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Hybrid Modelling in Cell Biology

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Hybrid modelling is classically defined as the coupling of a continuous approach with a discrete one, in order to model a (complex) phenomenon that cannot be described in a standard homogeneous way. This is often the case with multiscale phenomena, where the most macroscopic part usually have a continuous nature (chemical fields, concentration of populations, *etc*) whereas the microscopic part reveals the discrete nature of its elements (particles, individuals, *etc*). Consequently, hybrid models usually take the form of a system of partial differential equations (PDEs, *e.g.* for reaction-diffusion equations), or a system of ordinary differential equations (ODEs, *e.g.* for kinetics reactions), coupled with an individual based model, such as a cellular automaton (CA) or an agent-based model (ABM) both operating from a set of either deterministic or stochastic rules. In a wider sense, hybrid modelling corresponds to any mixed approaches and this includes, for example, the coupling of deterministic and stochastic models which can either be discrete or continuous.

Back to the nineties, mathematical biology was mostly dominated by the use of PDEs and ODEs, *i.e.* continuous models of equations. The rise of discrete approaches occurred from this period and it coincides with the evolution of processors and the resulting computing capabilities of desktop computers that have permitted to simulate scientifically relevant discrete models. The shift from pure mathematical approaches (mostly continuous) to more computational approaches (mostly discrete) is observed from those years, and correspond to the emergence of a still growing number of hybrid models. We observe that as a consequence mathematical biology has, through the recent years, been overwhelmed by computational biology.

Multiscale modelling, and hence the development of hybrid models, was especially stimulated in the context of systems biology. This consists in studying a phenomenon as a whole, requiring the integration of the spatial scales from molecules (nanometre) to organs (centimetre) and temporal scales from reaction kinetics (microsecond) to developmental scales (months to years), rather than considering the phenomenon at the different scales independently, which would provide too little insights and make no sense in modern biology. In cell biology, hybrid modelling has permitted to reach a higher level of understanding between experimentalists and theoreticians, since the level of abstraction in the discrete part of the models is often lower. It usually consists in the definition of a set of rules that are based on direct experimental observations or measurements. It then makes it easier to compare both qualitatively and

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quantitatively experimental and simulation results. Since discrete models are in principle not amenable to mathematical analysis - in terms of identifying solutions unicity, stationary states, stability and bifurcations - alternative techniques are used to ensure the robustness of the results. Those techniques, mostly taken from statistics, are similar to those applied to the real experimental sets of data.

This review is specifically dedicated to hybrid models in cell biology and essentially concern cell migration and some aspects of cell differentiation. More than only presenting new hybrid model applications, this issue integrates some papers that express the growing concern for the development of new techniques, which better integrate the different scales, which provide an increased control on the system and which give some new means to analyse the results.

To ensure rapid publication in the electronic form, some of the papers of this special issue were reproduced on line before all papers were received. This implies that the order of the papers is not completely coherent. However, we suggest to the interested reader to read the papers in the following and more logical order.

As the opening of this special issue, we suggest the reader to start with the review on computational models of sprouting angiogenesis and cell migration by Heck, Vaeyens and Van Oosterwyck [6]. The review is a very good illustration of the numerous hybrid approaches used to model this fundamental biological processes. In particular most models combine discrete modelling of individual cells with continuous modelling of the extracellular matrix to highlight the role of various molecular factors involved in guidance cues or in mediating cell-cell interactions. This review particularly aims at stressing the still underestimated role of mechanics on the overall angiogenic process.

As a response to this demand, the paper by Stéphanou, Le Floc'h and Chauvière [7] presents a hybrid model of angiogenesis that specifically tests the importance of mechanical cues driving cell migration in angiogenesis. In this hybrid model cells are discrete elements that generate traction forces on the extracellular matrix which is considered as a homogeneous elastic medium whose rigidity (Young's modulus) can be locally altered by cell degradation. The respective roles of the cell traction force intensity and extracellular matrix rigidity on cell migration and hence on the resulting vascular networks, are the main focus of this paper.

Although individual cell migration was already considered in the two previous papers in the context of angiogenesis, the next three papers are devoted to cell migration, but this time in a context of populations.

The paper by Colombi, Scianna and Preziosi [1] presents a measure-theoretic approach to model the dynamics of a cell population with a finite number of cells. The approach consists in using a time-evolving probability measure describing the overall cell population rather than considering individual cell paths characteristics. The strength of this new approach is that there is no need to make *a priori* assumptions on the number of cells, since the modelling framework remains valid across all levels of representation. Such theoretical framework is therefore a crucial tool to address a vast range of multiscale issues. The authors present different examples that illustrate the potential of their framework and highlight the importance of the scale on the systems dynamics. They also show how this framework is well suited to describe multiple cell populations involving different scales and apply it to model the interaction of inactivated cell colony, described as continuum, with a small number of activated cells, reproduced with a discrete viewpoint. This hybrid continuum-discrete description implemented in the two-population cell system appears as very promising to model many biological and biomedical problems.

Another new theoretical modelling approach, to describe cell population dynamics, is presented in the paper by Guerrero and Alarcon [4]. The paper presents a methodology to formulate stochastic multiscale models in this context, as well as asymptotic and numerical methods for analysing the models. The different level of biological organisation considered are here related to the different time scales. The stochastic model couples cell population and intracellular dynamics *via* the level of oxygen. In this way, the cell-cycle rate depends on the level of oxygen and this determines the birth rate of the cells, based on a mean-first passage time approach. The progression of the cell into its cycle is modelled using standard chemical kinetics equations. The stochastic dynamics of the population of cells is formulated in terms of

an age-structured Master Equation. The aim of the paper is to address the issue of noise, by proposing a framework that provides a mean to formulate and analyse stochastic multiscale models.

The third and last paper devoted to cell population dynamics, especially focus on the comparison of different models of cell-density dependent migration strategies. Specifically, a lattice-gas cellular automaton (LGCA) is used to model two opposite strategies depending on cell density. In the first strategy, cell motility increases with the cell density whereas in the second strategy, the motility decreases as the cell density increases. A mean-field approximation is then used to quantify the corresponding spreading dynamics at the cell population level. Simulations of the derived mean-field partial differential equation corresponding to a degenerate diffusion equation are then compared with the LGCA dynamics for the different migration strategies and reveal a good agreement for specific parameter regimes.

The remaining two papers that form this issue present some applications of hybrid modelling related to blood hemodynamics and to hematopoiesis *i.e.* red blood cells differentiation, respectively.

The paper by Tosenberger, Bessonov and Volpert [2], investigates through a hybrid model, the influence of fibrinogen deficiency on clot formation. The model is based on the method of Dissipative Particle Dynamics to describe both platelets suspension and the plasma flow. The regulatory network responsible for blood coagulation is, in the other hand, represented by a system of partial differential equations. The simulations performed, specifically investigate the influence of the initial level of fibrinogen and of the fibrin production rate on the clot formation in flow.

Still on a blood-related subject, Eymard and Kurbatova [3] present multiscale hybrid models of hematopoiesis focusing on particular lineage leading to erythrocytes, *i.e.* red blood cells, and megakaryocytes, *i.e.* cells of the bone marrow responsible for the production of the previously mentioned platelets. Intracellular regulatory networks that determine the cell fate are described with ordinary differential equations, those networks can be influenced by the biochemical substances in the matrix modelled with partial differential equations, whereas the cells are considered as individual objects. The integration of the cells spatiality, enabled by the use of a discrete representation for the cells, allows the authors to show the importance of cell movement and positioning in cell choice between self-renewal, differentiation and apoptosis.

The seven papers that compose this special issue gives a large overview of different hybrid modelling methods. It will soon become pointless to make special issues on hybrid modelling since it is about to be the norm in biological and biomedical modelling, so it was just about time we did it.

We would like to conclude this short introduction by acknowledging the authors for contributing in this special issue. We are also very grateful to all the reviewers for all their time and efforts.

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