

Multiscale Modelling of Cellular Systems in the Competition between Tumor and Immune System

NICOLA BELLOMO

Department of Mathematics, Politecnico of Torino

Corso Duca degli Abruzzi 24, 10129, Torino, Italy

`nicola.bellomo@polito.it`

This Lecture deals with the analysis of multiscale modeling of cellular systems related to the competition at the cellular level between tumor and immune cells. The final objective is the development of a bio-mathematical theory based on a development of methods of mathematical kinetic theory for large systems with internal biological structure.

Indeed, the scientific community is aware that the great revolution of this century is going to be the mathematical formalization of phenomena belonging to the living matter, while the revolution of the past two centuries was the modeling of the behavior of the inert matter. Hints to develop a mathematical theory of biological systems can be recovered in various papers authored by scientists operating in the field of molecular and cellular biology. For instance, an interesting paper by Hartwell et alii [HA] deeply analyzes some concepts related to the above topic:

Although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences.

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.

More important, what really distinguish biology from physics are survival and reproduction, and the concomitant notion of function.

A specific hint recovered in [HAa] is that a system in biology cannot be simply observed and interpreted at a macroscopic level. A system constituted by millions of cells shows at the macroscopic level only the output of the cooperative and organized behaviors which may not, or are not, individually observed. A backward excursus to nonequilibrium statistical mechanics and kinetic theory to multiparticle systems is immediate. Indeed the mathematical kinetic theory is based on the essential idea that although particles cannot be individually observed an analysis of their statistical behavior may lead to the description of macroscopic variables also in conditions far from equilibrium.

Then a question can be naturally posed: Is it possible dealing with multicellular systems by suitable development of the methods of nonequilibrium statistical mechanics? Applied mathematicians are already engaged by the above fascinating idea and are already tackling the main difficulty

of this approach: the description in mathematical terms of the organized, somehow intelligent, behavior of the several cells of a biological system.

A specific and challenging field of investigation looks at the onset and development of cancer cells in the environment of a vertebrates well as to several related phenomena such as the competition with the immune system, aggregation of cells in solid forms, interactions with the outer environment with generation of angiogenesis phenomena, and so on.

It is plain that cells do not follow rules of Newtonian mechanics. Indeed, cells organize their dynamics and play a collective game which may end up either with the blow up of cells or their destruction due to the action of the immune defense. The paper by Greller, Tobin and Poste [GRa] provides some significant hints addressed to the description of multicellular systems by equations of statistical mechanics:

Tumor cellular populations are characterized by progression distributions, progression velocities and progression dependent growth rates. Major genetic changes after the tumor dynamics as each sub-population moves further away from genetic normality.

The modeling paradigm provides conceptual foundation not only for modeling progression and heterogeneity phenomena, but acts as a language for describing their complex phenomena.

To the degree that a model is an adequate representation of biological reality, it can be used to perform "experiments" that are impossible or impractical in the laboratory. The danger of discovering phenomena that are artifacts of the model must be always scrutinized, but the properties of a model may also foretell genuine biological situations that are yet to be observed.

Referring to general bibliography, the interested reader is addressed to the books edited by Adam and Bellomo [AB], and by Preziosi [PR], which report about the various mathematical approaches developed in recent years. The reader can immediately identify that the passage from the contents of [AB] to the one of [PR] clearly shows the fast evolution of mathematical methods applied to cancer modeling related to the immune competition and therapeutical actions.

While all scientists are aware that mathematics cannot solve problems of immunology and medicine, it seems that a useful support to experiments and quantitative analysis of external actions to control the neoplastic growth can be developed by applied mathematics. Specifically, models and simulations of particular behaviors of the immune competition can reduce the amount of experiments which are necessary for therapy developments. As a final target, an immune-mathematical theory can be developed in order to provide a detailed description of the evolution of the system hopefully focusing phenomena which may be difficult to observe experimentally.

Starting from the above remarks, this Lecture deals with the development of a mathematical theory based on a suitable generalization of the equations and methods of the kinetic theory to the modeling of the dynamics of large systems of interacting populations in a vertebrate. These models describe the evolution of the statistical distribution, for each cell population, of the microscopic state of the cells. Applied mathematicians have already been involved in the development of the above mathematical theory as it is documented in the pioneer paper by Bellomo and Forni [BF], further developed by various authors, as it documented in the review paper [BB].

The contents are developed according to the following index:

- Phenomenological description of the physical systems which will be mathematically dealt with this Lecture. The description is proposed having in mind a multiscale mathematical description of

a system constituted by a large number of interacting cells with special attention to the onset and growth of tumor cells which may be contrasted by immune cells and therapeutical actions.

- Mathematical representation of the above system. This means dealing with the selection of the variables which, in the mathematical model, have to represent the overall state of the complex system we are dealing with. It is a delicate problem considering that one has to reduce a large number of variables into a limited number of them with the target of providing an effective representation without generating computational problems which may not be practically handled. The representation is addressed to all scales characterizing the system, while the mesoscopic description based on the methods of the kinetic theory will be selected as the reference scale.
- Modeling of microscopic interactions between cells of the various interacting populations and derivation of kinetic type equation for a large system of interacting cells in the spatially homogeneous case.
- Qualitative and computational analysis of the above class of mathematical models. Some sample simulations visualize the outputs of the competition and of the influence of the biological and therapeutical parameters on the above asymptotic behavior.
- Generalization the above class of models to a description for models with a space dynamics. This mathematical representation will be then used to develop a suitable asymptotic theory to derive macroscopic equations toward the representation of the system in its condensed phase which is reached when tumor cells aggregate into a solid form.
- Research perspectives to be developed having in the background the above contents with special attention to the development of a new statistical mechanics theory for large systems with internal structure, and to the multiscale modeling of new therapies.

References

- [AB] J. Adam and N. Bellomo, Eds., **A Survey of Models on Tumor Immune Systems Dynamics**, (Birkhäuser, Boston, 1996).
- [BF] N. Bellomo and G. Forni, Dynamics of tumor interaction with the host immune system, *Math. Comp. Modelling*, 20, 107–122, (1994).
- [BB] Bellomo N., Bellouquid A. and De Angelis E., Lecture notes on the modeling of the immune competition by generalized (Boltzmann) models, *Math. Comp. Modelling*, 37, 65–86, (2003).
- [GR] L. Greller, F. Tobin, and G. Poste, Tumor heterogeneity and progression: conceptual foundation for modeling, *Invasion and Metastasis*, 16, 177–208, (1996).
- [HA] H.L. Hartwell, J.J. Hopfield, S. Leibner, and A.W. Murray, From molecular to modular cell biology, *Nature*, 402, c47–c52, (1999).
- [PR] L. Preziosi, **Modeling Cancer Growth**, (CRC-Press - Chapman Hall, Boca Raton, 2003).