mechanical interactions.

Section 2.6 deals with discretized models which are obtained by replacing the continuous mechanical and biological variables by discrete variables.

Section 2.7 analyzes the general mathematical framework proposed in this chapter with reference to some specific models, thus showing how it includes, as special cases, a variety of models of interest in the biological sciences. Out of the above critical analysis the applicability of the framework for deriving models suitable for describing complex biological phenomena is discussed.

Some specific mathematical models derived within the general framework offered in Sections 2.4 to 2.6 will be proposed in Chapter 3.

2.2 Mathematical Representation

This section provides some preliminary definitions. These definitions refer to a large system of interacting cells and concern the concept of a microscopic state and the statistical distribution over such a microscopic state as an alternative, in terms of collective description, to the individual deterministic modelling of each cell, which in the whole ensemble may not even be identified.

Consider a large system of interacting cells organized into several populations. The description of the system by methods of mathematical kinetic theory essentially means defining the microscopic state of the cells and the distribution function over the above state.

Definition 2.2.1. *The system is constituted by n interacting **cell populations** labelled by the index $i = 1, \ldots, n$. Each population is characterized by a distinct way of organizing its peculiar activities, as well as its interactions with the other populations.*

Definition 2.2.2. *The physical variable denoting the state of each cell is called the **microscopic state**, and is denoted by $\mathbf{w}$, which is formally written as follows:*

$$\mathbf{w} = \{\mathbf{z}\,,\, \mathbf{q}\,,\, \mathbf{u}\} \in D_{\mathbf{w}} = D_{\mathbf{z}} \times D_{\mathbf{q}} \times D_{\mathbf{u}}\,, \tag{2.2.1}$$

*where $\mathbf{z}$ is the **geometrical microscopic state**, e.g., position, orientation, etc., $\mathbf{q}$ is the **mechanical microscopic state**, e.g., linear and angular velocities, and $\mathbf{u}$ is the **biological microscopic state**. The space of the microscopic states is called the **state space**.*

Definition 2.2.3. *The description of the overall state of the system is given by the one-cell distribution function*

$$f_i = f_i(t, \mathbf{w}) = f_i(t, \mathbf{z}, \mathbf{q}, \mathbf{u})\,, \tag{2.2.2}$$

which will be called the ***generalized distribution function****, for* $i = 1, \ldots, n$*, and such that* $f_i(t, \mathbf{w})\, d\mathbf{w}$ *denotes the number of cells whose state, at time* t*, is in the interval* $[\mathbf{w}, \mathbf{w} + d\mathbf{w}]$*.*

Definition 2.2.4. ***Interactions*** *are considered between pairs of cells. The first one will be called the* ***test cell****, while the second one will be the* ***field cell****. The distribution function defined in Definition 2.2.3 refers to the test cell.*

In some cases, the geometrical and mechanical microscopic states refer simply to position $\mathbf{x}$ and velocity $\mathbf{v}$; see Figure 2.1. Then $f_i = f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})$.

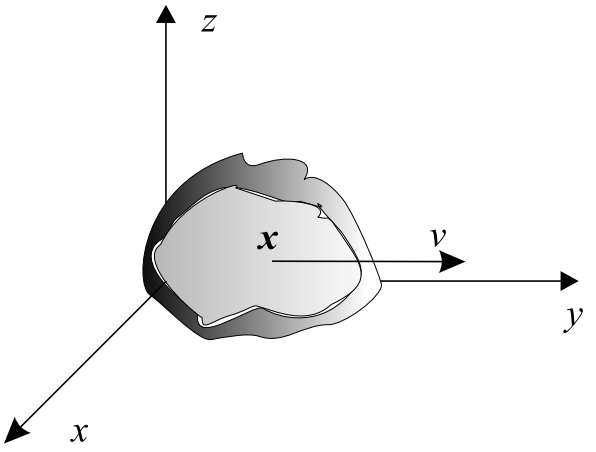

Fig. 2.1. Mechanical state of a cell.

Calculations developed in what follows refer, for simplicity of notation, to the above specific case; generalizations to more complicated cases, where geometrical and microscopic states refer not only to position and velocity, are merely technical and do not modify the following considerations.

If f_i is known, then macroscopic gross variables can be computed, under suitable integrability conditions, as moments weighted by the above distribution function. For instance, the ***local size*** of the i^{th} population is given by

$$n_i[f_i](t, \mathbf{x}) = \int_{D_\mathbf{v} \times D_\mathbf{u}} f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})\, d\mathbf{v}\, d\mathbf{u}\,. \tag{2.2.3}$$

The local initial size of the i^{th} population, at $t = 0$, is denoted by n_{i0}, while

the local size for all population is denoted by n_0 and is given by

$$n_0(\mathbf{x}) = \sum_{i=1}^{n} n_{i0}(\mathbf{x})\,. \tag{2.2.4}$$

Integration over the volume $D_{\mathbf{x}}$ containing the cells gives the ***total size*** of the i^{th} population:

$$N_i[f_i](t) = \int_{D_{\mathbf{x}}} n_i(t,\mathbf{x})\,d\mathbf{x}\,, \tag{2.2.5}$$

which may depend on time due to proliferating or destructive interactions, as well as the flux of cells through the boundaries of the volume. The total size of all populations N_0 is given by the sum of all N_i. In all practical cases it may be convenient to normalize the distributions f_i with respect to the total size N_0 at $t = 0$, so that each size is related to an initial condition.

Marginal densities may refer either to the generalized distribution over the mechanical state

$$f_i^m(t,\mathbf{x},\mathbf{v}) = \int_{D_{\mathbf{u}}} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\,d\mathbf{u}\,, \tag{2.2.6}$$

or to the generalized distribution over the biological state:

$$f_i^b(t,\mathbf{u}) = \int_{D_{\mathbf{z}}\times D_{\mathbf{q}}} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\,d\mathbf{x}\,d\mathbf{v}\,. \tag{2.2.7}$$

First-order momenta give either ***linear mechanical macroscopic*** quantities or ***linear biological macroscopic*** quantities. For instance, the mass velocity of cells, at the time t at the position $\mathbf{x}$, is defined by

$$\mathbf{U}[f_i](t,\mathbf{x}) = \frac{1}{n_i[f_i](t,\mathbf{x})}\int_{D_{\mathbf{v}}\times D_{\mathbf{u}}} \mathbf{v}\, f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\,d\mathbf{v}\,d\mathbf{u}\,. \tag{2.2.8}$$

Focusing on biological functions, linear momenta related to each j^{th} component of the state $\mathbf{u}$, related to the i^{th} populations, will be called ***activations*** at the time t at the position $\mathbf{x}$, and are computed as follows:

$$A_{ij} = A_j[f_i](t,\mathbf{x}) = \int_{D_{\mathbf{v}}\times D_{\mathbf{u}}} u_j f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\,d\mathbf{v}\,d\mathbf{u}\,, \tag{2.2.9}$$

while the ***activation density*** is given by the activation relative to the size of the i^{th} population:

$$\mathcal{A}_{ij} = \mathcal{A}_j[f_i](t,\mathbf{x}) = \frac{A_j[f_i](t,\mathbf{x})}{n_i[f_i](t,\mathbf{x})}\,, \tag{2.2.10}$$

and it allows us to identify the size of the mean value of the activation.

Similar calculations can be developed for higher order momenta. For instance, ***quadratic progressions*** can be computed as second-order momenta:

$$E_{ij} = E_j[f_i](t, \mathbf{x}) = \int_{D_\mathbf{v} \times D_\mathbf{u}} u_j^2 f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u})\, d\mathbf{v}\, d\mathbf{u}\,, \tag{2.2.11}$$

while the ***quadratic progression density*** is given by

$$\mathcal{E}_{ij} = \mathcal{E}_j[f_i](t, \mathbf{x}) = \frac{E_j[f_i](t, \mathbf{x})}{n_i[f_i](t, \mathbf{x})}\,. \tag{2.2.12}$$

2.3 Modelling Microscopic Interactions

Modelling microscopic interactions is preliminary to the derivation of evolution equations. This section deals with the design of a mathematical framework suitable for including a large variety of models at the microscopic level. Essentially, we treat ***short-range binary interactions*** which refer to the mutual actions between test and field cells, when the test cell enters into the action domain $\Lambda_\mathbf{x}$ of the field cell; $\Lambda_\mathbf{x}$ is relatively small and only binary encounters are assumed to be relevant.

Another type of microscopic interactions are ***mean field interactions***. These refer to the action over the test cell applied by all field cells which are in the action domain Ω of the field subject. This means that the density is sufficiently large relative to Ω so that more than one field cell may act over the test cell, but the action is still of the type of binary encounters.

In this book, we focus on applications with a short-range interaction type. In this chapter, we propose and develop the framework for the short-range interaction modelling; in next chapters we will propose some specific models. The analysis of mean field interactions is developed in the last chapter.

We consider the following classifications:

• ***Conservative interactions*** which modify the state, mechanical and/or biological, of the interacting cells, but not the size of the populations.

• ***Proliferating*** or ***destructive interactions*** which result in the death or birth of cells due to pair interactions.

Consider first ***conservative interactions*** between the test cell with state $\mathbf{w}_1$ belonging to the i^{th} population and the field cell with state $\mathbf{w}_2$

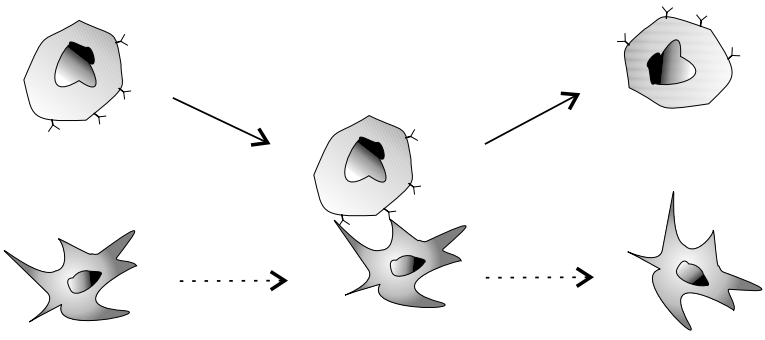

Fig. 2.2. Conservative interactions. A T cell interacts with a dendritic cell that does not present the specific antigen. After the encounter neither the T cell nor the dendritic cell change their state.

belonging to the j^{th} population, where $\mathbf{w} = \{\mathbf{x}, \mathbf{v}, \mathbf{u}\}$. The dynamics of conservative interactions are visualized in Figure 2.2. Modelling of microscopic interactions is based on the knowledge of the following two quantities:

- The ***encounter rate***

$$\eta_{ij}(\mathbf{w}_1, \mathbf{w}_2) \; : \quad D_{\mathbf{w}} \times D_{\mathbf{w}} \; \rightarrow \; \mathbb{R}_+ \, , \tag{2.3.1}$$

depending both on the states and on the type of populations of the interacting pairs;

- The ***transition density function***

$$\varphi_{ij}(\mathbf{w}_1, \mathbf{w}_2; \mathbf{w}) \; : \quad D_{\mathbf{w}} \times D_{\mathbf{w}} \times D_{\mathbf{w}} \; \rightarrow \; \mathbb{R}_+ \, , \tag{2.3.2}$$

which is such that $\varphi_{ij}(\mathbf{w}_1, \mathbf{w}_2; \mathbf{w})\, d\mathbf{w}$ denotes the probability density that a test cell with state $\mathbf{w}_1$ belonging to the i^{th} population falls into the state $\mathbf{w}$ after an interaction with a field cell with state $\mathbf{w}_2$ belonging to the j^{th} population. The function φ_{ij} has the structure of a probability density function with respect to the variable $\mathbf{w}$

$$\forall\, i, j \, , \quad \forall\, \mathbf{w}_1, \mathbf{w}_2 \; : \quad \int_{D_{\mathbf{w}}} \varphi_{ij}(\mathbf{w}_1, \mathbf{w}_2; \mathbf{w})\, d\mathbf{w} = 1 \, . \tag{2.3.3}$$

The knowledge of the above quantities allows us to compute the flux rate $\mathcal{C}^+$ and $\mathcal{C}^-$ of cells which enter or leave the elementary volume $d\mathbf{w}$ of

the state space due to local interactions. Technical calculations yield

$$\mathcal{C}_i^+[\mathbf{f}](t,\mathbf{w}) = \sum_{j=1}^{n} \int_{D\times D} \eta_{ij}(\mathbf{w}_1,\mathbf{w}_2)\varphi_{ij}(\mathbf{w}_1,\mathbf{w}_2;\mathbf{w}) \times f_i(t,\mathbf{w}_1) f_j(t,\mathbf{w}_2)\, d\mathbf{w}_1\, d\mathbf{w}_2\,, \tag{2.3.4}$$

$$\mathcal{C}_i^-[\mathbf{f}](t,\mathbf{w}) = f_i(t,\mathbf{w}) \sum_{j=1}^{n} \int_{D} \eta_{ij}(\mathbf{w},\mathbf{w}_2) f_j(t,\mathbf{w}_2)\, d\mathbf{w}_2\,, \tag{2.3.5}$$

where $D = \Lambda_{\mathbf{x}} \times D_{\mathbf{v}} \times D_{\mathbf{u}}$, and where $\mathbf{f}$ denotes the set of all distribution functions: $\mathbf{f} = \{f_i\}$.

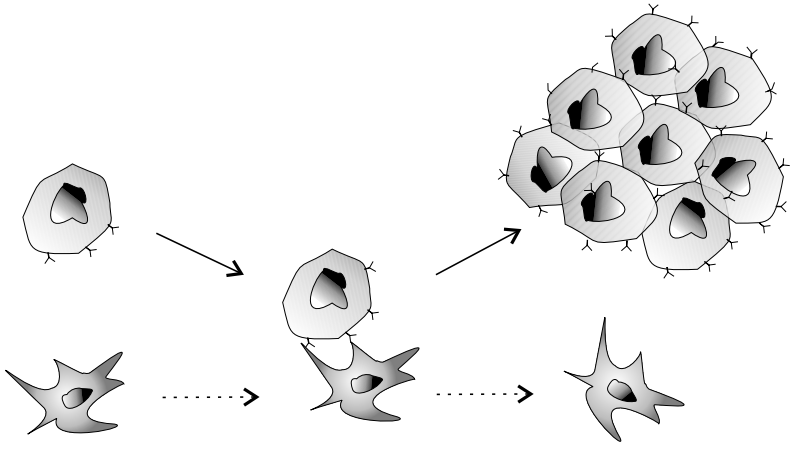

Fig. 2.3. Proliferating interactions. A T-helper cell is induced to proliferate after the interaction with a dendritic cell presenting the specific antigen.

Consider now ***nonconservative interactions*** between the test cell with state $\mathbf{w}_1$ belonging to the i^{th} population and the field cell with state $\mathbf{w}_2$ belonging to the j^{th} population, which occur with the above defined encounter rate. The dynamics of nonconservative interactions are visualized in Figures 2.3 and 2.4. Proliferating and/or destructive encounters can be modelled by the ***source/sink short-range distribution function***

$$\psi_{ij}(\mathbf{w}_1,\mathbf{w}_2;\mathbf{w}) = \mu_{ij}(\mathbf{w}_1,\mathbf{w}_2)\delta(\mathbf{w}-\mathbf{w}_1)\,, \tag{2.3.6}$$

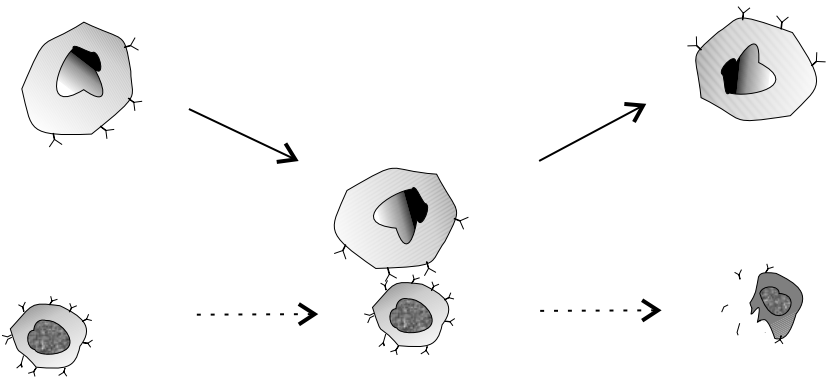

Fig. 2.4. Destructive interactions. An activated T citotoxic cell recognizes its specific target and kills the foreign cell.

where μ is the proliferation (or destruction) rate generated by the interaction of the test cells belonging to the i^{th} population with state $\mathbf{w}_1$ with a field cell belonging to the j^{th} population with state $\mathbf{w}_2$. Proliferating and destructive processes occur in the microscopic state of the test cell.

Calculations analogous to those we have seen for equations (2.3.4) and (2.3.5) provide the flux rate $\mathcal{I}$ due to proliferating or destructive interactions:

$$\mathcal{I}_i[\mathbf{f}](t,\mathbf{w}) = f_i(t,\mathbf{w}) \sum_{j=1}^{n} \int_D \eta_{ij}(\mathbf{w},\mathbf{w}_2)\mu_{ij}(\mathbf{w},\mathbf{w}_2) f_j(t,\mathbf{w}_2)\, d\mathbf{w}_2 \,. \quad (2.3.7)$$

The above general expressions, where the terms η, φ, and μ depend on the whole set of microscopic variables, need to be particularized according to the phenomenology of the system we are dealing with. Specifically, the following particularizations are proposed:

- The encounter rate depends, for each pair of interacting populations, on the relative velocity

$$\eta_{ij} = c_{ij}|\mathbf{v}_1 - \mathbf{v}_2|\delta(\mathbf{x}_1 - \mathbf{x}_2)\,, \qquad c_{ij} = constant\,. \quad (2.3.8)$$

- The transition probability density φ_{ij} is given by the product of the two transition densities related respectively to mechanical variables and biological variables. Defining $\mathcal{M}_{ij}$ as the ***transition probability density related to mechanical variables*** and $\mathcal{B}_{ij}$ as the ***transition probability density related to biological variables*** yields

$$\varphi_{ij} = \mathcal{M}_{ij}(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}|\mathbf{u}_1,\mathbf{u}_2)\delta(\mathbf{x}-\mathbf{x}_1)\mathcal{B}_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u})\,, \quad (2.3.9)$$

where δ denotes Dirac's delta function, and where the output of the mechanical interactions depends on the input velocity and biological states only, while biological interactions depend on the input biological states only. Of course mechanics also has an influence over biological interactions through the encounter rate.

- The proliferating/destruction term μ_{ij} depends on the biological states only:

$$\mu_{ij} = \mu_{ij}(\mathbf{u}_1, \mathbf{u}_2)\,. \tag{2.3.10}$$

Remark 2.3.1. The above particularizations are essentially based on the assumption that biological interactions are affected by mechanical interactions only through the encounter rate, while mechanical interactions depend on the biological state: cells select a strategy to move within their environment based on the biological state of the interacting pair. The output of the interaction is assumed to be localized in the same point of the test cell according to the assumption of short-range interactions.

The above particularizations allow relatively more precise calculations of the fluxes defined in equations (2.3.4) and (2.3.9). Specifically, referring to conservative interactions, one has

$$\begin{aligned}\mathcal{C}_i^+[\mathbf{f}](t,\mathbf{x},\mathbf{v},\mathbf{u}) = \sum_{j=1}^{n} \int_{(D_\mathbf{v}\times D_\mathbf{u})^2} & c_{ij}|\mathbf{v}_1-\mathbf{v}_2|\mathcal{M}_{ij}(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}|\mathbf{u}_1,\mathbf{u}_2) \\ & \times \mathcal{B}_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u}) f_i(t,\mathbf{x},\mathbf{v}_1,\mathbf{u}_1) \\ & \times f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\, d\mathbf{v}_1\, d\mathbf{v}_2\, d\mathbf{u}_1\, d\mathbf{u}_2\,,\end{aligned} \tag{2.3.11}$$

and

$$\begin{aligned}\mathcal{C}_i^-[\mathbf{f}](t,\mathbf{x},\mathbf{v},\mathbf{u}) = f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \sum_{j=1}^{n} \int_{D_\mathbf{v}\times D_\mathbf{u}} & c_{ij}|\mathbf{v}-\mathbf{v}_2| \\ & \times f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_2\,.\end{aligned} \tag{2.3.12}$$

Referring to proliferating or destructive interactions, it follows that

$$\begin{aligned}\mathcal{I}_i[\mathbf{f}](t,\mathbf{x},\mathbf{v},\mathbf{u}) = f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) \sum_{j=1}^{n} \int_{D_\mathbf{v}\times D_\mathbf{u}} & c_{ij}|\mathbf{v}-\mathbf{v}_2|\,\mu_{ij}(\mathbf{u},\mathbf{u}_2) \\ & \times f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_2\,.\end{aligned} \tag{2.3.13}$$

2.4 Mathematical Frameworks

This section deals with the derivation of the evolution equations corresponding to short-range interactions. They should be regarded as a mathematical framework to be used to design specific models simply by specializing the various microscopic interaction functions, equations (2.3.8) and (2.3.10), that we have seen in the previous section. The evolution equation for the distribution function can be formally written as

$$\mathcal{L}_i f_i = \mathcal{N}_i f_i \,, \quad \forall\, i = 1 \,, \ldots \,, n \,, \tag{2.4.1}$$

where $\mathcal{L}_i$ and $\mathcal{N}_i$ are linear and nonlinear operators which can be properly defined by a suitable balance equation obtained by equating the rate of variation of the distribution function in the elementary volume of the state space to the inlet and outlet flux due to microscopic interactions. The scheme for short-range interactions is represented in Figure 2.5, where the first box refers to the free transport, while the others correspond to the net fluxes in the elementary volume of the state space due to conservative and proliferating/destructive interactions, and to the inlet from the outer environment.

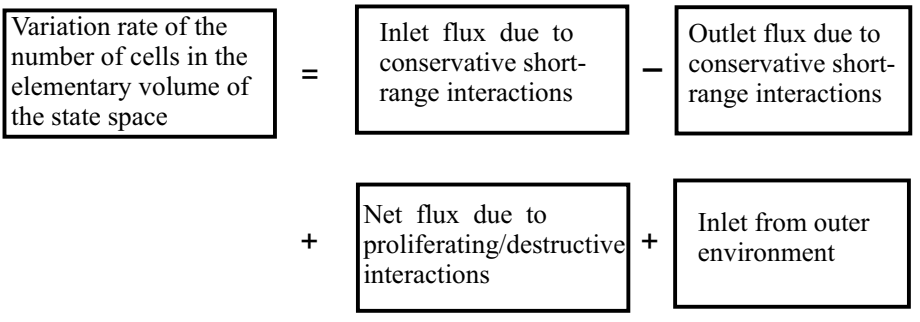

Fig. 2.5. Mass balance in the state space: short-range interactions.

The class of equations dealt with in what follows refers to the relatively more detailed models of microscopic interactions proposed by equations (2.3.8) and (2.3.10) for short-range interactions.

Consider the evolution of a multicellular system where cells are all subject to short-range microscopic interactions and suppose, in addition, that nothing external is acting on the cells. The scheme of the flowchart in Figure 2.5 corresponds, in the absence of inlet flux from the outer environment,

to the following equation:

$$\frac{df_i}{dt} = J_i[\mathbf{f}] = \sum_{j=1}^{n} J_{ij}[\mathbf{f}] = \mathcal{C}_i^+[\mathbf{f}] - \mathcal{C}_i^-[\mathbf{f}] + \mathcal{I}_i[\mathbf{f}]\,, \tag{2.4.2}$$

for $i = 1, \ldots, n$. Then, considering that

$$\frac{df_i}{dt} = \frac{\partial f_i}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_i\,, \tag{2.4.3}$$

and using the expression of the terms corresponding to microsopic interactions given by equations (2.3.11)–(2.3.13), the following class of evolution equations is obtained:

$$\begin{aligned}
&\left(\frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}}\right) f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) = J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \\
&\quad = \sum_{j=1}^{n} \int_{(D_{\mathbf{v}} \times D_{\mathbf{u}})^2} c_{ij} |\mathbf{v}_1 - \mathbf{v}_2| \mathcal{M}_{ij}(\mathbf{v}_1, \mathbf{v}_2; \mathbf{v} | \mathbf{u}_1, \mathbf{u}_2) \\
&\qquad\qquad \times \mathcal{B}_{ij}(\mathbf{u}_1, \mathbf{u}_2; \mathbf{u}) f_i(t, \mathbf{x}, \mathbf{v}_1, \mathbf{u}_1) f_j(t, \mathbf{x}, \mathbf{v}_2, \mathbf{u}_2)\, d\mathbf{v}_1\, d\mathbf{u}_1\, d\mathbf{v}_2\, d\mathbf{u}_2 \\
&\quad - f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \sum_{j=1}^{n} \int_{D_{\mathbf{v}} \times D_{\mathbf{u}}} c_{ij} |\mathbf{v} - \mathbf{v}_2| f_j(t, \mathbf{x}, \mathbf{v}_2, \mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_2 \\
&\quad + f_i(t, \mathbf{x}, \mathbf{v}, \mathbf{u}) \sum_{j=1}^{n} \int_{D_{\mathbf{v}} \times D_{\mathbf{u}}} c_{ij} |\mathbf{v} - \mathbf{v}_2| \mu_{ij}(\mathbf{u}, \mathbf{u}_2) \\
&\qquad\qquad \times f_j(t, \mathbf{x}, \mathbf{v}_2, \mathbf{u}_2)\, d\mathbf{v}_2\, d\mathbf{u}_2\,.
\end{aligned} \tag{2.4.4}$$

If an inlet flux from the outer environment is present, then a suitable source term needs to be added to the right-hand side of equation (2.4.4).

2.5 Some Simplified Models

This section reports two technical simplifications related to the mathematical framework proposed in Section 2.4. The first one refers to models with

dominant biological interactions, where the distribution over the mechanical state is uniform or constant in time. The second one refers to models with dominant mechanical interactions, with uniform or constant in time distributions over the biological state. Another possible simplification is the discretization technique, which will be treated in the next section.

The above particular classes of models are proposed in view of specific applications. The modelling is developed in the absence of external actions and source terms. Inserting these additional terms is simply a matter of technical calculations.

The class of models proposed in Section 2.4 can be, in some cases, simplified with reference to physical situations where some specific phenomena are relatively less relevant (or negligible) with respect to others. Indeed, this is the case for cellular systems in the spatially homogeneous case with a distribution over the velocity variable that is uniform or constant in time, i.e., with ***dominant biological interactions***. The evolution equations are obtained by integrating over the domain of the velocity variable in a physical condition such that the distribution over the velocity variable is constant in time and uniform in the space variable:

$$f_i(t,\mathbf{v},\mathbf{u}) = f_i^b(t,\mathbf{u})P(\mathbf{v})\,, \qquad \int_{D_\mathbf{v}} P(\mathbf{v})\,d\mathbf{v} = 1\,. \tag{2.5.1}$$

Using the above assumptions by substituting (2.5.1) into (2.4.4) yields, after an integration over the velocity variable, the mathematical model for a system on n cell populations:

$$\begin{aligned}\frac{\partial f_i^b}{\partial t}(t,\mathbf{u}) = &\sum_{j=1}^{n} \eta_{ij}^0 \int_{D_\mathbf{u}\times D_\mathbf{u}} \mathcal{B}_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u}) f_i^b(t,\mathbf{u}_1) f_j^b(t,\mathbf{u}_2)\,d\mathbf{u}_1\,d\mathbf{u}_2 \\ &- f_i^b(t,\mathbf{u}) \sum_{j=1}^{n} \int_{D_\mathbf{u}} \eta_{ij}^0 \big[1-\mu_{ij}(\mathbf{u},\mathbf{u}_2)\big] f_j^b(t,\mathbf{u}_2)\,d\mathbf{u}_2\,, \end{aligned} \tag{2.5.2}$$

where

$$\eta_{ij}^0 = \int_{D_\mathbf{v}\times D_\mathbf{v}} c_{ij}|\mathbf{v}-\mathbf{v}_2| P(\mathbf{v}_2)P(\mathbf{v})\,d\mathbf{v}_2\,d\mathbf{v}\,. \tag{2.5.3}$$

An analogous argument can be applied to the case of ***dominant mechanical interactions***. This is the case of cellular systems with a uniform or constant in time distribution over the biological variable. In other words, rules covering mechanical interactions depend on the biological states of the interacting pair. However, the distribution over the biological state is not influenced by interactions. In this case, the evolution equation is the one over the mechanical variable obtained by integrating over the domain of

the biological variable. Calculations are analogous to those we have seen above. Now, the preliminary assumption is

$$f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) = f_i^m(t,\mathbf{x},\mathbf{v})P(\mathbf{u})\,, \qquad \int_{D_\mathbf{u}} P(\mathbf{u})\,d\mathbf{u} = 1\,. \tag{2.5.4}$$

Moreover, the proliferation term is equal to zero: $\mu_{ij} = 0$. Then, substitution into (2.4.4) and averaging over the biological variable yields

$$\begin{aligned}\frac{\partial}{\partial t} f_i^m(t,\mathbf{x},\mathbf{v}) = \sum_{j=1}^{n} \int_{D_\mathbf{v}\times D_\mathbf{v}} & c_{ij}|\mathbf{v}_1-\mathbf{v}_2|\mathcal{M}_{ij}^m(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}) \\ & \times f_i^m(t,\mathbf{x}_1,\mathbf{v}_1) f_j^m(t,\mathbf{x}_2,\mathbf{v}_2) d\mathbf{v}_1\, d\mathbf{v}_2 \\ & - f_i^m(t,\mathbf{x},\mathbf{v}) \sum_{j=1}^{n} \int_{D_\mathbf{v}} c_{ij}|\mathbf{v}-\mathbf{v}_2| f_j^m(t,\mathbf{x}_2,\mathbf{v}_2) d\mathbf{v}_2\,, \end{aligned} \tag{2.5.5}$$

where

$$\mathcal{M}_{ij}^m(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}) = \int_{D_\mathbf{u}\times D_\mathbf{u}} \mathcal{M}_{ij}(\mathbf{v}_1,\mathbf{v}_2;\mathbf{v}|\mathbf{u}_1,\mathbf{u}_2) P(\mathbf{u}_1)P(\mathbf{u}_2)\,d\mathbf{u}_1\,d\mathbf{u}_2\,. \tag{2.5.6}$$

2.6 Discrete Models

Biological cellular systems may in some cases be characterized by a discrete, rather than continuous, biological state. For instance, in some cases biological functions may be identified by two states: an active state and a totally suppressed state.

The discretization is motivated by various considerations. Specifically, it is sometimes useful in computational treatments to reduce the computational complexity of the continuous equations. In other cases, it is motivated by the biological analysis: this happens when the microscopic state, rather than being represented by a continuous distribution, can attain only a finite number of values.

A systematic analysis of the discretization of generalized kinetic models was proposed by Bertotti and Delitala (2004), where well-posedness problems are discussed and an application to modelling social competition is proposed.

It can be anticipated, referring to the continuous and discrete Boltzmann equations proposed in the Appendix, that the evolution equation for the discretized distribution function is a system of partial differential equations corresponding to the integro-differential system which describes the evolution of the continuous distribution function. On the other hand, in the spatially homogeneous case, the evolution equation for the discretized function is a system of ordinary differential equations. In principle, if the number of populations is greater than one, the model can even be a hybrid one with continuous distributions for some populations (or at least, one population) and discrete distributions for others, leading to a system mixing partial differential and integro-differential equations.

The contents will be organized in two subsections. The first one refers to the spatially homogeneous case corresponding to the discretization for a system with more than one population and with biological dominant interactions; the second subsection generalizes the above analysis to the discretization to a nonhomogeneuosly distributed system.

2.6.1 Discrete Space Homogeneous Systems

Consider a model with dominant biological interactions. A discrete model in the spatially homogeneous case means that the biological variable is discretized into a set of values

$$I_{\mathbf{u}} = \{\mathbf{u}_1 \, , \, \dots \, , \, \mathbf{u}_i \, , \, \dots \, \mathbf{u}_p\} \, , \tag{2.6.1}$$

while the evolution equation refers to the densities f_i^α, corresponding to the α^{th} population and to the i^{th} state. The original system of n integro-differential equations is replaced by a system of $n \times p$ ordinary differential equations.

The derivation follows the same line we have seen for the continuous model. The first step is the modelling of microscopic interactions, which are described by the following quantities:

- The ***encounter rate***: $\eta_{\alpha\beta}$, for each pair of interacting populations α, β;
- The ***transition probability density***:

$$\mathcal{B}_{hk;i}^{\alpha\beta} = \mathcal{B}(\mathbf{u}_h, \mathbf{u}_k; \mathbf{u}_i) \, : \quad I_{\mathbf{u}} \times I_{\mathbf{u}} \times I_{\mathbf{u}} \, \rightarrow \, \mathbb{R}_+ \, , \tag{2.6.2}$$

which is the probability density for a ***test*** individual of the α^{th} population with state $\mathbf{u}_h$ to fall into the state $\mathbf{u}_i$ (in the same population) after an interaction with a ***field*** individual of the β^{th} population with state $\mathbf{u}_k$. The transition density functions have the structure of a probability density

with respect to the variable $\mathbf{u}_i$:

$$\forall\, h,k,\alpha,\beta\ :\quad \sum_{i=1}^{n}\mathcal{B}_{hk;i}^{\alpha\beta}=1\,. \tag{2.6.3}$$

• The ***source/sink term*** $\mu_{ik}^{\alpha\beta}$ is the self-proliferation or self-destruction rate of a test individual of the α^{th} population with state $\mathbf{u}_i$ due to its interactions with the field individual of the β^{th} population with state $\mathbf{u}_k$. Interactions occur with the above-defined encounter rate.

Applying the same balance equation we have seen for the continuous model yields

$$\frac{df_i^\alpha}{dt}=\sum_{\beta=1}^{n}\sum_{h,k=1}^{p}\eta_{\alpha\beta}\mathcal{B}_{hk;i}^{\alpha\beta}f_h^\alpha f_k^\beta-f_i^\alpha\sum_{k=1}^{p}\sum_{\beta=1}^{n}\eta_{\alpha\beta}\left[1-\mu_{ik}^{\alpha\beta}\right]f_k^\beta\,, \tag{2.6.4}$$

for $i=1,\dots,p$ and $\alpha=1,\dots,n$.

The above modelling, which is here simply outlined, can be generalized to the case of models such that the microscopic state also depends on space and velocity.

2.6.2 Discrete Space Non-homogeneous Systems

For simplicity, consider now the case of one single interacting population in which the evolution of the system in space cannot be neglected, so that the discrete distribution function also depends on the velocity variable

$$f_{ij}(t,\mathbf{x})=f(t,\mathbf{x},\mathbf{u}_i,\mathbf{v}_j)\,, \tag{2.6.5}$$

where the discretization is such that $i=1,\dots,n$ for the biological variable and $j=1,\dots,m$ for the velocity. In this case, the encounter rate can be modelled as depending on the relative velocity of the interacting pair:

$$\eta_{hk}=\eta_0|\mathbf{v}_h-\mathbf{v}_k|\,, \tag{2.6.6}$$

where η_0 is a constant. Moreover, as in the spatially homogeneous case, one can define the transition probability density:

$$A_\sigma^{ij}=A(\mathbf{u}_h,\mathbf{v}_r,\mathbf{u}_k,\mathbf{v}_s;\mathbf{u}_i,\mathbf{v}_j)\,,\qquad \sum_{i=1}^{n}\sum_{j=1}^{m}A_\sigma^{ij}=1\,, \tag{2.6.7}$$

where $\sigma=\{h,k,r,s\}$. The transition probability density A_σ^{ij} defines the probability density that a subject with state $(\mathbf{u}_h,\mathbf{v}_r)$ interacting with a subject with state $(\mathbf{u}_k,\mathbf{v}_s)$ falls into the state $(\mathbf{u}_i,\mathbf{v}_j)$.

Following the same reasoning developed in the preceding section generates the following system of partial differential equations:

$$\frac{\partial f_{ij}}{\partial t} + \mathbf{v}_j \nabla_{\mathbf{x}} f_{ij} = \sum_{\sigma} \eta_{rs} A_{\sigma}^{ij} f_{hr} f_{ks} - f_{ij} \sum_{k=1}^{n} \sum_{s=1}^{m} \eta_{js} f_{ks} + f_{ij} \sum_{k=1}^{n} \sum_{s=1}^{m} \eta_{js} \mu_{ik} f_{ks} \,, \qquad (2.6.8)$$

for $i = 1, \ldots, n$ and $j = 1, \ldots, m$.

2.7 Critical Analysis

A general mathematical framework has been proposed in this chapter to model, by systems of integro-differential equations, the evolution of large systems of interacting cells organized into several populations. The description is derived from the distribution functions over the microscopic states, biological and mechanical, of the cells.

It is worth stressing that the above-mentioned equations should be regarded as a general framework that can be particularized into specific models. The models can be obtained by specifying the populations which participate, as well as the type of microscopic interactions, so the specific model is related to the observed biological phenomena by defining the participating populations and the microscopic interaction rules among them.

Models generated by the above framework are intended to describe biological systems constituted by several interacting entities. The overall evolution of the system is determined by the above-mentioned interactions. The applications dealt with in the chapter which follows essentially refer to the immune competition, in particular to the competition between tumor and immune cells. However, these applications have to be regarded as particular ones. Additional examples can hopefully be developed using the mathematical framework developed in this chapter; some additional examples will be given in the last chapter.

The class of equations proposed in Section 2.4 is derived on the basis of the assumption of a continuous dependence on the microscopic state, while the class of equations derived in Section 2.6 assumes that the microscopic state can attain a finite number of states. This choice is not simply induced by the need for reducing the computational complexity related to the application of models, but by the aim of dealing with specific biological states

which may be effectively observed to attain discrete values. More generally, it is possible to deal with hybrid systems, such that for some populations the distribution is continuous while for others it is discrete.

The class of equations proposed in Section 2.5 refers to relatively less complex physical situations, such as the spatially homogeneous case; however, several interesting phenomena can still be mathematically described by these models, as we shall see in the next chapters.

It may be useful, in view of the applications proposed in the next chapters, to analyze the above framework with respect to technically different approaches known in the literature. This critical analysis is developed through two steps: first the mathematical framework is compared with different structures, and then it is shown how it can be particularized into specific models, described by equations belonging to the so-called generalized kinetic (Boltzmann) theory.

Generally, the modelling of complex biological systems, and in particular multicellular systems, requires integrating processes occurring across a range of spatial and temporal scales. Phenomena resulting from cellular interactions, such as dynamics of cellular tissue and tumors, cannot be deduced from experimental analysis only; they need to be fitted into a collaborative context with experiments related to mathematical models.

The simplest approach consists of describing biological phenomena by coupled systems of ordinary differential equations in which one assumes that the system is "well-stirred," so that all spatial information is lost and all individuals (cells or biological molecules) are assumed to have identical spaces. The limit of this approach is that all individuals are supposed to be identified by an identical microscopic state constant in time. Only the number of individuals may change in time, referring to various interacting populations, each characterized by a certain microscopic state.

Several models are available in the literature: among others, Nani and Freedmann (2000); D'Onofrio (2005 and 2006); and De Pillis, Radunskaya, and Wiseman (2005). These models in some cases are able to describe overall macroscopic phenomena. Certainly, the above-cited papers have this ability; on the other hand, the description at a cellular scale is lost.

A relatively more sophisticated approach is to model large systems of interacting individuals with an internal state which is assumed to be the same for all individuals. The modelling is driven by partial differential equations; this mathematical approach is well documented in the works by Webb (1985), (1986), and (1987) and is still an object of interest to applied mathematicians as documented in a variety of recent papers, e.g., Michel (2006) and Kheifetz, et al. (2006).

The framework proposed in this chapter will generate individual-based models, in which each element may represent an individual with assigned characteristics that can vary from one individual to the next. This approach allows for populations' behavior to respond and adapt to individual-level

interactions.

It can be shown how the framework includes, as specific applications, some models well known in the literature. This type of analysis may be useful in understanding how the mathematical approach can be used towards modelling complex biological systems by acting as a general paradigm.

An immediate application is Jager and Segel's model (1992), which describes the behavior of colonies of insects which in time evolve towards small groups of dominant insects which organize the behavior of groups below them. This particular behavior is experimentally observed by Hogeweg and coworkers (1981), who report a variety of empirical data which are properly described by this model.

Specifically, Jager and Segel's model refers to the mathematical structure (2.5.2) when the microscopic state is a scalar and the model refers to one population only. That is, the model can be written as

$$\frac{\partial f}{\partial t}(t,u) = \int_0^1 \int_0^1 \eta^0 \mathcal{B}_{ij}(u_1,u_2;u) f(t,u_1) f(t,u_2)\, du_1 du_2 - f(t,u) \int_0^1 \eta^0 f(t,u_2)\, du_2 \,, \tag{2.7.1}$$

in absence of proliferating or destructive events. The microscopic state u is defined in the interval $[0,1]$, where $u = 0$ corresponds to the lowest level of domination, while the greatest level corresponds to $u = 1$. The authors suggest in their paper the use of models with discrete states, thus corresponding to the structures proposed in Section 2.6.1.

Another particularization which is worth mentioning is the "velocity jump model" proposed by Othmer, et al. (1988, 1997, 2002) to describe the motion of microorganisms.

The model is written as

$$\left(\frac{\partial}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}}\right) f(t,\mathbf{x},\mathbf{v}) = -\lambda f(t,\mathbf{x},\mathbf{v}) + \lambda \int_{D_{\mathbf{v}}} T(\mathbf{v},\mathbf{v}_2) f(t,\mathbf{x},\mathbf{v}_2)\, d\mathbf{v}_2 \,, \tag{2.7.2}$$

where it is assumed that the random velocity changes are the result of a Poisson process of intensity λ so that λ^{-1} is the mean run length time between the random choices of direction. Finally, the kernel $T(\mathbf{v},\mathbf{v}_2)$ represents the probability of change in velocity from $\mathbf{v}_2$ to $\mathbf{v}$. T is taken to be nonnegative and normalized, so that

$$\int_{D_{\mathbf{v}}} T(\mathbf{v},\mathbf{v}_2)\, d\mathbf{v} = 1 \,. \tag{2.7.3}$$

It is also assumed that T is independent of the time interval between two consecutive jumps.

The above models are characterized by the absence of proliferating or destructive phenomena. On the other hand, the models dealt with in the chapters which follow include these specific events, which play a relevant role in several biological phenomena.

Let us now complete our analysis by showing how aggregation and fragmentation phenomena of clusters of cells can be described by models still related to the frameworks proposed in this chapter. The modelling can be written as follows:

$$\frac{\partial c}{\partial t}(t,x) = \frac{1}{2}\int_0^x K(y, x-y)\, c(t,y)\, c(t, x-y)\, dy - c(t,x)\int_0^\infty K(x,y)\, c(t,y)\, dy\,, \tag{2.7.4}$$

where $c(t,x)$ denotes the concentration of individuals of a certain population with size x at time t. The first term on the right-hand side of (2.7.4) represents coagulation of individuals of size x by means of binary encounters with individuals of sizes y and $(x-y)$ respectively. The mechanism by which aggregation occurs is encoded in the choice of the coagulation kernel $K(x,y)$. On the other hand, the second term describes the loss of x-sized individuals through encounters with individuals of any size $y > 0$, which results in the formation of clusters of size $(x+y)$. In many physical situations, when clusters grow sufficiently large, fragmentation effects (which introduce reversibility into the process) become relevant. These are contained in (2.7.4) but could easily be accounted for by adding suitable integral terms.

Originally, the model was introduced by means of discrete equations by Smoluchowski (1916); see also Chandrasekhar (1943) for an illuminating review. Equation (2.7.4) and its discrete counterpart

$$\frac{dc_k}{dt} = \frac{1}{2}\sum_{i+j=k} a_{ij} c_i c_j - c_k \sum_{j=1}^{\infty} a_{kj} c_j \qquad (k \geq 1)\,, \tag{2.7.5}$$

where c_k is the size of the clusters, has been extensively used to analyze a number of problems in population dynamics.

The above examples can be regarded as simple particularizations, while those dealt with in the chapters which follow aim at dealing with relatively more complex phenomena. The various examples shown above describe systems in the spatially homogeneous case. Their generalization to

space-dependent phenomena can be dealt with by appropriate techniques, as documented in the book by Arlotti, et al. (2003).

3

Modelling the Immune Competition and Applications

... history of life can be described as the evolution of systems that manipulate one set of symbols representing inputs into another set of symbols that represent outputs.

— Hartwell, et al.

3.1 Introduction

The analysis developed in Chapter 2 has provided a general mathematical framework which can be used as a background to model specific biological phenomena related to complex multicellular systems. Mathematical models can be designed by identifying the cell populations which participate, and then, according to the specific biological phenomena, by modelling pair interactions at the microscopic level between cells of the same or different populations.

An effective criterion for defining the populations which are involved in the competition can be found by following the suggestions of the paper by Hartwell, et al. (1999): every cell population will be identified essentially by the ***functional modules*** which it performs. Hartwell says,

> "A functional module is a discrete entity whose function is separable from those of others modules. Modules can be insulated from or connected to each other; the connectivity allows one function to influence another, and the higher-level properties of the cells will be described by the pattern of connections among their functional modules."

However, the above modelling technique needs to take into account several complexity problems, originating, for instance, from the large number of cell populations involved, the large number of cells in each population, and the interplay between the mechanical and biological variables characterizing the cells' microscopic states.

As mentioned in Chapter 2 and in the Appendix, a way to overcome the complexity arising from the mathematical representation of a system at the microscopic scale can be found in the statistical description of the system, applying the tools typical of mathematical kinetic theory. The system is described as a swarm of various interacting cell populations where each cell is characterized by a certain microscopic biological state, statistically distributed among the cells.

The system is described by a distribution function over the microscopic state of the interacting cells. The derivation of the equations describing the evolution of the above distribution is obtained from conservation equations in the space of the microscopic states, while the fluxes of cells in the elementary volume of this space are computed by taking advantage of models of microscopic interactions.

This chapter deals with the mathematical modelling of the immune competition. Specifically, it deals with the competition between immune cells and cells which are carriers of a pathology. The contents are developed in four sections:

Section 3.2 provides a phenomenological description of the physical system which is going to be modelled using the various mathematical tools developed in Chapter 2.

Section 3.3 deals with the derivation of mathematical models suitable for describing the evolution and competition between cells of the immune system and cells which are carriers of a certain pathology.

Section 3.4 shows how some particularizations of the general model derived in Section 3.3 provide specific, relatively simpler models which can describe particular, though interesting, aspects of the immune competition.

Section 3.5 develops a critical analysis of the contents of Sections 3.3 and 3.4, in view of further derivation of new models.

3.2 Phenomenological Description

The ***immune system***, in multicellular organisms, is an organ system that acts as a defense against foreign pathogens (viruses, bacteria, parasites) as well as against internal cellular disorder.

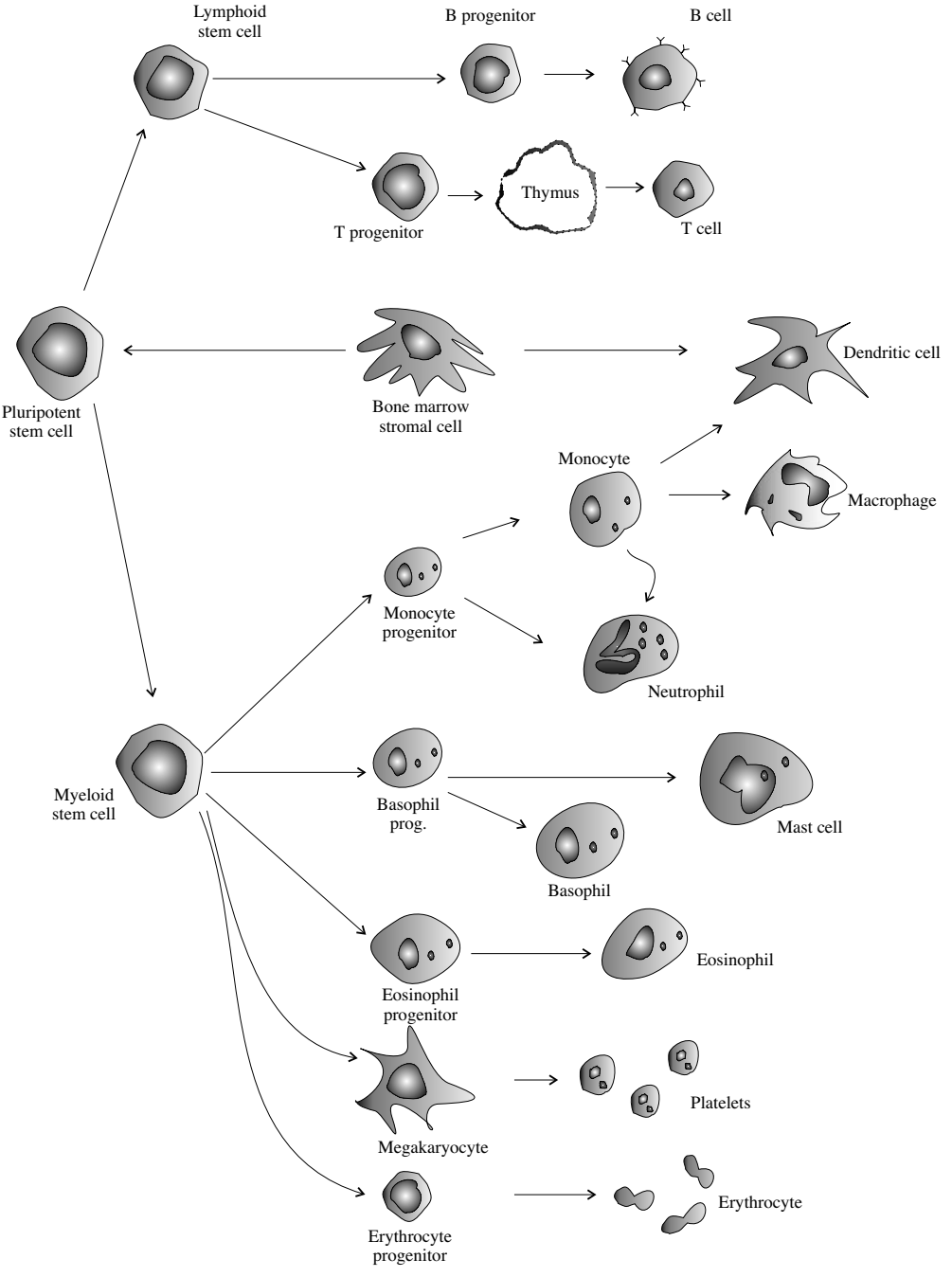

Fig. 3.1. The immune system involves different populations of cells.

The immune system can be regarded as an organization of substances and cooperating cells with specialized roles for the defense against infection. The immune system plays its defensive role through the recognition of ***non-self*** substances, detecting particular molecular patterns, the ***antigens***, which are associated with the foreign pathogen agents.

The process is quite a sophisticated one, as the immune system needs to evolve and change in time, recognizing some non-self substances as non-offending elements (i.e., cellular feeding substances, growing embryos in the mother) and learning to identify new pathogen agents not previously encountered. The task is performed by several populations of specialized cells as well as by biochemical substances (proteins, enzymes etc.). Figure 3.1 shows some of the most common subpopulations of cells of the immune system. For a short description of their roles, the reader is referred to the Glossary.

The immune system reacts to pathogen agents by means of two different kinds of response: innate response and acquired response. The ***innate response*** is quickly activated and occurs every time the infectious agent is encountered and detected through the recognition of its specific molecular pattern. The innate response uses two main components to fight the infection: specialized cells of the family of leukocytes and the complement system. The complement system is a large family of low–molecular weight proteins and cytokines: it responds to the detected infection with a reaction chain that starts increasing blood flow in the area, then attracts phagocytic cells by releasing molecules that active chemotaxis, and finally attempts to perforate the membrane of the target cell. The leukocytes involved in the innate response are phagocytic cells, like neutrophils and macrophages; cells that release inflammatory mediators, like basophils and eosinophils; and "natural killer" (cytotoxic) cells. They act by engulfing the pathogen agent or lysing it.

Figure 3.2 shows a macrophage which engulfs a pathogen agent and then exposes fragments of it to stimulate the production of specific antibodies.

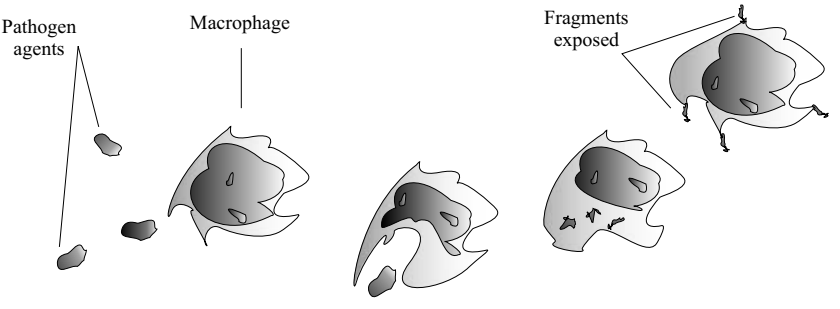

Fig. 3.2. Phagocytosis.

The ***acquired response*** is activated after repeated exposures to a given infection, and uses the mechanism of proliferation of B and T cells, lymphocytes of the family of leukocytes. B cells, stem cells which matured into the bone marrow, retain memory of the specific pathogen patterns encountered during the primary immune response and can produce specific antibodies. T cells are stem cells which matured in the thymus, and are divided into "helper" and "killer" T cells. T-helper cells may recognize virally infected or neoplastic cells, or may be activated by a macrophage which exposes fragments of a pathogen that it previously engulfed. The T cell compares the exposed structure to similar structures on the cell membrane of a B cell, and, if there is a matching pair, it activates the B cell; then both T and B cells migrate out of the lymph nodes in which they reside and proliferate.

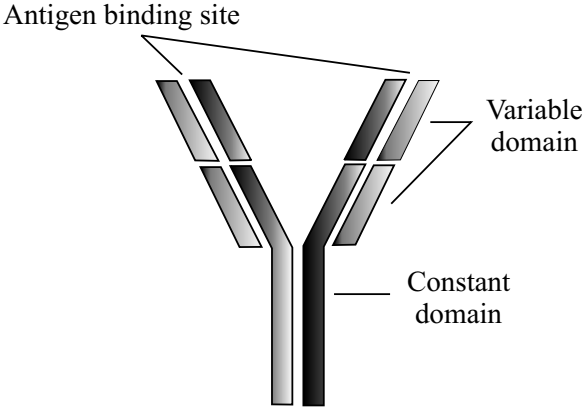

Fig. 3.3 Antibody.

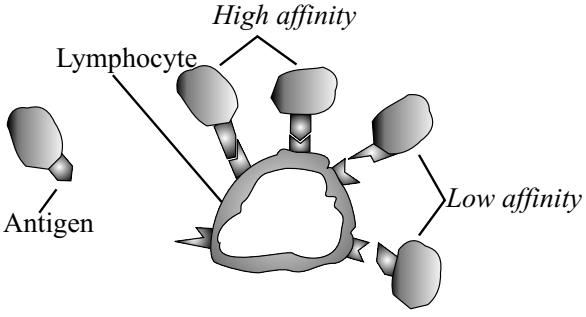

Fig. 3.4 Binding process.

B cells produce specific antibodies against the recognized antigens. An-

tibodies attack pathogens by binding them at the variable binding domain, the end of the "Y" antibody shape (Figure 3.3), and cooperate to destroy them by directly eliminating extracellular microorganisms or by facilitating the binding to the constant domain by the other immune cells, (Figure 3.4). Antibodies are specific to only one antigen, and in binding to it, they cause "agglutination" of antibody–antigen products prime for phagocytosis by macrophages.

The acquired response is divided into the "humoral immune response" and the "cellular immune response" (or "cell-mediated immune response"). Both responses are controlled by T-helper cells, and they occur when the T-helper cell is activated and releases a specific cytokine. In the humoral immune response the cytokine stimulates B cells to proliferate and to differentiate into "plasma cells," which secrete free-flowing antibodies. In the cellular immune response, the cytokine activates the T-killer (cytotoxic) cells, which attack the infected body cells, lysing them or committing them to apoptosis. Figures 3.5 and 3.6 show a schema of the humoral immune response and the cellular immune response.

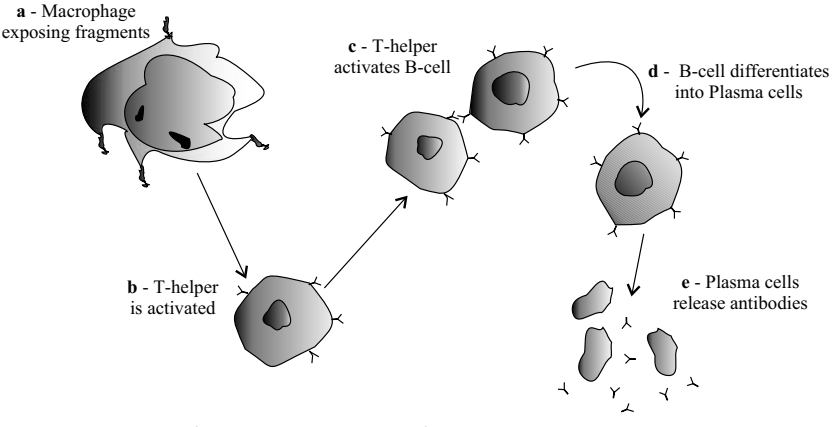

Fig. 3.5. Humoral immune response.

The activated lymphocytes are long-term survivors, thus retaining a "memory" of the infection and allowing a fast response in the case of repetition of the infection, while the innate response lacks of this kind of immunologic memory.

Innate and acquired responses work together against the infection; in both cases the defense starts from the recognition of the pathogen agents. It is a complex process in which several components of the immune system cooperate in order to reach the objective, from the detection of the infection to the proliferation of the leukocytes specialized against the pathology.

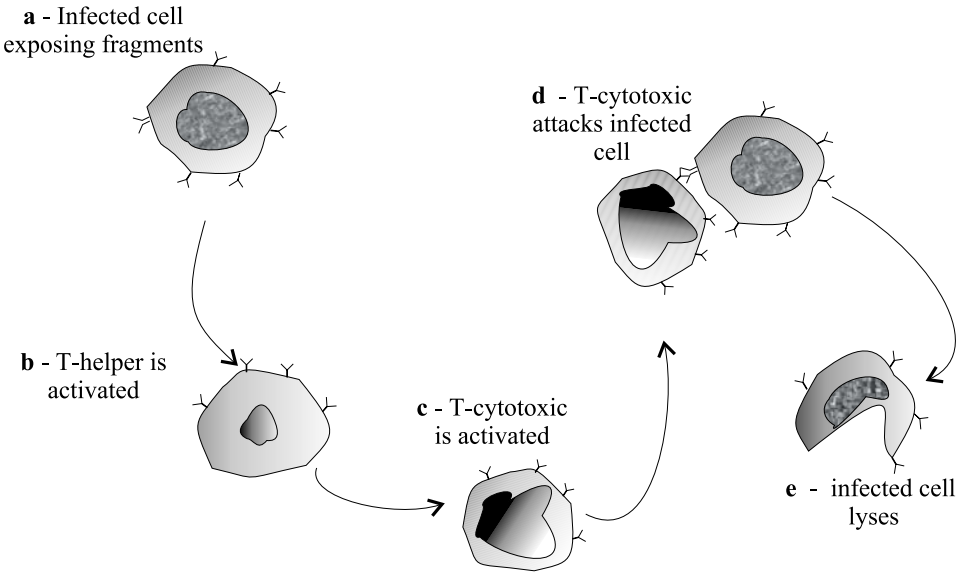

Fig. 3.6. Cell-mediated immune response.

On the other hand, ***abnormal cells***, i.e., cells that are carriers of a particular pathology, virally infected or neoplastic cells, may proliferate, rapidly increasing the number of infecting individuals or inhibiting in some way the functionality of the immune system. In this point of view, the neoplastic invasion may be described as a kind of infection, and the competition between neoplastic and immune cells is ruled by the dynamics of the two interacting systems. Tumor cells may be regarded as an aggressive host, at least at early stage of the tumor.

A ***tumor*** may be generally defined as a disease originated through some kind of cellular disorder, which allows certain cellular populations to manifest deviant characteristics. The life of each cell is regulated by the genes contained in its nucleus; when signals stimulate receptors on the cell surface and are transmitted to the nucleus of the cell, the genes can either be activated or inhibited. Typically a series of several genetic mutations is required before a cell becomes a tumor cell. The process involves both oncogenes and tumor suppressor genes: oncogenes promote tumors when activated by a genetic mutation, whereas tumor suppressor genes prevent tumors unless inhibited by a mutation. In general, mutations in both types of genes are necessary, as a mutation limited to an oncogene would be suppressed by normal cell-life control. A normal cell may start to deviate from genetic normality through slow degradation and variation of the genome or through some catastrophic event. The degenerated cells receive the signal of apoptosis, the natural way of death of the cell, but they may bypass

the signal because they are able, by synthesizing for themselves suitable proteins, to "escape" the natural checks to avoid uncontrolled corruption and proliferation. Once the genetic mutations are concluded, the tumor starts its clonal proliferation; the newborn cells remain genetically almost constant and start growing in number and volume.

At this stage, tumor cells start to compete with the immune system, and, if not recognized and depleted, start to condense into a solid form: this is the passage from the microscopic (cellular) scale to the macroscopic scale. Figure 3.7 shows a "live" picture of a T cell competing with a tumor cell and thus attempting to neutralize the pathogen agent.

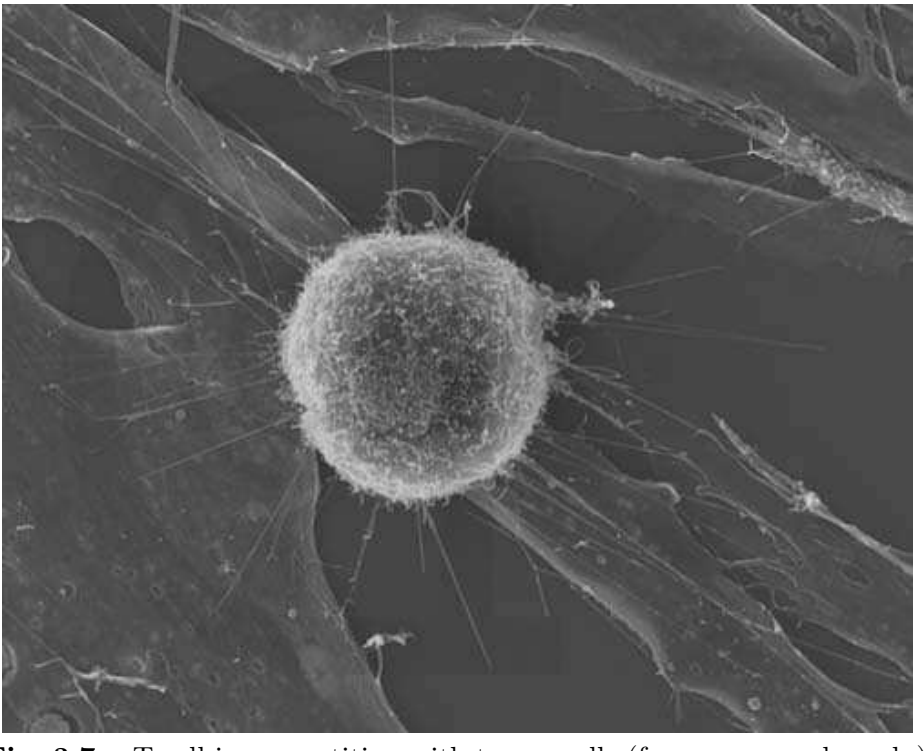

Fig. 3.7. T cell in competition with tumor cells (from www.med.sc.edu).

The competition between the immune system and a pathogen agent is quite a complicated process, where cellular and subcellular phenomena play a relevant role in the evolution of the competition. It may be described through the interactions of several cellular populations, related to immune system cells as well as to abnormal cells: if some differences at multiple levels of cellular biological organization (genetic, phenotypic, cellular, etc.) among individuals of the same population are exhibited, leading to progressively increasing cellular heterogeneities (genotypic, phenotypic, spatial and temporal), the immune cells are activated and the competition starts. See, among others, Greller, Tobin, and Poste (1996), Herberman

(1982), and Forni, et al. (1994).

The paper by Greller, Tobin, and Poste (1996) provides some significant hints addressed to the description of multicellular systems by equations of statistical mechanics. Their approach provides a schema for building conceptual models of the evolution of tumors, combining three phenomenological features: genetic instability of the cells, growth of the tumor, and its progression. The ***progression*** is the complex of the phenotypic changes which may be observed in a large spectrum of tumor properties, and describes, through an aggregate property, the degeneration of normal cells toward replicant and eventually metastatic states.

Models can be built for different tumor situations through the study of the interactions of the three driving elements, genetic heterogeneity, growth of the tumor, and its progression; moreover, these elements can be used to explore the dynamic changes in cellular populations during tumor progression. As Greller, et al. say, "The modeling paradigm acts as a consistent descriptive language for describing the complex interactions between genetic heterogeneity of the cells and progression of the tumor."

That language can be further converted into mathematical equations, and, to the degree that a model is an adequate representation of biological reality, it can be used to explore hypotheses and perform *in silico* experiments that are impractical *in vitro*.

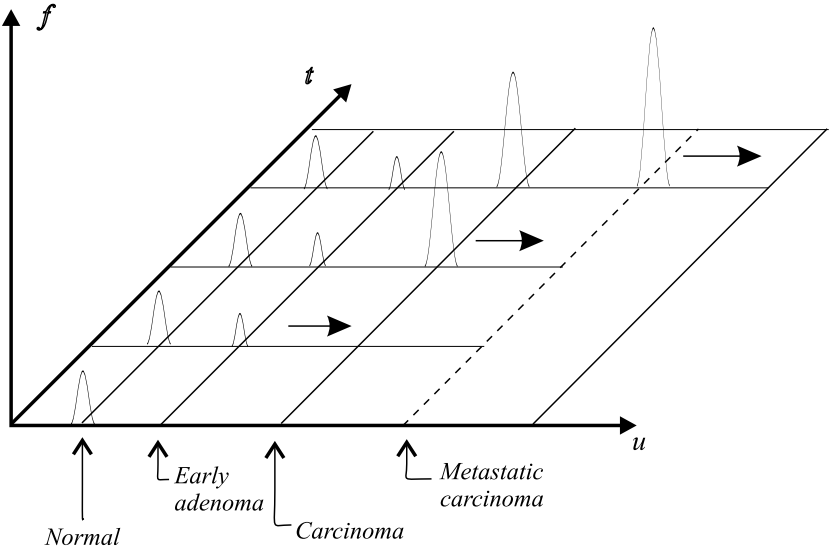

Fig. 3.8. Evolution of progression distributions.

The progression of a tumor, due to random irreversible genetic mutations, may provide a criterion for describing the collective changes that will

develop in the tumor: in this way, it is possible to compare two tumors that may evolve similarly. As stated in the paper by Greller, Tobin, and Poste (1996), "Tumor cellular populations are characterized by progression distributions, progression velocities, and progression-dependent growth rates. Major genetic changes alter the tumor dynamics as each subpopulation moves further away from genetic normality."

Figure 3.8 summarizes these concepts in a schematic representation of the progression distribution for a tumor progressing over time to a metastatic competence.

The mathematical model discussed below refers to the immune competition. It deals with the dynamics between immune cells and abnormal cells, carriers of different types of pathology, and the formulation offers a relatively broad mathematical framework for the competition between the immune system and many types of pathology. In Chapter 5, a suitable selection of the parameters of the model will define a specific application of the model to the tumor–immune competition and to the concept of progression.

3.3 Modelling the Immune Competition

Given the various phenomena described in Section 3.2, the general framework proposed in Chapter 2 can be specialized to model the immune competition at the cellular level between immune cells and abnormal cells.

As discussed in the previous section, the immune system involves several different subpopulations of cells; however to simplify the complexity induced by considering a large number of subpopulations, we will consider the immune cells as only one population. Therefore, this population develops activities which really are distributed among several particular subpopulations. An analogous simplification will be carried out for the cells or particles that are carriers of a pathology.

As mentioned in the previous chapter, each cell is characterized by a certain microscopic biological state. Cell interactions may either modify the state of each cell or the number of cells in each population by proliferation/destruction phenomena.

The formal framework proposed in Chapter 2 is specialized into a specific model by detailed assumptions based on a mathematical interpretation of the phenomenological behavior of the system. Bearing all of the above in mind, the following assumptions are proposed.

Assumption 3.3.1. *(**Cell populations**) The system is constituted by two interacting cell populations: environmental and immune cells, labelled, respectively, by the indexes $i = 1$ and $i = 2$. Cells are homogeneously distributed in space.*

Assumption 3.3.2. *(**Cell state**) The functional state of each cell is described by a real variable $u \in (-\infty, \infty)$. For the environmental cells, the above variable refers to the **natural** state (normal endothelial cells) for negative values of u and to the **abnormal** or pathological state (abnormal cells or cells which have lost their differentiated state and become pathological cells) for positive values of u. For the immune cells, negative values of u correspond to nonactivity or **inhibition**; positive values of u correspond to **activation**.*

Assumption 3.3.3. *(**Statistical description**) The statistical description of the system is defined by the normalized distribution density functions*

$$f_i^b(t,u) = \frac{1}{n_{10}^b} N_i^b(t,u)\,, \tag{3.3.1}$$

where the densities $N_i^b = N_i^b(t,u)$ are such that $dn_i^b = N_i^b(t,u)\,du$ denotes the number of cells per unit volume whose state is, at time t, in the interval $[u, u+du]$, and n_{10}^b is the number per unit volume of environmental cells at $t = 0$.

According to the above assumptions, the reference framework is the one proposed in Section 2.5, which corresponds to biological dominant interactions.

Before going further, some notations need to be specified. In the following discussion the superscript b which characterizes the distribution function will be dropped: $f^b(t,u) = f(t,u)$, because the biological interaction is predominant. Moreover, since there are no more mechanical variables, the microscopic states of the test cell and the field cell will be denoted respectively by v and w (instead of u_1 and u_2), so that the transition density function is denoted by $\mathcal{B}_{ij}(v,w;u)$. In this simplified notation, the subscript number will refer only to populations involved in the competition.

Equation (2.5.2) can be rewritten, according to the above notation, as follows:

$$\begin{aligned}\frac{\partial}{\partial t} f_i(t,u) = &\sum_{j=1}^{2} \eta_{ij}^0 \int_{D_u \times D_u} \mathcal{B}_{ij}(v,w;u) f_i(t,v) f_j(t,w)\, dv\, dw \\ &+ f_i(t,u) \sum_{j=1}^{2} \eta_{ij}^0 \int_{D_u} [\mu_{ij}(u,w) - 1] f_j(t,w)\, dw\,. \end{aligned} \tag{3.3.2}$$

Specific models are generated by a detailed modelling of cell interactions.

Assumption 3.3.4. *The **encounter rate** is assumed to be constant and equal to unity for all interacting pairs, hence* $\eta_{ij}^0 = \eta = 1$, $\forall\, i, j = 1, 2$.

Introducing the stepwise function $U_{[a,b]}(z)$ such that $U_{[a,b]}(z) = 1$ if $z \in [a, b]$ and $U_{[a,b]}(z) = 0$ if $z \notin [a, b]$, and referring to assumptions 3.3.1 and 3.3.2, we state the following assumptions in order to model the conservative and proliferating microscopic interactions:

Assumption 3.3.5. *The transition probability density related to **conservative interactions** is assumed to be a Gaussian distribution function with the most probable output defined by the mean value* $m_{ij}(v, w)$*, which may depend on the microscopic state of the interacting pair, and with a finite variance* s_{ij}*:*

$$\mathcal{B}_{ij}(v, w; u) = \frac{1}{\sqrt{2\pi s_{ij}}} \exp\left\{ -\frac{(u - m_{ij}(v, w))^2}{2 s_{ij}} \right\}. \tag{3.3.3}$$

Specifically, referring to every possible conservative pair interaction:

• ***Interactions between cells of the first population:*** Cells of the first population show a tendency to degenerate with most probable output given as follows:

$$v, w \in \mathbb{R} : \quad m_{11} = v + \alpha_{11}\,, \tag{3.3.4}$$

where α_{11} is a parameter related to the inner tendency of both a normal and an abnormal cell to degenerate.

• ***Interactions between cells of the first population with the cells of the second population:*** It is assumed that if a cell of the first population is normal, $v < 0$, then its state does not change due to interactions with immune cells. Moreover, if the cell is abnormal, $v \geq 0$, then the state of the cell does not change if the immune cell is not active, $w < 0$:

$$v < 0\,,\, w \in \mathbb{R}\,, \quad v \geq 0\,,\, w < 0 : \quad \mathcal{B}_{12} = \delta(u - v)\,. \tag{3.3.5}$$

On the other hand, for an abnormal cell, i.e., for positive values of v, if the immune cell is active, i.e., $w \geq 0$, then the most probable output is given as follows:

$$v, w \geq 0 : \quad m_{12} = v - \alpha_{12}\,, \tag{3.3.6}$$

where α_{12} is a parameter which indicates the ability of the immune system to reduce the state of cells of the first population.

• ***Interactions between cells of the second population with cells of the first population:*** Immune cells do not change state due to interactions

with normal endothelial cells, $w < 0$. Moreover, if the cell is inhibited, its state also does not change if it interacts with abnormal cells:

$$v \in \mathbb{R}\,,\ w < 0\,, \quad v < 0\,, w \geq 0: \quad \mathcal{B}_{21} = \delta(u - v)\,. \tag{3.3.7}$$

For positive values of w, the transition probability density is a Gaussian distribution, as in (3.3.3), with the most probable output given as follows:

$$v \geq 0\,, w \geq 0: \quad m_{21} = v - \alpha_{21}\,, \tag{3.3.8}$$

where α_{21} is a parameter which indicates the ability of abnormal cells to inhibit immune cells.

• ***Interactions between cells of the second population:*** It is assumed that the interactions between cells of the second population have a trivial output:

$$v, w \in \mathbb{R}: \quad \mathcal{B}_{22} = \delta(u - v)\,. \tag{3.3.9}$$

Assumption 3.3.6. ***Proliferating and destructive interactions*** *in the microscopic state u of the test cell are described by the following models of the proliferation and destruction rates.*

Specifically, referring to every possible nonconservative pair interaction:

• ***Interactions between cells of the first population:*** The proliferation rate of normal endothelial cells, $v < 0$, due to encounters with other endothelial cells, is equal to zero. On the other hand, abnormal cells with $v \geq 0$ proliferate due to encounters with normal cells, which show a feeding ability. Encounters between abnormal cells lead to no proliferation or destruction:

$$\mu_{11}(v, w) = \beta_{11} U_{[0,\infty)}(v) U_{(-\infty,0)}(w)\,, \tag{3.3.10}$$

where β_{11} is a parameter which characterizes the proliferating ability of abnormal cells.

• ***Interactions between cells of the first population with the cells of the second population:*** The proliferation rate of normal cells, $v < 0$, due to encounters with immune cells, is equal to zero. When $v \geq 0$, abnormal cells are partially destroyed due to encounters with active immune cells:

$$\mu_{12}(v, w) = -\beta_{12} U_{[0,\infty)}(v) U_{[0,\infty)}(w)\,, \tag{3.3.11}$$

where β_{12} is a parameter which characterizes the destructive ability of active immune cells.

• ***Interactions between cells of the second population with the cells of the first population:*** The proliferation rate of inhibited immune cells,

$v < 0$, due to encounters with cells of the first population, is equal to zero. When immune cells are active, $v \geq 0$, they proliferate due to encounters with abnormal cells:

$$\mu_{21}(v,w) = \beta_{21} U_{[0,\infty)}(v) U_{[0,\infty)}(w)\,, \tag{3.3.12}$$

where β_{21} is a parameter which characterizes the proliferating ability of immune cells.

• ***Interactions between cells of the second population:*** Encounters between immune cells have always a trivial output, $\mu_{22} = 0$.

Based on the above modelling of cell interactions, the evolution equation (3.3.2) is rewritten as follows:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = \dfrac{n_1(t)}{\sqrt{2\pi s_{11}}} \displaystyle\int_{-\infty}^{\infty} \exp\left\{ -\frac{(u-(v+\alpha_{11}))^2}{2s_{11}} \right\} f_1(t,v)\,dv \\ \qquad\qquad + \dfrac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \displaystyle\int_{0}^{\infty} \exp\left\{ -\frac{(u-(v-\alpha_{12}))^2}{2s_{12}} \right\} f_1(t,v)\,dv \\ \qquad\qquad - f_1(t,u) n_1(t) \\ \qquad\qquad + f_1(t,u) \left[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t) \right] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = \dfrac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \displaystyle\int_{0}^{\infty} \exp\left\{ -\frac{(u-(v-\alpha_{21}))^2}{2s_{21}} \right\} f_2(t,v)\,dv \\ \qquad\qquad + (\beta_{21}-1) U_{[0,\infty)}(u) f_2(t,u) n_1^T(t)\,, \end{cases} \tag{3.3.13}$$

where

$$n_1(t) = \int_{-\infty}^{\infty} f_1(t,u)\,du\,, \qquad n_2(t) = \int_{-\infty}^{\infty} f_2(t,u)\,du\,, \tag{3.3.14}$$

are the zeroth-order momenta representing the densities of each cell population. More specifically,

$$n_1^E(t) = \int_{-\infty}^{0} f_1(t,u)\,du\,, \quad n_1^T(t) = \int_{0}^{\infty} f_1(t,u)\,du\,, \tag{3.3.15}$$

are the densities of normal endothelial cells and abnormal endothelial cells, respectively;

$$n_2^I(t) = \int_{-\infty}^{0} f_2(t,u)\,du\,, \quad n_2^A(t) = \int_{0}^{\infty} f_2(t,u)\,du\,, \tag{3.3.16}$$

are the densities of normal immune cells and active immune cells, respectively.

If the variance goes to zero, a deterministic output in the conservative interaction functions is obtained:

$$s_{ij} \to 0 \quad \Longrightarrow \quad \mathcal{B}_{ij}(v, w; u) = \delta(u - m_{ij}(v, w)) \,. \tag{3.3.17}$$

In this particular case, the evolution equations (3.3.13) reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t)[f_1(t, u-\alpha_{11}) - f_1(t,u)] \\ \qquad\qquad + n_2^A(t) f_1(t, u+\alpha_{12}) U_{[0,\infty)}(u+\alpha_{12}) \\ \qquad\qquad + f_1(t,u)\left[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)\right] U_{[0,\infty)}(u) \,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) f_2(t, u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + (\beta_{21} - 1) n_1^T(t) f_2(t,u) U_{[0,\infty)}(u) \,. \end{cases} \tag{3.3.18}$$

The above model is characterized by six positive phenomenologic parameters, which are small with respect to one:

α_{11} corresponds to the tendency of endothelial cells to degenerate.

α_{12} corresponds to the ability of the active immune cells to reduce the state of abnormal cells.

α_{21} corresponds to the ability of abnormal cells to inhibit the active immune cells.

β_{11} corresponds to the proliferation rate of abnormal cells.

β_{12} corresponds to the ability of immune cells to destroy abnormal cells.

β_{21} corresponds to the proliferation rate of immune cells.

The α parameters are related to conservative encounters, while the β parameters are related to proliferation and destruction phenomena. The next section will show how a suitable specialization of the above parameters can provide models able to describe some particular interesting aspects of the immune competition.

The evolution equations for the densities $n_1^T(t)$ and $n_1^E(t)$ are obtained from (3.3.14)–(3.3.16) by integration of the first equation of (3.3.18) re-

spectively on $\mathbb{R}^+$ and on $\mathbb{R}^-$:

$$\begin{cases} \dfrac{\partial n_1^T(t)}{\partial t} = n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du - n_2^A(t) \int_0^{\alpha_{12}} f_1(t,u)\,du \\ \qquad\qquad + n_1^T(t)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right], \\ \dfrac{\partial n_1^E(t)}{\partial t} = -\,n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du + n_2^A(t) \int_0^{\alpha_{12}} f_1(t,u)\,du\,. \end{cases} \tag{3.3.19}$$

Applying the same procedure to the second equation of (3.3.18) yields the evolution equation for $n_2^A(t)$ and $n_2^I(t)$:

$$\begin{cases} \dfrac{\partial n_2^A(t)}{\partial t} = n_1^T(t)\left[\beta_{21} n_2^A(t) - \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\right], \\ \dfrac{\partial n_2^I(t)}{\partial t} = n_1^T(t) \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\,. \end{cases} \tag{3.3.20}$$

Remark 3.3.1. Systems (3.3.19) and (3.3.20) are not in a closed form, since $f_1(t,u)$ and $f_2(t,u)$ are unknown. However, the above equations are useful, as we shall see in Chapter 4, in view of the qualitative analysis and the study of the asymptotic behavior of the solution of the initial value problem of model (3.3.18).

Remark 3.3.2. Model (3.3.18) can be technically generalized and developed. For instance, we may consider an open system such that the inlet from the outer environment keeps the number of normal cells of the first population constant in time. Moreover, assumption 3.3.6 can be modified by considering a decay of the number of immune cells when the number of abnormal cells also declines.

3.4 Some Technical Particularizations

The mathematical model described in Section 3.3, although it has a very simple structure, can describe several stages of the immune competition: a preliminary stage when cells of the two interacting populations simply modify their respective biological functions, and later the onset of proliferating or destructive phenomena which may end up with the blowup or destruction of the aggressive, maybe invasive, host. The output of the competition

mostly depends on the ability of immune cells to identify and destroy the invading host.

Bearing all of the above in mind, various examples of particularization of the general model proposed in the previous section are reported below with attention to the biological counterpart.

Example: Model C

This first example, called **Model C**, is related to (prevalent) conservative interactions and it is obtained simply equating to zero all β parameters. Thus, as it is characterized only by conservative α parameters, it corresponds to a competition where no proliferation or destruction occurs while interactions only modify and affect the biological functions.

The model, derived from equation (3.3.18), is written as

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t)[f_1(t,u-\alpha_{11}) - f_1(t,u)] \\ \qquad\qquad + n_2^A(t) f_1(t,u+\alpha_{12}) U_{[0,\infty)}(u+\alpha_{12}) \\ \qquad\qquad - f_1(t,u) n_2^A(t) U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) f_2(t,u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad - n_1^T(t) f_2(t,u) U_{[0,\infty)}(u)\,. \end{cases} \tag{3.4.1}$$

The equations for the densities (3.3.19)–(3.3.20) reduce to the following system:

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du - n_2^A(t) \int_0^{\alpha_{12}} f_1(t,u)\,du\,, \\ \dfrac{\partial n_1^E}{\partial t}(t) = -n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du + n_2^A(t) \int_0^{\alpha_{12}} f_1(t,u)\,du\,, \\ \dfrac{\partial n_2^A}{\partial t}(t) = -n_1^T(t) \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\,, \\ \dfrac{\partial n_2^I}{\partial t}(t) = n_1^T(t) \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\,. \end{cases} \tag{3.4.2}$$

System 3.4.2 is not closed, considering that f_1 and f_2 are not known.

Model C can be applied to analyze latent immune competitions when cells degenerate before the onset of relevant proliferation phenomena which give evidence of the presence of a pathological state.

∎

Example: Model P

An analogous reasoning can be applied to the modelling of a stage characterized by the fact that the distribution over the biological functions is almost constant (or slowly varying), while the proliferating or destructive events are predominant. This predominant proliferating or destructive model, later called **Model P**, is obtained from the general model (3.3.18) by setting equal to zero all α-type parameters.

It is related to (prevalent) proliferative/destructive interactions: the biological counterpart is that the cells do not show a natural tendency to degenerate, since $\alpha_{11} = 0$. Moreover, an eventual pathological state is not opposed by immune cells, since $\alpha_{12} = 0$, and abnormal cells cannot inhibit immune cells, since $\alpha_{21} = 0$. In this case, the evolution equation for the distribution function is written as follows:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = f_1(t,u)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = \beta_{21} n_1^T(t) f_2(t,u) U_{[0,\infty)}(u)\,. \end{cases} \tag{3.4.3}$$

This particular model, integrated over the biological variable u, gives four closed equations and thus provides a population dynamic model:

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = n_1^T(t)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right]\,, \\ \dfrac{\partial n_1^E}{\partial t}(t) = 0\,, \\ \dfrac{\partial n_2^A}{\partial t}(t) = \beta_{21} n_1^T(t) n_2^A(t)\,, \\ \dfrac{\partial n_2^I}{\partial t}(t) = 0\,. \end{cases} \tag{3.4.4}$$

In this case, the system is closed and can be analyzed by classical methods of ordinary differential equations.

This model can be used to analyze the last stage of the competition, when both cell populations have reached a fixed stage of the biological functions, and only proliferating or destructive phenomena are relevant.

∎

Both Model C and Model P refer to the mathematical description of the immune competition when certain phenomena are prevalent with respect to the others. Not only is the particularization useful for capturing specific

biological phenomena, but it can be used for the identification of the parameters of the model by comparison between theory and experiment. The idea of separately identifying the parameters corresponding to conservative and proliferative phenomena was suggested by Bellomo and Forni (1994).

The model stated in equation (3.3.18), with both conservative and nonconservative parameters, can be particularized by acting on the α parameters. The selection of the particular examples proposed in what follows does not cover all conceivable possibilities, but it aims to illustrate the ability of the model to describe various aspects of the immune competition.

Three particular models are derived from (3.3.18), setting two of the α parameters equal to zero, while keeping the third one different from zero:

Example: Model I ($\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} > 0$).

Since $\alpha_{11} = 0$, cells do not show a natural tendency to degenerate. Moreover, the pathological state is not opposed by immune cells, as $\alpha_{12} = 0$, while abnormal cells have the ability to inhibit immune cells as $\alpha_{21} > 0$. The evolution equations (3.3.18) reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = f_1(t,u)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) f_2(t, u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) \\ \qquad\qquad + (\beta_{21}-1) n_1^T(t) f_2(t,u) U_{[0,\infty)}(u)\,, \end{cases} \tag{3.4.5}$$

while the equations for the densities become

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = n_1^T(t)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right]\,, \\ \dfrac{\partial n_1^E}{\partial t}(t) = 0\,, \\ \dfrac{\partial n_2^A}{\partial t}(t) = n_1^T(t)\left[\beta_{21} n_2^A(t) - \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\right]\,, \\ \dfrac{\partial n_2^I}{\partial t}(t) = n_1^T(t) \displaystyle\int_0^{\alpha_{21}} f_2(t,u)\,du\,. \end{cases} \tag{3.4.6}$$

Again, as pointed out in Remark 3.3.1, these equations for the densities are not in a closed form; nevertheless they are useful for the study of the asymptotic behavior of the model developed in next chapter.

This model describes competitions where the destructive ability of immune cells, represented by the parameter β_{12}, is progressively reduced by

the inhibition ability of cells which are carriers of a certain pathology. Then the output of the competition can generate a blowup of abnormal cells, although these cells have no tendency to degenerate.

∎

Example: Model II ($\alpha_{11} > 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$).

Since $\alpha_{11} > 0$, cells show a natural tendency to degenerate. This trend is not opposed by immune cells, as $\alpha_{12} = 0$, while abnormal cells cannot inhibit immune cells, as $\alpha_{21} = 0$. The evolution equations (3.3.18) reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t)[f_1(t,u-\alpha_{11}) - f_1(t,u)] \\ \qquad\qquad + f_1(t,u)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = \beta_{21} n_1^T(t) f_2(t,u) U_{[0,\infty)}(u)\,, \end{cases} \tag{3.4.7}$$

while those for the densities reduce to

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du + n_1^T(t)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right]\,, \\ \dfrac{\partial n_1^E}{\partial t}(t) = -n_1(t) \displaystyle\int_{-\alpha_{11}}^{0} f_1(t,u)\,du\,, \\ \dfrac{\partial n_2^A}{\partial t}(t) = \beta_{21} n_1^T(t) n_2^A(t)\,, \\ \dfrac{\partial n_2^I}{\partial t}(t) = 0\,, \end{cases} \tag{3.4.8}$$

which is not closed.

The model is able to describe how the proliferation of abnormal cells may or may not be opposed by immune cells which are not progressively inhibited. In this case, the immune system keeps its destructive ability.

∎

Example: Model III ($\alpha_{11} = 0$, $\alpha_{12} > 0$, $\alpha_{21} = 0$).

Since $\alpha_{11} = 0$, cells do not show a natural tendency to degenerate. The pathological state is opposed by immune cells, as $\alpha_{12} > 0$, while abnormal cells do not inhibit immune cells, as $\alpha_{21} = 0$. The evolution equations (3.3.18) reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_2^A(t) f_1(t, u+\alpha_{12}) U_{[0,\infty)}(u+\alpha_{12}) \\ \qquad\qquad + f_1(t,u)\left[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t)\right] U_{[0,\infty)}(u)\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = \beta_{21} n_1^T(t) f_2(t,u) U_{[0,\infty)}(u)\,, \end{cases} \tag{3.4.9}$$

while those for the densities reduce to

$$\begin{cases} \dfrac{\partial n_1^T}{\partial t}(t) = -n_2^A(t) \displaystyle\int_0^{\alpha_{12}} f_1(t,u)\,du + n_1^T(t)\left[\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right]\,, \\ \dfrac{\partial n_1^E}{\partial t}(t) = n_2^A(t) \displaystyle\int_0^{\alpha_{12}} f_1(t,u)\,du\,, \\ \dfrac{\partial n_2^A}{\partial t}(t) = n_1^T(t)\beta_{21} n_2^A(t)\,, \\ \dfrac{\partial n_2^I}{\partial t}(t) = 0\,, \end{cases} \tag{3.4.10}$$

which is not closed.

This model is able to describe how abnormal cells which do not degenerate may or may not be countered by immune cells.

∎

The above particularizations cover only a part of the potential ability of the model to describe phenomena of the immune competition, as each of them corresponds to a well-defined pathology. This matter will be discussed in more detail in Chapter 5, where the interested reader will find numerical simulations and additional biological interpretations related to the models proposed above. Moreover, in that chapter, Model P will be interpreted as a way of modelling and describing the interplay between immune and progressing (tumor) cells.

The table which follows summarizes the main properties of the various models proposed in this chapter, and should allow a rapid interpretation of them. Additional specific models can be obtained by following the guidelines proposed in this chapter.

Table 3.1. Properties of the Models.

Model C: $\beta_{11} = 0$, $\beta_{12} = 0$, $\beta_{21} = 0$.
The competition between populations is still latent and degeneration of cells does not cause the onset of proliferating/destructive phenomena.
Model P: $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$.
Both populations of cells have reached a fixed stage of their biological functions, and only proliferating/destructive phenomena are relevant.
Model I: $\alpha_{11} > 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$.
The destructive ability of immune cells is progressively reduced by the inhibition ability of abnormal cells.
Model II: $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} > 0$.
The immune system maintains its destructive ability, and the proliferation of abnormal cells may be opposed by immune cells.
Model III: $\alpha_{11} = 0$, $\alpha_{12} > 0$, $\alpha_{21} = 0$.
Active immune cells may counter abnormal cells, which do not show a tendency to degenerate.

3.5 Critical Analysis and Additional Applications

It can be stressed that this chapter was devoted to the modelling of the competition between immune cells and cells of an aggressive, maybe proliferating, invasive host.

Mathematical models described in this chapter refer to the framework proposed in Chapter 2. The models are obtained by starting from a detailed description of microscopic interactions and are derived on the basis of a mathematical interpretation of the phenomenology of the interactions. The models are characterized by various parameters, with a well-defined physical meaning, related to mass conservative interactions and to encounters which modify the biological functions of the interacting cells.

It has been shown how the general model can be particularized into specific models obtained by setting some of the parameters equal to zero. These examples describe specific phenomena which may be experimentally observed. The qualitative and computational analysis of mathematical problems related to the application of models is able to provide, as we shall see in Chapters 4 and 5, a detailed description of the above phenomena.

The general framework is actually the one offered by equation (3.3.18), while models C, P, I, II, and III should be regarded as particularizations of the model. Additional models can be generated by setting other parameters equal to zero. The interested reader can work out these specific cases and analyze them on the basis of the mathematical methods developed in Chapters 4 and 5.

Although the proposed model shows the ability to describe several interesting phenomena related to the immune competition, it does not claim to cover the whole variety of applications which can be generated by the mathematical framework proposed in Chapter 2. For instance, one may enlarge the number of cell populations to specify in more detail the biological functions involved in the phenomena which are analyzed.

Therefore, the class of mathematical models proposed in this chapter should be regarded as a tool suitable for describing certain aspects of the immune competition, as well as being the starting basis for technical developments suitable for increasing the ability of mathematical equations to describe phenomena.

Specifically, a quite natural development refers to the mathematical simulation of therapeutical actions. This matter can be dealt with by adding new populations which apply a specific action against cells which are carriers of a pathological state. For instance, an additional population may refer to the actions of proteins which contribute to activating the immune defense. Useful hints are offered by the literature in the fields of pharmaceutical sciences; among others, Relling and Darvieux (2001), Weinshilboum (2003), and Evans, et al. (2003). These papers clearly show how the biological dynamics essentially refers to the cellular and subcellular scale, and, moreover, that modelling doses and time of application may be crucial to obtaining the expected output of the competition.

A specific example will be given, as already mentioned, in Chapter 7, where an additional population is considered to activate the immune response by cytokine signals.

Of course, the above remarks should be regarded simply as a hint on developing a research project aimed at deriving new models for describing therapeutical actions, and possibly developing a proper control theory.

Finally, let us remark that the analysis proposed in this chapter can be further developed to model additional complex phenomena in biology. A challenging topic is the modelling of the immune competition against HIV particles. This subject is generally dealt with by models stated in terms of ordinary differential equations; see, among others, Kirschner and Panetta (1998). The modelling approach is then developed at the macroscopic scale for a system considered as a whole, while biological events occur at the cellular scale. This challenging topic will be considered again in Chapter 5, after the development of various simulations which will enlarge the description of the predictability of the class of models proposed in this chapter.

4

On the Cauchy Problem

As in physics, understanding the complex, nonlinear systems in cancer biology will require interactive research in which mathematical models guide experimental design and interpretation.

— Gatenby and Maini

4.1 Introduction

This chapter develops a qualitative analysis of the initial value problem for the various mathematical models proposed in Chapter 3. The problem is stated by linking the evolution equations to suitable initial conditions. The analysis is developed with classical methods of functional analysis (see Zeidler 1995), and provides the background for the simulations which will be proposed in Chapter 5.

Specifically, the qualitative analysis problem will be addressed in the following manner:

i) showing the well-posedness of the mathematical problems generated by application of the model, i.e., initial value problems;
ii) analyzing the asymptotic behavior of the solutions.

It is clear that the above asymptotic analysis may play an interesting role in the interaction between medicine and mathematics. Indeed, while mathematicians cannot contribute to the design of specific therapeutic treatments, they can develop an analysis of the parameters which play a relevant role in determining the qualitative asymptotic behavior of the system. As we shall see, some parameters may separate two different asymptotic behaviors: growth of the number of abnormal or tumor cells and progressive inhibition of the immune system, or progressive destruction of abnormal or tumor cells due to the activation of the immune system.

These parameters have a well-defined physical meaning and may possibly be modified by therapeutic actions.

The qualitative analysis developed in this chapter already provides some useful information which can be related to interesting biological information. However, a full description of the scenarios offered by the class of models proposed in this book is completed by the quantitative information offered by the simulations proposed in the next chapter. Therefore, the biological interpretation is not dealt with here, but it is postponed until the next chapter.

The contents of this chapter are developed through two more sections:

Section 4.2 deals with an analysis of the well-posedness and global existence of the initial value problem of the general model of immune competition proposed in Chapter 3.

Section 4.3 develops an analysis of the asymptotic behavior of the solutions of the specific models identified in Chapter 3.

4.2 The Cauchy Problem

This section deals with the qualitative analysis of the initial value problem for the model of immune competition of Chapter 3 proposed in equation (3.3.13). An analysis of this initial value problem is dealt with in the first subsection. Then the second subsection analyzes a variety of specific models described in the examples of Chapter 3. This type of analysis is not only technical, because each parameter has a well-defined physical meaning: consequently, the particular models which will be analyzed in what follows correspond to different aspects of the immune competition related to the response to different types of pathology.

4.2.1 Well-Posedness of the Initial Value Problem

The initial value problem related to equation (3.3.13) can be written as follows:

$$\begin{cases} \dfrac{\partial f}{\partial t} = N(f), \\ f(t=0,u) = f_0(u), \end{cases} \tag{4.2.1}$$

where $f = (f_1, f_2)$, $f_0(u) = (f_{10}(u), f_{20}(u))$, and the operator N is defined as

$$N(f)(t) = \{N_1(f)(t), N_2(f)(t)\}^T, \tag{4.2.2}$$

where

$$N_1(f)(t) = \frac{n_1(t)}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp\left\{ -\frac{(u-(v+\alpha_{11}))^2}{2s_{11}} \right\} f_1(t,v)\, dv$$
$$+ \frac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \int_{0}^{\infty} \exp\left\{ -\frac{(u-(v-\alpha_{12}))^2}{2s_{12}} \right\} f_1(t,v)\, dv$$
$$- f_1(t,u) n_1(t) + f_1(t,u) U_{[0,\infty)} \left[\beta_{11} n_1^E(t) - (1+\beta_{12}) n_2^A(t) \right] ,$$

and

$$N_2(f)(t) = \frac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \int_{0}^{\infty} \exp\left\{ -\frac{(u-(v-\alpha_{21}))^2}{2s_{21}} \right\} f_2(t,v)\, dv$$
$$+ (\beta_{21}-1) U_{[0,\infty)}(u) f_2(t,u) n_1^T(t) .$$

The analysis of problem (4.2.1) requires the definition of some suitable function spaces. Specifically,

- $L_1(\mathbb{R})$ is the Lebesgue space of measurable, real-valued functions which are integrable on $\mathbb{R}$. The norm is denoted by $\| \cdot \|_1$.
- $\mathcal{X} = L_1(\mathbb{R}) \times L_1(\mathbb{R}) = \{ f = (f_1, f_2) : f_1 \in L_1(\mathbb{R}), f_2 \in L_1(\mathbb{R}) \}$ is the Banach space endowed with the norm

$$\| f \| = \| f_1 \|_1 + \| f_2 \|_1 \ .$$

- $\mathcal{X}_+ = \{ f = (f_1, f_2) \in \mathcal{X} : f_1 \geq 0, f_2 \geq 0 \}$ is the positive cone of $\mathcal{X}$.
- $\mathcal{Y} = C([0,T], \mathcal{X})$ and $\mathcal{Y}_+ = C([0,T], \mathcal{X}_+)$ are the space of the functions continuous on $[0,T]$ with values, respectively, in a Banach space $\mathcal{X}$ and $\mathcal{X}_+$, equipped with the norm

$$\| f \|_{\mathcal{Y}} = \sup_{t \in [0,T]} \| f \| \ .$$

Local existence and uniqueness of the solution to the initial value problem are stated by the following:

Theorem 4.2.1. *Let $f_0 \in \mathcal{X}_+$. Then there exist two positive constants T and a_0 such that the initial value problem* (4.2.1) *has a unique solution $f \in C([0,T], \mathcal{X}_+)$. The solution f satisfies*

$$f(t) \in \mathcal{X}_+, \quad t \in [0,T] , \tag{4.2.3}$$

and

$$\| f \| \leq a_0 \| f_0 \|, \quad \forall\, t \in [0,T]\,. \tag{4.2.4}$$

Proof. Equation (4.2.1) can be written in the form of the integral equation

$$f = M(f) = f_0(u) + \int_0^t N(f)(s)\, ds = f_0(u) + \Psi(g)(t)\,. \tag{4.2.5}$$

Then the proof can be obtained by application of classical fixed point methods. The following estimates hold true:
i) Ψ is a continuous map from $\mathcal{Y}$ into $\mathcal{Y}$ and $\exists\, C_1 > 0$ such that

$$\| \Psi(f) \|_{\mathcal{Y}} \leq C_1 T \, \| f \|^2_{\mathcal{Y}}\,, \tag{4.2.6}$$

ii) Ψ is a contraction in $\mathcal{Y}$

$$\| \Psi(f) - \Psi(g) \|_{\mathcal{Y}} \leq C_1 T (\| f \|_{\mathcal{Y}} + \| g \|_{\mathcal{Y}}) \, \| f - g \|_{\mathcal{Y}}\,, \tag{4.2.7}$$

where C_1 is a constant depending on β_{ij}.

The technical proof of the above estimates will be given in Lemma 4.2.1. By exploiting them, it is possible to show that M is a contraction in a ball of $\mathcal{Y}$. In fact, M maps $\mathcal{Y}$ into itself. Moreover:

$$\| M(f) \|_{\mathcal{Y}} \leq \| f_0 \| + C_1 T \, \| f \|^2_{\mathcal{Y}}\,, \tag{4.2.8}$$

$$\| M(f) - M(g) \|_{\mathcal{Y}} \leq \, C_1 T (\| f \|_{\mathcal{Y}} + \| g \|_{\mathcal{Y}}) \, \| f - g \|_{\mathcal{Y}} \ . \tag{4.2.9}$$

This implies that there exist constants a_0, T, determined only by C_1 and $\| f_0 \|$, such that M is a contraction on a ball in $\mathcal{Y}$ of radius a_0. Thus, there exists a unique local solution $f(t)$ of equation (4.2.1) on $[0,T]$.

Positivity of solutions has now to be proved. Bearing this objective in mind, consider the operators $K = t_{(K_1,K_2)}$ and $B = t_{(B_1,B_2)}$ defined as follows:

$$K_1(f)(t) = n_1(t) + (1+\beta_{12}) n_2^A(t) U_{[0,\infty)}(u)\,, \tag{4.2.10}$$

$$K_2(f)(t) = n_1^T(t) U_{[0,\infty)}(u)\,, \tag{4.2.11}$$

$$\begin{aligned} B_1(f)(t) =& \frac{n_1(t)}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp\left\{ -\frac{(u-(v+\alpha_{11}))^2}{2 s_{11}} \right\} f_1(t,v)\, dv \\ &+ \frac{n_2^A(t)}{\sqrt{2\pi s_{12}}} \int_0^{\infty} \exp\left\{ -\frac{(u-(v-\alpha_{12}))^2}{2 s_{12}} \right\} f_1(t,v)\, dv \\ &+ \beta_{11} f_1(t,u)\, U_{[0,\infty)}(u) n_1^E\,, \end{aligned} \tag{4.2.12}$$

and

$$B_2(f)(t) = \frac{n_1^T(t)}{\sqrt{2\pi s_{21}}} \int_0^\infty \exp\left\{ -\frac{(u - v + \alpha_{21}))^2}{2s_{21}} \right\} f_2(t,v)\, dv$$
$$+ \beta_{21} f_2(t,u)\, U_{[0,\infty)}(u) n_1^T \,. \tag{4.2.13}$$

The map M satisfies the integral relation

$$M(f) = \exp\left\{ -\int_0^t K(f) \right\} f_0(u)$$
$$+ \int_0^t \exp\left\{ \int_t^\tau K(f)(s)\, ds \right\} B(f)(\tau)\, d\tau \,. \tag{4.2.14}$$

Then due to the nonnegativity of operator B, it is clear that M maps $\mathcal{X}_+$ into itself if the initial datum (condition) is positive. To complete the proof, the fixed point theorem in $\mathcal{Y}_+$ can be applied again using inequalities (i) and (ii).

∎

Lemma 4.2.1. *Ψ is a continuous map from $\mathcal{Y}$ into $\mathcal{Y}$ and $\exists\, C_1 > 0$ such that*

$$\| \Psi(f) \|_{\mathcal{Y}} \le C_1 T \, \| f \|_{\mathcal{Y}}^2, \tag{4.2.15}$$

$$\| \Psi(f) - \Psi(g) \|_{\mathcal{Y}} \le C_1 T (\| f \|_{\mathcal{Y}} + \| g \|_{\mathcal{Y}}) \, \| f - g \|_{\mathcal{Y}} \ . \tag{4.2.16}$$

The proof of Lemma 4.2.1 is based on the following:

Lemma 4.2.2. *Let f and g in $\mathcal{X}$. Then*
i) *$N(f) \in \mathcal{X}$ and*
ii) *there exists a constant C_1 such that*

$$\| N(f) \| \le C_1 \, \| f \|^2, \tag{4.2.17}$$

and

$$\| N(f) - N(g) \| \le C_1 (\| f \| + \| g \|) \, \| f - g \| \,. \tag{4.2.18}$$

Proof. Taking into account equation (4.2.2) yields

$$\| N(f) \| \le \frac{| n_1(t) |}{\sqrt{2\pi s_{11}}} \int_{-\infty}^\infty \int_{-\infty}^\infty \exp\left\{ -\frac{(u - (v + \alpha_{11}))^2}{2s_{11}} \right\} | f_1(t,v) | \ dv\, du$$

$$
\begin{aligned}
&+ \frac{|\, n_2^A(t)\,|}{\sqrt{2\pi s_{12}}} \int_{-\infty}^{\infty}\int_{0}^{\infty} \exp\left\{-\frac{(u-(v-\alpha_{12}))^2}{2s_{12}}\right\} |\, f_1(t,v)\,|\; dv\, du \\
&+ |\, n_1(t)\,| \int_{-\infty}^{\infty} |\, f_1(t,u)\,|\; du \\
&+ \left[\beta_{11}\, |\, n_1^E(t)\,| + (1+\beta_{12})\, |\, n_2^A(t)\,|\right] \int_{0}^{\infty} |\, f_1(t,u)\,|\; du \\
&+ \frac{|\, n_1^T(t)\,|}{\sqrt{2\pi s_{21}}} \int_{-\infty}^{\infty}\int_{0}^{\infty} \exp\left\{-\frac{(u-(v-\alpha_{21}))^2}{2s_{21}}\right\} |\, f_2(t,v)\,|\; dv\, du \\
&+ (1-\beta_{21})\, |\, n_1^T(t)\,| \int_{0}^{\infty} |\, f_2(t,u)\,|\; du\,.
\end{aligned}
$$

Using the Fubini–Tonelli theorem and the following estimates,

$$
\frac{1}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{+\infty} \exp\left\{-\frac{(u-(v+\alpha_{11}))^2}{2s_{11}}\right\} du = 1\,,
$$

$$
\frac{1}{\sqrt{2\pi s_{12}}} \int_{-\infty}^{+\infty} \exp\left\{-\frac{(u-(v-\alpha_{12}))^2}{2s_{12}}\right\} du = 1\,,
$$

$$
\frac{1}{\sqrt{2\pi s_{21}}} \int_{-\infty}^{+\infty} \exp\left\{-\frac{(u-(v-\alpha_{21}))^2}{2s_{21}}\right\} du = 1\,,
$$

and

$$
|\, n_i\,| \leq \|\, f\,\|\,, \quad i = 1, 2\,,
$$

implies that $N(f) \in \mathcal{X}$ and

$$
\|\, N(f)\,\| \leq (\beta_{11} + \beta_{12} - \beta_{21} + 6)\, \|\, f\,\|^2\ .
$$

By using the same arguments, it is easy to show that

$$
\|\, N(f) - N(g)\,\| \leq (\beta_{11} + \beta_{12} - \beta_{21} + 6)(\|\, f\,\| + \|\, g\,\|)\, \|\, f - g\,\|\ .
$$

∎

Proof of Lemma 4.2.1. It is easy to prove estimates (4.2.15) and (4.2.16), so that the Lemma 4.2.1 is proved by Lemma 4.2.2. Let $s, t \in [0, T]$. One gets, by Lemma 4.2.2,

$$
\|\, \Psi(f)(t) - \Psi(f)(s)\,\|_{\mathcal{Y}} \leq C_1\, |\, t - s\,|\, \|\, f\,\|_{\mathcal{Y}}^2,
$$

which gives the continuity of Ψ.

∎

4.2.2 Global Existence

Global existence and the analysis of the asymptotic behavior are obtained by analyzing the influence of the parameters of the model on the qualitative behavior of the solutions. The above analysis can be developed for specific models. Global existence can be always proved for Models C, P, I, and II, while such a general theorem cannot be proved for Model III. A detailed analysis of this model can be developed in connection with the study of the asymptotic behavior.

Theorem 4.2.2. *Let*

$$\alpha_{12} = 0. \tag{4.2.19}$$

Then, $\forall\ T > 0$ there exists a unique solution $f \in C([0,T], \mathcal{X})$ of (3.3.18) with the initial data, $f_0 \in \mathcal{X}_+$. The solution satisfies

$$f(t) \in\ \mathcal{X}_+, \quad \forall\, t \in [0,T], \tag{4.2.20}$$

and, for some constant C_T depending on T and on the initial data,

$$\sup_{t\in[0,T]} f(t) \le C_T\,. \tag{4.2.21}$$

Proof. Given the results of Theorem 4.2.1, it remains to find *a priori* estimates for the solution. Integrating the first equation of (3.3.18) with respect to u yields

$$\frac{\partial n_1(t)}{\partial t} = n_1^T \left(\beta_{11} n_1^E(t) - \beta_{12} n_2^A(t)\right)\,. \tag{4.2.22}$$

From the second equation of (3.3.19), taking into account (4.2.19), it follows that $n_1^E \le n_1^E(0)$, which combined with (4.2.22) yields

$$\frac{\partial n_1}{\partial t}(t,u) \le \beta_{11} n_1^E(0) n_1, \quad n_1 \le n_1(0)\exp(\beta_{11} n_1^E(0) t)\,. \tag{4.2.23}$$

Hence the total number of abnormal cells is bounded on each finite interval $[0,T]$. Integrating the second equation of (3.3.18) with respect to u yields

$$\frac{\partial n_2(t)}{\partial t} = \beta_{21} n_1^T(t) n_2^A. \tag{4.2.24}$$

It follows, from equations (4.2.23) and (4.2.24), that

$$n_2(t) \leq n_2(0) \exp\left(\frac{\beta_{21} n_1(0)}{\beta_{11} n_1^E(0)} (\exp(\beta_{11} n_1^E(0) t) - 1)\right),$$

which yields that $n_2(t)$ is bounded on each finite time interval $[0, T]$. This gives (4.2.21) with C_T given by

$$\begin{aligned} C_T = {} & n_1(0) \exp\left(\beta_{11} n_1^E(0) T\right) \\ & + n_2(0) \exp\left(\frac{\beta_{21} n_1(0)}{\beta_{11} n_1^E(0)} (\exp(\beta_{11} n_1^E(0) T) - 1)\right). \end{aligned} \tag{4.2.25}$$

∎

Remark 4.2.1. As a consequence of Theorem 4.2.2, the initial value problems for equations (3.4.4)–(3.4.5) and (3.4.7), corresponding to Models P, I, and II, have a global solution. The solution of Model III may not exist globally in time, due to the possibility of growth. Nevertheless, in some cases, we can get the global existence as it will be discussed in remark 4.3.1.

Referring to Model C, it is conservative and satisfies the following estimate:

$$\| f \| = \| f_0 \| \tag{4.2.26}$$

which guarantees global existence. Thus:

Theorem 4.2.3. *There exists a unique, nonnegative, strong solution $f(t)$ of problem* (3.4.1) *in $(L_1(\mathbb{R}))^2$, for $t > 0$, and for every $f_0 \geq 0$ in $(L_1(\mathbb{R}))^2$. Moreover, equality* (4.2.26) *is satisfied.*

4.3 Asymptotic Behavior

The analysis of the asymptotic behavior of the solutions refers to particular models obtained by letting only one of the conservative parameters be different from zero. Thus, in the subsections which follow we will deal with the asymptotic behavior of Models I, II, III, P, and C.

4.3.1 Model I. Asymptotic behavior

It is useful, in developing the analysis of the asymptotic behavior of Model I, i.e., equation (3.4.5), to introduce the following quantities:

$$\delta = \beta_{11} n_1^E(0) - \beta_{12} n_2^A(0)\,, \quad \gamma^\star = \frac{\beta_{21}\beta_{11}}{\beta_{12}} n_1^E(0)\,. \tag{4.3.1}$$

Theorem 4.3.1. *Consider the initial value problem for Model I defined in equation* (3.4.5).

- *If* $\beta_{12} = 0$, *then* n_1^T *increases,* $n_1^E =$ *constant and* n_2 *satisfies the following*

$$n_2^A(t) \geq n_2^A(0) \exp((\beta_{21} - 1) n_1^T(0) t). \tag{4.3.2}$$

Moreover if
  - $\beta_{21} = 0$, *then* n_2^A *decreases.*
  - $\beta_{21} = 1$, *then* n_2^A *increases.*

- *If* $\beta_{12} \neq 0$, *then three cases are possible:*
  - $\delta < 0$
    - *If* $\beta_{21} = 0$, *then* n_2^A *decreases and if* $n_1^T(0) \neq 0$, *then,* $\exists\, t_0$ *such that* n_1^T *decreases in* $[0, t_0]$ *and increases in* $[t_0, T]$, $\forall\, T > 0$.
    - *If* $\beta_{21} = 1$, *then* n_2^A *increases and* n_1^T *decreases:*

$$n_1^T(t) \leq n_1^T(0) \exp(\delta t)\,. \tag{4.3.3}$$

    - *If* $\beta_{21} \neq 0$ *and* $\beta_{21} \neq 1$, *then*
      - *If* $\beta_{11} = 0$, *then* n_1^T *decreases and* $n_2^A(t)$ *satisfies*

$$n_2^A(t) \leq n_2^A(0) \exp(\beta_{21} n_1^T(0) t). \tag{4.3.4}$$

Moreover, $\forall\, T > 0$, $\exists\, \beta_{21} \in (0,1)$ *and* $r > 0$ *such that* $n_2^A(t)$ *increases in* $[0, T]$, *if*

$$\sup_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)\, du \leq r\,.$$

      - *If* $\beta_{11} \neq 0$, *then* $\forall\ T > 0$, $\exists\, n_1^{(0)}$, $\beta_{11}^{(0)}$, $\beta_{12}^{(0)}$, *such that if* $n_1(0) \leq n_1^{(0)}$, $\beta_{11} \leq \beta_{11}^{(0)}$ *and* $\beta_{12} \leq \beta_{12}^{(0)}$, *then* $\exists\, \beta_{21} \in (0,1)$ *such that* n_1^T *decreases in* $[0, T]$ *and*

$$n_2^A(t) \geq \frac{\gamma^\star}{\beta_{21}}\,. \tag{4.3.5}$$

Moreover, if $\exists\,\gamma(\gamma \leq \gamma^\star)$ *such that if* $\sup_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)\,du \leq \gamma$, *then* n_2^A *increases in* $[0,T]$*:*

$$n_2^A(t) \geq n_2^A(0). \tag{4.3.6}$$

– $\delta > 0$
  · *If* $\beta_{21} = 0$, *then* n_2^A *decreases and* n_1^T *increases.*
  · *If* $\beta_{21} \neq 0$, *then* $\forall\ T > 0$, $\exists\,\beta_{11}^{(0)}$ *such that if* $\beta_{11} \leq \beta_{11}^{(0)}$, $\exists\,\beta_{21} \in (0,1)$ *such that* n_1^T *increases in* $[0,T]$ *and*

$$n_2^A(t) \leq \frac{\gamma^\star}{\beta_{21}}. \tag{4.3.7}$$

Moreover, if $\exists\,\gamma(\gamma \geq \gamma^\star)$ *such that* $\sup_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)\,du \geq \gamma$, *then* n_2^A *decreases and*

$$n_2^A(t) \leq n_2^A(0). \tag{4.3.8}$$

– $\delta = 0$
  · *If* $\beta_{21} = 0$, *then* n_2^A *decreases and* n_1^T *increases.*
  · *If* $\beta_{21} = 1$, *then* n_2^A *increases and* n_1^T *decreases.*
  · *If* $\beta_{21} \neq 0$ *and* $\beta_{21} \neq 1$, *then* $\forall\ T > 0$, $\exists\, n_1^{(0)}, \beta_{11}^{(0)}$ *and* $r > 0$ *such that if* $n_1(0) \leq n_1^{(0)}$, $\beta_{11} \leq \beta_{11}^{(0)}$ *and* $\sup_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)\,du \leq r$, *then* n_2^A *increases and* n_1^T *decreases.*

We need, in order to prove Theorem 4.3.1, the following lemmas which give the asymptotic behavior in the case $\beta_{ij} \neq 0\ \forall\ i,j$.

Lemma 4.3.1. *Let* $\delta < 0$ *and let* T *fixed. Consider the function* h *in* $[0,1]$ *defined as follows*

$$h(x) = (x-1)T\Bigg[n_1(0)\exp(\beta_{11}n_1^E(0)T) + n_2(0)\exp\left(\frac{(n_1(0))x}{\beta_{11}n_1^E(0)}(\exp(\beta_{11}n_1^E(0)T)-1)\right)\Bigg]. \tag{4.3.9}$$

If h *is increasing in* $[0,1]$, *then* $\exists\,\beta_{12}^{(0)}$ *such that if* $\beta_{12} \leq \beta_{12}^{(0)}$, *then there exists a unique solution* $x \in (0,1)$ *of the equation*

$$h(x) = \ln\left(\frac{\beta_{11}n_1^E(0)}{\beta_{12}n_2^A(0)}\right). \tag{4.3.10}$$

Proof. The function h is continuously increasing in x and maps $[0,1]$ into

$$[-T(n_1(0)\exp(\beta_{11}n_1^E(0)T)+n_2(0)),0]\,.$$

As $\delta<0$, equation (4.3.10) has a solution only if

$$\ln\left(\frac{\beta_{12}n_2^A(0)}{\beta_{11}n_1^E(0)}\right)\le T\left(n_1(0)\exp(\beta_{11}n_1^E(0)T)+n_2(0)\right). \tag{4.3.11}$$

Considering that

$$T(n_1(0)\exp(\beta_{11}n_1^E(0)T)+n_2(0))>Tn_2^A(0)\,,$$

then the condition (4.3.11) is satisfied if

$$\beta_{12}\le\frac{\beta_{11}n_1^E(0)}{n_2^A(0)}\exp(Tn_2^A(0))=\beta_{12}^{(0)}. \tag{4.3.12}$$

∎

Lemma 4.3.2. *Consider the function h given by* (4.3.9). *Then* $\exists\, n_1^{(0)},\beta_{11}^{(0)}$ *such that if* $n_1(0)\le n_1^{(0)},\beta_{11}\le\beta_{11}^{(0)}$, h *is increasing in* $[0,1]$.

Proof. The function h can be written in the following form:

$$h(x)=(x-1)T(A+n_2(0)\exp(Bx)), \tag{4.3.13}$$

where the constants A and B are given by

$$A=n_1(0)\exp(\beta_{11}n_1^E(0)T)\,, \tag{4.3.14a}$$

$$B=\frac{n_1(0)}{\beta_{11}n_1^E(0)}(\exp(\beta_{11}n_1^E(0)T)-1)\,. \tag{4.3.14b}$$

The derivative of h is defined as follows:

$$h^{'}(x)=Tn_2(0)\exp(Bx)(Bx+1-B)+TA.$$

For ε small, $\exists\,\eta>0$ such that if $\beta_{11}n_1^E(0)T\le\eta$, we have

$$B-n_1(0)T<\varepsilon\,.$$

Let $n_1(0)T<1-\varepsilon$; then $B<1$. Therefore

$$h^{'}(x)>Tn_2(0)\exp(Bx)(1-B)+TA>0\,.$$

∎

Lemma 4.3.3. *Let $r > 0$ and consider the functions $k(x)$ and $m(x)$ defined in $(0,1]$ by*

$$k(x) = h(x) + \ln(xn_2^A(0)), \tag{4.3.15}$$

and

$$m(x) = n_1^T(0)T(x-1) + \ln(xn_2^A(0)). \tag{4.3.16}$$

Consider the equations

$$k(x) = \ln(r), \tag{4.3.17a}$$

$$m(x) = \ln(r). \tag{4.3.17b}$$

Then

i) *$\exists\, n_1^{(0)}, \beta_{11}^{(0)}$ such that if $n_1(0) \le n_1^{(0)}$, $\beta_{11} \le \beta_{11}^{(0)}$, equation* (4.3.17a) *has a solution in $(0,1]$ if $r < n_2^A(0)$.*

ii) *Equation* (4.3.17b) *has a solution in $(0,1]$ if $r < n_2^A(0)$.*

Proof. The derivative of $k(x)$ is given by

$$k^{'}(x) = h^{'}(x) + \frac{n_2^A(0)}{x}. \tag{4.3.18}$$

Using Lemma 4.3.2, k is increasing for $n_1(0) \le n_1^{(0)}$, $\beta_{11} \le \beta_{11}^{(0)}$, and k maps $(0,1]$ into $(-\infty, \ln(n_2^A(0))]$, then, if $r < n_2^A(0)$, equation (4.3.17a) has a solution. In the same way, it is plain that if m is continuous, increases in $(0,1]$ and maps $(0,1]$ into $(-\infty, \ln(n_2^A(0))]$, then equation (4.3.17b) has a solution in $(0,1]$ if $r < n_2^A(0)$.

∎

Lemma 4.3.4. *Let $\delta > 0$ and let be T fixed. Consider the function g in $[0,1]$ given by*

$$\begin{aligned} g(x) = {} & xTn_1(0)\exp(\beta_{11}n_1^E(0)T) \\ & + xTn_2(0)\exp\left(\frac{xn_1(0)}{\beta_{11}n_1^E(0)}(\exp(\beta_{11}n_1^E(0)T) - 1)\right). \end{aligned} \tag{4.3.19}$$

Then, $\exists\, \beta_{11}^{(0)}$ such that if $\beta_{11} \le \beta_{11}^{(0)}$, there exists a unique solution $x \in (0,1)$ of the equation

$$g(x) = \ln\left(\frac{\beta_{11}n_1^E(0)}{\beta_{12}n_2^A(0)}\right). \tag{4.3.20}$$

Proof. The proof follows the same arguments. The function g is increasing from $[0,1]$ into $[0, g(1)]$. As $\delta > 0$, equation (4.3.20) has a solution if

$$\ln\left(\frac{\beta_{11}n_1^E(0)}{\beta_{12}n_2^A(0)}\right) \le g(1)\,, \tag{4.3.21}$$

which, as $g(1) > Tn_2^A(0)$, can be written as follows:

$$\beta_{11} \leq \frac{\beta_{12} n_2^A(0)}{\beta_{11} n_1^E(0)} \exp(T n_2^A(0)). \tag{4.3.22}$$

∎

Proof of Theorem 4.3.1. The equations satisfied by n_1^T, n_2^A, and n_1^E are the following:

$$\frac{\partial n_1^T}{\partial t} = n_1^T(\beta_{11} n_1^E - \beta_{12} n_2^A), \tag{4.3.23}$$

$$\frac{\partial n_1^E}{\partial t} = 0, \tag{4.3.24}$$

$$\frac{\partial n_2^A}{\partial t} = n_1^T \left(\beta_{21} n_2^A - \int_0^{\alpha_{21}} f_2(t,u)\, du \right). \tag{4.3.25}$$

Case $\beta_{12} = 0$: From (4.3.23), we deduce that n_1^T is given by

$$n_1^T(t) = n_1^T(0) \exp(\beta_{11} n_1^E(0) t), \tag{4.3.26}$$

and so $n_1^T(t)$ is increasing.

Noting that

$$n_2^A(t) \geq \int_0^{\alpha_{21}} f_2(t,u)\, du, \tag{4.3.27}$$

then equation (4.3.25) yields the estimate (4.3.2). Equation (4.3.25) shows that if $\beta_{21} = 0$, n_2^A decreases, and if $\beta_{21} = 1$ with (4.3.27), n_2^A increases.

Case $\beta_{12} \neq 0$: Let $\delta < 0$; if $\beta_{21} = 0$; then n_2^A decreases. Let $n_1^T(0) \neq 0$, so $n_1^T \neq 0$ and

$$\frac{\partial n_1^T}{\partial t} = 0 \Leftrightarrow n_2^A(t) = \frac{\beta_{11} n_1^E(0)}{\beta_{12}}. \tag{4.3.28}$$

Let $t \in [0,T]$; as $\delta < 0$ and n_2^A is decreasing, it follows that

$$n_2^A(T) < \frac{\beta_{11} n_1^E(0)}{\beta_{12}} = n_2^A(t) \leq n_2^A(0). \tag{4.3.29}$$

The function n_2^A is continuous and decreases in $[0,T]$; then from (4.3.29), there exists a unique $t_0 \in [0,T]$ such that

$$n_2^A(t_0) = \frac{\beta_{11} n_1^E(0)}{\beta_{12}}\,, \tag{4.3.30}$$

and n_1^T decreases in $[0, t_0]$ and increases in $[t_0, T]$.

If $\beta_{21} = 1$, it is easy to see that n_2^A increases and n_1^T decreases. Now let $\beta_{21} \neq 0$ and $\beta_{21} \neq 1$; then from (4.3.25), the following estimate holds true $\forall\, T > 0$:

$$\frac{\partial n_2^A}{\partial t} \geq n_1^T(\beta_{21} - 1)n_2^A \geq C_T(\beta_{21} - 1)n_2^A\,,$$

where the constant C_T is given by (4.2.25). Therefore

$$n_2^A \geq n_2^A(0)\exp((\beta_{21} - 1)C_T t)\,,$$

which, substituted into (4.3.23), yields

$$\frac{\partial n_1^T}{\partial t} \leq n_1^T(\beta_{11}n_1^E(0) - \beta_{12}n_2^A(0)\exp((\beta_{21} - 1)C_T t)). \tag{4.3.31}$$

If $\beta_{11} \neq 0$, then it follows from (4.3.31) that there exists

$$t_0 = \frac{1}{C_T(\beta_{21} - 1)}\ln\left(\frac{\beta_{11}n_1^E(0)}{\beta_{12}n_2^A(0)}\right)$$

such that, if $t \leq t_0$, one has

$$\frac{\partial n_1^T}{\partial t} \leq 0 \quad \text{for}\, t \leq t_0\,. \tag{4.3.32}$$

The decreasing property of n_1^T in $[0, T]$ for any $T > 0$ is equivalent to

$$h(\beta_{21}) = \ln\left(\frac{\beta_{11}n_1^E(0)}{\beta_{12}n_2^A(0)}\right), \tag{4.3.33}$$

where h is given by (4.3.9). Therefore Lemmas 4.3.1 and 4.3.2 give the existence of $n_1^{(0)}, \beta_{11}^{(0)}$, and $\beta_{12}^{(0)}$ such that if $n_1(0) \leq n_1^{(0)}$, $\beta_{11} \leq \beta_{11}^{(0)}$, and $\beta_{12} \leq \beta_{12}^{(0)}$, then there exists $\beta_{21} \in (0, 1)$ such that $t_0(T) = T$, and n_1^T decreases in $[0, T]$. From equation (4.3.23), equation (4.3.5) follows; from equation (4.3.25), it follows

$$\frac{\partial n_2^A}{\partial t} \geq n_1^T\left(\gamma^\star - \int_0^{\alpha_{21}} f_2(t, u)\,du\right). \tag{4.3.34}$$

Moreover, let γ be such that $\gamma \leq \gamma^\star$ and suppose that

$$\sup_{t\in[0,T]}\int_0^{\alpha_{21}} f_2(t, u)\,du \leq \gamma\,,$$

then n_2^A increases and satisfies (4.3.6) for $t \in [0, T]$.

If $\beta_{11} = 0$, then from (4.3.23) it follows that n_1^T is decreasing and by (4.3.25), n_2^A satisfies (4.3.4) and

$$\frac{\partial n_2^A}{\partial t} \geq n_1^T(\beta_{21} n_2^A(0) \exp(n_1^T(0)(\beta_{21} - 1)t) - r) \tag{4.3.35}$$

$\forall\, r > 0$ such that $\sup\limits_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t, u)\, du \leq r$. Let $r < \beta_{21} n_2^A(0)$; then from (4.3.35), we get the existence of

$$t_0 = \frac{1}{n_1^T(0)(\beta_{21} - 1)} \ln\left(\frac{r}{\beta_{21} n_2^A(0)}\right)$$

(now $\beta_{21} \neq 1$) such that n_2^A increases for $t \leq t_0$. The increase in $[0, T]$ is equivalent to $m(\beta_{21}) = \ln(r)$ (m is given by (4.3.16)). As $r < n_2^A(0)$, Lemma 4.3.3 gives the existence of $\beta_{21} \in (0, 1)$ such that n_2^A increases in $[0, T]$.

Now let $\delta > 0$. In this case we have $\beta_{11} \neq 0$. Let $\beta_{21} \neq 0$ (the case $\beta_{21} = 0$ is trivial). Then by using equation (4.3.25), it follows that $\forall\, T > 0$:

$$n_2^A(t) \leq n_2^A(0) \exp(\beta_{21} C_T t). \tag{4.3.36}$$

Substituting (4.3.36) into (4.3.23) yields

$$\frac{\partial n_1^T}{\partial t} \geq n_1^T\left(\beta_{11} n_1^E(0) - \beta_{12} n_2^A(0) \exp(\beta_{21} C_T t)\right), \tag{4.3.37}$$

which implies that there exists

$$t_0 = \frac{1}{\beta_{21} C_T} \ln\left(\frac{\beta_{11} n_1^E(0)}{\beta_{12} n_2^A(0)}\right)$$

such that if $t \leq t_0$ we have $\dfrac{\partial n_1^T}{\partial t} \geq 0$. As above, the increase in $[0, T]$ is equivalent to

$$g(\beta_{21}) = \ln\left(\frac{\beta_{11} n_1^E(0)}{\beta_{12} n_2^A(0)}\right), \tag{4.3.38}$$

where g is given by (4.3.19). Therefore Lemma 4.3.4 gives the existence of $\beta_{11}^{(0)}$ such that if $\beta_{11} \leq \beta_{11}^{(0)}$, there exists $\beta_{21} \in (0, 1)$ such that n_1^T

increases in $[0,T]$ and equation (4.3.23) gives (4.3.7), which we substitute into (4.3.25) to have

$$\frac{\partial n_2^A}{\partial t} \leq n_1^T \left[\gamma^\star - \int_0^{\alpha_{21}} f_2(t,u)\,du\right]. \tag{4.3.39}$$

Let

$$\sup_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)\,du \geq \gamma \geq \gamma^\star\,; \tag{4.3.40}$$

then from (4.3.39) it follows that n_2^A decreases and satisfies (4.3.8).

Let $\delta = 0$. The equation satisfied by n_1^T is written in the form

$$\frac{\partial n_1^T}{\partial t} = \beta_{12} n_1^T (n_2^A(0) - n_2^A(t)). \tag{4.3.41}$$

Let $\beta_{21} \neq 0$ (the case $\beta_{21} = 0$ or $\beta_{21} = 1$ are trivial), $r < \beta_{21} n_2^A(0)$, and suppose that $\sup\limits_{t\in[0,T]} \int_0^{\alpha_{21}} f_2(t,u)du \leq r$; then there exists t_0:

$$t_0 = \frac{1}{C_T(\beta_{21}-1)} \ln\left(\frac{r}{\beta_{21} n_2^A(0)}\right)$$

such that n_2^A is increasing in $[0,t_0]$. The decreasing in $[0,T]$ is equivalent to

$$k(\beta_{21}) = \ln(r), \tag{4.3.42}$$

where k is given by (4.3.15). Let $n_1(0)$, β_{11} be small as in Lemma 4.3.3. As $r < n_2^A(0)$, the solution of (4.3.42) exists due to Lemma 4.3.3 and so n_2^A increases, and by (4.3.41), n_1^T decreases.

∎

4.3.2 Model II. Asymptotic behavior

In order to study the asymptotic behavior of Model II, equation (3.4.7), let us introduce the quantity λ:

$$\lambda = (1+\beta_{11}) n_1^E(0) - \beta_{12} n_2^A(0). \tag{4.3.43}$$

Theorem 4.3.2. *Consider the initial value problem for Model II, equation (3.4.7). Then n_2^A increases, n_1^E decreases, and*

- *If $\beta_{12} = 0$, then n_1^T increases.*

• *If* $\beta_{12} \neq 0$, *then*

$$n_1^T \leq \exp(\lambda t)\left(n_1^T(0) + \frac{(n_1^E(0))^2}{\lambda}\right) - \frac{(n_1^E(0))^2}{\lambda}. \tag{4.3.44}$$

In particular if $\lambda < 0$, *then we have the following estimate for* $n_1^T(\infty)$*:*

$$n_1^T(\infty) \leq -\frac{(n_1^E(0))^2}{\lambda}. \tag{4.3.45}$$

Proof. The equations satisfied by n_1^T, n_2^A, and n_1^E are the following:

$$\frac{\partial n_1^T}{\partial t} = n_1 \int_{-\alpha_{11}}^0 f_1(t,u)\,du + n_1^T(\beta_{11}n_1^E - \beta_{12}n_2^A), \tag{4.3.46}$$

$$\frac{\partial n_1^E}{\partial t} = -n_1(t) \int_{-\alpha_{11}}^0 f_1(t,u)\,du, \tag{4.3.47}$$

$$\frac{\partial n_2^A}{\partial t} = \beta_{21} n_1^T n_2^A. \tag{4.3.48}$$

If $\beta_{12} = 0$, then from (4.3.46)–(4.3.48) it follows that n_1^T, n_2^A increases, and n_1^E decreases. Let $\beta_{12} \neq 0$; it is easy to prove by using $n_1 = n_1^E + n_1^T$ and by

$$\int_{-\alpha_{11}}^0 f_1(t,u)\,du \leq n_1^E \tag{4.3.49}$$

the following estimate:

$$\partial_t n_1^T \leq (n_1^E(0))^2 + n_1^T((1+\beta_{11})n_1^E(0) - \beta_{12}n_2^A(0)) = (n_1^E(0))^2 + \lambda n_1^T\,. \tag{4.3.50}$$

Using the Gronwall lemma yields

$$n_1^T \leq \exp(\lambda t) n_1^T(0) - \frac{(n_1^E(0))^2}{\lambda}(1 - \exp(\lambda t))\,, \tag{4.3.51}$$

which is the expected estimate (4.3.44).

∎

4.3.3 Model III. Asymptotic behavior

Referring to Model III, it useful to introduce the quantities ℓ and θ given by

$$\begin{aligned}\ell &= \beta_{11} n_1^E(0) - (1+\beta_{12}) n_2^A(0),\\ \theta &= \beta_{11}\left(n_1^E(0) - \frac{1}{\beta_{21}} n_2^A(0)\right).\end{aligned} \tag{4.3.52}$$

Theorem 4.3.3. *Consider the initial value problem for Model III, equation (3.4.9). Then*

- *If $\beta_{21} = 0$, then n_1^E increases and $n_2 = n_2^A(0)$.*
  - *If $\beta_{11} = 0$, then n_1^T decreases.*
  - *If $\beta_{11} \neq 0$, then*

$$n_1^T(t) \leq n_1^T(0) \exp\left(\beta_{11} \int_0^t n_1^E(s)\, ds\right). \tag{4.3.53}$$

  Moreover if $\ell \geq 0$, then n_1^T increases and

$$n_1^T(t) \geq n_1^T(0) \exp(\ell t). \tag{4.3.54}$$

- *If $\beta_{21} \neq 0$, then n_1^E and n_2^A increases. Moreover, if $\dfrac{\beta_{11}}{\beta_{21}} - \beta_{12} \leq 0$ ($\beta_{11} < \beta_{21}$) and $\theta \leq 0$, then n_1^T decreases and*

$$n_1^T(t) \leq n_1^T(0) \exp(\theta t). \tag{4.3.55}$$

Proof. The equations satisfied by n_1^T, n_2^A, and n_1^E are the following:

$$\frac{\partial n_1^T}{\partial t} = -n_2^A \int_0^{\alpha_{12}} f_1(t,u) du + n_1^T(\beta_{11} n_1^E - \beta_{12} n_2^A), \tag{4.3.56}$$

$$\frac{\partial n_1^E}{\partial t} = n_2^A \int_0^{\alpha_{12}} f_1(t,u)\, du\,, \tag{4.3.57}$$

and

$$\frac{\partial n_2^A}{\partial t} = \beta_{21} n_1^T n_2^A. \tag{4.3.58}$$

Let $\beta_{21} = 0$; then from the above equation, it is obvious that $n_2^A = n_2^A(0)$ and n_1^E increases.

If $\beta_{11} = 0$, it is easy to see that n_1^T decreases. Let $\beta_{11} \neq 0$; then we get

$$\frac{\partial n_1^T}{\partial t} \leq \beta_{11} n_1^T n_1^E \,, \tag{4.3.59}$$

which gives (4.3.53). Moreover, considering that

$$\int_0^{\alpha_{12}} f_1(t,u)\, du \leq n_1^T \,,$$

then n_1^T satisfies

$$\frac{\partial n_1^T}{\partial t} \geq \ell n_1^T \,, \tag{4.3.60}$$

which gives (4.3.54).
Let $\beta_{21} \neq 0$; then, from equations (4.3.57)–(4.3.58), we have

$$\frac{\partial n_1^E}{\partial t} \leq n_2^A n_1^T = \frac{1}{\beta_{21}} \frac{\partial n_2^A}{\partial t} \,,$$

and so

$$n_1^E(t) \leq n_1^E(0) - \frac{1}{\beta_{21}} n_2^A(0) + \frac{1}{\beta_{21}} n_2^A(t) \,, \tag{4.3.61}$$

which we combine with (4.3.56) to obtain

$$\frac{\partial n_1^T}{\partial t} \leq n_1^T (\beta_{11} n_1^E(0) - \frac{\beta_{11}}{\beta_{21}} n_2^A(0) + \frac{\beta_{11}}{\beta_{21}} n_2^A(t) - \beta_{12} n_2^A). \tag{4.3.62}$$

Now let

$$\frac{\beta_{11}}{\beta_{21}} - \beta_{12} \leq 0 \quad (\beta_{11} < \beta_{21}) \,,$$

and

$$\beta_{21} n_1^E(0) - n_2^A(0) \leq 0 \,.$$

Then it follows from (4.3.62) that n_1^T decreases and satisfies (4.3.55).

∎

Remark 4.3.1. The solution of Model III may not exist globally in time, due to the possibility of growth. Nevertheless, in some cases we can get the global existence. For example, in the case when $\beta_{11} = 0$, or in the case $\beta_{21} \neq 0$ and $\frac{\beta_{11}}{\beta_{21}} - \beta_{12} \leq 0$ and $\theta \leq 0$ (see (4.3.52)), we obtain $n_1(t) \leq n_1(0)$, and by using (4.2.24), we have that n_2 is bounded on each finite time interval $[0, T]$. Thus, using the technique of the proof of Theorem 4.2.2, we get the global existence of the solution.

4.3.4 Model P. Asymptotic behavior

This subsection is devoted to analyzing the asymptotic behavior of Model P, equation (3.4.3).

The analysis of the asymptotic behavior refers, as in the previous subsections, to the time evolution of the densities n_1^T, n_1^E, and n_2^A. A parameter which plays a relevant role is, as in Model I, equation (3.4.5), the following:

$$\delta = \beta_{11} n_1^E(0) - \beta_{12} n_2^A(0). \tag{4.3.63}$$

Referring to the initial value problem, the following results can be proved.

Theorem 4.3.4. *Consider the initial value problem for the model defined in equation (3.4.4). Then*

• *If $\beta_{21} = 0$, then $n_2^A = constant, n_1^E = constant$, and n_1^T satisfies the equality*

$$n_1^T(t) = n_1^T(0) \exp(\delta t)\,; \tag{4.3.64}$$

thus, if $\delta \geq 0$, then n_1^T increases, and if $\delta < 0$, then n_1^T decreases.

• *If $\beta_{21} \neq 0$, then*
- *If $\beta_{12} = 0$, then n_1^T increases, $n_1^E = constant$, and n_2 increases.*
- *If $\beta_{12} \neq 0$, then $n_1^E = constant$, n_2^A increases, and*
  - *If $\delta \leq 0$, then n_1^T decreases and satisfies the following estimate:*

$$n_1^T(t) \leq n_1^T(0) \exp(\delta t). \tag{4.3.65}$$

  - *If $\delta > 0$: if $n_1^T(0) \neq 0$, then $\exists\, t_0$ such that n_1^T increases in $[0, t_0]$ and n_1^T decreases in $[t_0, T]$ $\forall\, T > 0$.*

Proof. The equations satisfied by n_1^T, n_2^A, and n_1^E are the following:

$$\frac{\partial n_1^T}{\partial t} = n_1^T(\beta_{11} n_1^E - \beta_{12} n_2^A), \tag{4.3.66}$$

$$\frac{\partial n_1^E}{\partial t} = 0, \tag{4.3.67}$$

$$\frac{\partial n_2^A}{\partial t} = \beta_{21} n_1^T n_2^A. \tag{4.3.68}$$

If $\beta_{21} = 0$, then from (4.3.67)–(4.3.68) we deduce that $n_2^A = n_2^A(0)$, and $n_1^E = n_1^E(0)$, which, substituted into (4.3.66), gives (4.3.64).

Let $\beta_{21} \neq 0$; if $\beta_{12} = 0$, it is easy to see from (4.3.66) that n_1^T increases. Let $\beta_{12} \neq 0$; then two cases are possible: if $\delta \leq 0$, then from (4.3.66) follows

(4.3.65). Now let $\delta > 0$ (which implies $\beta_{11} \neq 0$) and $T > 0$. If $n_1^T(0) = 0$, then it follows that $n_1^T = 0$. Now let $n_1^T(0) \neq 0$, so that $n_1^T \neq 0$ and

$$\frac{\partial n_1^T}{\partial t} = 0 \Leftrightarrow n_2^A(t) = \frac{\beta_{11} n_1^E(0)}{\beta_{12}}. \tag{4.3.69}$$

Let $t \in [0, T]$; as $\delta > 0$ and n_2^A is increasing, it follows that

$$n_2^A(0) < \frac{\beta_{11} n_1^E(0)}{\beta_{12}} = n_2^A(t) \leq n_2^A(T)\,.$$

Since n_2^A is continuous, increasing in $[0, T]$, then we get the existence of a unique $t_0 \in [0, T]$ such that

$$n_2^A(t_0) = \frac{\beta_{11} n_1^E(0)}{\beta_{12}}, \quad t_0 = (n_2^A)^{-1}\left(\frac{\beta_{11} n_1^E(0)}{\beta_{12}}\right). \tag{4.3.70}$$

From (4.3.70) we get that n_1^T increases in $[0, t_0]$ and decreases in $[t_0, T]$. ∎

In the next chapter, we will show that the above theorems provide a description of various phenomena interesting from the viewpoint of immunology, and that they also give some interesting information toward the development of therapeutic actions.

4.3.5 Model C. Asymptotic behavior

In this subsection we focus on two particular cases of the conservative model, Model C1 and C2, obtained from the Model C, equation (3.4.1), by setting equal to zero α_{12} and α_{11}, respectively.

Model C1 ($\alpha_{12} = 0, \alpha_{11} > 0, \alpha_{21} > 0$). In this particular case, the evolution equations for the Model C reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t)[f_1(t, u - \alpha_{11}) - f_1(t,u)], \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t)(f_2(t, u + \alpha_{21}) U_{[0,\infty)}(u + \alpha_{21}) - f_2(t,u) U_{[0,\infty)}(u))\,. \end{cases} \tag{4.3.71}$$

Theorem 4.3.5. *Consider the initial value problem for the model defined in equation (4.3.71). Then*

i) n_2^A *is decreasing, and* n_1^T *is increasing.*

ii) *Moreover* $n_1^T(t)$ *and* $n_2^A(t)$ *satisfies, in the limit* $t \longrightarrow +\infty$, *the following estimate:*

$$\lim_{t\longrightarrow+\infty} n_1^T(t) \geq \int_{-\alpha_{11}}^{+\infty} f_{10}(u)\,du > n_1^T(0), \tag{4.3.72}$$

$$\lim_{t\longrightarrow+\infty} n_2^A(t) \leq \int_{\alpha_{21}}^{+\infty} f_{20}(u)\,du < n_2^A(0). \tag{4.3.73}$$

Remark 4.3.2. Note that the number density $n_1^T(t)$ at any time $t > 0$ is always greater than the initial number density $n_1^T(0)$.

In the same spirit, the number density $n_2^A(t)$ at any time $t > 0$ is always less than the initial number density $n_2^A(0)$.

Proof. The proof needs some preliminary estimates which are cited in the following lemma:

Lemma 4.3.5. *One gets the following estimates for* f_1*:*

$$\int_{-\alpha_{11}}^{0} f_1(t,u)\,du \geq \exp(-n_1(0)t)\int_{-\alpha_{11}}^{0} f_{10}(u)\,du, \tag{4.3.74}$$

$$\int_{0}^{+\infty} f_1(t,u)\,du \geq \int_{-\alpha_{11}}^{+\infty} f_{10}(u)\,du - \exp(-n_1(0)t)\int_{-\alpha_{11}}^{0} f_{10}(u)\,du. \tag{4.3.75}$$

and the following estimates for f_2*:*

$$\int_{0}^{\alpha_{21}} f_2(t,u)\,du \geq \exp\left(-\int_0^t n_1^T(s)\,ds\right)\int_{0}^{\alpha_{21}} f_{20}(u)\,du, \tag{4.3.76}$$

$$\int_{0}^{+\infty} f_2(t,u)\,du \leq \int_{\alpha_{21}}^{+\infty} f_{20}(u)\,du + \exp\left(-\int_0^t n_1^T(s)\,ds\right)\int_{0}^{\alpha_{21}} f_{20}(u)\,du. \tag{4.3.77}$$

Proof. Integrating (4.3.71) over u in $(-\alpha_{11}, 0)$ yields

$$\begin{aligned}\partial_t \int_{-\alpha_{11}}^{0} f_1(t,u)\,du &= n_1(0)\left(\int_{-2\alpha_{11}}^{-\alpha_{11}} f_1(t,u)\,du - \int_{-\alpha_{11}}^{0} f_1(t,u)\,du\right)\\ &\geq -n_1(0)\int_{-\alpha_{11}}^{0} f_1(t,u)\,du\,.\end{aligned}$$

Therefore, the estimate (4.3.74) is obtained by applying the Gronwall lemma.
Integrating (4.3.71) in $(0,\infty)$ and using (4.3.74) yields

$$\partial_t \int_0^{+\infty} f_1(t,u)\,du \geq n_1(0)\exp(-n_1(0)t)\int_{-\alpha_{11}}^{0} f_{10}(u)\,du\,,$$

which, once integrated over time in $(0,t)$, yields the estimate (4.3.75).

The proof of (4.3.76) is easily obtained by an integration of the second equation of (4.3.71) over u in $(0,\alpha_{21})$:

$$\begin{aligned}\partial_t \int_0^{\alpha_{21}} f_2(t,u)\,du &= n_1^T(t)\left(\int_{\alpha_{21}}^{2\alpha_{21}} f_2(t,u)\,du\right) - \left(\int_0^{\alpha_{21}} f_2(t,u)\,du\right) n_1^T(t)\\ &\geq -n_1^T(t)\int_0^{\alpha_{21}} f_2(t,u)\,du\,.\end{aligned}$$

The expected estimate (4.3.76) follows from the Gronwall lemma.

Integrating the second equation of (4.3.71) in $(0,\infty)$ and using (4.3.76), one gets

$$\partial_t \int_0^{+\infty} f_2(t,u)\,du \leq -\left(\int_0^{\alpha_{21}} f_{20}(u)\,du\right) n_1^T(t)\exp\left(-\int_0^t n_1^T(s)\,ds\right). \tag{4.3.78}$$

Noting that

$$-n_1^T(t)\exp\left(-\int_0^t n_1^T(s)\,ds\right) = \frac{d}{dt}\exp\left(-\int_0^t n_1^T(s)\,ds\right), \tag{4.3.79}$$

and integrating (4.3.78) over t, using (4.3.79), we find that

$$\begin{aligned}&\int_0^{+\infty} f_2(t,u)\,du - \int_0^{+\infty} f_{20}(u)\,du\\ &\qquad\leq \left[\exp\left(-\int_0^t n_1^T(s)\,ds\right) - 1\right]\int_0^{\alpha_{21}} f_{20}(u)\,du\,,\end{aligned}$$

which is the expected estimate (4.3.77).

The proof of Theorem 4.3.5 is easily deduced from Lemma 4.3.5.

∎

Model C2 ($\alpha_{11} = 0$, $\alpha_{12} > 0$, $\alpha_{21} > 0$). In this particular case the evolution equations for the Model C, equation (3.4.1), reduce to

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_2^A(t)(f_1(t,u+\alpha_{12})U_{[0,\infty)}(u+\alpha_{12}) - f_1(t,u)U_{[0,\infty)}(u)), \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t)(f_2(t,u+\alpha_{21})U_{[0,\infty)}(u+\alpha_{21}) - f_2(t,u)U_{[0,\infty)}(u)). \end{cases} \tag{4.3.80}$$

Theorem 4.3.6. *Consider the initial value problem for Model C2 defined in equation (4.3.80). Then*

i) n_2^A *and* n_1^T *decrease.*
ii) *Moreover* $n_1^T(t)$ *and* $n_2^A(t)$ *satisfy in the limit* $t \to +\infty$ *the following estimates:*

$$\lim_{t\to+\infty} n_1^T(t) \le \exp\left(-\frac{n_2^A(0)}{n_1^T(0)}\right)\int_0^{\alpha_{12}} f_{10}(u)\,du + \int_{\alpha_{12}}^{+\infty} f_{10}(u)\,du, \tag{4.3.81}$$

$$\lim_{t\to+\infty} n_2^A(t) \le \exp\left(-\frac{n_1^T(0)}{n_2^A(0)}\right)\int_0^{\alpha_{12}} f_{20}(u)\,du + \int_{\alpha_{21}}^{+\infty} f_{20}(u)\,du\,. \tag{4.3.82}$$

The proof of the above theorem is based on the following lemmas.

Lemma 4.3.6. *The following estimates for* f_1 *hold true:*

$$\partial_t \int_0^{+\infty} f_1(t,u)\,du = -n_2^A(t)\int_0^{\alpha_{12}} f_1(t,u)\,du \le 0, \tag{4.3.83}$$

$$\begin{aligned} \int_0^{+\infty} f_1(t,u)\,du \le &\exp\left(-\int_0^t n_2^A(s)\,ds\right)\int_0^{\alpha_{12}} f_{10}(u)\,du \\ &+ \int_{\alpha_{12}}^{+\infty} f_{10}(u)\,du, \end{aligned} \tag{4.3.84}$$

and

$$\int_0^t n_1^T(s)\,ds \ge \frac{n_1^T(0)}{n_2^A(0)}(1-\exp(-n_2^A(0)t)). \tag{4.3.85}$$

Proof. The proof of (4.3.83) is easy. To prove (4.3.84), we integrate the first equation of (4.3.80) over u in $(0,\alpha_{12})$:

$$\begin{aligned} \partial_t \int_0^{\alpha_{12}} f_1(t,u)\,du &= n_2^A(t)\left(\int_{\alpha_{12}}^{2\alpha_{12}} f_1(t,u)\,du - \int_0^{\alpha_{12}} f_1(t,u)\,du\right) \\ &\ge -n_2^A(t)\int_0^{\alpha_{12}} f_1(t,u)\,du\,. \end{aligned}$$

The application of the Gronwall lemma yields

$$\int_0^{\alpha_{12}} f_1(t,u)\,du \geq \exp\left(-\int_0^t n_2^A(s)\,ds\right)\int_0^{\alpha_{12}} f_{10}(u)\,du\,. \tag{4.3.86}$$

Using (4.3.83) and taking into account (4.3.86) yields

$$\partial_t \int_0^{+\infty} f_1(t,u)\,du \leq -n_2^A(t)\exp\left(-\int_0^t n_2^A(s)\,ds\right)\int_0^{\alpha_{12}} f_{10}(u)\,du\,. \tag{4.3.87}$$

Noting that

$$\frac{d}{dt}\exp\left(-\int_0^t n_2^A(s)\,ds\right) = -n_2^A(t)\exp\left(-\int_0^t n_2^A(s)\,ds\right)$$

and integrating (4.3.87) over s in $(0,t)$ yields (4.3.84).
Using (4.3.83) and the fact that $n_2^A(t)$ is decreasing yields

$$\partial_t n_1^T(t) \geq -n_2^A(0)n_1^T(t)\,,$$

which gives

$$n_1^T(t) \geq n_1^T(0)\exp(-n_2^A(0)t)\,. \tag{4.3.88}$$

Finally, integrating (4.3.88) in $(0,t)$ yields (4.3.85).

∎

Lemma 4.3.7. *The following estimates for f_2 hold true:*

$$\partial_t \int_0^{+\infty} f_2(t,u)\,du = -n_1^T(t)\int_0^{\alpha_{21}} f_2(t,u)\,du \leq 0, \tag{4.3.89}$$

$$\int_0^t n_2^A(s)\,ds \geq \frac{n_2^A(0)}{n_1^T(0)}(1-\exp(-n_1^T(0)t)). \tag{4.3.90}$$

Proof. The proof of (4.3.89) is easily obtained. For the proof of (4.3.90), we use the same technique as in Lemma 4.3.6. Using (4.3.89) and the fact that $n_1^T(t)$ is decreasing yields

$$\partial_t n_2^A(t) \geq -n_1^T(0)n_2^A(t)\,.$$

This gives

$$n_2^A(t) \geq n_2^A(0)\exp(-n_1^T(0)t)\,,$$

which, after integration in $(0,t)$, yields (4.3.90).

∎

Proof of Theorem 4.3.6. The proof of (i) comes from (4.3.83) and (4.3.89).
Using (4.3.84), (4.3.90), and the fact that

$$\exp\left(-\int_0^t n_2^A(s)\,ds\right) \le \exp\left(-\frac{n_2^A(0)}{n_1^T(0)}(1-\exp(-n_1^T(0)t))\right)$$
$$\to \exp\left(-\frac{n_2^A(0)}{n_1^T(0)}\right) \quad \text{for} \quad t \to +\infty$$

yields (4.3.81).

In the same way, using (4.3.85) and the fact that

$$\exp\left(-\int_0^t n_1^T(s)\,ds\right) \le \exp\left(-\frac{n_1^T(0)}{n_2^A(0)}\right)(1-\exp(-n_2^A(0)t))$$
$$\to \exp\left(-\frac{n_1^T(0)}{n_2^A(0)}\right) \quad \text{for} \quad t \to +\infty$$

yields (4.3.82).

∎

4.4 Perspectives

The qualitative analysis developed in this chapter relates to the general model proposed in Chapter 3, but also to some specific particularizations. The specializations of the model have been proposed to focus on different particular aspects of the immune competition with special attention to phenomena which can be experimentally observed.

This is certainly an interesting application, but not the only conceivable one. It aims to show how analytic methods can be developed not simply as mathematical speculations, but also towards a deeper understanding of complex biological phenomena. Bearing all of the above in mind, this chapter can be regarded as a bridge between Chapter 3, devoted to modelling, and Chapter 5, where some simulations will be proposed to complete the qualitative analysis.

As we have seen, the analysis has been devoted mainly to working out the asymptotic behavior of the solutions with special attention to analyzing

the role of the parameters of the model and the initial conditions over the output of the competition between the immune system and the carriers of a pathological state.

It is worth stressing that the qualitative analysis does not cover the whole panorama of models and examples which can be obtained from the general model proposed in Chapter 3, and, although it offers a variety of interesting results, it still needs the additional support of computational simulations. As a matter of fact, it refers to the evolution of the density of the cell populations, while higher order moments can be computed by computational simulations. Chapter 2 has shown that higher order moments have a well-defined biological meaning, so that it is worth completing the analysis developed in this chapter by adding simulations of the evolution of the whole distribution function and eventually of higher order moments. Of course, additional analysis is required for models with space structure. The contents of Chapter 6 will be devoted to this difficult issue.

5

Simulations, Biological Interpretations, and Further Modelling Perspectives

In the physical sciences, mathematical theory and experimental investigation have always marched together. Mathematics has been less intrusive in the life sciences because they have been largely descriptive, lacking the invariance principles and fundamental constants of physics.

Increasingly, in recent decades, however, mathematics has become pervasive in biology, taking many different forms: statistics in experimental design; pattern seeking in bioinformatics; models in evolution, ecology and epidemiology: and much else ...

— R.M. May

5.1 Introduction

A qualitative analysis of the initial value problem for various models of the immune competition against an aggressive host was developed in Chapter 4. The analysis showed that the problem is locally well posed, while special attention was devoted to identifying the output of the competition and, in particular, the influence of the parameters of the model over the above-mentioned asymptotic behavior.

The above analysis should not be regarded as a simple mathematical speculation, because well-defined biological interpretations can be linked to the analysis of the asymptotic behavior. This means identifying the parameters which play a role in recognizing and combating the aggressive host. Therapeutic actions can possibly be addressed to act over the biological factors related to the identified parameters.

The analysis also proved suitable regularity properties and, in some particular cases, the global existence and asymptotic behavior of the solutions. This means that there exist biological situations where the immune system can counteract the carriers of the pathology.

The above qualitative analysis enables us to develop appropriate computational methods to obtain simulations of the initial value problems. The computational analysis will be used to obtain additional information on the asymptotic behavior of the solution.

Simulations are developed to enlarge the description delivered by the theorems proposed in Chapter 4, with a relatively more detailed analysis of the role of the parameters. In particular, while the qualitative analysis refers to the evolution of the densities, simulations also show the behavior of the distribution function.

Simulations are obtained using the so-called ***generalized collocation method***.

Considering that the computational problem is not technically difficult, it does not seem necessary to provide a detailed description of such method. We simply state that the variable u is discretized into a suitable set of collocation points, and that the dependent variables, the distribution functions, are interpolated by Sinc functions. Then the integral terms are approximated by means of algebraic weighted sums in the nodal points of the discretization. The particularization of the evolution equation in each node and the enforcing of the initial conditions has transformed the integro-differential initial value problem into an initial value problem for ordinary differential equations, describing the evolution of the values of the distribution functions in the nodes of the collocation. The latter technically is solved with standard methods for ordinary differential equations. Further details on numerical methods can be found, for instance, in Canuto, Yousuff, Quarteroni, Zang (1988), Lund and Bowers (1992), and Bellomo (1997).

According to the above computational approach, the continuous distribution is obtained by interpolations. Moments, which as we have seen have a well-defined physical meaning, are computed by weighted sums.

It is worth stressing that the simulations developed in this chapter with their biological interpretations do not cover the whole variety of conceivable competitions. Simulations refer to some particularizations of model 3.3.18; some of them are developed with various levels of detail, while various hints are brought to the attention of the reader. The contents of this chapter are as follows:

Section 5.2 deals with simulations related to Model I, II, III, and C. The computational analysis is organized as already described in the above introduction. Various hints are indicated, for each model, for extending the analysis, thus obtaining a complete panorama of the prediction offered by each model.

Section 5.3 concerns the analysis of a specific model. In particular, it shows how Model P may be interpreted as a model of competition between immune cells and some particular progressing (neoplastic) cells.

Section 5.4 analyzes the delicate problem of the validation of parameters by experimental data. The main problem, as we shall see, consists of correlating empirical data at the macroscopic level with the microscopic behavior described by the model.

Section 5.5 develops a critical analysis for inquiring about the possibility of developing additional simulations and enlarging the class of models proposed in this book to the modelling of complex biological systems other than those considered so far.

5.2 Simulation of Immune Competition

This section is devoted to simulations and biological interpretations of the model of immune competition proposed in Chapter 3. Each simulation is illustrated by three graphs. A 2D graph shows the evolution in time of the densities of the system: the continuous line is the evolution of the density of abnormal cells, while the dashed line is the evolution of the immune density. A 3D graph on the left shows the evolution of f_1, and the one on the right shows the evolution of f_2; the axis corresponds to the time and the value of the state.

In addition to the simulations delivered with reference to each specific model, some suggestions for additional analysis are offered to the interested reader. Some of the suggestions can be regarded as a proper research perspective, with the aim of focusing the description of particular phenomena which may be delivered by the model.

The proposed simulations, as already mentioned in Section 5.1, do not cover the whole panorama related to the sensitivity analysis of all parameters. However, various aspects of interest for the biological sciences are covered, while the methodological approach can be further developed by the interested reader as discussed in the last section of this chapter.

The following subsections will analyze respectively the following three models: Models I–III, proposed in (3.4.5)–(3.4.9) and analyzed in Theorems 4.3.1–4.3.3; and Model C, proposed in (3.4.1)–(3.4.2) and analyzed in Theorems 4.3.5–4.3.6. For each model, some simulations and a biological interpretation are given.

5.2.1 Simulations of Model I.

The mathematical model. The model describes the competition when normal cells do not autonomously increase their degeneration, and immune cells do not have the ability to reduce the above microscopic state, while abnormal cells have some ability to inhibit the activation of immune cells.

Expected behavior. In general, we should expect a growth of abnormal cells and an inhibition of immune cells. Of course, the growth occurs if the initial number of abnormal cells is sufficiently large.

Simulations related to Theorem 4.3.1. The above expected behavior is the one delivered by Theorem 4.3.1, which gives a detailed description of the asymptotic scenario; see (4.3.5) and (4.3.7).

$$\text{If } \delta > 0 : \qquad \begin{cases} \forall\, T \geq 0 : n_1^T(t) \uparrow \quad \text{in } [0,T]\,, \\ n_2^A(t) \leq \dfrac{\gamma^*}{\beta_{21}}\,, \end{cases}$$

where, recalling (4.3.1), δ is given by

$$\delta = \beta_{11} n_1^E(0) - \beta_{12} n_2^A(0)\,,$$

and

$$\gamma^\star = \frac{\beta_{21}\beta_{11}}{\beta_{12}} n_1^E(0)\,.$$

$\delta > 0$ means that initially, at $t = 0$, the number of normal endothelial cells is sufficiently large with respect to the number of immune cells, respectively weighted with the parameters β_{11} and β_{12} related to the proliferation ability of abnormal cells and the ability of immune cells to counter abnormal cells. In this case, when $\delta > 0$, a growth of abnormal cells n_1^T is observed. It is indicated in Figures 5.1a–c, which also show how the maximum value of f_2 moves progressively toward lower values of the microscopic state u.

The opposite behavior is observed when $\delta < 0$ (Figures 5.2a–c), where abnormal cells are depleted while immune cells grow in number since they are not sufficiently inhibited.

$$\text{If } \delta < 0 : \qquad \begin{cases} \forall\, T > 0 : n_1^T(t) \downarrow \quad \text{in } [0,T]\,, \\ n_2^A(t) \geq \dfrac{\gamma^*}{\beta_{21}}\,. \end{cases}$$

Biological interpretation. The model corresponds to a competition where the immune system is inhibited by abnormal cells. However, despite

this inhibition, immune cells are still able to counter the invasive host, depending both on the initial state and on the ability of abnormal cells to proliferate and on the ability of immune cells to combat against the invader.

This result suggests therapeutic actions related to the ability to reduce proliferation of abnormal cells (by reducing β_{11}) or to increase the immune activity (by increasing β_{12}).

The model also shows that if the therapeutic action increases the number of active immune cells beyond a certain threshold, then the immune system is able to complete the destructive action on the abnormal cells.

Suggestions for additional qualitative and computational analysis. Additional simulations can be developed to enrich the panorama of the description offered by Theorem 4.3.1 with special attention to the role of the β-type parameters. Further analysis, qualitative and/or computational, may identify the asymptotic behavior when $\alpha_{11} > 0$, which should generate a relatively more complex behavior due to the progressive degeneration of abnormal cells; or when $\alpha_{21} > 0$, should show a relatively more favorable situation for the immune system due to its ability to reduce the state of abnormal cells.

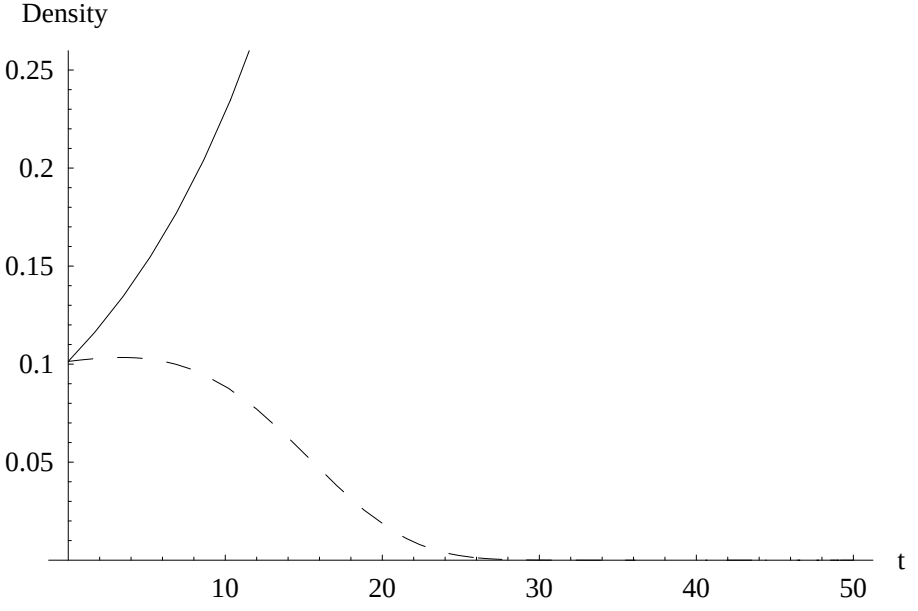

Fig. 5.1a. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta > 0$. Growth of abnormal cells and immune inhibition.

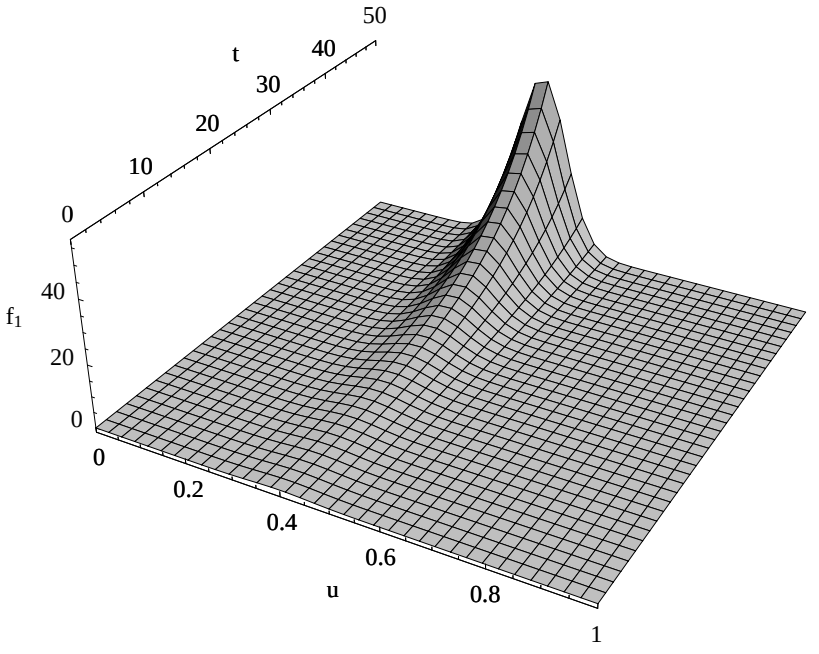

Fig. 5.1b. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta > 0$. Growth of abnormal cells.

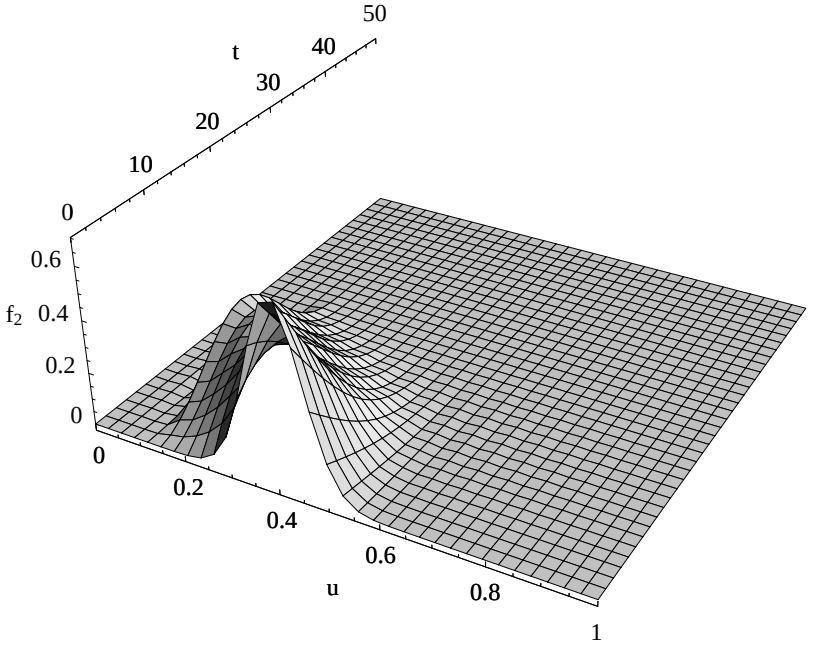

Fig. 5.1c. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta > 0$. Immune inhibition.

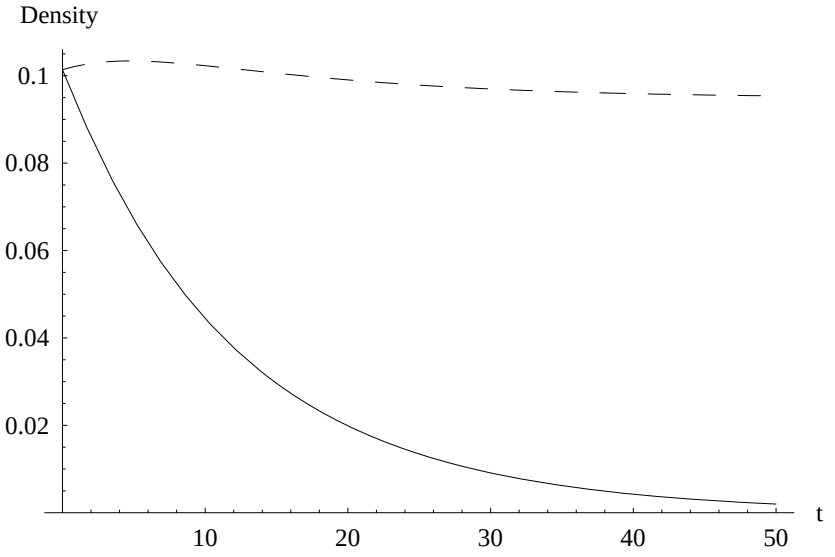

Fig. 5.2a. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta < 0$. Depletion of abnormal cells and immune activation.

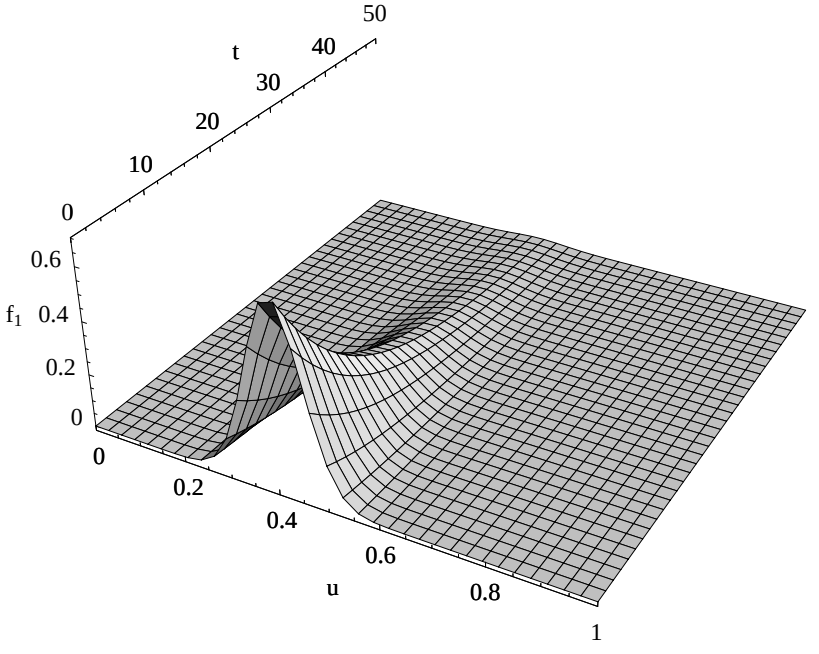

Fig. 5.2b. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta < 0$. Final depletion of abnormal cells.

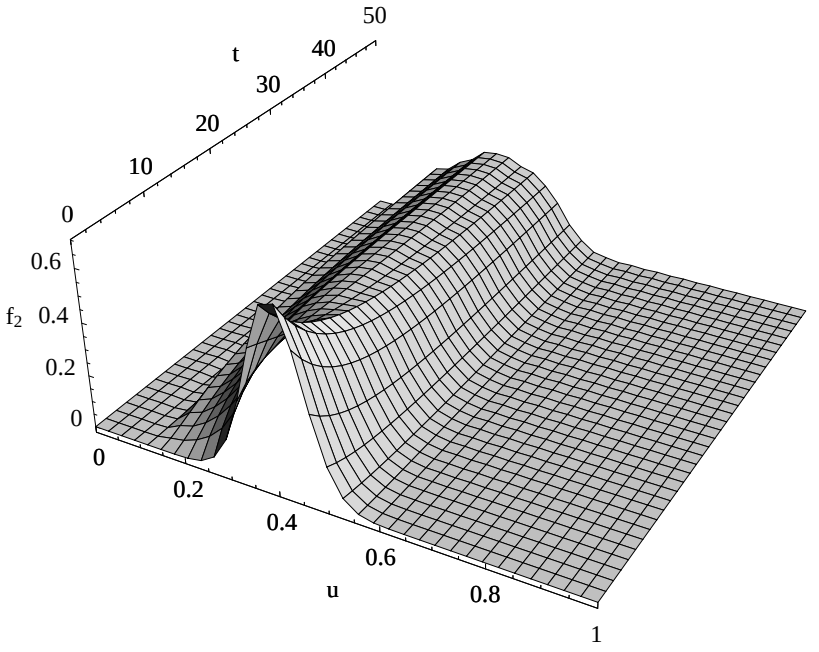

Fig. 5.2c. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0.1$, and $\delta < 0$. Evolution of immune distribution.

5.2.2 Simulations of Model II.

The mathematical model. The model describes the competition when cells of the first population, both normal and already abnormal cells, show a natural tendency to degenerate. In addition, the competition between abnormal cells and immune cells is influenced by the values of the nonconservative parameters only.

Expected behavior. The tendency to degenerate of the normal endothelial cells is not countered by immune cells, as $\alpha_{12} = 0$, and abnormal cells cannot inhibit immune cells, as $\alpha_{21} = 0$. For some sets of the β-type parameters and the initial conditions, a reduction of abnormal cells is expected.

Simulations related to Theorem 4.3.2. The above expected behavior is predicted by Theorem 4.3.2, based on the following *a priori* estimates; see (4.3.45).

$$\text{If } \lambda = (\delta + n_1^E(0)) < 0 : \quad \begin{cases} n_1^T(\infty) \le -\dfrac{(n_1^E(0))^2}{\lambda}, \\ n_2^A(t) \uparrow, \end{cases}$$

where, according to (4.3.43), $\lambda = (1 + \beta_{11})n_1^E(0) - \beta_{12}n_2^A(0)$.

In this case, simulations show the total depletion of abnormal cells with a growth in number of immune cells (Figures 5.3a–c).

Conversely, if the non-conservative parameters and the initial conditions are chosen in such a way that $\lambda > 0$, Theorem 4.3.2 gives no information and from the computational analysis we obtain an increase of the state of abnormal cells, while their density, after an initial growth, is reduced by the competition with immune cells which are stimulated to grow (Figures 5.4a–c). Thus, the density of abnormal cells, after a growth stage, is eventually reduced by immune cells.

Biological interpretation. The above results show that when abnormal cells are not able to inhibit immune cells, they are asymptotically destroyed. Note that once the density of abnormal cells reaches a certain threshold (which may be identified in comparison with suitable experimental and medical results), the attacked host may survive no longer.

Suggestions for additional qualitative and computational analysis. Additional analysis, qualitative and/or computational simulations can be developed with the introduction of the capability of immune cells to counter abnormal cells, i.e., $\alpha_{12} > 0$. In this case, the natural tendency of endothelial cells to degenerate is countered by the immune system and a competition starts. The magnitude of the initial conditions and the values of the parameters play an important role in determining the final scenario.

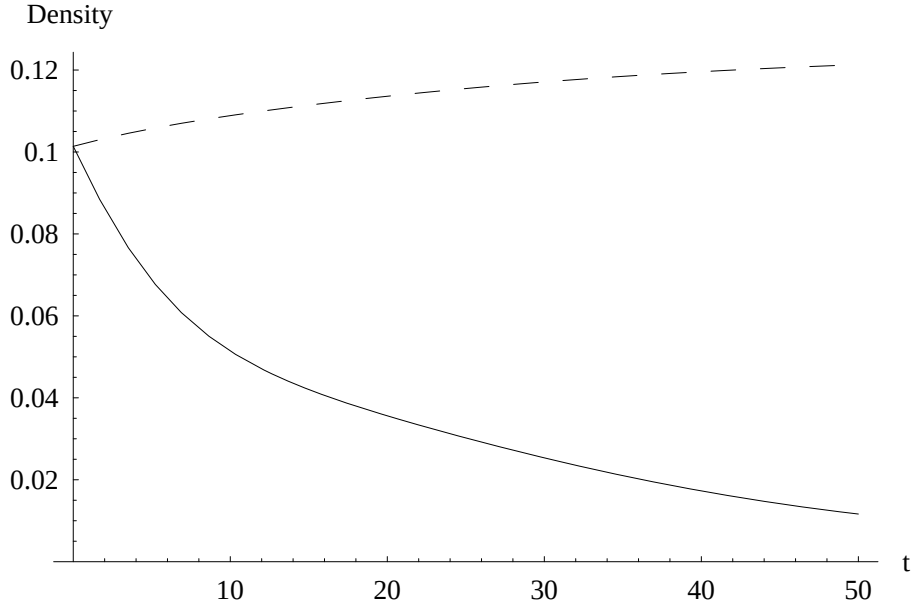

Fig. 5.3a. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda < 0$.
Final depletion of abnormal cells and immune activation.

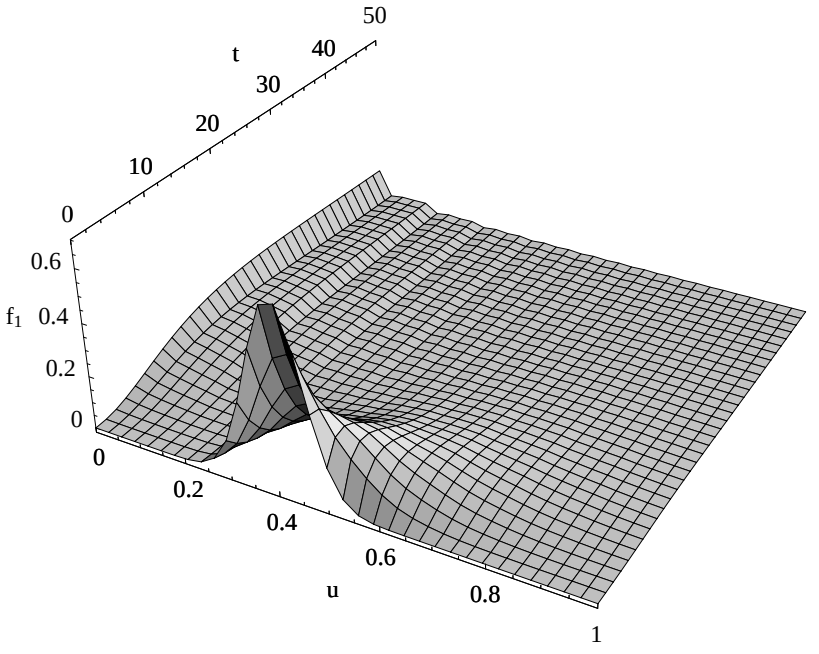

Fig. 5.3b. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda < 0$. Final depletion of abnormal cells.

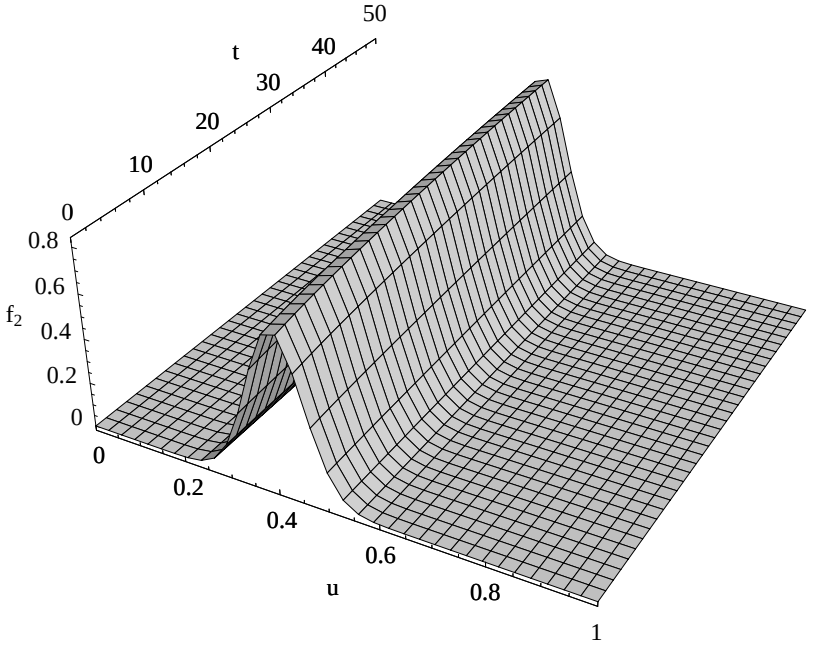

Fig. 5.3c. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda < 0$. Immune activation.

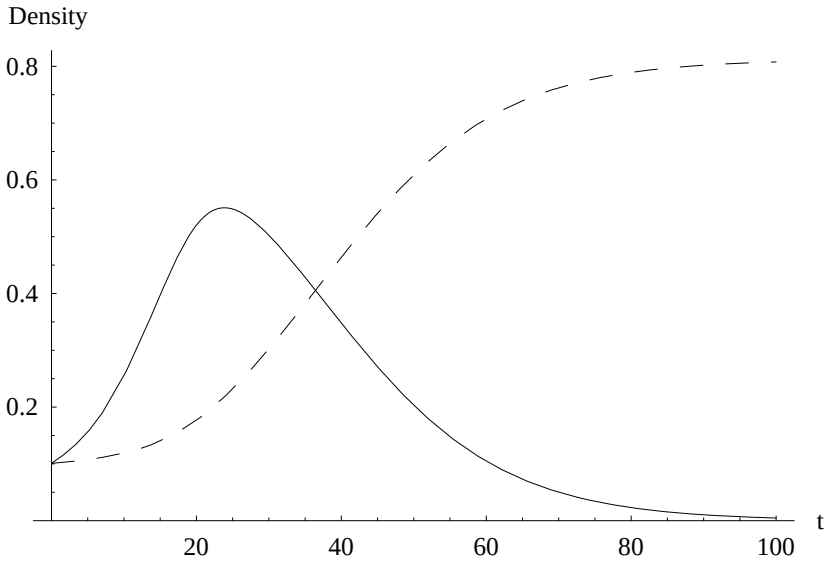

Fig. 5.4a. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda > 0$. Depletion of abnormal cells and immune activation.

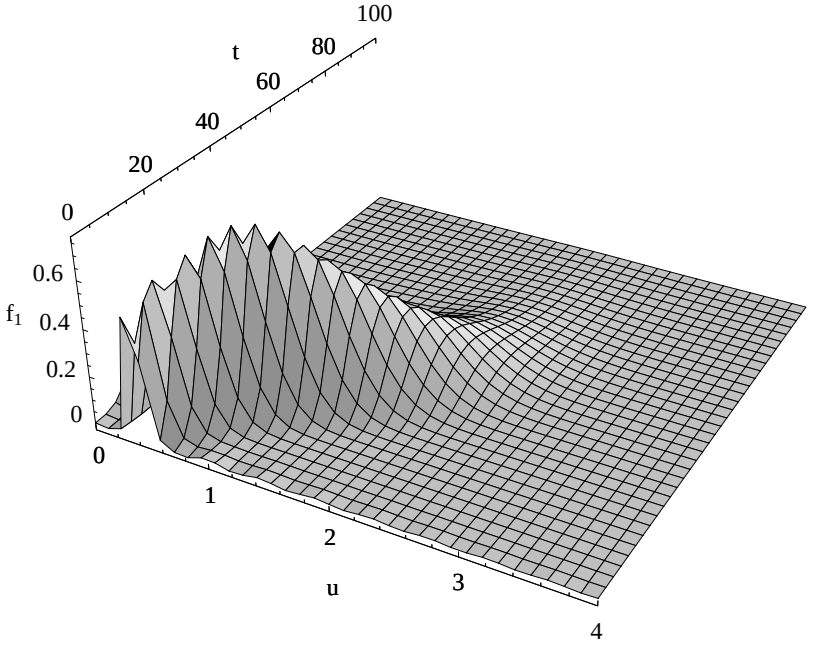

Fig. 5.4b. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda > 0$. Abnormal cells increase their state but finally are depleted.

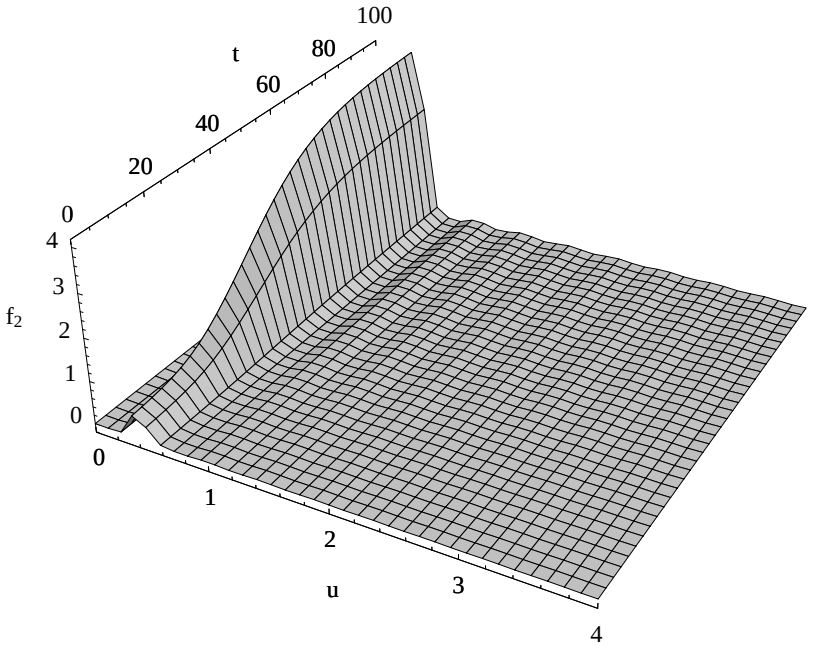

Fig. 5.4c. $\alpha_{11} = 0.1$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\lambda > 0$. Immune activation.

5.2.3 Simulations of Model III.

The mathematical model. In this case endothelial cells do not show a natural tendency to degenerate. The abnormal cells are countered by immune cells, while they do not inhibit immune cells.

Expected behavior. Abnormal cells do not degenerate and are not able to inhibit immune cells, which conversely are stimulated to reproduce themselves. Thus the expected behavior is the depletion of abnormal cells.

Simulations related to Theorem 4.3.3. The *a priori* estimates obtained from Theorem 4.3.3 provide only partial information on the depletion of abnormal cells; see (4.3.52) and (4.3.55).

$$\text{If } \theta \le 0 : \qquad \begin{cases} n_1^T \downarrow & \text{and} \quad n_1^T \le n_1^T(0)\exp(\theta t)\,, \\ n_2^A(t) \uparrow\,, \end{cases}$$

where, according to (4.3.52),

$$\theta = \beta_{11}\left(n_1^E(0) - \frac{1}{\beta_{21}} n_2^A(0)\right)\,.$$

The computational analysis shows that the growth of abnormal cells is always countered by immune cells. The number of immune cells grows and they are able to control, from the beginning, the proliferation of abnormal cells. This behavior is shown in Figures 5.5a–c.

If $\theta > 0$, abnormal cells initially grow in number, but since the proliferation of immune cells is also stimulated, when the number of the immune cells reaches a threshold, abnormal cells start to be reduced until their complete depletion; see Figures 5.6a–c.

Biological interpretation. The situation is the most favorable one for the host. Abnormal cells do not degenerate any more (the maximum degenerated state is at the beginning) and are not able to inhibit immune cells, which conversely are stimulated to reproduce themselves. The final outcome is always the depletion of abnormal cells. The values of the non-conservative parameters and of the initial condition play a significant role in determining the initial evolution; for instance, there might be an initial growth of abnormal cells before their final depletion; see Figures 5.6a–c.

Suggestions for additional qualitative and computational analysis. It appears interesting to analyze the evolution when α_{21} is also positive and different from zero, i.e., the case $\alpha_{11} = 0$, $\alpha_{12} > 0$, $\alpha_{21} > 0$. It is expected that there exists a bifurcating parameter such that if the ability of immune cells to reduce abnormal ones is set at a critical value, the final scenario is the depletion of abnormal cells. Conversely, if it is below the critical value, the final expected outcome is the growth of abnormal cells and immune inhibition.

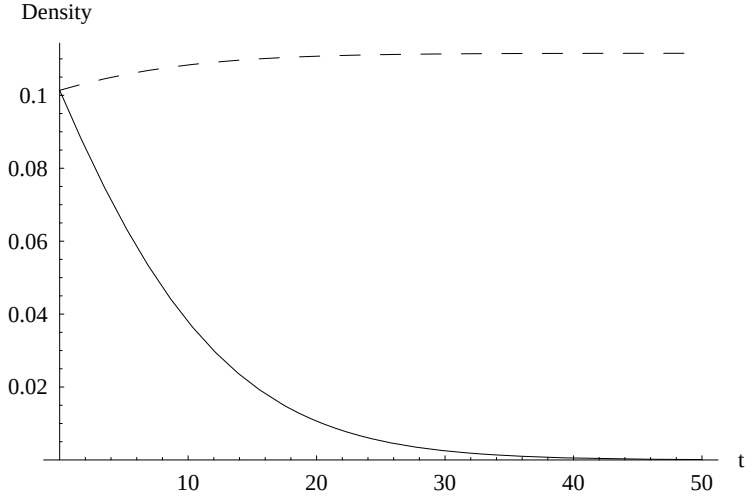

Fig. 5.5a. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta < 0$. Depletion of abnormal cells and immune activation.

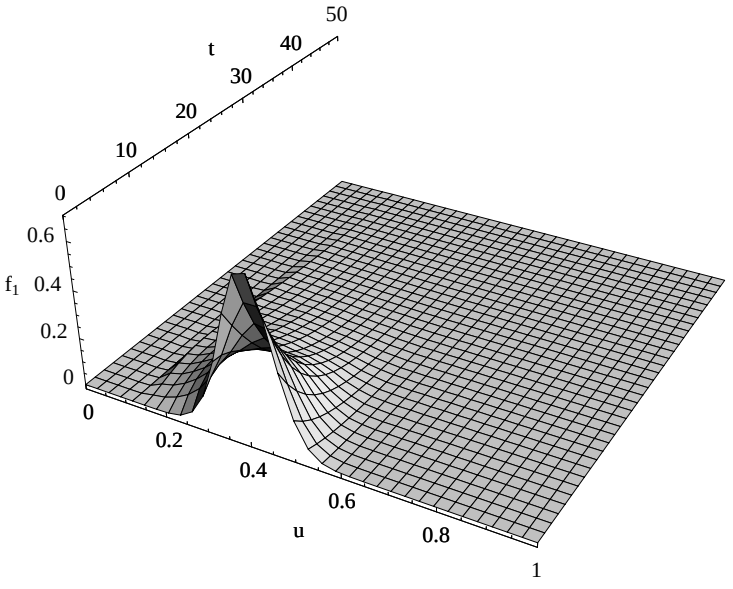

Fig. 5.5b. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta < 0$. Final depletion of abnormal cells.

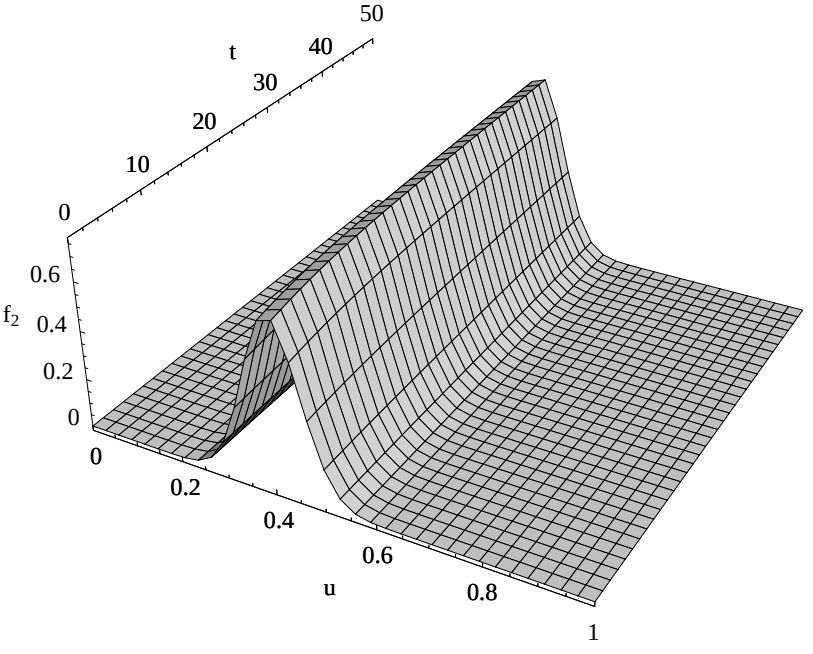

Fig. 5.5c. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta < 0$. Evolution of immune distribution.

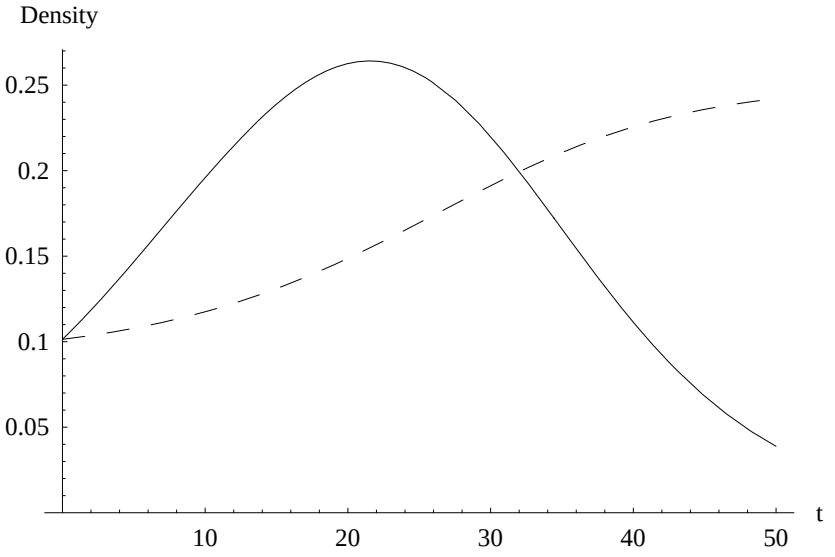

Fig. 5.6a. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta > 0$.
Final depletion of abnormal cells and immune activation.

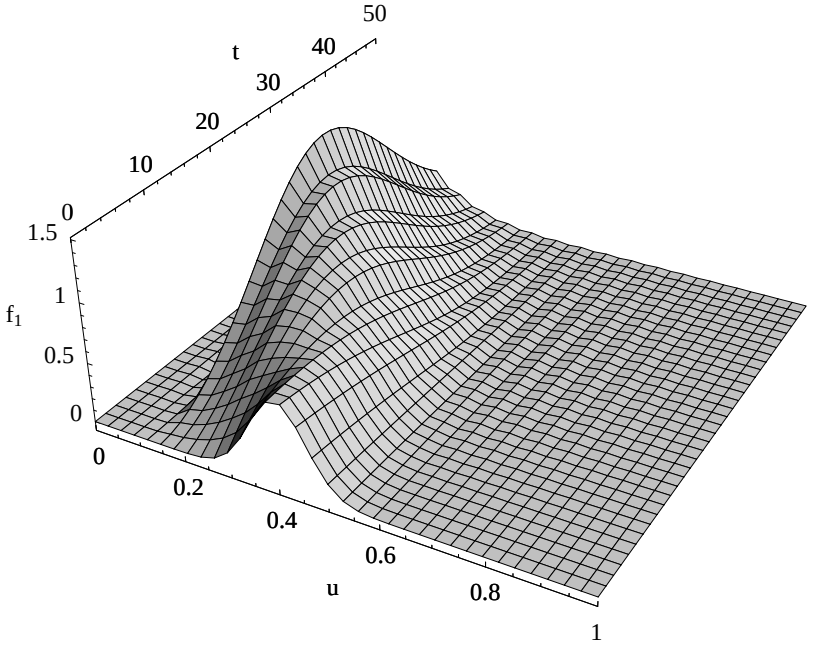

Fig. 5.6b. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta > 0$.
Final depletion of abnormal cells.

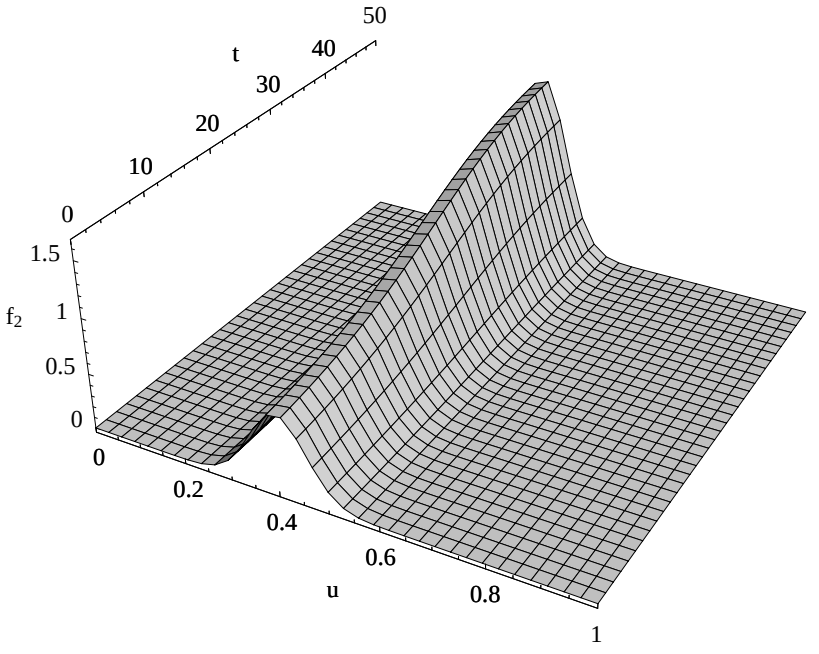

Fig. 5.6c. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0$, and $\theta > 0$. Immune activation.

5.2.4 Simulations of Model C.

The mathematical model. Model C is characterized by the fact that the number of cells is constant in time, while the distribution function over the microscopic state shifts toward higher or lower values.

Expected behavior. The evolution is ruled by the evolution of the states and not by destruction/proliferation phenomena. The expected behavior strongly depends on the ability of abnormal/immune cells to inhibit the competitor cells (immune/abnormal cells), and thus on the ratio between α_{21} and α_{12}. An additional role is played by the parameter related to the tendency of endothelial cells to degenerate, α_{11}. Thus, we expect a complex scenario strongly depending on the parameters.

We focus on Model C2, defined in equation (4.3.80), corresponding to the situation in which no degeneration occurs ($\alpha_{11} = 0$) and only the parameters α_{21} and α_{12} are different from zero. The qualitative scenario of this model is studied in Theorem 4.3.6, which states that

$$n_2^A \downarrow \quad \text{and} \quad n_1^T \downarrow .$$

Simulations related to Theorem 4.3.6. As expected, both abnormal and immune cells are reduced during the competition (since no proliferation may occur). However, the asymptotic scenario is such that only one cell population survives and the other is completely depleted. The ratio between the values of α_{21} and α_{12}, as well as the initial conditions, defines which of the populations will survive.

Consider the same initial condition for abnormal and immune cells. If $\alpha_{21} > \alpha_{12}$, the ability of abnormal cells to inhibit immune cells is greater than the ability of immune cells to reduce the state of abnormal cells. The final output is a complete inhibition of immune cells and a final survival of abnormal cells, as shown in Figures 5.7a–c.

If $\alpha_{21} < \alpha_{12}$, the final scenario is a reduction of the state of abnormal cells until their complete depletion and a final survival of immune cells, as shown in Figures 5.8a–c.

Biological interpretation. In this situation, the time is so short that no proliferation occurs. The final scenario depends on which of the two populations is the "strongest" in inhibiting the competitor population.

Suggestions for additional qualitative and computational analysis. It is interesting to develop a complete picture taking into account the self-degeneration of endothelial cells, i.e., $\alpha_{11} \neq 0$.

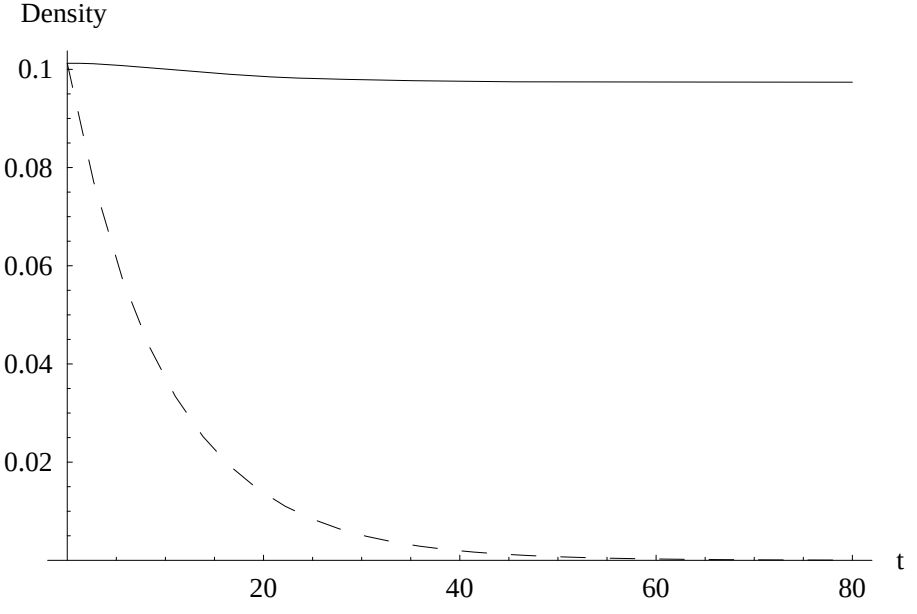

Fig. 5.7a. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0.9$.
Complete immune depression and density evolution of abnormal cells.

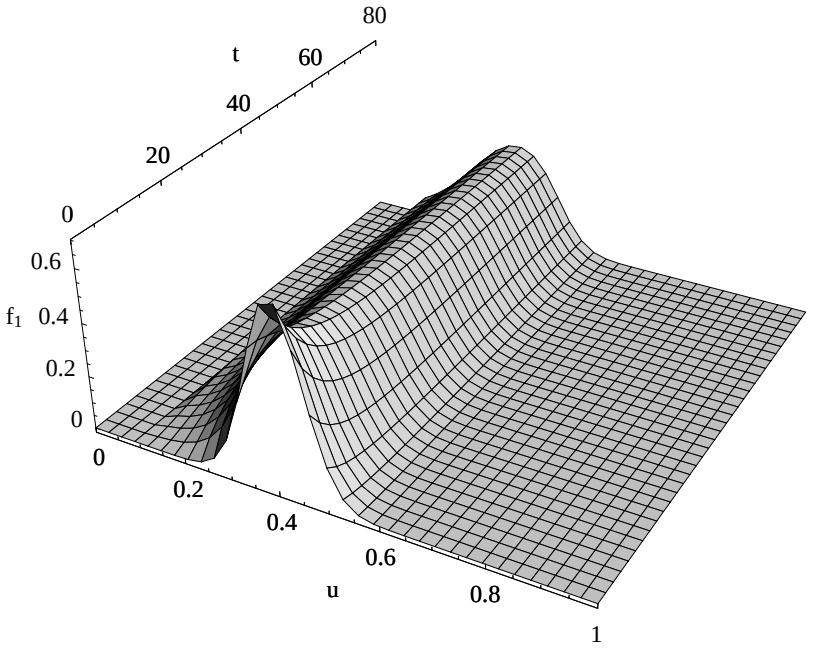

Fig. 5.7b. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0.9$.
Evolution of abnormal cells.

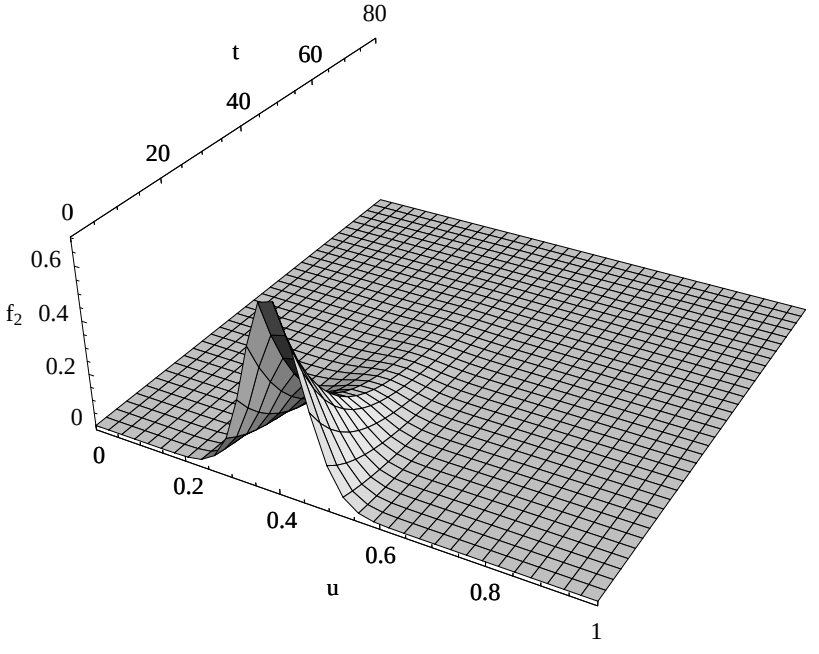

Fig. 5.7c. $\alpha_{11} = 0$, $\alpha_{12} = 0.1$, $\alpha_{21} = 0.9$.
Immune inhibition.

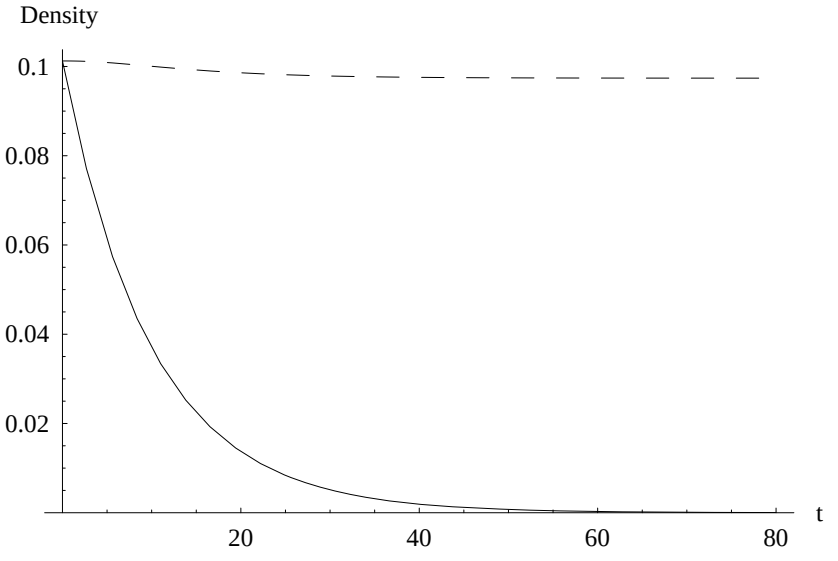

Fig. 5.8a. $\alpha_{11} = 0$, $\alpha_{12} = 0.9$, $\alpha_{21} = 0.1$.
Immune survival and total depletion of abnormal cells.

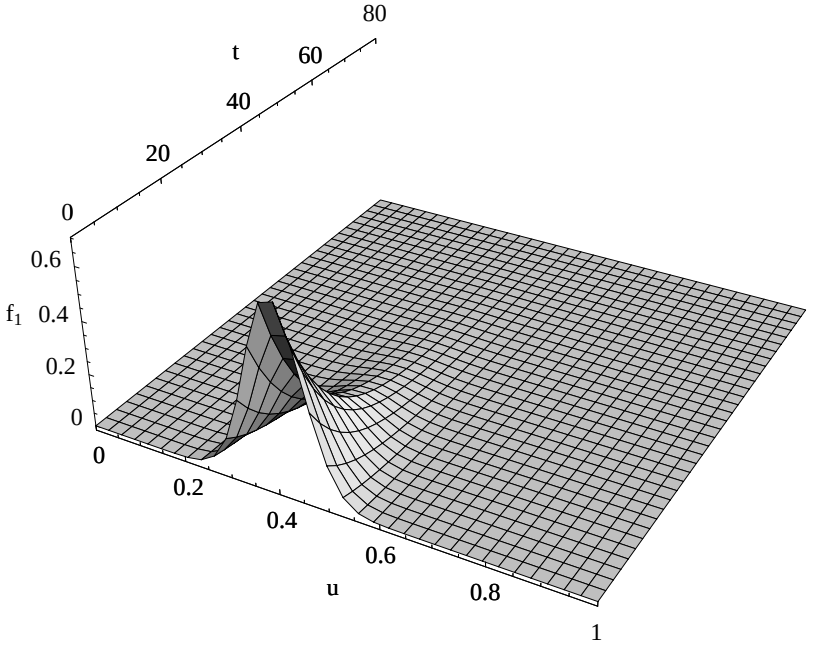

Fig. 5.8b. $\alpha_{11} = 0$, $\alpha_{12} = 0.9$, $\alpha_{21} = 0.1$.
Reduction of abnormal cells.

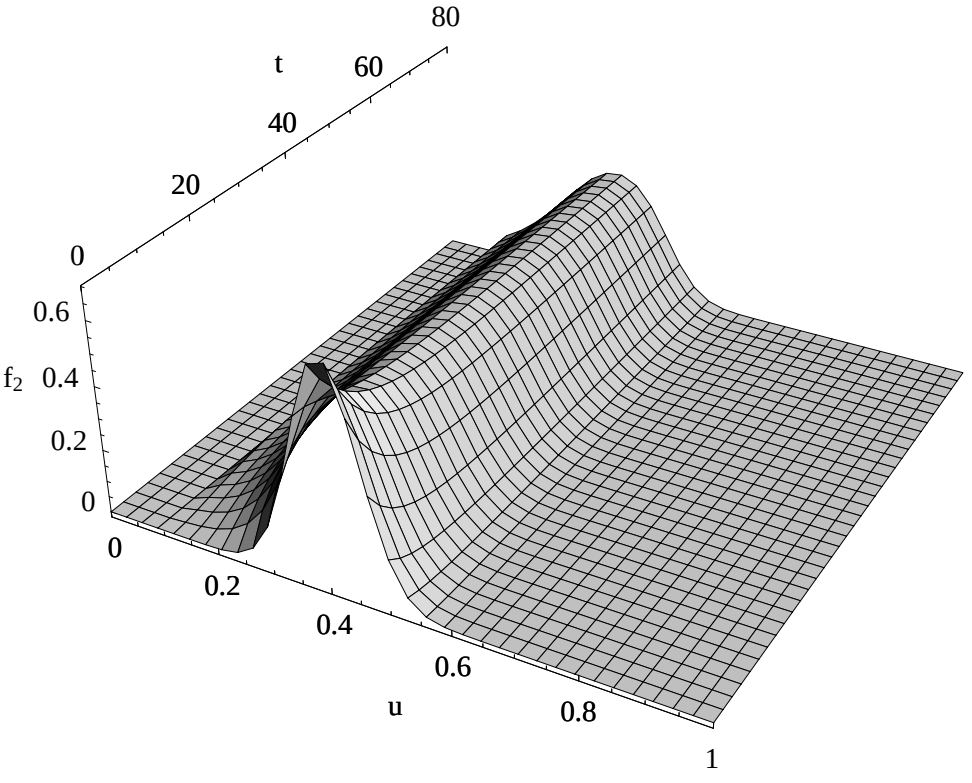

Fig. 5.8c. $\alpha_{11} = 0$, $\alpha_{12} = 0.9$, $\alpha_{21} = 0.1$. Immune survival.

The table which follows summarizes the biological meaning and the asymptotic (in time) behavior of the models proposed in this chapter, thus allowing their biological interpretation.

Table 5.1. Biological meaning and asymptotic behavior of the models.

Model C2	The model is (prevalent) conservative, and the evolution is ruled by the evolution of the states. No degeneration occurs ($\alpha_{11} = 0$). No proliferation phenomena occur, since the observation time is short: the final scenario is related to the ability of each of the two populations to inhibit its competitor.

Model I	Normal cells do not degenerate autonomously, and immune cells do not have the ability to reduce their microscopic state, while abnormal cells have the ability to inhibit the activation of immune cells. Despite the inhibition of immune cells by abnormal cells, they are still able to counter the invasive host depending both on the initial state and on the proliferating ability of abnormal cells.
Model II	Cells of the first population show a natural tendency to degenerate. The competition between abnormal cells and immune cells is influenced only by the values of the nonconservative parameters. Abnormal cells are not able to inhibit immune cells, so after an initial growth stage, they are progressively destroyed.
Model III	Endothelial cells do not show a natural tendency to degenerate. Abnormal cells are countered by immune cells, while they do not inhibit immune cells. The evolution of the competition shows that abnormal cells, after an initial growth stage, are completely depleted.

5.3 Tumor–Immune Competition

This section is devoted to the biological interpretations and simulations of Model P given by equation (3.4.3). The analysis shows how Model P may describe the competition between immune cells and tumor cells. Specifically, we consider the evolution of cells which have lost their differentiated state and become tumor cells, or ***progressing*** cells as specifically discussed in Section 3.2.

Let us assume that

i) The progressing cells do not show a natural tendency to increase their progression. This means that either the cells do not show a tendency to degenerate at all, or the phenotypic changes occur so rarely that they are negligible with respect to the time scale of the model (and thus to the survival time of the host). According to the above biological interpretation, this means assuming $\alpha_{11} = 0$.

ii) The active immune cells are not able to reduce the progression of tumor cells. This means that either the immune cells are able to destroy the progressing cells (destructive interaction), or they are unable to counter the progression. In other words, the immune system is not able to partially "repair" the genetic degradation of the progressing cell. According to the above biological interpretation of the parameters of the general model, this means assuming $\alpha_{12} = 0$.

iii) The progressing cells are not able to inhibit the immune cells; referring to the biological interpretation of the parameters of the general model, this means assuming $\alpha_{21} = 0$.

The model is not to be considered as a general model of tumor–immune competition, but only as a way of modelling some aspects of the competition between particular progressing cells and immune cells.

In this way, the general model (3.3.18) reduces to a model where only the nonconservative parameters are different from zero: this is Model P. These parameters should be related to specific types of progressing cells.

The quantitative analysis which follows is developed in three subsections. The first one provides some biological interpretations of Theorem 4.3.4 on the solution of the Cauchy problem. The second subsection shows some simulations and develops a computational analysis of the model. Finally, the third subsection shows how the model can be compared with experimental results and how some parameters can be identified.

5.3.1 Biological interpretations

In this subsection, we provide an interpretation from the biological point of view of Theorem 4.3.4. Specifically, Theorem 4.3.4 shows that the asymptotic behavior depends, in a rather complicated way, on the size of the initial condition and on the β-type parameters related to the proliferation ability.

According to definition (4.3.1) of the parameter

$$\delta = \beta_{11} n_1^E(0) - \beta_{12} n_2^A(0)\,,$$

which plays a relevant role in defining the asymptotic scenario, a ***critical***

immune density $n_{2_C}^A = \beta^*$ can be defined, such that

$$\beta^* = \frac{\beta_{11}}{\beta_{12}} n_1^E(0)$$

is the product of the initial number of environmental cells (both normal and abnormal endothelial cells) and the ratio of the proliferation rate of tumor cells and the ability of immune cells to destroy tumor cells. Then, the results of Theorem 4.3.4 can be summarized as follows:

$$\text{If } n_2^A(0) < n_{2_C}^A = \beta^* \, (\delta > 0) \, : \begin{cases} n_2^A(t) \uparrow, \\ \\ \exists \; t_0 \; : \; n_1^T \uparrow, \forall \; t \in [0, t_0] \quad \text{and} \\ \qquad n_1^T \downarrow, \forall \; t \in [t_0, T], \forall \; T > 0 \, . \end{cases}$$

$$\text{If } n_2^A(0) \geq n_{2_C}^A = \beta^* \, (\delta \leq 0) \, : \begin{cases} n_2^A(t) \uparrow, \\ \\ n_1^T(t) \downarrow; \exists \delta \leq 0 : n_1^T(t) \leq n_1^T(0) \exp(\delta t) \, , \end{cases}$$

Thus, according to Theorem 4.3.4, in the presence of an aggressive host, the immune system is stimulated to grow and its density increases, while the following two behaviors are predicted by the model:

- If $n_2^A(0) \geq \beta^*$, i.e., $\delta \leq 0$, then the number of tumor cells decreases and the rate of decrease is given by estimate (4.3.65), which shows that this rate is related to the values of β^*.
- If $n_2^A(0) < \beta^*$, i.e., $\delta > 0$, at first the number of tumor cells grows, since the number of immune cells is not sufficient to counter them. Nevertheless, since the immune cells are stimulated to proliferate by the presence of the host, after a certain critical time t_0 their number will be great enough to reduce the number of tumor cells. Of course this critical time t_0 is, at this stage, purely mathematical, while it should be linked to the survival time of the individual. In principle, the asymptotic behavior always shows an increase and then a decrease of the tumor cells, but in reality this critical time may be too long, so that one sees only the first step of tumor growth.

Some computational analysis may be useful to complete the above interpretation.

5.3.2 Simulations

Simulations have been obtained, as mentioned in the introduction of this chapter, by using the generalized collocation methods. We are interested in the evolution of the size of the populations $n_1^T(t)$, $n_1^E(t)$. The solution of equation (3.4.4) will be evaluated in a compact subset of $\mathbb{R}^+ \times \mathbb{R}$: the choice of this set is biologically justified because we are considering early-stage tumor cells and an infinite progression state has no biological counterpart.

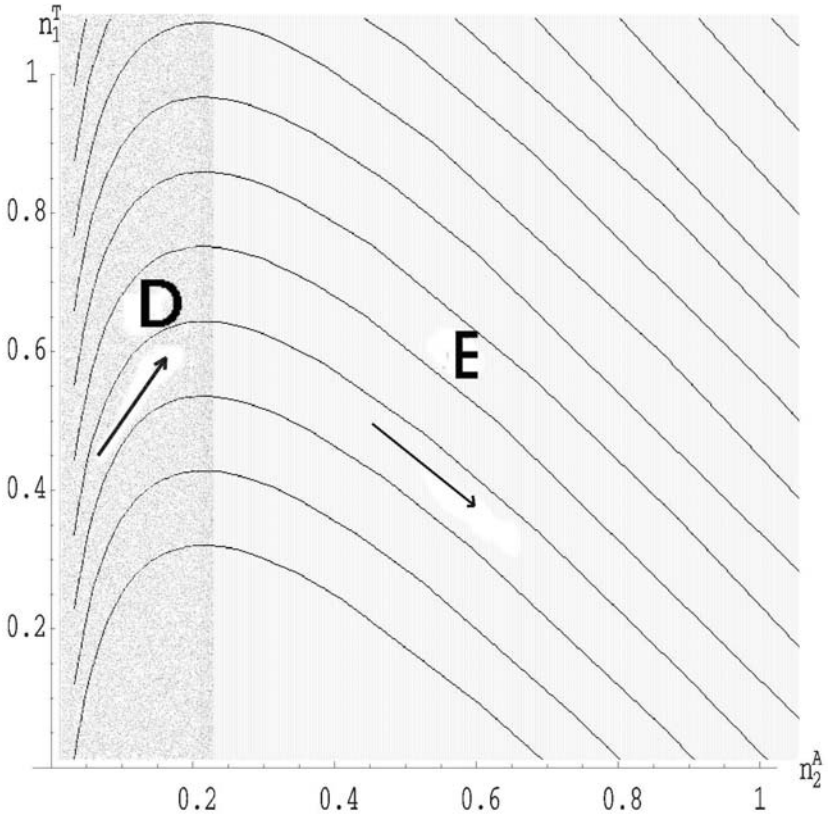

Fig. 5.9. Phase portrait of the density of tumor cells and immune cells.

Specifically, Figure 5.9 is the phase portrait related to the model described by equations (3.4.4). On the abscissa it reports the immune density and the tumor density is on the ordinate. As known in the theory of

ordinary differential equations, starting from a point of the phase space, which corresponds to fixing the initial condition of the initial value problem, there is only one orbit which describes the evolution of the system, as the system is autonomous. The arrows in the figures indicate the direction of the evolution in time of the orbits.

Figure 5.9 shows the phase portrait for fixed values of β^* and for fixed $\beta_{21} > 0$. In this situation immune cells increase, and we can distinguish two areas, Area D and E, which differentiate the evolution. Specifically, Area D refers to the initial values of immune density less than the critical value. In this case, the tumor is able to grow in the first stage, but when the immune cells, stimulated to proliferate by the presence of the progressing cells, reach the critical value, then the tumor cells start to decrease and finally are depleted.

Area E refers to the initial values of immune density greater than the critical value. If the initial condition belongs to Area E, then only the second stage occurs; namely the tumor reduction toward complete depletion.

It needs to be stressed that the phase portraits refer to a chosen set of the parameters defining β^* and β_{21}. A change of these values slightly modifies the portraits, namely the dimension and shape of the above-mentioned areas. The change shifts the position of the critical immune density and the position of the above-mentioned "threshold orbit," but the qualitative behavior does not change and it is always possible to identify the above-mentioned areas.

Therefore, it can be remarked that the above representation fully describes the qualitative influence of the parameters on the evolution of the immune competition. Specifically, Figure 5.9 illustrates the theoretical predictions given in Theorem 4.3.4.

Of course the same result can be visualized by showing the evolution of the distribution function. Indeed, this simulation shows the evolution of the distribution function, thus providing a deeper look at the inner structure of the system, giving additional information with respect to the theorem and the phase portrait referred to the evolution of the densities, which are the moments of the distribution function.

Thus, if $\delta \leq 0$ for the density we get a decrease from the initial number of abnormal cells and an increase for the number of immune cells; see Figure 5.10a. The same results is obtained for the distribution function where, since in Model P only proliferative/destructive encounters occur, no shift in the state of the distribution function occurs (Fig. 5.10b,c).

The opposite behavior is obtained if $\delta > 0$, where immune cells are stimulated to proliferate while abnormal cells increase at first and after a certain critical time start to be depleted; see Figures 5.11a–c.

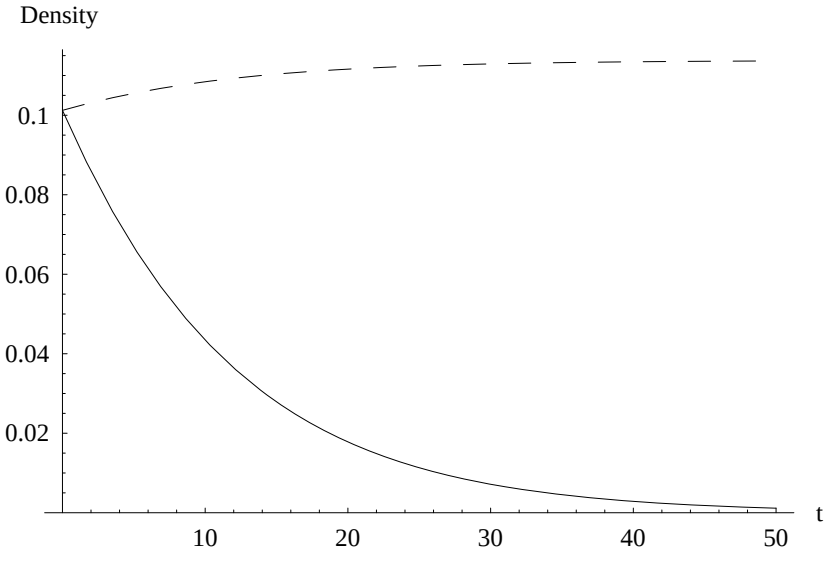

Fig. 5.10a. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta < 0$. Immune cell proliferation and depletion of abnormal cells.

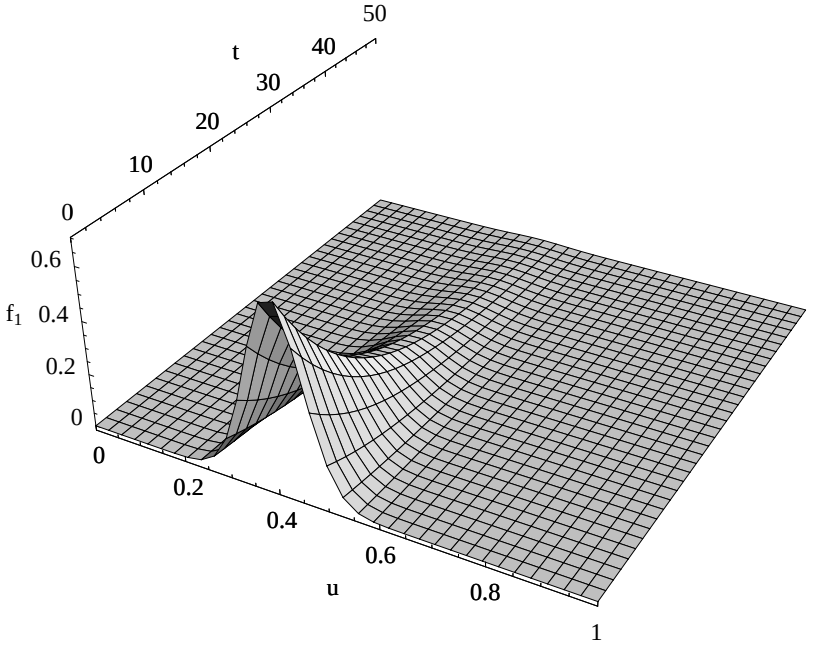

Fig. 5.10b. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta < 0$. Depletion of abnormal cells.

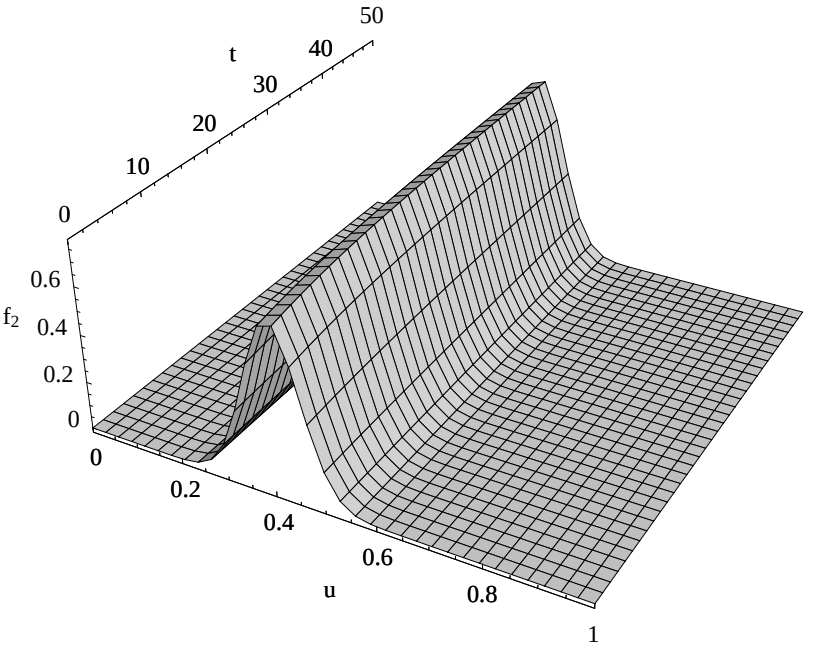

Fig. 5.10c. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta < 0$.
Immune cell proliferation.

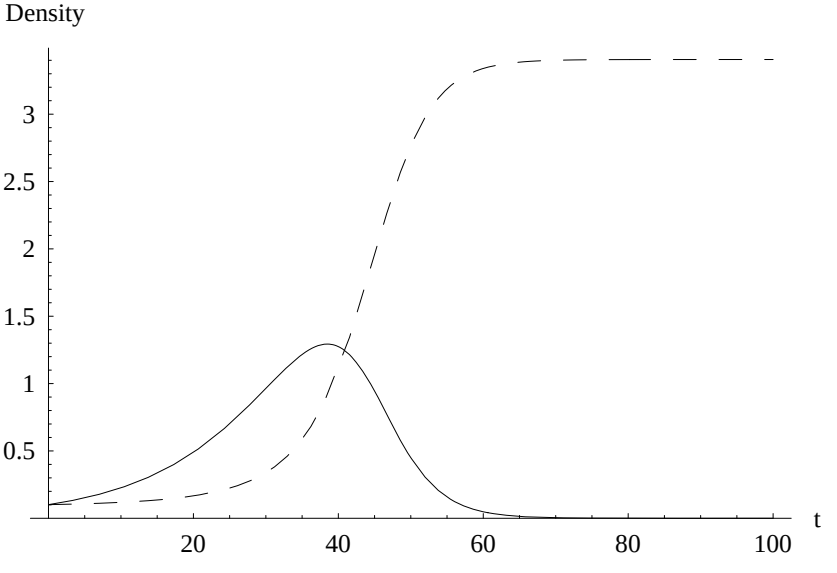

Fig. 5.11a. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta > 0$.
Immune proliferation and initial increase and final depletion of abnormal cells.

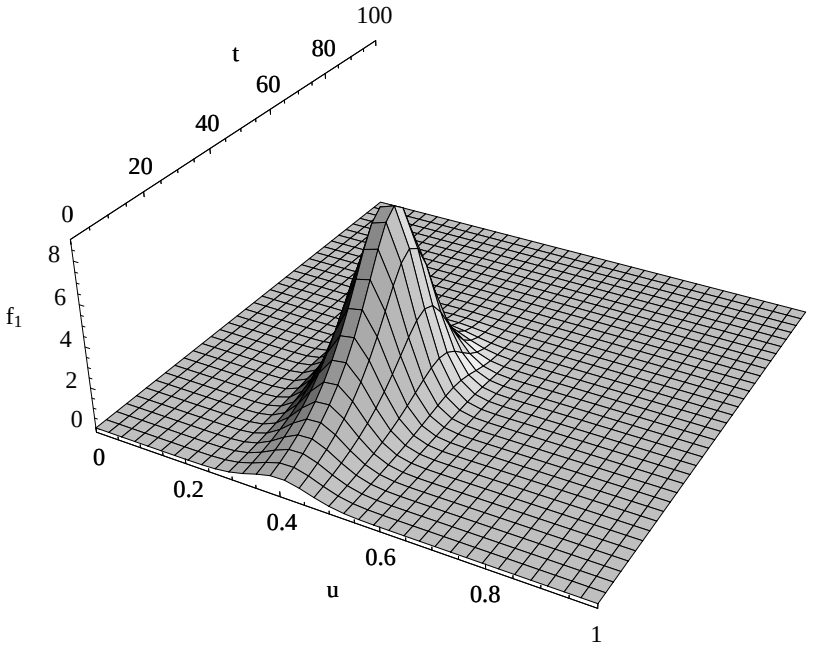

Fig. 5.11b. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta > 0$. Initial increase and final depletion of abnormal cells.

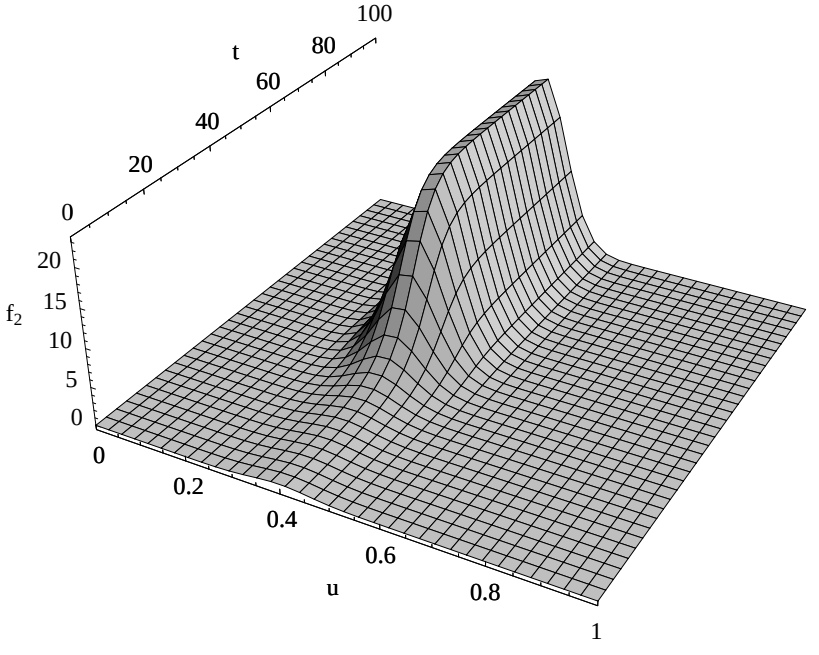

Fig. 5.11c. $\alpha_{11} = 0$, $\alpha_{12} = 0$, $\alpha_{21} = 0$, and $\delta > 0$. Immune proliferation.

5.4 Comparison with Experimental Data

The class of mathematical models proposed in this book has shown the ability to describe several interesting phenomena of the immune competition. However, a detailed quantitative description can be obtained only if the parameters of the model are properly identified.

Of course, the above identification can be realized if the competition is specialized to a well-defined phenomenon. The analysis proposed in this section refers to the competition between tumor and immune cells. However, the generalization to other types of competition can be properly analyzed, as we shall discuss in Section 5.5.

It is necessary, before dealing technically with the above problem, to analyze the difficulties, and maybe even the impossibility, of achieving some useful data. The articles published in the special issue of the journal *La Recherche* can contribute to a deep understanding of the above-mentioned difficulties.

Specifically, we refer to the article by Gillet (2005), which points out the impossibility of analyzing *in vivo* cellular cancer phenomena, while experiments *in vitro* do not reproduce what really happens *in vivo*. This is due to the fact that experiments observe macroscopic behaviors, while relevant biological phenomena occur at the cellular scale. This is not a peculiarity of cancer phenomena only, but of several immune competitions when cellular phenomena play a relevant role.

Returning to the model analyzed in Section 5.3, it is clear that some macroscopic output can be described through changing the selection of the parameters related to microscopic interactions. On the other hand, it is possible to reproduce specific competitions involving only one or two parameters, while the role of the others can be neglected. In this case, it is possible to organize the identification of each parameter.

The above method was proposed in Bellomo and Forni (1994) and consists of analyzing the evolution of a tumor induced in a population of immuno-depressed mice and in a population of normal mice.

We assume, to be consistent with Model P, and in particular with the assumption $\alpha_{11} = 0$, that the time of the observation of the experimental measurement is small enough to suppose that no genetic degeneration occurs, i.e., there is no change of the progression state of the cells during the experiment.

The experimental results are reported in Figure 5.12, where triangular dots refer to the first population and circular dots refer to the second popu-

lation. A suitable comparison between experimental data and the results provided by the mathematical model allows us to identify the parameters.

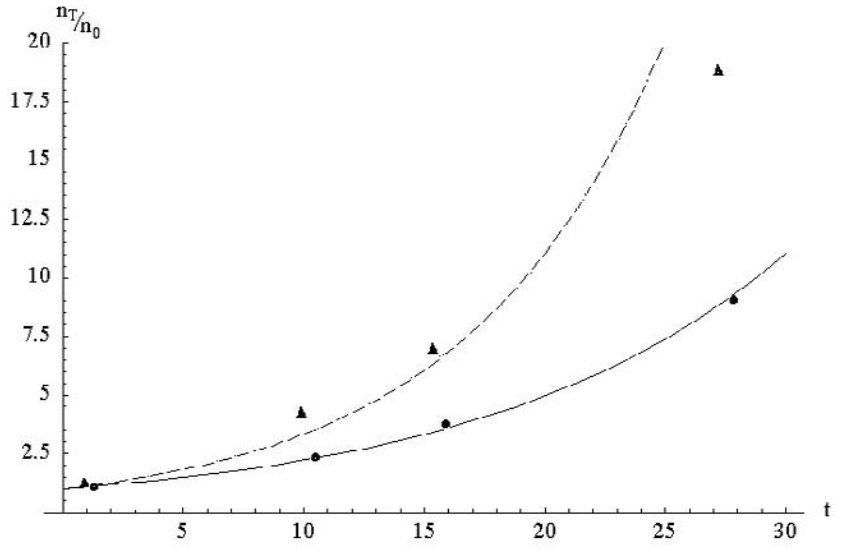

Fig. 5.12. Comparison between theoretical results and experimental data of growth of a tumor in nontreated mice (dots) and in irradiated mice (triangles).

Specifically, referring to the first population of immuno-depressed mice, $n_2^A(0) = 0$, the evolution equations (3.4.4) lead to an exponential growth of tumor cells of the type

$$n_1^T(t)/n_1^T(0) = \exp[\beta_{11} n_1^E(0) t] \,.$$

A comparison (Fig. 5.12), between the experimental results, the triangles and the output of the model (dashed line), allows us to the identify the product of β_{11} and the initial size of endothelial cells: $\beta_{11} n_1^E(0) = 0.12$. Of course the identification depends on the particular experiment carried out; as β^* is related to β_{11}, the proliferation rate of tumor cells, depending on to the aggressiveness of the particular tumor induced in the mice.

The same approach can be used to analyze the experimental results for the second population, nontreated mice (dots), with the output of the model (continuum line), so that the value of $\beta_{12} n_2^A(0) = 0.04$ is obtained.

In addition to the above specific identification, which should be regarded as just one example among various conceivable ones, it is worth remarking that the simulations in this chapter provide a description of relevant

biological events, and can effectively contribute to a deeper understanding of this complex phenomenology. The description is also supported by theorems which have a wide generality.

Stressing again some of the concepts already proposed in the previous sections, the following remarks are again brought to the attention of the reader.

- The role of the initial number of abnormal cells is ruled by the parameter δ, where this number is weighted by the proliferating ability of abnormal cells and by the destructive ability of active immune cells. Positive values of δ are related to situations which are dangerous for the vertebrate affected by a pathology. This means that a large number of weakly proliferating abnormal cells can possibly be countered by active immune cells, while a small number of cells with great proliferation ability can overcome the immune defense.
- The ability of immune cells to identify abnormal cells plays a crucial role in the competition. This specific role is represented by the parameter α_{12}, and must be related to the above-mentioned role of the initial number of abnormal cells.

The above remarks can be regarded as a speculation on the stimulating article by Gillet (2005). Indeed, modelling at the cellular scale can focus events which are consistent with the biological phenomenology of the system we are dealing with, but which cannot be carefully observed through macroscopic experiments. Therefore, we may optimistically observe that when a model achieves the above target, then the bridge between mathematical and biological sciences is effectively crossed.

5.5 Developments and Perspectives

The various simulations offered in the preceding sections have given an interesting overview of several biological events which characterize the immune competition, and which can be described by the class of models proposed in Chapter 3. As we have seen, simulations enlarge and increase the precision of the information given by qualitative analysis.

The analysis of this chapter should also be regarded as a methodological approach which may be technically developed for different models obtained by generalizations and possible improvements to include additional features

and the ability to describe phenomena which are not covered by the models proposed in this book.

For instance, the number of populations characterizing the immune system can be enlarged in order to specialize the specific activity to each subpopulation. Moreover, additional cells or populations can be inserted to model therapeutic actions. For instance, populations of cytokines or specific proteins may be taken into account to model the activation of the immune system, while particles acting over tumor cells may simulate chemotherapy treatments. Indeed, the model proposed in Chapter 3 should be regarded as the basic model to be further generalized to include a variety of conceivable technical developments. An account of some developments and research perspectives will be given in Chapter 7.

The methodological approach to mathematically analyze these developments is the same: a qualitative analysis of the initial value problem, based on methods of functional analysis, provides a careful description of the evolution of the systems, and this analysis is completed and enriched by computational simulations.

Analogous reasoning can be addressed to simulations, and specifically to those proposed in this chapter. The various simulations should be regarded as computational experiments, designed to visualize specific features of the immune competition. Additional computations can be developed, according to the suggestions given at the end of each subsection concerning certain types of simulations.

Particularly interesting is the case of simulations developed by setting all parameters except one equal to zero: the analysis of the model is then focused on one particular phenomenon, while the others are not relevant. If suitable experiments can be linked to these types of simulations, then the parameters can be identified. Indeed, this is the case for the identification process developed in this chapter.

Moreover, the analysis can be addressed to particular biological competitions. Certainly the modelling of the competition between HIV particles and the immune system is a challenging research problem; see Campello de Souza (1999) on modelling the dynamics of HIV-1 and CD4 and CD8 lymphocytes. The dynamics of the competition shows how the number of HIV particles first grows countered by immune cells, which have the ability of weakening them; then a second increase of the viral particles is again countered by the lymphocytes, while the competition may last for a very long period, as discussed in the article by Coisne (2005).

Models developed at a macroscopic scale, documented in the review by Hethcote (2000), can possibly describe the above specific aspects of the competition. However, macroscopic models cannot relate biological phenomena to specific cellular properties.

The various simulations developed in this chapter show how the behavior

of the dynamics of HIV-1 and CD4 and CD8 lymphocytes can be reproduced through a suitable characterization of the class of models proposed in this book. Certainly it is an interesting perspective, related to one of the great challenges of this century.

6

Models with Space Structure and the Derivation of Macroscopic Equations

The power of modeling methodology comes from the channelling of the description of the phenomena into a consistent descriptive language.

— Greller, Tobin, and Poste

6.1 Introduction

The various mathematical models proposed and analyzed in the preceding chapters describe multicellular systems in the spatially homogeneous case. As we have seen, these models are able to describe several interesting phenomena related to several aspects of the immune competition. On the other hand, a space structure is needed to model cellular motion, as well as to recover macroscopic models from the underlying microscopic description.

Deriving macroscopic equations, generally partial differential equations, is particularly important for describing the evolution of cells when they aggregate into solid form. This phenomenon is visualized in Figure 6.1.

The mathematical literature on the modelling of cellular motion phenomena includes several valuable papers which analyze specific issues. Most of them are modelled by kinetic-type equations which can be regarded as particular cases of the very general framework proposed in Chapter 2. Among others, Othmer and Stevens (1997) analyze aggregation and collapse of cellular populations, Chalub, et al. (2001, 2004) derive from kinetic-type equations macroscopic diffusion equations, while Capasso and Morale (2005) obtain macroscopic models from stochastic models of cellular motion. Hyperbolic models are obtained by Filbet, Laurencot, and

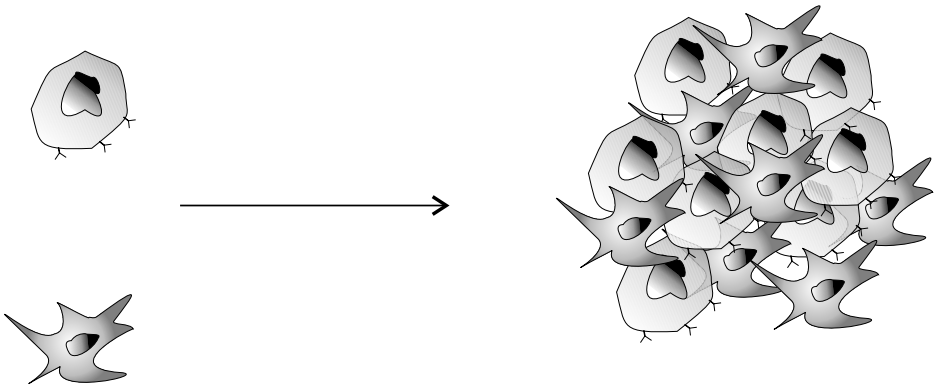

Fig. 6.1. From microscopic to macroscopic description.

Perthame (2005). Valuable surveys, mainly on mathematical topics, are proposed by Perthame (2004) and Chalub, et al. (2006). The above analysis refers to models with a constant number of particles; these models are essentially based on a transport model based on a velocity jump process proposed by Hillen and Othmer (2000), which will be analyzed in Section 6.2.

The derivation of macroscopic equations from kinetic cellular models appears to be a relatively more complex problem, due to the evolution in time both of the biological functions and of the number of cells. As we shall see, the ratio between the various rates characterizing every evolution—biological, mechanical, and proliferating/destructive—plays an important role in assessing the structure of mathematical macroscopic equations derived from the underlying microscopic equations.

Generally macroscopic models are obtained via methods of continuum mechanics. This means writing the system of conservation equations for mass, momentum, and energy to be closed by suitable phenomenological models describing the material behavior of the biological systems assumed to be continuous.

In some cases, the biological material may even be characterized by growing mass phenomena. The paper by Humphrey and Rajagopal (2002) provides original ideas and methods toward the continuum mechanics approach to the derivation of the macroscopic equations suitable for describing the behavior of the above mechanical systems. The review paper by Bellomo, De Angelis, and Preziosi (2003) reports the existing literature on macroscopic models of tissues of tumor systems. Specific models and applications are reported, among others, in the papers by De Angelis and Preziosi (2000), Chaplain and Sherrat (2001), Anderson and Chaplain (2003), Ber-

tuzzi, Fasano and Gandolfi (2004), and Alarcon, Byrne, and Maini (2005).

An alternative approach to the derivation of macroscopic models stems from mathematical kinetic theory. This method consists, as documented in Arlotti, Bellomo, De Angelis, and Lachowicz (2003), of deriving macroscopic models by suitable limits, or averaging methods, of Boltzmann-type equations related to the statistical microscopic description. Hopefully this approach may capture properties and behaviors of the material which are hidden, at least in some cases, by models derived through the traditional approach of continuum mechanics. Indeed, different equations correspond, as we shall see, to different scalings and modelling of microscopic phenomena related to cell populations interacting in biological tissues.

Methods of kinetic theory have been recently used to recover macroscopic models from the mesoscopic description by suitable asymptotic theories for multicellular systems. In particular, various authors have proposed mathematical methods towards the above theory; among others, Hillen and Othmer (2000), Hillen (2002), Lachowicz (2002) and (2005), and Filbet, Laurencot, and Perthame (2005). These methods deal with multicellular systems in the absence of an internal biological microscopic structure. On the other hand, recently Bellomo, Bellouquid, and Herrero (2006) developed the above analysis for multicellular systems such that interactions modify the microscopic state and generate phenomena with destruction and proliferation of cells. Specifically, interactions which modify the velocity of cells are assumed to be stochastic in a way which will be made precise later.

The main difficulty, as already mentioned, is induced by the need for including the evolution of biological functions and of proliferating/destructive processes.

This chapter deals with revisiting and critically analyzing the above mathematical analysis and provides some suggestions for future research perspectives. Indeed, the problem of developing the above analysis in the more general case of the mathematical structures dealt with in Chapter 2 appears, at this stage, still open.

Section 6.2 deals with the description of a class of evolution equations which include space dynamics in addition to biological interactions, and with the analysis of a linear operator related to the modelling of space dynamics.

Section 6.3 deals with the scaling of the equations described in Section 6.2 and develops the asymptotic analysis for mass conservative systems, showing how different diffusion equations correspond, at different scaling, to the underlying microscopic description offered by the model.

Section 6.4 deals with the asymptotic analysis for models with proliferation and destruction interactions, showing how the presence of source or sink terms, related to the growth or death of cells, modifies the macroscopic equations derived for systems with constant overall mass.

Section 6.5 proposes a simple application with the aim of showing how

the method can be technically applied to the analysis of a specific model in the cases of conservative interactions only. It is a simple exercise proposed to show some technical aspects related to the application of the method.

Section 6.6 deals with a critical analysis with special attention to research perspectives on open problems. Indeed, the contents of this chapter should be regarded as an introduction to the challenging research field of modelling the macroscopic behavior of living tissues, including the case of growing matter.

6.2 Models with Space Dynamics

This section deals with the modelling of multicellular systems such that the microscopic state includes position and velocity, in addition to variables related to biological functions. Specifically, referring to Chapter 2, consider a physical system constituted by a large number of cells interacting in the environment of a vertebrate (or in an *in vitro* experiment). The physical variable used to describe the state of each cell, already called the ***microscopic state***, is denoted by $\mathbf{w} = \{\mathbf{x}\,, \mathbf{v}\,, u\}$, where $\{\mathbf{x}, \mathbf{v}\}$ is the ***mechanical microscopic state*** and $u \in D_u \subseteq \mathbb{R}$ is the ***biological microscopic state***. The biological state is here assumed to be a scalar, referring to the models of Chapter 3.

The statistical collective description of the system is, in the case of one population only, identified (see Chapter 2), by the statistical distribution $f = f(t, \mathbf{x}, \mathbf{v}, u)$, which has been called the ***generalized distribution function***. Weighted moments permit, under suitable integrability properties, the calculation of macroscopic variables by technical calculations already reported in Chapter 2. The evolution of f, according to Bellomo, Bellouquid, and Herrero (2005), can be modelled as follows:

$$\begin{aligned}
&\left(\frac{\partial}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}}\right) f(t,\mathbf{x},\mathbf{v},u) \\
&\quad = \nu\left[\int_{D_{\mathbf{v}}} T(\mathbf{v},\mathbf{v}^*) f(t,\mathbf{x},\mathbf{v}^*,u) - T(\mathbf{v}^*,\mathbf{v}) f(t,\mathbf{x},\mathbf{v},u)\right] d\mathbf{v}^* \\
&\qquad + \eta\left[\int_{D_u}\int_{D_u} \varphi(u_*,u_{**},u) f(t,\mathbf{x},\mathbf{v},u_*) f(t,\mathbf{x},\mathbf{v},u_{**})\, du_*\, du_{**}\right. \\
&\qquad \left. - f(t,\mathbf{x},\mathbf{v},u)\int_{D_u} f(t,\mathbf{x},\mathbf{v},u_{**})\, du_{**}\right], \qquad (6.2.1)
\end{aligned}$$

which can be formally written as follows:

$$\frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f = \nu \mathcal{L} f + \eta \mathcal{N}[f, f]\,. \tag{6.2.2}$$

The linear term $\mathcal{L}$ has been proposed by various authors to model the dynamics of biological organisms modelled by a velocity-jump process, where ν is the turning rate or turning frequency (hence $\tau = \frac{1}{\nu}$ is the mean run time), and $T(\mathbf{v}, \mathbf{v}^*)$ is the probability kernel for the new velocity $\mathbf{v} \in D_{\mathbf{v}}$, given the previous velocity $\mathbf{v}^*$. This corresponds to the assumption that cells choose any direction with bounded velocity. Specifically the set of possible velocities is denoted by $D_{\mathbf{v}}$, where $D_{\mathbf{v}} \subset \mathbb{R}^3$, and it is assumed that $D_{\mathbf{v}}$ is bounded and spherically symmetric (i.e., $\mathbf{v} \in D_{\mathbf{v}} \Rightarrow -\mathbf{v} \in D_{\mathbf{v}}$).

Referring to the term related to the biological interactions, η denotes the biological interaction rate, which for simplicity is here assumed to be constant; while the term φ models the transition probability density of the test cell with state u_* into the state u after the interaction with the cell with state u^*. Interactions occur within the action domain Ω of the test cell. Ω is assumed to be relatively small so that only binary localized encounters are relevant. We recall that φ is not symmetric with respect to u and has the structure of a probability density only for mass conservative systems.

The above model generalizes the transport model with a velocity jump proposed by Othmer and Hillen (2000) to a mathematical description of multicellular systems which include biological functions in the microscopic scale.

This model can be rewritten as a system of two coupled equations (see Chapter 3). The model, in the case of conservative encounters only, can be written as follows:

$$\begin{aligned}
&\left(\frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}}\right) f_1(t, \mathbf{x}, \mathbf{v}, u) \\
&\quad = \nu \int_{D_{\mathbf{v}}} \Big[T(\mathbf{v}, \mathbf{v}^*) f_1(t, \mathbf{x}, \mathbf{v}^*, u) - T(\mathbf{v}^*, \mathbf{v}) f_2(t, \mathbf{x}, \mathbf{v}, u) \Big] d\mathbf{v}^* \\
&\qquad + (\mathcal{G}_{11} - \mathcal{L}_{11} + \mathcal{G}_{12} - \mathcal{L}_{12})(f, f)(t, \mathbf{x}, \mathbf{v}, u)\,, \\
&\left(\frac{\partial}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}}\right) f_2(t, \mathbf{x}, \mathbf{v}, u) \\
&\quad = \nu \int_{D_{\mathbf{v}}} \Big[T(\mathbf{v}, \mathbf{v}^*) f_2(t, \mathbf{x}, \mathbf{v}^*, u) - T(\mathbf{v}^*, \mathbf{v}) f_1(t, \mathbf{x}, \mathbf{v}, u) \Big] d\mathbf{v}^* \\
&\qquad + (\mathcal{G}_{21} - \mathcal{L}_{21} + \mathcal{G}_{22} - \mathcal{L}_{22})(f, f)(t, \mathbf{x}, \mathbf{v}, u)\,,
\end{aligned} \tag{6.2.3}$$

where the operators $\mathcal{G}$ and $\mathcal{L}$ are defined as follows:

$$\mathcal{G}_{ij}(f,f) = \int_{D_u}\int_{D_u} \eta_{ij}\varphi_{ij}(u_*,u^*;u) f_i(t,\mathbf{x},\mathbf{v},u_*) f_j(t,\mathbf{x},\mathbf{v},u^*)\, du_*\, du^*\,, \tag{6.2.4}$$

and

$$\mathcal{L}_{ij}(f,f) = f_i(t,\mathbf{x},\mathbf{v},u)\int_{D_u} \eta_{ij} f_j(t,\mathbf{x},\mathbf{v},u^*)\, du^*\,. \tag{6.2.5}$$

The above set of equations describes the evolution in the space $\mathbf{x} \in \mathbb{R}^3$ and in the biological state $u \in D_u \subseteq \mathbb{R}$ of a large system of two interacting cell populations. Specifically, $\mathcal{G}$ and $\mathcal{L}$ correspond, respectively, to the gain and loss of cells in the state u due to conservative encounters, namely to encounters which modify the biological state without generating proliferation or destruction phenomena.

The analysis developed in what follows refers to the model with conservative interactions only. After this analysis, some technical developments for models with proliferating and destructive terms will be dealt with.

Let us now define the following operators:

$$\Gamma(f,f) = (\mathcal{G}_{11} - \mathcal{L}_{11} + \mathcal{G}_{12} - \mathcal{L}_{12}, \mathcal{G}_{21} - \mathcal{L}_{21} + \mathcal{G}_{22} - \mathcal{L}_{22})(f,f)\,,$$

and

$$\mathcal{L}(f) = (\mathcal{L}_1(f), \mathcal{L}_2(f))\,,$$

where

$$\mathcal{L}_1(f) = \int_{D_\mathbf{v}} \Big[T(\mathbf{v},\mathbf{v}^*) f_1(t,\mathbf{x},\mathbf{v}^*,u) - T(\mathbf{v}^*,\mathbf{v}) f_2(t,\mathbf{x},\mathbf{v},u)\Big] d\mathbf{v}^*\,, \tag{6.2.6}$$

and

$$\mathcal{L}_2(f) = \int_{D_\mathbf{v}} \Big[T(\mathbf{v},\mathbf{v}^*) f_2(t,\mathbf{x},\mathbf{v}^*,u) - T(\mathbf{v}^*,\mathbf{v}) f_1(t,\mathbf{x},\mathbf{v},u)\Big] d\mathbf{v}^*\,. \tag{6.2.7}$$

Then the evolution equation (6.2.3) for $f = (f_1, f_2)$ can be formally written as follows:

$$\frac{\partial f}{\partial t} + \sum_{j=1}^{3} V_j \frac{\partial f}{\partial \mathbf{x}_j} = \nu \mathcal{L} f + \Gamma(f,f)\,, \tag{6.2.8}$$

where $V_j = \mathrm{diag}(\mathbf{v}_j, \mathbf{v}_j)$, $j = 1,2,3$.

A detailed qualitative analysis of the operator K is preliminary to the asymptotic analysis. K is defined as follows:

$$Kf = \int_{D_{\mathbf{v}}} \Big(T(\mathbf{v}, \mathbf{v}^*) f(t, \mathbf{x}, \mathbf{v}^*, u) - T(\mathbf{v}^*, \mathbf{v}) f(t, \mathbf{x}, \mathbf{v}, u) \Big) d\mathbf{v}^*, \quad (6.2.9)$$

where $f : D_{\mathbf{v}} \longrightarrow \mathbb{R}$.

Let us now state some properties of this operator. Let $h, g, N : D_{\mathbf{v}} \longrightarrow \mathbb{R}$, and let

$$\Psi_1[N] = \frac{T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*) + T(\mathbf{v}^*, \mathbf{v})N(\mathbf{v})}{2}, \quad (6.2.10a)$$

and

$$\Psi_2[N] = \frac{T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v})N(\mathbf{v})}{2} \quad (6.2.10b)$$

denote, respectively, the symmetric and antisymmetric parts of the term $T(\mathbf{v}, \mathbf{v}^*)N(\mathbf{v}^*)$. The following result is given in Bellomo, Bellouquid, and Herrero (2005):

Lemma 6.2.1. *The operator K satisfies the following relation:*

$$\begin{aligned} \int_{D_{\mathbf{v}}} K(Ng) \frac{h(\mathbf{v})}{N(\mathbf{v})} d\mathbf{v} = & \frac{1}{2} \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \Psi_1[N](g(\mathbf{v}^*) - g(\mathbf{v})) \\ & \times \left(\frac{h(\mathbf{v})}{N(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{N(\mathbf{v}^*)} \right) d\mathbf{v}\, d\mathbf{v}^* \\ & + \frac{1}{2} \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \Psi_2[N](g(\mathbf{v}) + g(\mathbf{v}^*)) \\ & \times \left(\frac{h(\mathbf{v})}{N(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{N(\mathbf{v}^*)} \right) d\mathbf{v}\, d\mathbf{v}^*. \quad (6.2.11) \end{aligned}$$

Proof of Lemma 6.2.1: The proof is a straightforward computation. In fact, using equations (6.2.10) yields

$$\begin{aligned} \int_{D_{\mathbf{v}}} K(Ng) \frac{h(\mathbf{v})}{N(\mathbf{v})} d\mathbf{v} = & \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \Psi_1[N](g(\mathbf{v}^*) - g(\mathbf{v})) \frac{h(\mathbf{v})}{N(\mathbf{v})}\, d\mathbf{v}\, d\mathbf{v}^* \\ & + \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \Psi_2[N](g(\mathbf{v}) + g(\mathbf{v}^*)) \frac{h(\mathbf{v})}{N(\mathbf{v})} d\mathbf{v}\, d\mathbf{v}^*. \end{aligned}$$

Then, interchanging $\mathbf{v}$ and $\mathbf{v}^*$, using the symmetry properties of $\Psi_1[N]$ and $\Psi_2[N]$, yields (6.2.11).

The following assumption on the leading turning operator is essential to the analysis developed in what follows:

Assumption 6.2.1. *There exists a bounded velocity distribution* $M(\mathbf{v}) > 0$*, independent of* $\mathbf{x}$ *and* t*, such that the detailed balance*

$$T(\mathbf{v}^*, \mathbf{v})M(\mathbf{v}) = T(\mathbf{v}, \mathbf{v}^*)M(\mathbf{v}^*) \tag{6.2.12}$$

holds. The flow produced by this equilibrium distribution vanishes, and M *is normalized:*

$$\int_{D_\mathbf{v}} \mathbf{v}M(\mathbf{v})\, d\mathbf{v} = 0, \qquad \int_{D_\mathbf{v}} M(\mathbf{v})\, d\mathbf{v} = 1\,. \tag{6.2.13}$$

The kernel $T(\mathbf{v}, \mathbf{v}^*)$ *is bounded, and there exists a constant* $\sigma > 0$ *such that*

$$T(\mathbf{v}, \mathbf{v}^*) \geq \sigma M, \quad \forall (\mathbf{v}, \mathbf{v}^*) \in D_\mathbf{v} \times D_\mathbf{v}, \quad \mathbf{x} \in I\!R^3,\ t > 0\,. \tag{6.2.14}$$

The above assumption allows the proof of the following lemmas:

Lemma 6.2.2. *If* (6.2.12) *of assumption* 6.2.1 *holds true, then the following equalities hold:*

$$\int_{D_\mathbf{v}} K(f)\frac{h(\mathbf{v})}{M(\mathbf{v})}d\mathbf{v} = -\frac{1}{2}\int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Psi_1[M]\left(\frac{f(\mathbf{v})}{M(\mathbf{v})} - \frac{f(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right) \times \left(\frac{h(\mathbf{v})}{M(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right) d\mathbf{v}\, d\mathbf{v}^*\,, \tag{6.2.15}$$

and

$$\int_{D_\mathbf{v}} K(h)\frac{h(\mathbf{v})}{M(\mathbf{v})}d\mathbf{v} = -\frac{1}{2}\int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Psi_1[M]\left(\frac{h(\mathbf{v})}{M(\mathbf{v})} - \frac{h(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right)^2 d\mathbf{v}\, d\mathbf{v}^*\,. \tag{6.2.16}$$

Proof of Lemma 6.2.2: Equality (6.2.15) is an application of lemma 6.2.1 with $f = Ng$ and $N = M$. The detailed balance assumption in (6.2.12) is equivalent to $\Psi_2 = 0$.

Let $L^2(D_\mathbf{v}, \mathbf{v}) \times L^2(D_\mathbf{v}, \mathbf{v})$ be the space of the functions $f = (f_1, f_2)$, with $f_i \in L^2(\mathbf{v})$, and let the scalar product be defined by

$$\langle f, g\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})} = \sum_{i=1}^{2} \langle f_i, g_i\rangle_{L^2(\mathbf{v})}. \tag{6.2.17}$$

Lemma 6.2.3. *The following equality holds:*

$$\Big\langle \mathcal{L}f, \frac{g}{M} \Big\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})} = \Big\langle Kf_1, \frac{g_1}{M} \Big\rangle_{L^2(\mathbf{v})} + \Big\langle Kf_2, \frac{g_2}{M} \Big\rangle_{L^2(\mathbf{v})} + \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} T(\mathbf{v}^*, \mathbf{v})(f_1(\mathbf{v}) - f_2(\mathbf{v})) \times \left(\frac{g_1(\mathbf{v})}{M(\mathbf{v})} - \frac{g_2(\mathbf{v})}{M(\mathbf{v})} \right) d\mathbf{v}\, d\mathbf{v}^* . \qquad (6.2.18)$$

Proof of Lemma 6.2.3: Using the definition of scalar product (6.2.17) yields:

$$\begin{aligned}
&\Big\langle \mathcal{L}f, \frac{g}{M} \Big\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})} \\
&\quad = \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} \frac{g_1(\mathbf{v})}{M(\mathbf{v})} \big[T(\mathbf{v}, \mathbf{v}^*) f_1(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v}) f_2(\mathbf{v}) \big] d\mathbf{v}\, d\mathbf{v}^* \\
&\qquad + \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} \frac{g_2(\mathbf{v})}{M(\mathbf{v})} \big[T(\mathbf{v}, \mathbf{v}^*) f_2(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v}) f_1(\mathbf{v}) \big] d\mathbf{v}\, d\mathbf{v}^* \\
&\quad = \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} \big[T(\mathbf{v}, \mathbf{v}^*) f_1(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v}) f_1(\mathbf{v}) \big] \frac{g_1(\mathbf{v})}{M(\mathbf{v})} d\mathbf{v}\, d\mathbf{v}^* \\
&\qquad + \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} \big[T(\mathbf{v}, \mathbf{v}^*) f_2(\mathbf{v}^*) - T(\mathbf{v}^*, \mathbf{v}) f_2(\mathbf{v}) \big] \frac{g_2(\mathbf{v})}{M(\mathbf{v})} d\mathbf{v}\, d\mathbf{v}^* \\
&\qquad + \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} T(\mathbf{v}, \mathbf{v}^*) \big[f_1(\mathbf{v}) - f_2(\mathbf{v}) \big] \frac{g_1(\mathbf{v})}{M(\mathbf{v})} d\mathbf{v}\, d\mathbf{v}^* \\
&\qquad + \int_{D_\mathbf{v}} \int_{D_\mathbf{v}} T(\mathbf{v}, \mathbf{v}^*) \big[f_2(\mathbf{v}) - f_1(\mathbf{v}) \big] \frac{g_2(\mathbf{v})}{M(\mathbf{v})} d\mathbf{v}\, d\mathbf{v}^* .
\end{aligned}$$

The above equation, taking into account (6.2.9), corresponds to equality (6.2.18).

∎

Lemma 6.2.4. *Let* (6.2.12) *and* (6.2.13) *of assumption* 6.2.1 *hold. Then the following properties and equalities related to the operator* $\mathcal{L}$ *hold true:*

i) $\mathcal{L}$ *is a self-adjoint operator with respect to the scalar product in the space*

$$L^2(D_\mathbf{v}, \frac{d\mathbf{v}}{M}) \times L^2(D_\mathbf{v}, \frac{d\mathbf{v}}{M}) ;$$

ii) *Let* $\psi = (1, 1)$*; then* $\langle \mathcal{L}f, \psi \rangle = 0$*;*

iii) *Moreover if*

$$T(\mathbf{v},\mathbf{v}^*) = T_1(\mathbf{v})T_2(\mathbf{v}^*)\,, \tag{6.2.19}$$

then $N(\mathcal{L}) = \mathrm{vect}(M(\mathbf{v})\psi)$.

Proof of Lemma 6.2.4: The proof of i) is obtained by application of (6.2.15) and (6.2.18). Consider now

$$\begin{aligned}\langle \mathcal{L}f,\psi\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})} =& \langle \mathcal{L}_1 f\rangle_{L^2(\mathbf{v})} + \langle \mathcal{L}_2 f\rangle_{L^2(\mathbf{v})} \\ =& \int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Big[T(\mathbf{v},\mathbf{v}^*)f_1(\mathbf{v}^*) - T(\mathbf{v}^*,\mathbf{v})f_2(\mathbf{v})\Big]d\mathbf{v}^*d\mathbf{v} \\ &+ \int_{D_\mathbf{v}}\int_{D_\mathbf{v}} \Big[T(\mathbf{v},\mathbf{v}^*)f_2(\mathbf{v}^*) - T(\mathbf{v}^*,\mathbf{v})f_1(\mathbf{v})\Big]d\mathbf{v}^*d\mathbf{v}\,.\end{aligned}$$

Then interchanging $\mathbf{v}$ and $\mathbf{v}^*$ implies the equality ii). Moreover, using (6.2.13) of assumption 6.2.1 implies $M(\mathbf{v})\psi \in N(\mathcal{L})$. Let (6.2.19) hold true; then the operator $\mathcal{L}$ can be written as follows:

$$\mathcal{L}(f) = \big(T_1(\mathbf{v})\langle T_2 f_1\rangle_\mathbf{v} - T_2 f_2\langle T_1\rangle_\mathbf{v}, T_1(\mathbf{v})\langle T_2 f_2\rangle_\mathbf{v} - T_2 f_1\langle T_1\rangle_\mathbf{v}\big)\,. \tag{6.2.20}$$

Consider now $f \in N(\mathcal{L})$; then one has

$$T_1(\mathbf{v})\langle T_2 f_1\rangle_\mathbf{v} = T_2 f_2\langle T_1\rangle_\mathbf{v} \tag{6.2.21}$$

and

$$T_1(\mathbf{v})\langle T_2 f_2\rangle_\mathbf{v} = T_2 f_1\langle T_1\rangle_\mathbf{v}\,, \tag{6.2.22}$$

which, after integration with respect to $\mathbf{v}$, yield:

$$\langle T_2 f_1\rangle_\mathbf{v} = \langle T_2 f_2\rangle_\mathbf{v}\,. \tag{6.2.23}$$

Substituting (6.2.23) into (6.2.21) and (6.2.22) yields $f_1 = f_2$.

On the other hand, one obtains the following from Lemma 6.2.3:

$$\left\langle Kf_1, \frac{f_1}{M}\right\rangle + \left\langle Kf_2, \frac{f_2}{M}\right\rangle = 0\,,$$

which gives by (6.2.16)

$$\frac{f_1(\mathbf{v})}{M(\mathbf{v})} - \frac{f_1(\mathbf{v}^*)}{M(\mathbf{v}^*)} = 0\,. \tag{6.2.24}$$

Integrating (6.2.24) with respect to $\mathbf{v}$ yields

$$\rho_{f_1} = \frac{f_1(\mathbf{v}^*)}{M(\mathbf{v}^*)}, \qquad f_1 = M(\mathbf{v})\rho_{f_1}\,. \tag{6.2.25}$$

This completes the proof of iii). ∎

Lemma 6.2.5. *Let* (6.2.19) *and assumption* 6.2.1 *hold. Then the equation* $\mathcal{L}(f) = g$ *has a unique solution*

$$f \in L^2\left(D_{\mathbf{v}}, \frac{d\mathbf{v}}{M}\right) \times L^2\left(D_{\mathbf{v}}, \frac{d\mathbf{v}}{M}\right)$$

satisfying

$$f_1 = f_2, \qquad \int_{D_{\mathbf{v}}} f_1\, d\mathbf{v} = 0\,, \tag{6.2.26a}$$

if and only if

$$\int_{D_{\mathbf{v}}} g_1\, d\mathbf{v} + \int_{D_{\mathbf{v}}} g_2\, d\mathbf{v} = 0\,. \tag{6.2.26b}$$

In particular

$$\mathcal{L}(h_j) = MV_j\psi,\ j = 1, 2, 3 \tag{6.2.27}$$

has a unique solution given by

$$h_j(\mathbf{v}) = k_j(\mathbf{v})\psi, \quad \langle k_j(\mathbf{v})\rangle_{\mathbf{v}} = 0, \quad j = 1, 2, 3. \tag{6.2.28}$$

Proof of Lemma 6.2.5: The relation

$$\int_{D_{\mathbf{v}}} g_1\, d\mathbf{v} + \int_{D_{\mathbf{v}}} g_2\, d\mathbf{v} = 0$$

is a necessary condition for the solvability of $\mathcal{L}f = g$. From (6.2.14), (6.2.16), and (6.2.18), one has

$$\begin{aligned} -\left\langle \mathcal{L}f, \frac{f}{M}\right\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})} &= \frac{1}{2}\int_{D_{\mathbf{v}}}\int_{D_{\mathbf{v}}} \Psi_1[M]\left(\frac{f_1(\mathbf{v})}{M(\mathbf{v})} - \frac{f_1(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right)^2 d\mathbf{v}\, d\mathbf{v}^* \\ &\quad + \frac{1}{2}\int_{D_{\mathbf{v}}}\int_{D_{\mathbf{v}}} \Psi_1[M]\left(\frac{f_2(\mathbf{v})}{M(\mathbf{v})} - \frac{f_2(\mathbf{v}^*)}{M(\mathbf{v}^*)}\right)^2 d\mathbf{v}\, d\mathbf{v}^* \end{aligned}$$

$$
\begin{aligned}
&- \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \frac{T(\mathbf{v}^*, \mathbf{v})}{M(\mathbf{v})} (f_1(\mathbf{v}) - f_2(\mathbf{v}))^2 d\mathbf{v}\, d\mathbf{v}^* \\
&\geq \sigma \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} M(\mathbf{v}) M(\mathbf{v}^*) \left(\frac{f_1(\mathbf{v})}{M(\mathbf{v})} - \frac{f_1(\mathbf{v}^*)}{M(\mathbf{v}^*)} \right)^2 d\mathbf{v}\, d\mathbf{v}^* \\
&\quad + \sigma \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} M(\mathbf{v}) M(\mathbf{v}^*) \left(\frac{f_2(\mathbf{v})}{M(\mathbf{v})} - \frac{f_2(\mathbf{v}^*)}{M(\mathbf{v}^*)} \right)^2 d\mathbf{v}\, d\mathbf{v}^* \\
&\quad - \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \frac{T(\mathbf{v}^*, \mathbf{v})}{M(\mathbf{v})} (f_1(\mathbf{v}) - f_2(\mathbf{v}))^2 d\mathbf{v}\, d\mathbf{v}^* \\
&\geq \sigma \int_{D_{\mathbf{v}}} \left(\frac{f_1^2(\mathbf{v})}{M(\mathbf{v})} + \frac{f_2^2(\mathbf{v})}{M(\mathbf{v})} \right) d\mathbf{v} \\
&\quad - \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \big(f_1(\mathbf{v}) f_1(\mathbf{v}^*) - f_2(\mathbf{v}) f_2(\mathbf{v}^*) \big) d\mathbf{v}\, d\mathbf{v}^* \\
&\quad - \int_{D_{\mathbf{v}}} \int_{D_{\mathbf{v}}} \frac{T(\mathbf{v}^*, \mathbf{v})}{M(\mathbf{v})} (f_1(\mathbf{v}) - f_2(\mathbf{v}))^2 d\mathbf{v}\, d\mathbf{v}^* \,.
\end{aligned}
$$

For $f_1 = f_2$ and $\int f_1 d\mathbf{v} = 0$, the last inequality leads to the following estimate:

$$
\begin{aligned}
-\left\langle \mathcal{L} f, \frac{f}{M} \right\rangle_{L^2(\mathbf{v}) \times L^2(\mathbf{v})} &\geq \sigma \left(\int_{D_{\mathbf{v}}} \frac{f_1^2}{M} d\mathbf{v} + \int_{D_{\mathbf{v}}} \frac{f_2^2}{M} d\mathbf{v} \right) \\
&= \sigma \left\langle f, \frac{f}{M} \right\rangle_{L^2(\mathbf{v}) \times L^2(\mathbf{v})} . \qquad (6.2.29)
\end{aligned}
$$

The statement of the lemma is then a consequence of the Lax–Milgram theorem. Moreover, the condition of solvability is satisfied for the equation $\mathcal{L}(h_j) = MV_j\psi$ by (6.2.13) of assumption 6.2.1 and then there exists a unique solution $h_j(\mathbf{v}) = k_j(\mathbf{v})\psi$, $j = 1, 2, 3$.

∎

Remark 6.2.1. If $T(\mathbf{v}, \mathbf{v}^*) = T_1(\mathbf{v})$, then one can compute the solution of the equation $\mathcal{L}(h_j) = MV_j\psi$. Indeed, since

$$
\mathcal{L}(MV_j\psi) = (-M\mathbf{v}_j \langle T_1 \rangle_{\mathbf{v}}, -M\mathbf{v}_j \langle T_1 \rangle_{\mathbf{v}}) = -M \langle T_1 \rangle_{\mathbf{v}} V_j \psi \,,
$$

the solution is given by

$$
h_j(\mathbf{v}) = -\frac{1}{\langle T_1 \rangle_{\mathbf{v}}} MV_j\psi \,. \qquad (6.2.30)
$$

The technical results proposed in this section will be used to recover macroscopic equations.

6.3 Asymptotic Limits for Mass-Conserving Systems

The mathematical model described in Section 6.2 is characterized by two types of rates, the first one related to the dynamics of the mechanical variables, the second one to the biological ones. Experimental evidence suggests that we study the regimes such that the biological dynamics, i.e., η_{ij}, are of a smaller order with respect to the mechanical one, i.e., ν. In order to simplify we set $\eta_{11} = \eta_{22}$ and $\eta_{12} = \eta_{21}$, and

$$\eta_{11} = \varepsilon^q\,, \qquad \eta_{12} = \varepsilon^r\,,$$

with $r, q \geq 1$. Moreover,

$$\nu = \frac{1}{\varepsilon^p}\,, \quad \text{with } p \geq 1\,,$$

where ε is a small parameter which will be allowed to tend to zero. In addition, the slow diffusion scale time $\tau = \varepsilon t$ will be used so that the following scaled equation is obtained:

$$\begin{aligned}\varepsilon\,\frac{\partial}{\partial t} f_\varepsilon(t,\mathbf{x},\mathbf{v},u) + \sum_{j=1}^{3} V_j \frac{\partial}{\partial x_j} f_\varepsilon(t,\mathbf{x},\mathbf{v},u) \\ = \frac{1}{\varepsilon^p}\,\mathcal{L} f_\varepsilon + \varepsilon^q\,\Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) + \varepsilon^r\,\Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon)\,, \quad (6.3.1)\end{aligned}$$

where

$$\Gamma_{11}^{22} = (\Gamma_{11}, \Gamma_{22}) = \frac{1}{\eta_{11}}(\mathcal{G}_{11} - \mathcal{L}_{11}, \mathcal{G}_{22} - \mathcal{L}_{22})\,, \qquad (6.3.2)$$

and

$$\Gamma_{12}^{21} = (\Gamma_{12}, \Gamma_{21}) = \frac{1}{\eta_{12}}(\mathcal{G}_{12} - \mathcal{L}_{12}, \mathcal{G}_{21} - \mathcal{L}_{21}). \qquad (6.3.3)$$

The diffusion approximation asymptotic limit can be obtained by appropriate moments of f_ε. The main result is given by the following theorem:

Theorem 6.3.1. *Let equality* 6.2.19 *and assumption* 6.2.1 *hold, and let* $f_\epsilon(t, \mathbf{x}, \mathbf{v}, u)$ *be a sequence solutions to the scaled kinetic equation* (6.3.1) *such that* f_ϵ *converges, in the distributional sense, to a function* f *as* ε *goes to zero. Furthermore, assume that the moments*

$$\langle f_{\varepsilon i}\rangle, \quad \left\langle \frac{k(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f_{\varepsilon i} \right\rangle, \quad \langle \Gamma_{ij}(f_\varepsilon, f_\varepsilon)\rangle, \quad i, j = 1, 2$$

converge in the sense of distributions to the corresponding moments

$$\langle f_i\rangle, \qquad \left\langle \frac{k(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f_i \right\rangle, \qquad \langle \Gamma_{ij}(f, f)\rangle\,,$$

and that all formally small terms vanish. Then the asymptotic limit takes the form

$$f(t, \mathbf{x}, \mathbf{v}, u) = M(\mathbf{v})\rho(t, \mathbf{x}, u)\psi\,, \tag{6.3.4}$$

where $\rho(t, \mathbf{x}, u)$ *is the weak solution of the following equations:*

$p = q = r = 1$	$\partial_t \rho - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho)$ $= \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho)$ (6.3.5)
$p = r = 1,\ q > 1$	$\partial_t \rho - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho)$ $= \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} (\Gamma_{12} + \Gamma_{21})(\rho, \rho)$ (6.3.6)
$p = q = 1,\ r > 1$	$\partial_t \rho - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho)$ $= \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} (\Gamma_{11} + \Gamma_{22})(\rho, \rho)$ (6.3.7)
$p = 1,\ r > 1,\ q > 1$	$\partial_t \rho - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) = 0$ (6.3.8)
$r = q = 1,\ p > 1$	$\partial_t \rho = \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho)$ (6.3.9)
$r = 1,\ p > 1,\ q > 1$	$\partial_t \rho = \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} (\Gamma_{12} + \Gamma_{21})(\rho, \rho)$ (6.3.10)

$q = 1,\ p > 1,\ r > 1$	$\partial_t \rho = \frac{1}{2}\langle M^2 \rangle_{\mathbf{v}} (\Gamma_{11} + \Gamma_{22})(\rho, \rho)$ (6.3.11)
$p > 1,\ q > 1,\ r > 1$	$\partial_t \rho = 0$ (6.3.12)

where the terms Γ_{ij} *are defined by*

$$\Gamma_{ij}(\rho,\rho)(t,\mathbf{x},u) = \int_{D_u}\int_{D_u} \varphi_{ij}(u_*,u^*;u)\rho(t,\mathbf{x},u_*)\rho(t,\mathbf{x},u^*)\,du_*\,du^* - \rho(t,\mathbf{x},u)\int_{D_u}\rho(t,\mathbf{x},u^*)\,du^*\,, \tag{6.3.13}$$

and the diffusivity tensor D *is given by*

$$D = -\int_{D_{\mathbf{v}}} \mathbf{v}\otimes k(\mathbf{v})\,d\mathbf{v}, \tag{6.3.14}$$

where $k(\mathbf{v})$ *is a solution of equation* (6.2.27) *delivered by equation* (6.2.28) *in Lemma* 6.2.5.

Remark 6.3.1. One can prove that the tensor D is symmetric and positive definite. To see this, note that for any $\mathbf{x} \in \mathbb{R}^3$, one has

$$(D\mathbf{x})\cdot\mathbf{x} = -\int_V (\mathbf{v}\cdot\mathbf{x})(k(\mathbf{v})\cdot\mathbf{x})\,d\mathbf{v}. \tag{6.3.15}$$

Indeed, by (6.2.27), one has

$$\mathbf{v}_i = \frac{1}{2M}\Big(\mathcal{L}_1(k_i(\mathbf{v})\psi) + \mathcal{L}_2(k_i(\mathbf{v})\psi)\Big), \qquad i = 1,2,3. \tag{6.3.16}$$

Substituting (6.3.16) into (6.3.15) and using (6.2.29) yields

$$\begin{aligned}(D\mathbf{x})\cdot\mathbf{x} &= -\frac{1}{2}\left\langle \frac{1}{M}(\mathcal{L}_1(k(\mathbf{v})\cdot\mathbf{x}\psi) + \mathcal{L}_2(k(\mathbf{v})\cdot\mathbf{x}\psi)), k(\mathbf{v})\cdot\mathbf{x}\right\rangle_{L^2(\mathbf{v})}\\ &= -\frac{1}{2}\left\langle \frac{1}{M}\mathcal{L}(k(\mathbf{v})\cdot\mathbf{x}\psi), k(\mathbf{v})\cdot\mathbf{x}\psi\right\rangle_{L^2(\mathbf{v})\times L^2(\mathbf{v})}\\ &\geq \frac{1}{2\sigma}\left\langle k(\mathbf{v})\cdot\mathbf{x}\psi, \frac{k(\mathbf{v})\cdot\mathbf{x}\psi}{M}\right\rangle_{L^2(\mathbf{v})}.\end{aligned} \tag{6.3.17}$$

Suppose now that $k(\mathbf{v})\cdot\mathbf{x}$ are identically equal to zero for all $\mathbf{x} \neq 0$. Then by taking the scalar product of (6.2.27) with $\mathbf{x}$, $\mathbf{v}\cdot\mathbf{x}$ would be zero

for all $\mathbf{v} \in D_{\mathbf{v}}$, which is impossible by the spherical symmetry of $D_{\mathbf{v}}$. Thus the right-hand side of (6.3.17) is positive for each $\mathbf{x} \neq 0$. The symmetry of the matrix D is an immediate consequence of the fact that $\mathcal{L}$ is self-adjoint with respect to the scalar product in

$$L^2(\mathbf{v}, \frac{d\mathbf{v}}{M}) \times L^2(\mathbf{v}, \frac{d\mathbf{v}}{M}) .$$

Indeed, let $\mathbf{x}, \mathbf{z} \in \mathbb{R}^3$; then

$$\begin{aligned}(D \cdot \mathbf{x}) \cdot \mathbf{z} &= -\int_V (\mathbf{v} \cdot \mathbf{z})(k(\mathbf{v}) \cdot \mathbf{x})\, d\mathbf{v} \\ &= -\frac{1}{2} \left\langle \frac{1}{M}(\mathcal{L}_1(k(\mathbf{v}) \cdot \mathbf{z}\psi) + \mathcal{L}_2(k(\mathbf{v}) \cdot \mathbf{z}\psi)), k(\mathbf{v}) \cdot \mathbf{x} \right\rangle_{L^2(\mathbf{v})} \\ &= -\frac{1}{2} \left\langle \frac{1}{M}\mathcal{L}(k(\mathbf{v}) \cdot \mathbf{z}\psi), k(\mathbf{v}) \cdot \mathbf{x}\psi \right\rangle_{L^2(\mathbf{v}) \times L^2(\mathbf{v})} .\end{aligned}$$

The tensor D in general is nonisotropic (it is a nonscalar multiple of the identity). At the end of this chapter, an example will be given in which the tensor D is isotropic.

Remark 6.3.2. When both biological interactions have the same rate, which corresponds to $q = r$, then the above cases (6.3.5)–(6.3.12) simply reduce to the following: (6.3.5), (6.3.8), (6.3.9), and (6.3.12).

Let us now define the following quantities:

$$R_\varepsilon(t, \mathbf{x}) = \int_{\mathbb{R}^3 \times \mathbb{R}} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u)\, d\mathbf{v}\, du$$

and

$$R(t, \mathbf{x}) = \int_{\mathbb{R}} \rho(t, \mathbf{x}, u)\, du .$$

As $\varphi_{ij}(u_*, u^*; u)$ is a probability density

$$\int_{\mathbb{R}} \varphi_{ij}(u_*, u^*, u)\, du = 1,$$

one easily gets

$$\int_{\mathbb{R}} \Gamma_{ij}(\rho, \rho)(t, \mathbf{x}, u)\, du = 0 . \tag{6.3.18}$$

Integrating (6.3.5)–(6.3.8) over u yields

$$\frac{\partial R(t,\mathbf{x})}{\partial t} + \nabla_{\mathbf{x}} \cdot \langle k(\mathbf{v}) \otimes \mathbf{v} \cdot \nabla_{\mathbf{x}} R(t,\mathbf{x}) \rangle = 0\,, \tag{6.3.19}$$

while integrating (6.3.9)–(6.3.12) over u yields

$$\frac{\partial R(t,\mathbf{x})}{\partial t} = 0\,. \tag{6.3.20}$$

In the limit

$$\varepsilon \to 0\,, \quad \Rightarrow \quad R_\varepsilon(t,\mathbf{x}) \cong (R(t,\mathbf{x}), R(t,\mathbf{x}))\,,$$

which is a solution of the linear diffusion equation (6.3.19) or, respectively, of the mass conservative equation (6.3.20) and where (R,R) is the vector with components corresponding to the two components of f_ε.

Proof of Theorem 6.3.1: Multiplying equation (6.3.1) by ε^p, letting ε go to zero, and using the moment convergence assumptions yields $\mathcal{L}f = 0$. This implies that $f \in \mathrm{Ker}(\mathcal{L})$ and consequently can be written as in (6.3.4). Integrating equation (6.3.1) over $\mathbf{v}$ and using the fact that $\langle \mathcal{L}f, \psi \rangle = 0$ yields

$$\begin{aligned}\partial_t \langle f_\varepsilon, \psi \rangle + \sum_1^3 \partial_{\mathbf{x}_j} \left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle = {} & \varepsilon^{q-1} \langle \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon), \psi \rangle \\ & + \varepsilon^{r-1} \langle \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon), \psi \rangle\,. \end{aligned} \tag{6.3.21}$$

The asymptotic limit of $\left\langle V_j \dfrac{f_\varepsilon}{\varepsilon}, \psi \right\rangle$ has to be estimated to recover the limit in (6.3.21). Then, using Lemma 6.2.5, and recalling from i) of Lemma 6.2.4 that $\mathcal{L}$ is self-adjoint, we find that

$$\left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle = \left\langle \frac{\mathcal{L} f_\varepsilon}{\varepsilon}, \frac{k_j(\mathbf{v})}{M} \psi \right\rangle. \tag{6.3.22}$$

Eliminating $\mathcal{L}f_\varepsilon$ and using equation (6.3.1) yields

$$\begin{aligned}\frac{1}{\varepsilon}\mathcal{L}(f_\varepsilon) = {} & \varepsilon^p \frac{\partial f_\varepsilon}{\partial_t} + \varepsilon^{p-1} \sum_{j=1}^3 \frac{\partial V_j f_\varepsilon}{\partial \mathbf{x}_j} \\ & - \varepsilon^{p+q-1} \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) - \varepsilon^{p+r-1} \Gamma_{11}^{21}(f_\varepsilon, f_\varepsilon)\,. \end{aligned} \tag{6.3.23}$$

Finally, combining (6.3.22) and (6.3.23), the following result is obtained:

$$\sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle = \sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \left\langle \varepsilon^p \frac{\partial f_\varepsilon}{\partial t} + \varepsilon^{p-1} \sum_{k=1}^{3} \frac{\partial}{\partial \mathbf{x}_k} V_k f_\varepsilon \right.$$
$$\left. - \varepsilon^{p+q-1} \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) - \varepsilon^{p+r-1} \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon), \frac{k_j(\mathbf{v})}{M} \psi \right\rangle .$$

This term, with the hypothesis on the moments, converges to the following expression:

$$\sum_{j=1}^{3} \sum_{k=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \frac{\partial}{\partial \mathbf{x}_k} \langle V_k f, \frac{k_j(\mathbf{v})}{M} \psi \rangle = 2 \nabla_{\mathbf{x}} \cdot \langle k(\mathbf{v}) \otimes \mathbf{v} \cdot \nabla_{\mathbf{x}} \rho \rangle , \qquad (6.3.24)$$

when $p = 1$, or to 0 if $p > 1$.

The asymptotic quadratic term of (6.3.21) converges to the following expression:

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi \rangle + \langle \Gamma_{12}^{21}(M\rho, M\rho), \psi \rangle \quad \text{if } q = r = 1 ,$$

$$\langle \Gamma_{12}^{21}(M\rho, M\rho), \psi \rangle \quad \text{if } r = 1,\ q > 1 ,$$

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi \rangle \quad \text{if } q = 1,\ r > 1 ,$$

and to

$$0 \quad \text{if } r > 1,\ q > 1 .$$

This completes the proof.

∎

6.4 Models with Proliferation and Destruction

The various models of cell populations dealt with in Chapters 3 to 5 are characterized by a source term related to birth and death processes. Therefore it is useful to deal with the derivation of macroscopic equations in this relatively more general case.

The formal structure of the equations including birth and death processes terms (2.3.7), using the same notation we have seen in the preceding sections, is as follows:

$$\begin{aligned}
&\left(\frac{\partial}{\partial t}+\mathbf{v}\cdot\nabla_{\mathbf{x}}\right)f_1(t,\mathbf{x},\mathbf{v},u)\\
&\quad=\nu\int_{D_{\mathbf{v}}}\Big[T(\mathbf{v},\mathbf{v}^*)f_1(t,\mathbf{x},\mathbf{v}^*,u)-T(\mathbf{v}^*,\mathbf{v})f_2(t,\mathbf{x},\mathbf{v},u)\Big]d\mathbf{v}^*\\
&\qquad+(\mathcal{G}_{11}-\mathcal{L}_{11}+\mathcal{G}_{12}-\mathcal{L}_{12}+\mathcal{I}_{11}+\mathcal{I}_{12})(f,f)(t,\mathbf{x},\mathbf{v},u)\,,\\
&\left(\frac{\partial}{\partial t}+\mathbf{v}\cdot\nabla_{\mathbf{x}}\right)f_2(t,\mathbf{x},\mathbf{v},u)\\
&\quad=\nu\int_{D_{\mathbf{v}}}\Big[T(\mathbf{v},\mathbf{v}^*)f_2(t,\mathbf{x},\mathbf{v}^*,u)-T(\mathbf{v}^*,\mathbf{v})f_1(t,\mathbf{x},\mathbf{v},u)\Big]d\mathbf{v}^*\\
&\qquad+(\mathcal{G}_{21}-\mathcal{L}_{21}+\mathcal{G}_{22}-\mathcal{L}_{22}+\mathcal{I}_{21}+\mathcal{I}_{22})(f,f)(t,\mathbf{x},\mathbf{v},u)\,,
\end{aligned}\tag{6.4.1}$$

where the operators $\mathcal{G}$ and $\mathcal{L}$ are defined by (6.2.4) and (6.2.5) and $\mathcal{I}_{ij}$ is defined by

$$\mathcal{I}_{ij}(f,f)=f_i(t,\mathbf{x},\mathbf{v},u)\int_{D_u}\int_{D_u}\eta_{ij}\mu_{ij}f_j(t,\mathbf{x},\mathbf{v},u^*)\,du^*\,.\tag{6.4.2}$$

The mathematical model described by (6.4.1) is characterized by three types of rates, the first one related to the dynamics of the mechanical variables, and the second and third one to the biological rates. Experimental evidence suggests that we study those regimes such that the biological terms, η_{ij} and μ_{ij}, are of a smaller order with respect to the mechanical ones, i.e., ν_{ij}. In order to simplify the equations we take $\eta_{11}=\eta_{22}$, $\eta_{12}=\eta_{21}$, $\mu_{11}=\mu_{22}$, and $\mu_{12}=\mu_{21}$. Then we set

$$\eta_{11}=\varepsilon^q\,,\quad \eta_{12}=\varepsilon^r\,,\quad \mu_{11}=\varepsilon^\delta\,,\quad \mu_{12}=\varepsilon^\gamma,\quad q,r,\delta,\gamma\geq 0\,,$$

and

$$\nu=\frac{1}{\varepsilon^p},\quad p>0,$$

where ε is a small parameter which will be allowed to tend to zero. In addition, the slow diffusion scale time $\tau=\varepsilon t$ will be used so that the following scaled equation is obtained:

$$\varepsilon\frac{\partial}{\partial t}f_\varepsilon(t,\mathbf{x},\mathbf{v},u)+\sum_{j=1}^{3}V_j\frac{\partial}{\partial\mathbf{x}_j}f_\varepsilon(t,\mathbf{x},\mathbf{v},u)$$

$$= \frac{1}{\varepsilon^p}\,\mathcal{L}f_\varepsilon + \varepsilon^q\,\Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) + \varepsilon^r\,\Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon)$$

$$+ \varepsilon^{q+\delta} I_{11}^{22}(f_\varepsilon, f_\varepsilon) + \varepsilon^{r+\gamma} I_{12}^{21}(f_\varepsilon, f_\varepsilon)\,, \qquad (6.4.3)$$

where Γ_{11}^{22} and Γ_{12}^{21} are given by equations (6.3.2) and (6.3.3), respectively, and the terms I_{12}^{21} and I_{11}^{22} are given by

$$I_{11}^{22} = (I_{11}, I_{22}), \quad I_{12}^{21} = (I_{12}, I_{21}), \quad I_{ij} = \frac{\mathcal{I}_{ij}(f,f)}{\eta_{ij}\mu_{ij}}, \quad i,j = 1,2. \quad (6.4.4)$$

Suppose now that f_ε converges in the distributional sense to a function f as ε goes to zero. Moreover, assume that all moments of f_ε, $\Gamma_{ij}(f_\varepsilon, f_\varepsilon)$, and $I_{ij}(f_\varepsilon, f_\varepsilon)$ converge to the corresponding moments in the distributional sense and that all formally small terms vanish. Multiplying equation (6.4.3) by ε^p, letting ε go to zero, and using convergence assumptions yields $\mathcal{L}f = 0$. This implies that $f \in \mathrm{Ker}(\mathcal{L})$ and consequently it can be written as in (6.3.4). Integrating equation (6.4.3) over $\mathbf{v}$ and using the fact that $\langle \mathcal{L}f, \psi\rangle = 0$ yields

$$\frac{\partial}{\partial t}\langle f_\varepsilon, \psi\rangle + \sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j}\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi\rangle = J[f_\varepsilon]$$

$$= \varepsilon^{q-1}\langle \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon), \psi\rangle + \varepsilon^{r-1}\langle \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon), \psi\rangle$$

$$+ \varepsilon^{q+\delta-1}\langle I_{11}^{22}(f_\varepsilon, f_\varepsilon), \psi\rangle + \varepsilon^{r+\gamma-1}\langle I_{12}^{21}(f_\varepsilon, f_\varepsilon), \psi\rangle\,. \quad (6.4.5)$$

Before calculating the limit for $\varepsilon \to 0$ in the right-hand side of (6.4.5), we must take $r, q \geq 1$ and $\delta, \gamma \geq 0$. The asymptotic limit of $\left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle$ must be estimated to recover the limit in (6.4.5). Then, using Lemma 6.2.5, and recalling from i) of Lemma 6.2.4 that $\mathcal{L}$ is self-adjoint, we find that

$$\sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j}\left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle = \sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j}\left\langle \varepsilon^p \frac{\partial}{\partial t} f_\varepsilon + \varepsilon^{p-1} \sum_{k=1}^{3} \frac{\partial}{\partial \mathbf{x}_k} V_k f_\varepsilon \right.$$

$$- \varepsilon^{p+q-1}\Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) - \varepsilon^{p+r-1}\Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon) - \varepsilon^{q+\delta+p-1} I_{11}^{22}(f_\varepsilon, f_\varepsilon)$$

$$\left. - \varepsilon^{r+\gamma+p-1} I_{12}^{21}(f_\varepsilon, f_\varepsilon), \frac{k_j(\mathbf{v})}{M}\psi \right\rangle. \qquad (6.4.6)$$

The limit of (6.4.6) exists if $p \geq 1$. This term, under the hypothesis on the moments, converges to the expression (6.3.24) when $p = 1$, or to 0 if $p > 1$.

Remark 6.4.1. It is clear that if $r, q > 1$, then the asymptotic limit of the quadratic term of (6.4.5) converges to zero for any $\delta, \gamma \geq 0$, in which case one formally obtains the mass conservation equation or the linear diffusion equation depending of the values of p:

$$\frac{\partial \rho}{\partial t} + \nabla_{\mathbf{x}} \cdot \langle k(\mathbf{v}) \otimes \mathbf{v} \cdot \nabla_{\mathbf{x}} \rho \rangle = 0, \quad p = 1\,, \tag{6.4.7}$$

$$\frac{\partial \rho}{\partial t} = 0, \quad p > 1\,, \tag{6.4.8}$$

which are the same equations (6.3.8), (6.3.12) in the case of mass-conservating systems (6.2.3). Therefore, for any $\delta, \gamma \geq 0$, the presence of source terms in the case $r, q > 1$ does not affect the macroscopic limit equations.

Remark 6.4.2. One can compute the proliferating term in the limit $\varepsilon \to 0$. For any i, j,

$$\langle I_{ij}(f_\varepsilon, f_\varepsilon) \rangle_{\mathbf{v}} \longrightarrow \langle I_{ij}(M\rho, M\rho) \rangle_{\mathbf{v}} = \langle M^2(\mathbf{v}) \rangle_{\mathbf{v}} \rho \langle \rho \rangle_u\,. \tag{6.4.9}$$

The asymptotic limit of the quadratic term of (6.4.5) clearly depends on δ and γ. In order to simplify the analysis, we take $r = q$, and only the following cases will be analyzed.

I: $\gamma = 0\,,\ \delta \neq 0\,,\ q = 1$. In this case, the quadratic term of (6.4.5) converges to

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi \rangle + \langle \Gamma_{12}^{21}(M\rho, M\rho), \psi \rangle + \langle I_{12}^{21}(M\rho, M\rho), \psi \rangle\,.$$

II: $\delta = 0$, $\gamma \neq 0$, $q = 1$. In this case, the quadratic term of (6.4.5) converges to

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi \rangle + \langle \Gamma_{12}^{21}(M\rho, M\rho), \psi \rangle + \langle I_{11}^{22}(M\rho, M\rho), \psi \rangle\,.$$

Letting ε go to zero in (6.4.5), and using (6.4.6) and (6.4.9), one obtains the following result:

Theorem 6.4.1. *Let* (6.2.19) *and assumption* 6.2.1 *hold, suppose that* $q = 1, \gamma = 0, \delta \neq 0$ *or* $q = 1, \delta = 0, \gamma \neq 0$, *and let* $f_\epsilon(t, \mathbf{x}, \mathbf{v}, u)$ *be a sequence solutions to the scaled kinetic equation* (6.4.3) *such that* f_ϵ *converges, in*

the distributional sense, to a function f as ε goes to zero. Furthermore, assume that the moments

$$\langle f_{\varepsilon i}\rangle, \quad \left\langle \frac{k(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f_{\varepsilon i} \right\rangle, \quad \langle \Gamma_{ij}(f_\varepsilon, f_\varepsilon)\rangle, \quad \langle I_{ij}(f_\varepsilon, f_\varepsilon)\rangle, \quad i,j = 1,2$$

converge in the sense of distributions to the corresponding moments

$$\langle f_i\rangle, \quad \left\langle \frac{k(\mathbf{v})}{M(\mathbf{v})} \otimes \mathbf{v} f_i \right\rangle, \quad \langle \Gamma_{ij}(f, f)\rangle, \quad \langle I_{ij}(f, f)\rangle, \quad i,j = 1,2\,,$$

and that all formally small terms vanish. Then the asymptotic limit f takes the form (6.3.4) *where $\rho(t, \mathbf{x}, u)$ is the weak solution of the following equation:*

$$p = 1: \quad \frac{\partial \rho}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) = \frac{\langle M^2\rangle_{\mathbf{v}}}{2} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + \langle M^2\rangle_{\mathbf{v}} \rho \langle \rho\rangle_{\mathbf{u}}\,, \tag{6.4.10}$$

and

$$p > 1: \quad \frac{\partial \rho}{\partial t} = \frac{1}{2}\langle M^2\rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + \langle M^2\rangle_{\mathbf{v}} \rho \langle \rho\rangle_{u}\,, \tag{6.4.11}$$

where Γ_{ij} is defined by (6.3.13).

III: $q = 1, \delta = 0, \gamma = 0$. In this case, the quadratic term of (6.4.5) converges to

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi\rangle + \langle \Gamma_{12}^{21}(M\rho, M\rho), \psi\rangle + \langle I_{11}^{22}(M\rho, M\rho), \psi\rangle + \langle I_{12}^{21}(M\rho, M\rho), \psi\rangle \ .$$

The macroscopic description is defined by the following result:

Theorem 6.4.2. *Let $f_\epsilon(t, \mathbf{x}, \mathbf{v}, u)$ be a sequence solutions to the scaled kinetic equation* (6.4.3). *Let the assumptions of Theorem 6.4.1 hold, and suppose that $q = 1$ and $\gamma = \delta = 0$. Then the asymptotic limit f has the form* (6.3.4) *where $\rho(t, \mathbf{x}, u)$ is the weak solution of the following equations:*

$$p = 1: \quad \frac{\partial \rho}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) = \frac{\langle M^2\rangle_{\mathbf{v}}}{2} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + 2\langle M^2\rangle_{\mathbf{v}} \rho \langle \rho\rangle_{u}\,, \tag{6.4.12}$$

and

$$p > 1: \quad \frac{\partial \rho}{\partial t} = \frac{1}{2}\langle M^2 \rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + 2\langle M^2 \rangle_{\mathbf{v}} \rho \langle \rho \rangle_u \,. \tag{6.4.13}$$

IV: $q = 1, \delta \neq 0, \gamma \neq 0$. The asymptotic quadratic term of (6.4.5) converges to

$$\langle \Gamma_{11}^{22}(M\rho, M\rho), \psi \rangle + \langle \Gamma_{12}^{21}(M\rho, M\rho), \psi \rangle \,.$$

The macroscopic picture is now given by

Theorem 6.4.3. *Let $f_\epsilon(t, \mathbf{x}, \mathbf{v}, u)$ be a sequence solutions to the scaled kinetic equation* (6.4.3)*. Let the assumptions of Theorem 6.4.1 hold, and suppose that $q = 1, \gamma \neq 0$, and $\delta \neq 0$. Then the asymptotic limit f has the form* (6.3.4) *where $\rho(t, \mathbf{x}, \mathbf{u})$ is the weak solution of the following equations:*

$$p = 1: \quad \frac{\partial \rho}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) = \frac{\langle M^2 \rangle_{\mathbf{v}}}{2} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) \,, \tag{6.4.14}$$

and

$$p > 1: \quad \frac{\partial \rho}{\partial t} = \frac{1}{2}\langle M^2 \rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho). \tag{6.4.15}$$

Remark 6.4.3. In this case, the proliferating terms disappear in the limit and therefore they do not influence the behavior of the macroscopic limit equations.

Remark 6.4.4. The case $\gamma = \delta = 0$, which corresponds to $\mu_{11} = \mu_{12} = \mu_{21} = \mu_{22} = Constant = 1$ is particularly important in birth and death processes. Let $R(t, \mathbf{x})$ and $R_\varepsilon(t, \mathbf{x})$ be the functions defined as in remark 6.3.2. Integrating (6.4.12) and (6.4.13) over u yields

$$\frac{\partial R(t, \mathbf{x})}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} R(t, \mathbf{x})) = 2\langle M^2 \rangle_{\mathbf{v}} R^2(t, \mathbf{x}) \,, \tag{6.4.16}$$

or

$$\frac{\partial R(t, \mathbf{x})}{\partial t} = 2\langle M^2 \rangle_{\mathbf{v}} R^2(t, \mathbf{x}) \,. \tag{6.4.17}$$

In the limit

$$\varepsilon \longrightarrow 0 \,, \quad R_\varepsilon(t, x) = \int_{\mathbb{R}^3 \times \mathbb{R}} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u) \, d\mathbf{v} \, du \cong (R(t, \mathbf{x}), R(t, \mathbf{x})) \,,$$

which is a solution of the nonlinear diffusion equation (6.4.16) or respectively of the nonlinear evolution equation (6.4.17).

Remark 6.4.5. The macroscopic equation (6.4.15) can be obtained from kinetic model (6.4.1) in the case $p = 1$, without the diffusion time scaling and in the case $q = \delta = \gamma = 0$. In this case the model (6.4.1) becomes

$$\frac{\partial}{\partial t} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u) + \sum_{j=1}^{3} V_j \frac{\partial f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u)}{\partial \mathbf{x}_j} = \frac{1}{\varepsilon} \mathcal{L} f_\varepsilon + \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) + \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon) + I_{11}^{22}(f_\varepsilon, f_\varepsilon) + I_{12}^{21}(f_\varepsilon, f_\varepsilon)\,. \tag{6.4.18}$$

In the limit $\varepsilon \longrightarrow 0$,

$$f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u) \longrightarrow (M\rho, M\rho),$$

and

$$\left\langle \sum_{j=1}^{3} V_j \frac{\partial}{\partial \mathbf{x}_j} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u), \psi \right\rangle \longrightarrow 0.$$

The scalar product of equation (6.4.18) with ψ yields equation (6.4.15).

Example. Let us discuss a specific model for the turning kernel and compute explicit formulas for the diffusion coefficient. This task is straightforward for the relaxation time model

$$T(\mathbf{v}, \mathbf{v}^*) = \sigma M(\mathbf{v}), \qquad \sigma > 0\,. \tag{6.4.19}$$

In this case, the leading turning operator becomes

$$\mathcal{L}(f) = \sigma \Big(M\langle f_1 \rangle_{\mathbf{v}} - f_2, M\langle f_2 \rangle_{\mathbf{v}} - f_1 \Big)\,. \tag{6.4.20}$$

In particular one derives from equation (6.2.30) the following expression for the diffusion coefficient:

$$D = \frac{1}{\sigma} \int_{D_{\mathbf{v}}} \mathbf{v} \otimes \mathbf{v} M(\mathbf{v})\, d\mathbf{v}\,. \tag{6.4.21}$$

Moreover, if we assume rotational invariance of the equilibrium distribution, i.e., $M = M(|\,v\,|)$, one gets the isotropic tensor D:

$$D = \left(\frac{1}{3\sigma} \int_{D_{\mathbf{v}}} |\,\mathbf{v}\,|^2\, M(\mathbf{v})\, d\mathbf{v} \right) \cdot I\,. \tag{6.4.22}$$

For $q = 1, \gamma = \delta = 0$, the following nonlinear diffusion equation and nonlinear evolution equation are obtained:

$$p = 1: \quad \frac{\partial \rho}{\partial t} - d\Delta_x \rho = \frac{\langle M^2 \rangle_{\mathbf{v}}}{2} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + 2\langle M^2 \rangle_{\mathbf{v}} \rho \langle \rho \rangle_u \,, \quad (6.4.23)$$

and

$$p > 1: \quad \frac{\partial \rho}{\partial t} = \frac{1}{2}\langle M^2 \rangle_{\mathbf{v}} \sum_{i,j=1}^{2} \Gamma_{ij}(\rho, \rho) + 2\langle M^2 \rangle_{\mathbf{v}} \rho \langle \rho \rangle_u \,, \quad (6.4.24)$$

where

$$d = \frac{1}{3\sigma} \int_{D_{\mathbf{v}}} |\,\mathbf{v}\,|^2 \, M(\mathbf{v})\, d\mathbf{v} \,. \quad (6.4.25)$$

When $d \longrightarrow 0$, equation (6.4.24) formally reduces to (6.4.23). The question is, how can we get equation (6.4.24) in the case $p = 1$?

The following answer is proposed. For d very small, this means that σ is very large; let $\sigma = 1/\varepsilon^a$, $a > 0$. For $p = q = 1, \gamma = \delta = 0$, one gets the following model:

$$\varepsilon \frac{\partial}{\partial t} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u) + \sum_{j=1}^{3} V_j \frac{\partial}{\partial \mathbf{x}_j} f_\varepsilon(t, \mathbf{x}, \mathbf{v}, u) = \frac{1}{\varepsilon^{a+1}} L f_\varepsilon + \varepsilon \Big(\Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) + \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon) + I_{11}^{22}(f_\varepsilon, f_\varepsilon) + I_{12}^{21}(f_\varepsilon, f_\varepsilon) \Big) \,, \quad (6.4.26)$$

where $L = \mathcal{L}/\sigma$. By taking the scalar product of (6.4.26) with ψ, we obtain

$$\frac{\partial}{\partial t} \langle f_\varepsilon, \psi \rangle + \sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle = J[f_\varepsilon] = \langle \Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon), \psi \rangle + \langle \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon), \psi \rangle + \langle I_{11}^{22}(f_\varepsilon, f_\varepsilon), \psi \rangle + \langle I_{12}^{21}(f_\varepsilon, f_\varepsilon), \psi \rangle. \quad (6.4.27)$$

The asymptotic limit of $\left\langle V_j \dfrac{f_\varepsilon}{\varepsilon}, \psi \right\rangle$ has to be estimated to recover the limit in (6.4.27).

For $\varepsilon \to 0$, one has

$$J = \sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \left\langle V_j \frac{f_\varepsilon}{\varepsilon}, \psi \right\rangle \longrightarrow 0 \,, \quad (6.4.28)$$

where

$$J = \varepsilon^a \Bigg[\sum_{j=1}^{3} \frac{\partial}{\partial \mathbf{x}_j} \Big\langle \varepsilon \frac{\partial}{\partial t} f_\varepsilon + \sum_{k=1}^{3} \frac{\partial}{\partial \mathbf{x}_k} V_k f_\varepsilon - \varepsilon \Big(\Gamma_{11}^{22}(f_\varepsilon, f_\varepsilon) + \Gamma_{12}^{21}(f_\varepsilon, f_\varepsilon) + I_{11}^{22}(f_\varepsilon, f_\varepsilon) + I_{12}^{21}(f_\varepsilon, f_\varepsilon) \Big), \frac{k_j(\mathbf{v})}{M} \psi \Big\rangle \Bigg]. \tag{6.4.29}$$

This implies that the diffusion term vanishes and gives the macroscopic equation (6.4.24) in the limit $\sigma \to +\infty$. One concludes that equation (6.4.24) can be obtained from the kinetic model even in the case $p = 1$ in the regime $\sigma \to +\infty$.

6.5 Application

A methodological approach to the derivation of macroscopic equations from the mesoscopic description has been developed in the preceding sections by means of a suitable generalization of the methods of kinetic theory. This section proposes a simple application with the aim of showing how the method can be applied to the analysis of a specific model in the case of conservative interactions only. The reader may develop additional calculations related to models with proliferation and destruction of cells.

As we shall see, although nonconservative phenomena are neglected, the macroscopic description, derived according to the above method, clearly shows nonlinear features.

We consider the class of equations proposed in Chapter 2 in the case of two populations: endothelial cells which may start progressing, and tumor cells.

Specifically we refer to assumptions 3.3.1–3.3.6 of Chapter 3. Hence, the mathematical model consists of the following integro-differential ***evolution equation***:

$$\Big(\frac{\partial f_1}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f_1 - \nu \mathcal{L}_1 f \Big)(t, \mathbf{x}, \mathbf{v}, u) = \eta_{11} n_1(t, \mathbf{x}, \mathbf{v}) \Big(\frac{1}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp \Big\{ - \frac{(u - (\mathbf{w} + \alpha_{11}))^2}{2 s_{11}} \Big\}$$

$$\times f_1(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w} - f_1(t,\mathbf{x},\mathbf{v},u)\Big)$$

$$+ \eta_{12} n_2^A(t,\mathbf{x},\mathbf{v})\Big(\frac{1}{\sqrt{2\pi s_{12}}}\int_0^\infty \exp\Big\{-\frac{(u-(\mathbf{w}-\alpha_{12}))^2}{2s_{12}}\Big\}$$

$$\times f_1(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w}$$

$$- U_{[0,\infty)}(u) f_1(t,\mathbf{x},\mathbf{v},u)\Big)\,, \tag{6.5.1a}$$

and

$$\Big(\frac{\partial f_2}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_2 - \nu\mathcal{L}_2 f\Big)(t,\mathbf{x},\mathbf{v},u)$$

$$= \eta_{21} n_1^T(t,\mathbf{x},\mathbf{v})\Big(\frac{1}{\sqrt{2\pi s_{21}}}\int_0^\infty \exp\Big\{-\frac{(u-(\mathbf{w}-\alpha_{21}))^2}{2s_{21}}\Big\}$$

$$\times f_2(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w}$$

$$- U_{[0,\infty)}(u) f_2(t,\mathbf{x},\mathbf{v},u)\Big)\,, \tag{6.5.1b}$$

where $U_D(u)$ is the characteristic function and

$$n_1(t,\mathbf{x},\mathbf{v}) = \int_{-\infty}^{\infty} f_1(t,\mathbf{x},\mathbf{v},u)\,du\,, \tag{6.5.2}$$

$$n_2^A(t,\mathbf{x},\mathbf{v}) = \int_0^{+\infty} f_2(t,\mathbf{x},\mathbf{v},u)\,du\,, \tag{6.5.3}$$

and

$$n_1^T(t,\mathbf{x},\mathbf{v}) = \int_0^{\infty} f_1(t,\mathbf{x},\mathbf{v},u)\,du\,. \tag{6.5.4}$$

The model is characterized by three phenomenological parameters:

α_{11} refers to the variation of the progression due to encounters between endothelial cells. It describes the tendency of a normal cell to degenerate and to increase its progression.

α_{12} is the parameter corresponding to the ability of the active immune cells to reduce the progression of tumor cells.

α_{21} is the parameter corresponding to the ability of tumor cells to inhibit the active immune cells.

We are looking for the diffusive/hydrodynamic asymptotic limit of equation (6.5.1) when the parameters $\eta_{ij}, i,j=1,2$ are of a smaller order with respect to the mechanical one. We suppose that $\eta_{12}=\eta_{21}=\epsilon^r, \eta_{11}=\epsilon^q, r,q\geq 1$, and $\nu=\frac{1}{\epsilon^p}$, $p\geq 1$. Under the above assumption, model (6.5.1) can be rewritten as follows:

$$
\begin{aligned}
&\left(\varepsilon\frac{\partial f_1}{\partial t}+\mathbf{v}\cdot\nabla_{\mathbf{x}}f_1-\frac{1}{\varepsilon^p}\mathcal{L}_1 f\right)(t,\mathbf{x},\mathbf{v},u)\\
&\qquad=\varepsilon^q n_1(t,\mathbf{x},\mathbf{v})\left(\frac{1}{\sqrt{2\pi s_{11}}}\int_{-\infty}^{\infty}\exp\left\{-\frac{\left(u-(\mathbf{w}+\alpha_{11})\right)^2}{2s_{11}}\right\}\right.\\
&\qquad\qquad\qquad\qquad\left.\times f_1(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w}\right.\\
&\qquad\quad\left.-f_1(t,\mathbf{x},\mathbf{v},u)\right)\\
&\qquad\quad+\varepsilon^r n_2^A(t,\mathbf{x},\mathbf{v})\left(\frac{1}{\sqrt{2\pi s_{12}}}\int_{0}^{\infty}\exp\left\{-\frac{\left(u-(\mathbf{w}-\alpha_{12})\right)^2}{2s_{12}}\right\}\right.\\
&\qquad\qquad\qquad\qquad\left.\times f_1(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w}\right.\\
&\qquad\quad\left.-U_{[0,\infty)}(u)f_1(t,\mathbf{x},\mathbf{v},u)\right),\\
&\left(\varepsilon\frac{\partial f_2}{\partial t}+\mathbf{v}\cdot\nabla_{\mathbf{x}}f_2-\frac{1}{\varepsilon^p}\mathcal{L}_2 f\right)(t,\mathbf{x},\mathbf{v},u)\\
&\qquad=\varepsilon^r n_1^T(t,\mathbf{x},\mathbf{v})\left(\frac{1}{\sqrt{2\pi s_{21}}}\int_{0}^{\infty}\exp\left\{-\frac{\left(u-(\mathbf{w}-\alpha_{21})\right)^2}{2s_{21}}\right\}\right.\\
&\qquad\qquad\qquad\qquad\left.\times f_2(t,\mathbf{x},\mathbf{v},\mathbf{w})\,d\mathbf{w}\right.\\
&\qquad\quad\left.-U_{[0,\infty)}(u)f_2(t,\mathbf{x},\mathbf{v},u)\right).
\end{aligned}
\tag{6.5.5}
$$

The various results of Section 6.3 can be exploited to find the possible asymptotic limit equations. In particular, let $(M\rho(t,\mathbf{x},u),M\rho(t,\mathbf{x},u))$ be an approximation of f_ε; then some specific cases, among several ones, of different evolution equations for the density ρ are described below. Specifically, three different regimes will be dealt with, corresponding to different ratios between the biological and mechanical interaction rates. As we shall see, the more the biological interaction rate grows with respect to the mechanical one, the more the macroscopic evolution equation shifts from a

diffusion process to a local mass evolution. Specifically, the following cases will be examined:

Case I: $p = q = r = 1$, $\eta_{11} \cong \eta_{12} \cong \varepsilon$, $\nu \cong \frac{1}{\eta_{11}} \cong \frac{1}{\varepsilon}$;

Case II: $q, r > 1$, $p = 1\, \eta_{11} \cong \varepsilon^q, \eta_{12} \cong \varepsilon^r$, $\nu \cong \frac{1}{\varepsilon}$;

Case III: $q = r = 1$, $p > 1$, $\eta_{11} \cong \eta_{12} \cong \varepsilon$, $\nu \cong \frac{1}{\eta_{11}^p} \cong \frac{1}{\varepsilon^p}$.

The analysis provides the following results:

Case I: The following nonlinear diffusion equation is derived for $p = q = r = 1$:

$$\begin{aligned}
&\frac{\partial \rho}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) \\
&= \frac{\langle M^2 \rangle_{\mathbf{v}}}{2} \Bigg(\langle \rho \rangle_{\mathbf{u}} \Bigg(\frac{1}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp \Bigg\{ - \frac{(u - (\mathbf{v} + \alpha_{11}))^2}{2 s_{11}} \Bigg\} \rho(\cdot, \mathbf{v})\, d\mathbf{v} - \rho \Bigg) \\
&\quad + \langle U_{[0,\infty)}(u) \rho \rangle_u \Bigg(\frac{1}{\sqrt{2\pi s_{12}}} \int_0^{\infty} \exp \Bigg\{ - \frac{(u - (\mathbf{v} - \alpha_{12}))^2}{2 s_{12}} \Bigg\} \rho(\cdot, \mathbf{v})\, d\mathbf{v} \\
&\quad - U_{[0,\infty)}(u) \rho \Bigg) \\
&\quad + \langle U_{[0,\infty)}(u) \rho \rangle_u \Bigg(\frac{1}{\sqrt{2\pi s_{21}}} \int_0^{\infty} \exp \Bigg\{ - \frac{(u - (\mathbf{v} - \alpha_{21}))^2}{2 s_{21}} \Bigg\} \rho(\cdot, \mathbf{v})\, d\mathbf{v} \\
&\quad - U_{[0,\infty)}(u) \rho \Bigg) \Bigg) . \qquad (6.5.6)
\end{aligned}$$

Case II: Linear diffusion is obtained for $r > 1$, $q > 1$, and $p = 1$:

$$\frac{\partial \rho}{\partial t} - \nabla_{\mathbf{x}} \cdot (D \cdot \nabla_{\mathbf{x}} \rho) = 0 . \qquad (6.5.7)$$

This means that the ratio with respect to ν of the rates of biological interactions is of a smaller order. This means that nonlinear diffusion takes place only if the rate of biological interactions overcomes a critical value, i.e., case I.

Case III: Nonlinear evolution equations are obtained for $r = q = 1$ and $p > 1$:

$$\frac{\partial \rho}{\partial t} = \frac{\langle M^2 \rangle_{\mathbf{v}}}{2} \Bigg(\langle \rho \rangle_u \Bigg(\frac{1}{\sqrt{2\pi s_{11}}} \int_{-\infty}^{\infty} \exp \Bigg\{ \frac{-(u - (\mathbf{v} + \alpha_{11}))^2}{2 s_{11}} \Bigg\} \rho(\cdot, \mathbf{v})\, d\mathbf{v} - \rho \Bigg)$$

$$+ \langle U_{[0,\infty)}(u)\rho\rangle_u \left(\frac{1}{\sqrt{2\pi s_{12}}} \int_0^\infty \exp\left\{ - \frac{(u-(\mathbf{v}-\alpha_{12}))^2}{2s_{12}} \right\} \rho(\cdot,\mathbf{v})\, d\mathbf{v} \right.$$

$$\left. - U_{[0,\infty)}(u)\rho \right)$$

$$+ \langle U_{[0,\infty)}(u)\rho\rangle_u \left(\frac{1}{\sqrt{2\pi s_{21}}} \int_0^\infty \exp\left\{ - \frac{(u-(\mathbf{v}-\alpha_{21}))^2}{2s_{21}} \right\} \rho(\cdot,\mathbf{v})\, d\mathbf{v} \right.$$

$$\left. - U_{[0,\infty)}(u)\rho \right) \Bigg) . \tag{6.5.8}$$

This corresponds to the opposite situation with respect to the previous two cases. Now the rate of mechanical interactions becomes relatively greater than those corresponding to cases I and II.

Remark 6.5.1. It is worth stressing again that the biological interpretation of the above result is that the diffusion process, which may generate invasion, only occurs when biological interactions become predominant with respect to mechanical ones.

6.6 Critical Analysis

This chapter has shown how different macroscopic equations (with different mathematical structures) can be derived corresponding to rates between the biological and mechanical interactions terms.

The analysis may appear tediously formal, and somehow far removed from biological sciences. On the other hand, the mathematical approach is technically necessary for a rigorous derivation of macroscopic equations from microscopic descriptions. The reader who is not interested in the mathematical analysis may skip over all the technical calculations and reach the final conclusion of Sections 6.3 and 6.4 which deal, respectively, with equations in the absence and presence of proliferation terms. The mathematical structure of the evolution equations (parabolic, hyperbolic, partial differential equations, ordinary differential equations) is directly related to the rates between mechanical and biological interactions terms. These rates can be experimentally determined.

The derivation of macroscopic models from underlying microscopic descriptions is necessary for overcoming purely heuristic reasoning which may lead to an incorrect description of biological matter. Applied mathematicians are getting more and more involved in this difficult research field as documented in the recent paper by Lachowicz (2005).

It is worth stressing that the analysis developed in this chapter is based on assumption 6.2.1 of Section 6.2, which has to be verified for the specific system which is object of the modelling process. Generalizations of the mathematical approach with the above assumption removed do not appear to be tractable. On the other hand, using the same approach to derive macroscopic equations from underlying microscopic descriptions for models technically different from those dealt with in the preceding chapters appears to be an interesting research perspective, which may possibly lead to a deeper understanding of the mathematical structure of biological growing tissues. Possibly even the traditional approach of continuum mechanics may take advantage of some ideas proposed in this chapter.

It is worth mentioning that the several biological phenomena which have a macroscopic appearance, such as pattern formation or tumor growth, are characterized by the time evolution of biological functions. Therefore the overall description of the system is given by equations which change in type, along the various model equations reported in Section 6.3.

The above reasoning is even more crucial in the case of the multiscale approach proposed by Alarcon, et al. (2004, 2005). Their approach describes the overall system of cancer modelling as a system of systems, each at different scales. Consequently the influence of the evolution of biological functions over the evolution of each specific subsystem is a specific peculiarity of the mathematical description. An interplay between the above-mentioned multiscale approach and the mathematical analysis proposed in this chapter is definitely an interesting research perspective.

7

Critical Analysis and Forward Perspectives

... mathematical models cannot be designed on the basis of a purely heuristic approach. They should be referred to well-defined mathematical structures, which may act as a mathematical theory.

— Bellomo and Forni (2006)

7.1 Critical Analysis

A general mathematical approach to the modelling of multicellular systems in view of applications to the mathematical description of complex biological systems has been developed in this book.

The modelling of the immune response is the application which has been analyzed in detail, with a focus also on interactions between cancer and immune cells. The modelling concerns a more detailed description of the phenomena developed at the cellular scale with respect to models which provide an overall macroscopic description. In particular, various mathematical models proposed in Chapter 3 are able to describe the competition between the immune system and pathogenic cells. One of them describes the progression of specific tumor cells in competition with the immune cells, as we have seen in Chapter 5.

Models have been derived on the basis of methods of mathematical kinetic theory to describe the evolution of the distribution function over the microscopic biological state of two cell populations, according to the general framework proposed in Chapter 2. Microscopic interactions modify the biological state of the interacting pairs and generate proliferation/destruction

processes. The evolution equations are derived from suitable balance equations related to the elementary volume of the state space. The inlet and outlet flux of cells is computed starting from the above-mentioned microscopic interactions.

A qualitative analysis of the initial value problems related to the application of the models to real biological phenomena has been developed in Chapter 4 to obtain a detailed description of the evolution of the immune competition. The overall analysis has been completed by the simulations and biological interpretations proposed in Chapter 5, which have given a detailed picture of the above qualitative behavior. The model has been shown to describe several interesting phenomena related to well-defined biological situations.

The above mathematical description provides a useful background for modelling the application of therapeutic actions, because it gives some indication of the parameters which have to be modified in order to recover the desired output of the competition. Of course, only medicine can appropriately modify the parameters of the model, while mathematics can only contribute to organizing and addressing the above mentioned therapeutic actions.

A crucial issue still remains: identifying the phenomenological parameters of the model. The analysis of Chapter 5 has shown how these parameters can be technically identified by suitable comparisons with experimental data. In principle, as suggested in Bellomo and Forni (2006), developing a mathematical theory of the immune competition may lead to the characterization of the above parameters by theoretical methods based on methods of immunology.

Chapter 6 has been devoted to the derivation of macroscopic equations from the microscopic kinetic equations. Several models of continuum mechanics for tumors growing *in vivo* have been developed: a variety of macroscopic models are reviewed, among others, by Bellomo, De Angelis, and Preziosi (2003). The models are obtained by different methodological approaches. All of them should be regarded as heuristic models considering that the evolution equations require a description of the material behavior from phenomenological models. On the other hand, the asymptotic theory dealt with in Chapter 6 has shown how different macroscopic models can be obtained according to different ways of modelling microscopic interactions. Therefore, a precise link between microscopic and macroscopic description is stated.

The immune competition, as reported in the review paper by Delves and Roitt (2000), involves several complex phenomena which occurr at the cellular and subcellular scale; moreover, some biological functions may be statistically distributed in the cell population; see Greller, Tobin, and Poste (1996). These features suggest, as already discussed in Chapter 1, the development of methods of nonequilibrium statistical mechanics, following the

suggestions given in the papers by Bellomo and Forni (2006) and Hartwell, Hopfield, Leibner, and Murray (1999). The variety of phenomena described in the models analyzed in Perelson and Weisbuch (1997) is a valuable reference framework.

A critical analysis is developed in this final chapter addressed to certain aspects of modelling. Moreover, some suggestions for alternative mathematical frameworks will be given. Finally, referring to the above-mentioned paper by Bellomo and Forni (2006), a critical analysis on the interplay between mathematical and biological sciences is brought to the reader's attention.

7.2 Developments Toward New Models

The class of mathematical models proposed in Chapter 3, although quite general, should be regarded as the conceptual background to be further developed toward relatively more sophisticated models designed to describe additional phenomena.

Reasoning about conceivable developments and research perspectives, we can point out the following:

- The number of populations of immune cells can be enlarged with the aim of specializing the biological functions within each population, rather than modelling the collective behavior of the whole system as one population only.
- The modelling of therapeutic actions can be obtained by adding further populations of particles which may activate the immune response, or which have the pharmakinetic ability to weaken cells which are carriers of a pathology (abnormal cells).

A specific development of these suggestions has been initiated in a recent paper by Bellouquid and Delitala (2005), where some examples of mathematical models are proposed referring specifically to the competition between immune and tumor cells. Here, we simply report one of the models proposed in this paper.

Specifically, consider a system where a third population, corresponding to cytokine signals, is added to the first two populations of the model proposed in Chapter 3. The modelling can be based on the same assumptions reported in Section 3.3 for interactions between endothelial and immune cells, while, referring to interactions with cells of the third population, the only interaction with nontrivial output is the encounter between an immune

cell and an active cytokine, i.e., a particle of the third population with positive state. In particular the immune cell (either inhibited or not) increases its state while the cytokine decreases ability of activating or inhibiting its specific target cells.

$$u_1, u_2 \in \mathbb{R}: \quad \varphi_{13} = \varphi_{31} = \varphi_{33} = \delta(u - u_1)\,. \tag{7.2.1}$$

$$u_1 > 0\,,\ u_2 \in \mathbb{R}\,, \quad m_{32} = u_1 - \alpha_{32}\,, \tag{7.2.2}$$

$$u_1 \in \mathbb{R}\,,\ u_2 > 0\,, \quad m_{23} = u_1 + \alpha_{23}\,. \tag{7.2.3}$$

The mathematical model, in the case where only conservative encounters are significant, is obtained through calculations we have seen in the preceding chapters. The resulting model is as follows:

$$\begin{cases} \dfrac{\partial f_1}{\partial t}(t,u) = n_1(t) f_1(t, u+\alpha_{11}) - f_1(t,u) n_1(t) - f_1(t,u) n_2^A(t) U_{[0,\infty)}(u) \\ \qquad\qquad + n_2^A(t) f_1(t, u+\alpha_{12}) U_{[0,\infty)}(u+\alpha_{12})\,, \\ \dfrac{\partial f_2}{\partial t}(t,u) = n_1^T(t) f_2(t, u+\alpha_{21}) U_{[0,\infty)}(u+\alpha_{21}) + n_3^A(t) f_2(t, u-\alpha_{23}) \\ \qquad\qquad - f_2(t,u) n_1^T(t) U_{[0,\infty)}(u) - n_3^A(t) f_2(t,u)\,, \\ \dfrac{\partial f_3}{\partial t}(t,u) = n_2(t)\big[f_3(t, u+\alpha_{32}) U_{[0,\infty)}(u+\alpha_{32}) - f_3(t,u) U_{[0,\infty)}(u)\big]\,. \end{cases} \tag{7.2.4}$$

The parameters α_{11}, α_{12}, and α_{21} have the same meaning as in the model proposed in Section 3.3, while α_{23} corresponds to the ability of cytokine signals to activate the immune defense ability and α_{32} is the parameter corresponding to the ability of immune cells to exploit cytokines to improve their reaction state.

The interested reader could also add proliferating and destructive interactions to obtain a model which can be analyzed by the qualitative and computational methods proposed in Chapters 4 and 5.

7.3 Mean Field Interactions

The mathematical framework proposed in Chapter 3 is based on the assumption that interactions between cells are localized in space. This may

be true when the movement of cells is limited to small migrations. In this case, the framework used in Chapter 6 to derive macroscopic equations is a valid tool for dealing with multicellular systems. On the other hand, various papers suggest the use of long-range interactions to analyze the movement of cells which may feel the presence of signals from other cells at a distance. It has been proposed that one could use short-range interaction schemes for the exchange of biological functions, while long-range interaction schemes can be used for cellular movement. This idea has generated a detailed mathematical analysis in Bellouquid and Delitala (2005), where a class of evolution equations has been derived referring to long-range interaction schemes.

Bearing all of the above in mind, it is worth reporting some results proposed in the above-cited paper, with the aim of completing the tools which are available toward the modelling of multicellular systems.

Specifically, mechanical interactions are assumed to be of a mean field type, considering that cells feel a reciprocal presence even at a long distance, while biological interactions are assumed to be of a short-range type, due to binding phenomena between cells which are possible only by contact.

Biological short-range interactions can be modelled following the same reasoning developed in this book, while, referring to the mechanical long-range interaction, the test cell of the i^{th} population is assumed to be subject to an ***action*** over the mechanical variables, $\mathcal{P}_{ij}^m = \mathcal{P}_{ij}^m(\mathbf{x}, \mathbf{x}_*, \mathbf{u}, \mathbf{u}_*)$, due to the interaction with field cells of the j^{th} population which are in a suitable interaction domain of the test cell.

The ***resultant mechanical action*** of the cells of the j^{th} population in the action domain Ω of the test particles is given by

$$\mathcal{F}_{ij}^m[\mathbf{f}](t, \mathbf{x}, \mathbf{u}) = \int_{\mathcal{D}} \mathcal{P}_{ij}^m(\mathbf{x}, \mathbf{x}_*, \mathbf{u}, \mathbf{u}_*)\, f_j(t, \mathbf{x}_*, \mathbf{v}_*, \mathbf{u}_*)\, d\mathbf{x}_*\, d\mathbf{v}_*\, d\mathbf{u}_*\,, \quad (7.3.1)$$

where $\mathcal{D} = \Omega \times D_{\mathbf{v}} \times D_{\mathbf{u}}$, and Ω is the interaction domain of the test cell: hence, $\mathbf{x}_* \notin \Omega \Rightarrow \mathcal{P}_{ij} = 0$.

As in the case of the purely short-range interactions presented in this book, the evolution equations are obtained by equating the rate of variation of the distribution function in the elementary volume of the state space to the inlet and outlet flux due to microscopic interactions, both mechanical and biological. Calculations yield

$$\frac{\partial}{\partial t} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f_i(t,\mathbf{x},\mathbf{v},\mathbf{u}) + \sum_{j=1}^{n} \mathcal{F}_{ij}^{m}[\mathbf{f}](t,\mathbf{x},\mathbf{u})\,\nabla_{\mathbf{v}}\Big(f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\Big) = \sum_{j=1}^{n}\int_{D\times D} c_{ij}|\mathbf{v}_1-\mathbf{v}_2|\mathcal{B}_{ij}(\mathbf{u}_1,\mathbf{u}_2;\mathbf{u}) f_i(t,\mathbf{x},\mathbf{v}_1,\mathbf{u}_1) \times f_j(t,\mathbf{x},\mathbf{v}_2,\mathbf{u}_2)\,d\mathbf{v}_1\,d\mathbf{u}_1\,d\mathbf{v}_2\,d\mathbf{u}_2 - f_i(t,\mathbf{x},\mathbf{v},\mathbf{u})\sum_{j=1}^{n}\int_{D} c_{ij}|\mathbf{v}-\mathbf{v}_2|\big[1-\mu_{ij}(\mathbf{u},\mathbf{u}_2)\big] \times f_j(t,\mathbf{x}_2,\mathbf{v}_2,\mathbf{u}_2)\,d\mathbf{v}_2\,d\mathbf{u}_2\,. \quad (7.3.2)$$

The general framework given in equation (7.3.2) can be used to model systems with mixed types of interactions. This means that specific models may describe certain interactions, say mechanical, by long-range models and other, say proliferating/destructive, by localized interactions. Of course, to build the specific model, suitable phenomenological assumptions have to be given for the terms specifying the transition probabilities of both mechanical and biological interactions. The guidelines are those offered in the preceding chapters.

7.4 On the Interaction Between Biology and Mathematical Sciences

This final section aims at reaching a deeper insight into the interactions between mathematical and biological sciences in order to develop a bio-mathematical theory for multicellular systems starting from the mathematical tools proposed in this book. In other words, it is worth analyzing what is still needed to obtain a mathematical theory for biological systems. Again we refer to the paper by Bellomo and Forni (2006), which is specifically devoted to this difficult topic.

Some of the ideas and reasoning proposed in the above-cited paper will be reported below and critically analyzed with reference to the contents of this book. The analysis is related to the corresponding problem of deriving a statistical mechanics theory for a multiparticle system belonging to living matter.

One of the first steps in the development of a mathematical theory for physical systems is the selection of the observation and representation scale. In classical mechanic, the microscopic scale corresponds to particles, while the macroscopic scale represents the continuum representation, where a finite number of particles is contained in the elementary volume. According to the fundamental paradigm of continuum mechanics, the ratio between the number of particles and the measure of the volume is finite even when the said volume tends to zero.

The dynamics at the microscopic scale are described by evolution equations, generally ordinary differential equations, which can be derived if the interaction rules between particles can be defined on the basis of a suitable physical theory. At the microscopic level, rather than describing the state of each particle (which may not be individually identified), one may look for evolution equations for the statistical distribution over the microscopic state. Mathematical kinetic theory provides such a framework in terms of systems of integro-differential equations. Also in this case, modelling requires a mathematical description of the microscopic interactions between particles.

Referring to classical particles, Newtonian mechanics provides the necessary background via equations describing particle interactions by attraction/repulsion potentials of the interacting particles, or by mechanical collisions which preserve mass, momentum, and energy. It is clear that the theory cannot avoid experiments: for instance interaction potentials can be obtained only from suitable experiments.

The substantial difference in dealing with multicellular systems, as opposed to multiparticle systems of classical mechanics, is that the microscopic state includes, in addition to the mechanical microscopic state, the biological functions of cells which have the ability to modify their mechanical behavior; this feature generally modifies the rules of classical mechanics due to the ability of cells to organize their dynamics.

This book has shown how a suitable mathematical framework can be derived to model the behavior of the complex biological system we are dealing with. Following the guidelines proposed in the above-cited paper, let us summarize the sequential steps followed to derive the evolution equation.

The first step consists of selecting the populations which participate: this means selecting, among a large variety of cell types, those which are effectively involved in the phenomenon which is the object of the biomathematical description. In some cases, various populations may be compacted into only one population linked to a biological function which is the

result of a collective behavior of various population. Indeed, this strategy may reduce the complexity of the mathematical structure.

The second step consists of linking to each population a specific biological function or set of functions.

The third step refers to the modelling of microscopic interactions for each type, i.e., short-range interactions must have a suitable mathematical description. The terms for these interactions should be identified on the basis of suitable biological theories rather then on phenomenological assumptions.

The fourth step is technical, and essentially consists of deriving the evolution equations for the distribution functions over the microscopic state of each cell population. The derivation is obtained from suitable conservation equations in the elementary volume of the state space.

It is clear that the crucial step is the third one. Indeed, it refers to the attempt to transform a biological theory into a bio-mathematical one. The application proposed in Chapter 3 fulfills, only partially, the requirements for obtaining such a theory. In fact, the assessment of microscopic interaction functions is based only on a phenomenological interpretation of physical reality. Therefore, the evolution equations should be regarded as mathematical structures suitable for designing specific models rather than the derivation of a proper bio-mathematical theory.

This is also the case when careful experiments are developed to identify the parameters of the model. A procedure for developing experiments, in the case of phenomena with predominantly biological interpretations, and a technical identification of parameters are reported in Chapter 5 with reference to a specific model. A careful identification of the parameters can generate a reliable model.

An important issue is the parameter sensitivity analysis to verify if, by a suitable selection of the parameters, a mathematical model is able to describe phenomena of interest in biological sciences. Some of these phenomena may be observed, but not quantitatively measured. Hopefully the mathematical model can, at least in some cases, visualize events which may be inferred, but not precisely observed. This aspect is an interesting issue in developing a dialogue between applied mathematicians and theoretical biologists.

However, the goal of developing a mathematical theory for biological sciences is not yet reached, while it can be claimed that the methodological approach which may contribute to such an ambitious aim has been proposed. This can be regarded as a suggestion for research activity in the field of theoretical biology. This means that biologists, in addition to their traditional, valuable research activity may include the conceptual analysis suitable for obtaining the description of the microscopic interaction terms, according to a robust biological theory.

Appendix

Basic Tools of Mathematical Kinetic Theory

1 Introduction

This Appendix gives a brief description of the Boltzmann equation and provides a preliminary analysis of its fundamental properties. Additional information on the derivation and the properties of Boltzmann equation can be found in the pertinent literature cited in Chapter 1, e.g., the books by Cercignani, Illner, and Pulvirenti (1994), Cercignani (1998), as well as in the review paper by Perthame (2004).

The Appendix is organized as follows:

Section 1 deals with a phenomenological analysis and modelling of the interaction between particles of a fluid and with the modelling of collision dynamics.

Section 2 introduces the concept of the distribution function as a statistical variable suitable for describing the properties of the system.

Section 3 deals with a simplified derivation of the Boltzmann equation as a mathematical model for a large system of identical physical particles.

Section 4 deals with an analysis of the mathematical properties of the Boltzmann equation with special attention to the characterization of equilibrium properties and to the tendency toward equilibrium.

Section 5 shows how the continuous distribution function can be properly discretized to generate a distribution function with discrete values. In particular, a derivation of the discrete Boltzmann equation is proposed.

This Appendix should be considered the mathematical background to Chapter 2, where a generalized Boltzmann equation is derived for a large system of interacting entities whose microscopic state is identified not only by geometrical and mechanical variables, but also by an additional (biological) microscopic variable which may assume different meanings corresponding to the specific system which is object of the modelling process.

2 Multiparticle Systems and Statistical Distribution

A physical fluid is an assembly of disordered interacting particles free to move in all directions, inside a space domain $\Omega \subseteq \mathbb{R}^3$ possibly equal to the whole space $\mathbb{R}^3$. Assuming that the position of each particle is correctly identified by the coordinates of its center of mass

$$\mathbf{x}_k\,, \qquad k = 1, \ldots, N\,, \tag{2.1}$$

the system may be reduced to a set of point masses relative to a fixed frame of reference. For instance, when the shapes of the particles are spherically symmetric, and hence rotational degrees of freedom can be ignored, the microscopic state $\mathbf{u}_k$ of each k-particle is identified by position and velocity

$$\mathbf{u}_k = \{\mathbf{x}_k, \mathbf{v}_k\}\,. \tag{2.2}$$

The overall state of the system is given by the state of all particles, a $6 \times N$ dimensional vector, and the modelling of the evolution of the system at the microscopic scale means deriving $6 \times N$ equations for the dynamics of the particles.

An additional difficulty occurs when the domain Ω is bounded; the particles interact with the boundaries of the domain. If Ω contains obstacles, say subdomains $\Omega^* \subset \Omega$ which restrict the free motion, then the particles also interact with the walls of Ω^*.

Consider the relatively simpler case of a fluid in an unbounded domain. In most fluids of practical interest, the state of each particle, atom, or molecule evolves according to the laws of classical mechanics which, for a system of N particles, correspond to the following set of ordinary differ-

ential equations:

$$\begin{cases} \dfrac{d\mathbf{x}_k}{dt} = \mathbf{v}_k \,, \\ m_k \dfrac{d\mathbf{v}_k}{dt} = \mathbf{F}_k(t, \mathbf{x}_k) = \mathbf{f}_k + \displaystyle\sum_{k'=1}^{N} \mathbf{f}_{k'k}(\mathbf{x}_k, \mathbf{x}_{k'}) \,, \end{cases} \tag{2.3}$$

where it has been assumed that interactions depend only on the positions of the particles and that only pair interactions are relevant. $\mathbf{F}_k$ is the force corresponding to the mass m_k acting on each particle and it may be expressed as the superposition of an external field $\mathbf{f}_k$ and of the force $\mathbf{f}_{k'k}$ acting on the k-particle due to the action of all other particles. In general, these forces are regular functions on the phase space, and $\mathbf{f}_{k'k}$ may be allowed to exhibit point discontinuities when the distance between particles is zero. Technically these forces are computed from suitable models of pair interaction potentials.

The evolution of the whole system is obtained by solving system (2.3) with initial conditions

$$\mathbf{x}_k(0) = \mathbf{x}_{k0} \,, \quad \mathbf{v}_k(0) = \mathbf{v}_{k0} \,, \quad k = 1, ..., N \,. \tag{2.4}$$

This approach requires that the system of equations (2.3) can be solved, and that the macroscopic properties of the fluid can be obtained as averages involving the microscopic information contained in such solutions.

However, it is very hard or even impossible, to obtain a numerical solution, without the introduction of suitable simplifications. Indeed, unavoidable inaccuracies in our knowledge of the initial conditions, the large value of N, and the mathematical complexity result in the impossibility of retrieving and manipulating all the microscopic information obtained from (2.3) and (2.4) and contained in $\{\mathbf{x}_k, \mathbf{v}_k\}$ for $k = 1, \ldots, N$.

Indeed, our interest is in extracting the information sufficient to compute the time and space evolution of a restricted number of macroscopic observables such as the following quantities:

Number density: $n = n(t, \mathbf{x})$;

Mass velocity: $\mathbf{U} = \mathbf{U}(t, \mathbf{x})$;

Temperature: $\Theta = \Theta(t, \mathbf{x})$;

Stress tensor: $\mathbf{P} = \mathbf{P}(t, \mathbf{x}) = [p_{ij}(t, \mathbf{x})]$, with $i, j = 1, 2, 3$.

However, recovering the macroscopic observables using the solutions to equation (2.3) is an almost impossible task, not only due to the initial difficulty in dealing with a large system of ordinary differential equations,

but also to the difficulty of computing the averages which correctly define the macroscopic quantities. For instance, the mean mass density $E(\rho)$ should be obtained, for a system of identical particles, by examining the ratio

$$E(\rho) = m \frac{\Delta n}{\Delta \mathbf{x}} \tag{2.5}$$

when the volume $\Delta \mathbf{x}$ tends to zero and the number of particles remains sufficiently large. Obviously, fluctuations cannot be avoided. Additional difficulties are related to the computation of the other macroscopic variables. Thus constitutive relations are needed.

Continuum fluid dynamics is another possible approach; see C. Truesdell and K.R. Rajagopal (2000). It consists of deriving the evolution equations related to the above macroscopic observables under several strong assumptions, including the hypothesis of continuity of matter (continuum assumption). This constitutes a good approximation of a real system only if the mean distance between pairs of particles is small with respect to the characteristic lengths of the system, e.g., the typical length of Ω or of Ω^*. Conversely, if the intermolecular distances are of the same order of such lengths, then the continuum assumption is no longer valid, and a discrepancy is expected between the description of continuum fluid dynamics and that obtained from equation (2.3).

An alternative way to understand the phenomenology of particle interactions and hence their mathematical description is offered by mathematical ***kinetic theory***. Let us consider the interaction of two particles with equal mass in the absence of an external force field. The first one will be called the ***test particle*** with velocity $\mathbf{v}$, while the second one, with velocity $\mathbf{w}$, will be called the ***field particle***.

A simple kinetic model, still related to laws of classic mechanics, is the ***localized collision model***, in which particles move (in the absence of an external force field) along straight lines until a localized collision obliges them to change suddenly directions, like a pair of billiard balls. The model leads to the derivation of the Boltzmann equation.

The collision model, which should be considered an approximation of physical reality, is based on the assumption that two interacting particles with velocities $\mathbf{v}$ and $\mathbf{w}$ follow a straight line until a local collision occurs; after the collision, they assume velocities $\mathbf{v}'$ and $\mathbf{w}'$, respectively, as sketched in Figure 1.

Considering that collisions are assumed to be elastic and that mass, momentum, and energy are preserved, the conservation equations for a collision process of two particles of simple gas $(\mathbf{v}, \mathbf{w}) \mapsto (\mathbf{v}', \mathbf{w}')$ can be

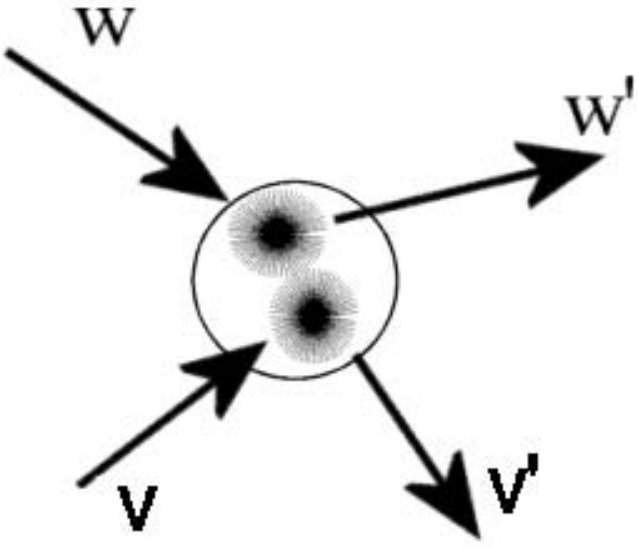

Fig. 1. Test and field particle interaction.

written as follows:

$$\begin{cases} \mathbf{v} + \mathbf{w} = \mathbf{v}' + \mathbf{w}' \,, \\ |\mathbf{v}|^2 + |\mathbf{w}|^2 = |\mathbf{v}'|^2 + |\mathbf{w}'|^2 \,. \end{cases} \tag{2.6}$$

Moreover, conservation of angular momentum can be used to compute the post-collision velocities. In fact, the system (2.6) provides four equations, while six equations are necessary for six scalar unknowns. The solution can be formally written as follows:

$$\begin{cases} \mathbf{v}' = \mathbf{v} + C\,\mathbf{n} \,, \\ \mathbf{w}' = \mathbf{w} - C\,\mathbf{n} \,, \end{cases} \tag{2.7}$$

where C is a scalar quantity and $\mathbf{n}$ is the unit vector in the direction of the axis through the centers of the two interacting particles, bisecting the angle between the relative velocities $\mathbf{q} = \mathbf{w} - \mathbf{v}$ and $\mathbf{q}' = \mathbf{w}' - \mathbf{v}'$. Substituting (2.7) into equation (2.6) and performing some calculations yields

$$\begin{cases} \mathbf{v}' = \mathbf{v} + \mathbf{n}(\mathbf{n} \cdot \mathbf{q}) \,, \\ \mathbf{w}' = \mathbf{w} - \mathbf{n}(\mathbf{n} \cdot \mathbf{q}) \,. \end{cases} \tag{2.8}$$

3 The Distribution Function

As we have seen in Section 2 it appears necessary to look for a model different from those of continuum fluid dynamics or of classical particle dynamics. Boltzmann's idea was to introduce the ***one-particle distribution function***

$$f = f(t, \mathbf{x}, \mathbf{v}) : \quad \mathbb{R}_+ \times \mathbb{R}^3 \times \mathbb{R}^3 \to \mathbb{R}_+ , \tag{3.1}$$

where $\mathbb{R}_+$ means the set $\{t \in \mathbb{R} , t \geq 0\}$. The distribution function, under suitable integrability assumptions, is such that the total number of particles is

$$N(t) = \int_{\mathbb{R}^3 \times \mathbb{R}^3} f(t, \mathbf{x}, \mathbf{v}) \, d\mathbf{x} \, d\mathbf{v} . \tag{3.2}$$

To simplify the notations, we will suppress the integration limits where obvious, e.g., equation (3.2) is written as

$$N(t) = \int \int f(t, \mathbf{x}, \mathbf{v}) \, d\mathbf{x} \, d\mathbf{v} .$$

The knowledge of the above distribution function leads to the computation of the physical quantities needed in a large variety of applications. The Boltzmann equation is an evolution equation for such a distribution. Indeed, if f is known and $\mathbf{v}f$ and $\mathbf{v}^2 f$ are in $L_1(\mathbb{R}^3 \times \mathbb{R}^3)$, then the macroscopic observables can be computed as expectation values of the corresponding microscopic functions. In particular

$$n(t, \mathbf{x}) = \int f(t, \mathbf{x}, \mathbf{v}) \, d\mathbf{v} , \tag{3.3}$$

and

$$\mathbf{U}(t, \mathbf{x}) = \frac{1}{n(t, \mathbf{x})} \int \mathbf{v} f(t, \mathbf{x}, \mathbf{v}) \, d\mathbf{v} \tag{3.4}$$

are, respectively, the ***mass density*** and the ***mass velocity***. The internal energy is given by

$$\mathcal{E}(t, \mathbf{x}) = \frac{1}{2\, n(t, \mathbf{x})} \int \big[\mathbf{v} - \mathbf{U}\big]^2 f(t, \mathbf{x}, \mathbf{v}) \, d\mathbf{v} . \tag{3.5}$$

In equilibrium conditions, for a monatomic gas (of identical particles), the energy can be related, according to Boltzmann's principle, to the temperature Θ,

$$\mathcal{E} = \frac{3}{2}\, k\, \Theta\,, \tag{3.6}$$

where k is the Boltzmann constant. Far from equilibrium it is reasonable to deal with mechanical energy rather than with temperature.

Similar calculations lead to the ***pressure tensor*** with elements

$$p_{ij}(t, \mathbf{x}) = \int (v_i, U_i)(v_j - U_j) f(t, \mathbf{x}, \mathbf{v})\, d\mathbf{v}\,, \tag{3.7}$$

corresponding to the $(i, j)^{th}$ components of $\mathbf{v}$ and $\mathbf{U}$.

Actually, one has to accept that the above kinetic type of modelling only approximates physical reality. For instance, the state of an N-particle gas is statistically described by the N-particle distribution function

$$f_N = f_N(t, \mathbf{x}_1, \mathbf{v}_1, \ldots, \mathbf{x}_k, \mathbf{v}_k, \ldots, \mathbf{x}_N, \mathbf{v}_N)\,. \tag{3.8}$$

The one-particle distribution function is obtained as the marginal density of the N-particle distribution function. A rigorous derivation of the evolution equation leads to a hierarchy of equations, the BBGKY hierarchy, involving all distributions from the first to the last one. Then, an evolution equation for the one-particle distribution function may only be an approximation, however useful, of physical reality.

In particular, the phenomenological derivation of the equation requires the assumption of factorization of the two-particle distribution function of the two particles involved in the collision, the so-called ***molecular chaos assumption***,

$$f_2 = f_2(\mathbf{x}_1, \mathbf{v}_1, \mathbf{x}_2, \mathbf{v}_2) = f_1(\mathbf{x}_1, \mathbf{v}_1) f_1(\mathbf{x}_2, \mathbf{v}_2)\,. \tag{3.9}$$

However, the above assumption is valid only for special initial conditions and short time intervals. Consequently the Boltzmann equation is not rigorously referred to Newtonian mechanics, but is intended as an approximation developed to model large systems of interacting particles.

4 On the Derivation of the Boltzmann Equation

The phenomenologic derivation of the Boltzmann equation is obtained by a continuity equation within the elementary volume $d\mathbf{x}\,d\mathbf{v}$ at the point $\mathbf{x}, \mathbf{v}$ of the six-dimensional phase space, i.e., the space of the physical and velocity coordinates. The above elementary volume contains all particles in $[\mathbf{x},\, \mathbf{x} + d\mathbf{x}]$ with velocity $[\mathbf{v},\, \mathbf{v} + d\mathbf{v}]$. Thus, the time derivative of f in a reference volume $d\mathbf{x}\,d\mathbf{v}$ is equated to the difference between the ***gain*** and ***loss*** terms of the particles which, due to the collisions, enter into the volume and leave it:

$$\frac{df}{dt} d\mathbf{x}\, d\mathbf{v} = (G[f,f] - L[f,f])\, d\mathbf{x}\, d\mathbf{v} = J[f,f] d\mathbf{x}\, d\mathbf{v}\,, \tag{4.1}$$

where the total derivative (the material time derivative) comprises local and convective effects:

$$\frac{df}{dt} = \frac{\partial f}{\partial t} + \mathbf{v} \cdot \nabla_{\mathbf{x}} f\,, \tag{4.2}$$

where the first term denotes the change of f for fixed $\mathbf{x}$ and the second one describes the change of f due to the motion.

To compute gains and losses, one has to determine the total number of collisions per unit time and unit volume. The detailed analysis of this task should include a technical analysis of the mechanics and geometry of the collision processes which goes beyond the scope of this book. Here, referring to the already cited technical literature for details, we briefly recall some of main steps of a phenomenological derivation of the Boltzmann equation.

The total number of collisions per unit time and unit volume is taken to be equal to the total number of field particles per unit volume $(f(t,\mathbf{x},\mathbf{w})d\mathbf{w})$ multiplied by the probability that any of them have a collision. This probability is proportional to the number of test particles per unit volume $(f(t,\mathbf{x},\mathbf{v})d\mathbf{v})$ times the "arrival volume" $(d\mathbf{v}'\, d\mathbf{w}')$. Thus

$$\begin{aligned} &\frac{\text{total number of collisions}}{\text{(unit volume) (unit time)}} \\ &\qquad = \mathcal{W}(\mathbf{v},\mathbf{w};\mathbf{v}',\mathbf{w}') f(t,\mathbf{x},\mathbf{v}) f(t,\mathbf{x},\mathbf{w}) d\mathbf{v}\, d\mathbf{w}\, d\mathbf{v}'\, d\mathbf{w}'\,, \end{aligned} \tag{4.3}$$

where $\mathcal{W}$ takes into account the collision process $(\mathbf{v},\mathbf{w}) \mapsto (\mathbf{v}',\mathbf{w}')$ and is determined from analytical mechanics by solving the collision problem for a given intramolecular force. Moreover, it is a symmetric function,

$$\mathcal{W}(\mathbf{v},\mathbf{w};\mathbf{v}',\mathbf{w}') = \mathcal{W}(\mathbf{v}',\mathbf{w}';\mathbf{v},\mathbf{w})\,. \tag{4.4}$$

This is a consequence of the hypothesis that at equilibrium the number of collisions $(\mathbf{v}, \mathbf{w}) \mapsto (\mathbf{v}', \mathbf{w}')$ is equal to the number of collisions $(-\mathbf{v}', -\mathbf{w}') \mapsto (-\mathbf{v}, -\mathbf{w})$ (symmetry of the equations of classical mechanics under time reversal) and this assumption is also adopted in the nonequilibrium settings. Moreover, the N-particle distribution function, as remarked in the last part of Section 3, is factorized according to the hypothesis of "molecular chaos."

The ***loss term*** takes into account all collisions where a particle with velocity in the range $d\mathbf{v}$ exits this range after the collision. Collisions of this type, occurring in $d\mathbf{x}$ per unit time, are expressed by

$$d\mathbf{x}\, d\mathbf{v} \int\int\int \mathcal{W}(\mathbf{v}, \mathbf{w}; \mathbf{v}', \mathbf{w}') f(t, \mathbf{x}, \mathbf{v}) f(t, \mathbf{x}, \mathbf{w})\, d\mathbf{w}\, d\mathbf{v}'\, d\mathbf{w}' \,. \tag{4.5}$$

The ***gain term*** takes into account all collisions which bring, into a velocity range $d\mathbf{v}$, particles which originally were outside, $(\mathbf{v}', \mathbf{w}') \mapsto (\mathbf{v}, \mathbf{w})$ with all possible $\mathbf{w}$, $\mathbf{v}'$, and $\mathbf{w}'$. The total number of such collisions per unit time is given by

$$d\mathbf{x}\, d\mathbf{v} \int\int\int \mathcal{W}(\mathbf{v}', \mathbf{w}'; \mathbf{v}, \mathbf{w}) f(t, \mathbf{x}, \mathbf{v}') f(t, \mathbf{x}, \mathbf{w}')\, d\mathbf{w}\, d\mathbf{v}'\, d\mathbf{w}' \,. \tag{4.6}$$

Therefore, the collision operator $J[f, f]$, according to the symmetry property of $\mathcal{W}$ discussed above is written as

$$\begin{aligned} J(f, f) = \int\int\int \mathcal{W}(\mathbf{v}, \mathbf{w}; \mathbf{v}', \mathbf{w}') [f(t, \mathbf{x}, \mathbf{v}') f(t, \mathbf{x}, \mathbf{w}') \\ - f(t, \mathbf{x}, \mathbf{v}) f(t, \mathbf{x}, \mathbf{w})]\, d\mathbf{w}\, d\mathbf{v}'\, d\mathbf{w}' \,. \end{aligned} \tag{4.7}$$

As already mentioned, $\mathcal{W}$ is still in a general form and takes into account the mechanics of the collision. To obtain a specific model, one has to give some assumptions on the collision. For a monatomic gas, this expression can be simplified by making some further assumptions about the collision process.

The so-called ***collision kernel*** $\mathcal{B}$ can be introduced. It can be specified by defining the interaction potential of the chosen collision model, and it has to satisfy some general properties: nonnegativity and explicit dependence at most on $\mathbf{n} \cdot \mathbf{q}$ and $|\mathbf{q}|$. For instance, an important collision kernel is the one corresponding to the hard sphere potential.

Denoting with $\mathbb{S}^2_+$ the integration domain of $\mathbf{n}$,

$$\mathbb{S}^2_+ = \{\mathbf{n} \in \mathbb{R}^3 : |\mathbf{n}| = 1\,,\, \mathbf{n} \cdot \mathbf{q} \geq 0\}\,, \tag{4.8}$$

the ***collision operator*** is written as

$$J(f,f) = \int_{\mathbb{R}^3} \int_{\mathbb{S}^2_+} \mathcal{B}(\mathbf{n}, |\mathbf{q}|)[f(t,\mathbf{x},\mathbf{v}')f(t,\mathbf{x},\mathbf{w}') - f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w})]\, d\mathbf{w}\, d\mathbf{n}\,. \tag{4.9}$$

Thus, the ***Boltzmann equation***, in the absence of an external force field, can be written as follows:

$$\frac{\partial f}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f = J[f,f]\,. \tag{4.10}$$

On the other hand, when an external field is applied, particles do not follow straight lines between two successive collisions and their trajectories are determined by laws of classical mechanics. The equation is then written as follows:

$$\frac{\partial f}{\partial t} + \mathbf{v}\cdot\nabla_{\mathbf{x}} f + \mathbf{F}\cdot\nabla_{\mathbf{v}} f = J[f,f]\,, \tag{4.11}$$

where $\mathbf{F} = \mathbf{F}(\mathbf{x})$ is the external positional field acting on each of the identical particles, and the collision operator is the same as above.

We have to point out that the idea behind this balance of losses and gains in the volume element $d\mathbf{x}d\mathbf{v}$ due to free streaming or collisions of particles is that the size of this volume element must be on the one hand so large that the number of particles contained in it justifies the use of statistical methods, and on the other hand so small that the information in it has a local character. In general, these two features are not compatible. Nevertheless, in the cases of practical interest, the molecular size falls in a range of values which are small when compared to those of the volume element $d\mathbf{x}d\mathbf{v}$, while it can be considered microscopic with respect to the observation scale.

5 Mathematical Properties of the Boltzmann Equation

Solving the mathematical problems related to the Boltzmann equation gives the distribution function and consequently the macroscopic observable.

Let us define the ***collision invariants*** as functions such that

$$\int J(f,f)\phi(\mathbf{v})\, d\mathbf{v} = 0\,. \tag{5.1}$$

It can be proved that the following property holds true:

$$\int J(f,f)\phi(\mathbf{v})\,d\mathbf{v} = \frac{1}{4}\int\int\int \mathcal{B}(\mathbf{n},|\mathbf{q}|) \times [f(t,\mathbf{x},\mathbf{v}')f(t,\mathbf{x},\mathbf{w}') - f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w})] \times [\phi(\mathbf{v}) + \phi(\mathbf{w}) - \phi(\mathbf{v}') - \phi(\mathbf{w}')]\,d\mathbf{n}\,d\mathbf{v}\,d\mathbf{w}\,. \quad (5.2)$$

Then the collision invariants correspond to functions ϕ such that

$$[\phi(\mathbf{v}) + \phi(\mathbf{w}) - \phi(\mathbf{v}') - \phi(\mathbf{w}')] = 0\,. \quad (5.3)$$

The ***Boltzmann–Gronwall theorem*** can be proved. This theorem states that the most general form of the collision invariants is

$$\phi(\mathbf{v}) = a + \mathbf{b}\cdot\mathbf{v} + c|\mathbf{v}|^2\,, \quad (5.4)$$

where a and c are constant scalars and $\mathbf{b}$ is a constant vector. The general collision invariant is a linear combination of five elementary collision invariants:

$$\phi_0(\mathbf{v}) = 1\,, \quad \phi_i(\mathbf{v}) = \mathbf{v}_i \quad i = 1,2,3\,, \quad \phi_4(\mathbf{v}) = |\mathbf{v}|^2\,, \quad (5.5)$$

which correspond to conservation of mass, momentum, and energy. In fact, multiplying the Boltzmann equation by ϕ, chosen as above in (5.5), and integrating over the velocities, we have formally:

- Conservation of mass:

$$\int\int f(t,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v} = \textit{constant} = \int\int f(0,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v}\,, \quad (5.6)$$

- Conservation of momentum:

$$\int\int \mathbf{v} f(t,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v} = \textit{constant} = \int\int \mathbf{v}\, f(0,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v}\,, \quad (5.7)$$

- Conservation of energy:

$$\int\int |\mathbf{v}|^2 f(t,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v} = \textit{constant} = \int\int |\mathbf{v}|^2\, f(0,\mathbf{x},\mathbf{v})\,d\mathbf{x}\,d\mathbf{v} \quad (5.8)$$

In order to study some features of irreversibility of the Boltzmann equation it is useful to show that the ***Boltzmann inequality***

$$\mathcal{S} = \int\int J(f,f)\,\ln f d\mathbf{v} \leq 0 \tag{5.9}$$

holds true.

Proof. Let $\phi(\mathbf{v}) = \ln f$ in the expression (5.2); we have

$$4\mathcal{S} = \int\int\int \mathcal{B}(\mathbf{n},|\mathbf{q}|)[f(t,\mathbf{x},\mathbf{v}')f(t,\mathbf{x},\mathbf{w}') - f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w})]$$
$$\times \left[\ln \frac{f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w})}{f(t,\mathbf{x},\mathbf{v}')(t,\mathbf{x},\mathbf{w}')}\right] d\mathbf{n}\,d\mathbf{v}\,d\mathbf{w}\ , \tag{5.10}$$

which can be rewritten as

$$\mathcal{S} = \frac{1}{4}\int\int\int \mathcal{B}(\mathbf{n},|\mathbf{q}|)f(t,\mathbf{x},\mathbf{w}')f(t,\mathbf{x},\mathbf{v}')[1-\mu]\ln\mu\, d\mathbf{n}\,d\mathbf{v}\,d\mathbf{w}\ , \tag{5.11}$$

where

$$\mu = \frac{f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w})}{f(t,\mathbf{x},\mathbf{v}')(t,\mathbf{x},\mathbf{w}')}\,.$$

Due to the property

$$y,z>0 \to (z-y)\ln\frac{y}{z} \leq 0\,, \tag{5.12}$$

inequality (5.9) is true for $f \geq 0$.

∎

The equality sign in (5.9) holds true if $z = y$, thus if and only if

$$f(t,\mathbf{x},\mathbf{v})f(t,\mathbf{x},\mathbf{w}) = f(t,\mathbf{x},\mathbf{v}')f(t,\mathbf{x},\mathbf{w}')\,. \tag{5.13}$$

Taking the logarithms on both sides of this equation, we obtain that $\phi(\mathbf{v})$ satisfies (5.3); thus in particular ϕ can be written, recalling the Boltzmann–Gronwall theorem, in the general form (5.4). Inverting $\phi(\mathbf{v}) = \ln f$ yields

$$f(\mathbf{v}) = \exp(a + \mathbf{b}\cdot\mathbf{v} + c|\mathbf{v}|^2)\,. \tag{5.14}$$

which is the ***Maxwellian***. Thus the functions which satisfy the equation $\mathcal{S} = 0$, i.e., are such that $J(f,f) = 0$, are Maxwellian.

Recalling that mass, momentum, and energy are constant in a system, i.e., (5.6)–(5.8), a natural Maxwellian can be constructed so that its macroscopic variables have exactly those values:

$$M(t,\mathbf{x},\mathbf{v}) = \frac{n(t,\mathbf{x})}{(2\pi\, k\, \Theta(t,\mathbf{x}))^{3/2}} \exp\left[-\frac{(\mathbf{v}-\mathbf{U}(t,\mathbf{x}))^2}{2\, k\, \Theta(t,\mathbf{x})}\right], \tag{5.15}$$

where n, Θ, and $\mathbf{U}$ are the macroscopic observables, density, temperature, and mean velocity, and k is the Boltzmann constant.

An obvious consequence of the inequality (5.9) is the ***H Theorem*** which states that the ***entropy*** functional

$$\mathcal{H} = \int\int f\, \ln f\, d\mathbf{v}\,, \tag{5.16}$$

in the spatially homogeneous situation, is monotone decreasing:

$$\frac{d\mathcal{H}}{dt} \leq 0\,. \tag{5.17}$$

Proof: Multiplying both sides of the Boltzmann equation by $\ln f$ and integrating over the velocities, one has

$$\frac{\partial}{\partial t}\int f\, \ln f\, d\mathbf{v} + \nabla_{\mathbf{x}} \cdot \int \mathbf{v}\, f\, \ln f\, d\mathbf{v} \leq 0\,, \tag{5.18}$$

due to inequality (5.9). In the spatially homogeneous case, this reduces to equation (5.17).

∎

Thus in the spatially homogeneous case, when there is no microscopic flow of $\mathcal{H}$ through the boundaries, $\mathcal{H}$ is a decreasing function in time and, recalling (5.15), it is constant only if f is a Maxwellian, i.e. the source term $\mathcal{S}$ is zero. Thus the entropy is monotone decreasing in time towards the stable equilibrium configuration (equality holds only at equilibrium). Of course in the general case, one has to integrate over the space domain and should take into account the boundary conditions.

This theorem shows the irreversibility of the Boltzmann equation. This is in apparent contrast to the fact that the molecules constituting the gas follow the reversible laws of the classical mechanics: it is due to the probabilistic character of the Boltzmann equation.

6 The Discrete Boltzmann Equation

This section provides an outline of some methods of discretizing classical models of the kinetic theory of gases. A specific model of mathematical kinetic theory is the so-called discrete Boltzmann equation which is based on the discretization of the velocity variable, amounting to the admissibility of only a finite number of discrete velocities.

The effect of the discretized approach is that the original continuous Boltzmann equation, which is an integro-differential equation, is transformed into a suitable set of partial differential equations, each one corresponding to a discrete velocity.

The discrete Boltzmann equation is generally designed to reduce the computational complexity of the original Boltzmann equation and to make it more flexible for modelling. The mathematical theory of discrete kinetic theory was systematically developed in the lecture notes by Gatignol (1975) and by Cabannes (1980), which provide a detailed analysis of the relevant aspects of the discrete kinetic theory: modelling, analysis of thermodynamic equilibrium, and application to fluid dynamics problems. The contents mainly refer to a simple monatomic gas and to the related thermodynamic aspects. After such a fundamental contribution, several developments have been proposed in order to deal with more general physical systems: gas mixtures, chemically reacting gases, particles undergoing multiple collisions and so on, as is documented, for instance, in various contributions edited in Bellomo and Gatignol (2003). The qualitative analysis of the initial value and of the initial-boundary value problem has been an object of continuous interest to applied mathematicians.

The discrete models of the Boltzmann equation are obtained assuming that particles are allowed to move with a finite number of velocities. The model is an evolution equation for the number densities N_i linked to the admissible velocities $\mathbf{v}_i$, for $i \in \mathbf{L} = \{1, \ldots, n\}$. The set $N = \{N_i\}_{i=1}^n$ corresponds, for certain aspects, to the one-particle distribution function of the continuous Boltzmann equation. This model is called the ***discrete Boltzmann equation***.

The formal expression of the evolution equation is as follows:

$$\left(\frac{\partial}{\partial t} + \mathbf{v}_i \cdot \nabla_{\mathbf{x}}\right) N_i = J_i[N]\,, \tag{6.1}$$

where

$$N_i = N_i(t, \mathbf{x}) : \quad (t, \mathbf{x}) \in [0, T] \times \mathbb{R}^3 \to \mathbb{R}_+\,, \quad i = 1, \ldots, n\,, \tag{6.2}$$

with t and $\mathbf{x} \in \mathbb{R}^3$ being the time and the space variables. $J_i[N]$ denotes the binary collision terms

$$J_i[N] = \frac{1}{2} \sum_{jhk=1}^{n} A_{ij}^{hk} (N_h N_k - N_i N_j) \,. \tag{6.3}$$

The terms A_{ij}^{hk} are the so-called ***transition rates*** corresponding to the binary collisions

$$(\mathbf{v}_i, \mathbf{v}_j) \mapsto (\mathbf{v}_h, \mathbf{v}_k) \,, \qquad i, j, h, k \in \mathbf{L} \,, \tag{6.4}$$

and the collision scheme must be such that momentum and energy are preserved. The transition rates are positive constants which, according to the indistinguishability property of the gas particles and to the reversibility of the collisions, satisfy the following relations:

$$\mathbf{A} = A_{ji}^{hk} = A_{ij}^{kh} = A_{ji}^{kh} = A_{hk}^{ij} \,. \tag{6.5}$$

As for the continuous Boltzmann equation, the following definitions can be used:

– A vector $\phi = \{\phi_i\}_{i \in \mathbf{L}} \in \mathbb{R}^m$ is defined to be ***collision invariant*** if

$$\langle \phi \,,\, J[N] \rangle = 0 \,, \quad J[N] = \{ J_{i \in \mathbf{L}} \in \mathbb{R}^m \} \,, \tag{6.6}$$

where the inner product is defined in $\mathbb{R}^m$ and m is the cardinality of the set $\mathbf{L}$. The set of the totality of collision invariants, denoted by $\mathcal{M}$, is called the ***space of the collision invariants*** and is a linear subspace of $\mathbb{R}^m$.

– Let $N_i > 0$ for any $i \in \mathbf{L}$; then the vector N is defined to be ***Maxwellian*** if $J[N] = 0$. Moreover, let $N_i > 0$ for any $i \in \mathbf{L}$; then the following three conditions are equivalent:

i) N is a Maxwellian;
ii) $\{\log N_i\}_{i \in \mathbf{L}} \in \mathcal{M}$;
iii) $J[N] = 0$.

The classical ***H–Boltzmann functional*** is defined as follows:

$$H = \sum_{i \in \mathbf{L}} c_i N_i \log N_i \,. \tag{6.7}$$

The evolution equation for the H–Boltzmann functional can be derived, as in the continuous case, by multiplying the discrete Boltzmann equation by $1 + \log N_i$ and taking the sum over $i \in \mathbf{L}$. It

can be technically verified that the time derivative of the above functional is nonpositive and that the equality holds if and only if N is a Maxwellian.

The above modelling corresponds to discretizing the velocity space into a suitable set of points by linking a number density to each velocity. Several applied mathematicians have attempted in the last decade to design models with an arbitrarily large number of velocities and hence to analyze convergence of discretized models toward the full Boltzmann equation. On the other hand, the specific structure of the model depends on the discretization scheme of the velocity variable. Several technical difficulties have to be tackled and some problems are still at least partially open.

Some specific examples of classical applications are discussed in the literature; see for instance Gatignol (1975). In particular there are available both regular plane models, e.g., the four-velocity model, and three-dimensional models, e.g., the six- and eight-velocity model. Of course many possible generalizations are possible and various applications can be designed corresponding to different types of discretization. Various models are reported in the lecture notes by Bellomo and Gatignol (2003).

Glossary

activation: the process by which morphology and functional activity of an immune system cell is altered (lymphocytes, macrophages, etc.). It is initiated by specific cytokines and various immunologic adjuvants.

angiogenesis: the formation of blood vessels from preexisting ones. It is a normal physiological process in growth and in wound healing, and is the crucial step in the transition from the early stage of tumors to a malignant state.

antibody: a protein which identifies an antigen complex and binds to it; each antibody recognizes a unique antigen that is specific to its target. Antibodies are secreted by B cells and plasma cells in response to infection or immunizations, and neutralize pathogens or prepare them for destruction by macrophages. Antibodies are free floating through the blood as part of the immune system.

antigen: a substance not recognized by the immune system, or recognized as part of a virus or bacterium, that induces an immune response.

antigen-binding site: the region at the surface of the antibody that makes physical contact with the antigen.

antigen-presenting cell (APC): a cell which can recognize pathogen molecular patterns on the surface of foreign microorganisms, typically a dendritic cell or a macrophage. The APC secretes molecules that behave as signals for the activation of T cells. The APC is also activated by the release of particular substances in virally infected cells or in necrotic cell death.

antigen processing: the degradation of antigen proteins into peptides that can bind to MHC molecules for the activation of the T cells.

apoptosis: the programmed death of a cell. Apoptosis occurs when a cell is infected with a virus or damaged beyond repair. The apoptosis can start from the cell itself, from its surrounding tissue, or from a cell that is part of the immune system. If a cell's capability for apoptosis is damaged by genetic mutation, or if the initiation of apoptosis is blocked by a virus, the damaged cell can continue dividing without restrictions, developing into a tumor.

B cells: lymphocytes involved in the acquired immune response. On activation by an antigen, B cells differentiate into cells producing antibody molecules. Each type of B cell has a unique receptor protein on its membrane that will bind to one particular antigen. Plasma B cells secrete free circulating antibodies which bind to the antigen of pathogens, making them easier targets for phagocytes, while memory B cells are specific to the antigen(s) encountered during the primary immune response.

basophil: the least common of the white blood cells. Basophils release inflammatory substances and are an important source of a specific cytokine, interleukin-4, critical in the production of IgE antibody by the immune system.

binding: a biological process that allows the linking of the specialized immune cell to the antigen complex.

bone marrow: the tissue comprising the center of large bones, where new blood cells are produced. It contains two types of stem cells: hemopoietic cells, which produce leukocytes, erythrocytes, and platelets, and stromal cells, which produce fat, cartilage, and bone. The bone marrow is the site of B cells' development in mammals and the source of stem cells which, upon migration to the thymus, produce T cells.

cell: the structural and functional unit of living organisms. All organisms are composed of one or more cells; all cells come from preexisting cells; all vital functions of an organism occur within cells; cells contain the hereditary information necessary for regulating cell functions and for transmitting information to the next generation of cells. Each cell is a self-contained and self-maintaining entity: it can take in nutrients, convert these nutrients into energy, carry out specialized functions, and reproduce as necessary. Each cell stores its own set of instructions for carrying out each of these activities.

cell-mediated immunity: immunity activated when a cell is infected by a virus or shows cellular heterogeneity. The cell-mediated immunity is performed by lymphocytes.

chemotaxis: a bio-chemical process activated by specific proteins of the complement system and lymphocytes: it is the attraction of a large number of phagocytic cells to the area of the detected infection.

clonal selection: the proliferation of antigen-specific lymphocytes in response to antigenic stimulation. The new lymphocytes then differentiate into antigen-specific effector cells and memory cells.

complement system: the group of proteins involved in immune response. The antigen–antibody complex starts the complement cascade, a series of reactions which end with the membrane perforing of the offending host.

cytokine: an extra-cellular protein, made by cells that affect the behavior of other cells. Its main role is mediating cell–cell communication, thus activating or inhibiting the proliferation of specific target cells.

dendritic cell: a tissue resident cell, part of the immune system. It derives from monocytes, which, depending on the right signal, can turn into dendritic cells or macrophages. Its main role is activating a helper T cell which has never encountered its antigen before.

diapedesis: the movement of blood cells from blood into the tissues.

endothelium: a sheet of thin, flat cells (called endothelial cells), which are the lining between the interior surface of blood vessels and circulating blood.

epitope: the region of an antigen which is recognized and bound by an antibody or by a T cell receptor.

gene: a segment of DNA which cells transcribe into RNA and translate, at least in part, into proteins. The genes are inherited from parents during reproduction, and encode information essential for the construction and regulation of proteins and other molecules that determine the growth and functioning of the organism.

humoral immunity: immunity that involves the production of specific antibodies (IgM and IgG) by the B cells.

immunoglobulin: see **antibody**.

leukocyte: see **white blood cell**.

lymphocyte: a cell of the immune system which is found in the blood and in the lymphatic system. Lymphocytes are B cells, T cells, and natural killer cells.

lymphoid organ: a specialized organ of the organism where the adaptive immune response is initiated.

macrophage: a large mononuclear blood cell devoted to clearing foreign substances which are not recognized as healthy tissues. It plays a crucial role in innate immunity and, as an effector cell, in humoral and cell-mediated immunity; moreover, it presents antigens of the destroyed substance on its surface, thus activating the creation of specific antibodies.

major histocompatibility complex (MHC): a large DNA region which contains many genes involved in immune system response; among others, the genes that encodes cell-surface antigen-presenting proteins. The proteins are displayed to the receptors of T cells, and, if they are recognized as "nonself" (antigens), the immune response is activated. T cells require the presentation of the antigens (while the B cell receptors bind to antigens directly); the task is performed by MHC molecules and MHC proteins.

mast cell: part of the immune system, it is a resident cell of connective tissue; it is very similar, in shape and functions, to a basophil.

mitosis: the process of chromosome segregation and nuclear division that follows replication of the genetic material in eukaryotic cells. It is accompanied by cell division, and each daughter cell receives a complete copy of the parent cell genome.

monocyte: a white blood cell which, after a short time in the bloodstream, migrates to tissues and matures into a macrophage.

necrosis: the death of cells due to chemical or physical injury, as opposed to apoptosis.

neutrophil: the most common leukocyte, it is an active phagocyte, capable of only one phagocytic event. Being highly motile, neutrophils quickly congregate at the focus of infection, attracted by cytokines expressed by activated endothelium, mast cells, and macrophages.

pathogen: a microorganism that can cause disease when it infects a host.

phagocytosis: a process in which specialized immune system cells (neutrophils, eosinophils, basophils, and monocytes) engulf pathogen cells and then destroy them by cellular digestion. The cells may ingest large objects, such as prey cells or dead organic matter, folding their membranes around them. These are sealed off into large vacuoles and digested.

plasma cell: the output of the activation and division of B cells in the humoral immune response. The plasma cells produce and secrete free antibodies.

presentation: the process by which a cell, displaying on its surface antigens of a foreign host, activates the T cells for the immune response; the cell is called the "antigen-presenting cell."

protein: a complex, high–molecular weight organic compound, which consists of amino acids joined by peptide bonds. Proteins are essential to the structure and function of all living cells and viruses, and are one of the classes of bio-macromolecules, the primary constituents of living matter.

repertoire: the total variety of antibody types in the body of an individual.

stem cell: a primal, undifferentiated cell which has the potential to produce any kind of cell. There are three types of stem cells: totipotent, pluripotent, and multipotent (or unipotent). A single totipotent stem cell can grow into an entire organism. Pluripotent stem cells cannot grow into a whole organism, but they are able to differentiate into different types of cells. Multipotent stem cells can only become certain types of cells (blood cells or bone cells).

T cells: a subset of lymphocytes. The main types of T cells are as follows:
• cytotoxic T cells (CD8+) have on their surfaces antigen receptors that can bind to fragments of antigens displayed by the molecules of virus-infected cells and tumor cells
• helper T cells (CD4+) proliferate to activate many other types of cells which act more directly in the response
• suppressor T cells turn off the immune response once an antigen has been eliminated from the body
• regulatory T cells help to prevent the activation of self-reactive lymphocytes that destroy the body's own cells.

thymus: the lymphoepithelial organ where the T cells mature.

variable region: the terminal chain of an antibody or a T cell receptor. The antigen-binding site is in the variable region.

virus: a pathogen agent, composed of a nucleic acid genome enclosed in a protein, which can replicate itself only in a living cell.

white blood cell: an immune system cell, circulating in the blood and in the lymphatic system, which can be recruited into a tissue when needed. The major types of white blood cells are as follows:
• granulocytes (neutrophils, basophils, and eosinophils) active in phagocytosis and able to release inflammatory substances;
• lymphocytes: B cells, T cells, and natural killer cells;
• monocytes, which are involved in phagocytosis as are the neutrophils, and present pieces of pathogens to lymphocytes so that an antibody response may be activated.

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