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Multiscale models for biological systems

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ABSTRACT

Life, amazingly rich in diversity of shapes and functions, explores the limits of extreme complexity in nature. In this review we shall discuss in general terms the use of multiscale mathematical and computer models to study the dynamics of biological systems. These models permit integration of the rapidly expanding knowledge concerning the molecular basis of biology and its complex, nonlinear relationship with the emerging shapes and functions of cells, tissues and organs in living organisms.

1. Introduction

Mathematical modeling of biological systems has a long and fruitful history. A large number of discrete, continuous, and spatially explicit models were designed for the description of subcellular systems, physiological dynamics, developmental and population biology. Almost always, these traditional models are focused on single biological scales.

In the last few decades, the biology came into a new age: the era of "omics" [1]. The advent of various high-throughput experimental technologies produced systems-level measurements for virtually all types of biomolecules and provided unprecedent views of cells working. Mainly, these large-data set begin to guide our efforts to integrate all the facets of biology, from the molecular scale to the whole organism level. Such an integrative agenda demands for new modeling approaches in which multiple scales are considered at once. The aim of this review is to discuss some of the multiscale models recently proposed to investigate relevant biological problems.

2. Multiple scales in biology

The hallmarks of life are self-organization and self-reproduction. In all multicellular organisms, self-organization extends from supramolecular structures at the subcellular scale to the tissue and organ levels. This hierarchy is shown in Fig. 1. A myriad of small molecules, mainly proteins, nucleic acid, and phospholipids, are self-assembled by the electromagnetic interaction in non-covalent supramolecular structures. Ribosomes, chromatin, filaments and tubules, vesicles and membranes, molecular motors and catalysts comprise all the organelles and engage the intricate networks of chemical reactions operating inside the cell. The ordered dynamics of the cell (or simply, its physiology) emerges from a combination of complex stereospecific interactions (deterministic self-assembly), that occur even at thermodynamical equilibrium, and a striking variety of dynamical interactions between molecules that require energy dissipation (self-organization) [2]. The spatial scale of cellular morphogenesis lies between the limits of 1 to 100 μm, far beyond the effective range of electromagnetic forces that are strongly screened in an aqueous medium. Hence, in addition to self-assembly, the formation of large-scale supramolecular cellular structures requires the differential activation of genes, in time and space. Cell morphogenesis is also the result of cell physiology.

At the next level, the cells integrate themselves into tissues through cell–cell adhesion and communication structures and the adhesion to surrounding extracellular matrices (ECMs) that are secreted by themselves and self-assembled by covalent (disulfide) and non-covalent (hydrogen) bonds [3].

Finally, various tissues arrange themselves into organs, many organs composing systems and apparels of an organism. Clearly, processes for pattern formation able to distribute differentiated cells in appropriate three-dimensional structures in space and time are required. At these levels, self-organization progress through Turing-like mechanisms [4]. In such a chemical morphogenesis scenario, different regulatory genes are switched on in distinct places, and, by their expression, develop different organs.

Summarizing, living organisms are organized in multiple, interrelated scales that no single one can be fully considered in isolation from the others. Indeed, molecular signals from the outside can elicit

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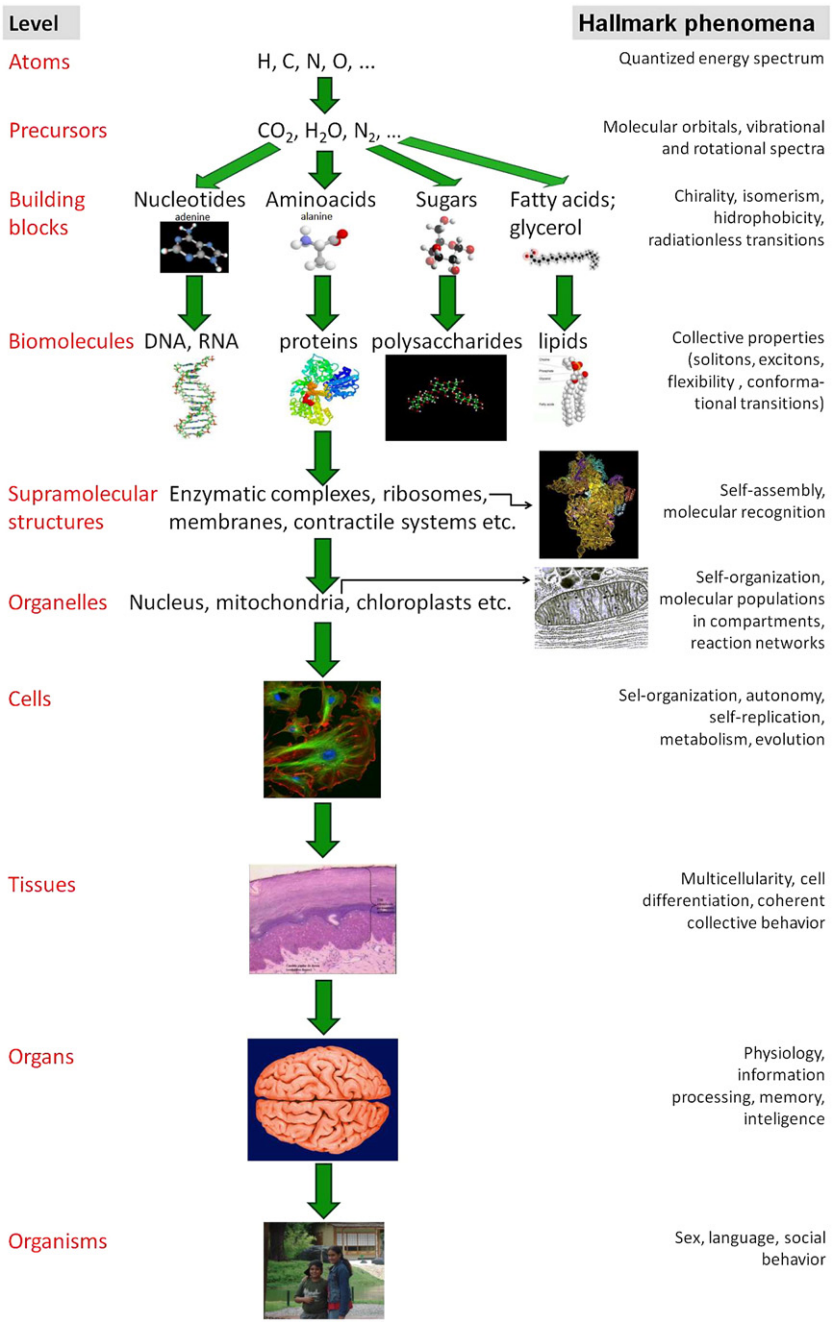

Fig. 1. The hierarchy of life from atoms to living organisms. New phenomena emerge at each upper level that cannot be seen at lower ones. Information flows both up and down these scales. This hierarchy connects to the hierarchy of inanimate matter through DNA and RNA macromolecules. They constitute the genome of all living systems, controlling their maintenance, replication and evolution.

changes in the cell metabolism and gene expression pattern; cells acquire identity from contact with other cells and ECMs; tissues are delineated and integrated with other tissues by specialized ECMs; and molecules carry messages from organ to organ. The time scales involved vary from seconds (for cell signaling) to years (for organism development and life span), and the spatial scales range from nanometers (for protein–DNA interactions) to meters (for nerve impulse propagation).

3. From biomolecules to cells

Fundamentally relevant biological processes start at the macromolecular level. Examples are protein folding, nucleic acid packaging and membrane remodeling. Such phenomena evolve on length and time scales ranging from 10 nm to tenth of microns and from micro to milliseconds. However, those processes are strongly coupled to atomic and/or molecular dynamics (e. g., fluctuations in side chain conformation) occurring at Angstrom length and picosecond time scales. Hence, the analysis of biomolecular structure formation and self-assembly of supramolecular complexes through a purely molecular dynamics (MD) approach is neatly unfeasible. Indeed, MD simulations involving many atoms reach at most nanosecond time and nanometer length scales [5].

In order to investigate the mesoscopic to nearly macroscopic dynamics that are critical to complex biomolecular systems, a variety of multiscale methods are currently being developed [6]. Essentially, these methods connect high-resolution atomistic models at small scales with coarse-grained representations at large scales in which particles are groups of molecules or even parts of the concerned

structures (e. g., one turn of a double helix) [7]. The coupling of the course-grained and atomistic-level models represents the crucial step in these multiscale approaches. It determines the way in which one level affects the other, i.e., how the information is transferred across various length and time scales. In general terms, three alternatives are used: (1) coarse-grained force fields are systematically derived from atomistic MD simulations through different methods such as reverse Monte Carlo [8] or "force matching" [9,10]; or (2) knowledge-based potentials are used as, for instance, Gō-type potentials that produce funnel pathways for protein folding [11–13]; or (3) the entire systems are described through elastic network models in which the biologically significant fluctuations are collective modes of these elastic materials [14–16].

Nowadays, multiscale approaches associated to enhanced computer power allow the simulation of biosystems of relevant length and time scales. Recent applications include modeling of DNA packaging into viral capsides [7], nucleosomal array folding [17], monomeric binding in homodimeric proteins [18••], folding and stability of β-sheet complexes [19], confining effects of chaperonin cages on the protein folding kinetics [20••], lipidic bilayer, micelles and vesicles formation [8], structural dynamics of protein–DNA complexes[21], movements of the ribosome [22] and of tRNA in ribosomal bound structures [23].

As can be inferred from this short list of applications, various multiscale studies have focused on the self-assembly of supramolecular structures and provided valuable insight into the interactions among proteins, nucleic acids and lipids. However, a quantitative model of the entire cell is yet a distant goal. Indeed, individual proteins carry out their function in complex networks of interacting macromolecules [24•]. Of special significance are the regulatory cascades in which membrane receptors stimulation triggers the assembly of signaling complexes on receptors down to the formation of transcriptional complexes that bind on DNA, regulating gene expression. In feedback, the outcomes of cell signaling lead to cytoskeletal reorganization, membrane remodeling, sequential transitions in the cell cycle and so on, thereby controlling central events in several physiological processes, such as cell metabolism, motility, migration, division, and differentiation.

At the level of metabolism (length and time scales of micrometer and second, or longer), the complex spatial and temporal dynamics of signaling pathways are modeled either through continuous (differential equations) [24•,25•] or discrete (cellular automata) [26] dynamical systems. In a multiscale approach, the ligand binding constants, reaction rates, diffusion coefficients and bound-states lifetimes parameterizing these dynamical systems are, in principle, determined by the structure and surface properties of the biomolecules and their macromolecular complexes. In turn, the network dynamics changes its own topology, consequently the cellular environment, protein synthesis and degradation, phosphorylation and dephosphorylation. So, self-organization and assembly of the macromolecules (protein folding, protein–protein docking, rearrangement upon ligand binding or after biochemical reactions) also change, affecting the parameters of the dynamical systems. Information moves both up and down the molecular and cellular scales.

4. From cells to organs

Biological tissues are complex composite materials. Neither the detailed microscopic description of million of cells nor the absolute negligence of subcellular effects represents an adequate approach to explain how these tissues and organs work. Again, multiscale methods seem to be appropriate tools to quantitatively explore functionality from the levels of gene to the physiology of organs and systems. Multiscale modeling the heart firmly confirms this point [27]. In this case, there are both detailed experimental information at the cellular level and reliable models of all the main types of cardiac myocytes and of the three-dimensional anatomy of the whole organ.

The main physiological feature of cardiac cells is their ability to form and transmit action potentials. A multiscale model approach [28••] successfully explains the physiology of ventricular action potentials. At the subcellular scale, the model assumes that ion channels stochastically transit between open, closed and inactive states corresponding to their discrete structural configurations. At the cell level, the rate of change of the membrane potential is described by a Hodgkin–Huxley type formalism [29] for the total ionic current associated to ion channels, pumps and exchangers, as in the Lou–Rudy model [30]. Thus, in one hand, the ventricular action potential at the cellular level is determined by the ionic currents through all the ion channels operating at the subcellular scale. On the other hand, since the dynamics of an ion channel is controlled by voltage dependent transition rates between its different conformations, the global cell response influences the subcellular level. Using this multiscale modeling strategy, it was possible to integrate ion channels (normal or mutant) into the whole cell and study how genetic defects lead to cardiac arrhythmias [27,28••], such as congenital long-QT syndrome due to a genetic mutation in the SCN5A gene [31].

Concerning the organ level, multiscale models for heart dynamics attempt to integrate cellular electrical activation, soft tissue mechanics, and ventricular and coronary fluid mechanics [32••]. Electrical activation processes are described in terms of Hodgkin–Huxley-like equations for the time-dependent gates controlling the flow of ions across the cell membrane, as mentioned in the preceding paragraph. Tissue models involve either discrete cells [33] or a continuous (syncytium) [34] ruled by partial differential equations coupling the transmembrane and the extracellular potentials. The myocardium is modeled as an incompressible elastic solid whose mechanical behavior is defined through constitutive laws specifying the relationship between active forces developed by cardiac myocytes and strains, strain rates, and strain history [35]. Finally, blood flow and the coronary circulation are governed by the Navier–Stokes equations [36]. The major challenges are imposed by moving boundary conditions (e.g., the ventricular endocardial surfaces), the intricate motion of the valve leaflets which plays a major role in vortex formation, and the coupling of blood pressure and velocity fields to the viscoelastic properties of arterial and venous blood vessel walls.

These multiscale models are now able to provide rather accurate reconstructions of, for instance, the spread of the electrical activation wavefront in the heart or the coronary circulation. Furthermore, they become valuable tools to help the design of new medical devices such as ventricular assist devices [37] and bioprosthetic and mechanical heart valves [38]. However, new structural and physiological features as, for instance, the sinus node, atrium, metabolic and signal transduction pathways, need to be incorporated in these models before significant progress can be made in supporting clinical diagnostic and drug discovery, since diseases and therapeutic drugs act at the level of proteins. Finally, multiscale simulation is now being done for a wide range of organs and systems such as the lung and the respiratory system [39], kidney [40], musculoskeletal system [41], and brain activity [42].

5. From models to therapies

Despite the extensive information on the genetic and molecular basis of diseases currently available, the integration of this information into the physiological environment of the functioning cell and tissue remains a major challenge. In the previous section, it was mentioned how mathematical models help us to meet this challenge in the context of cardiac excitation and arrhythmia. In turn, this section illustrates how multiscale modeling might be complementary (maybe necessary) tools to understand cancer growth and improve its therapy.

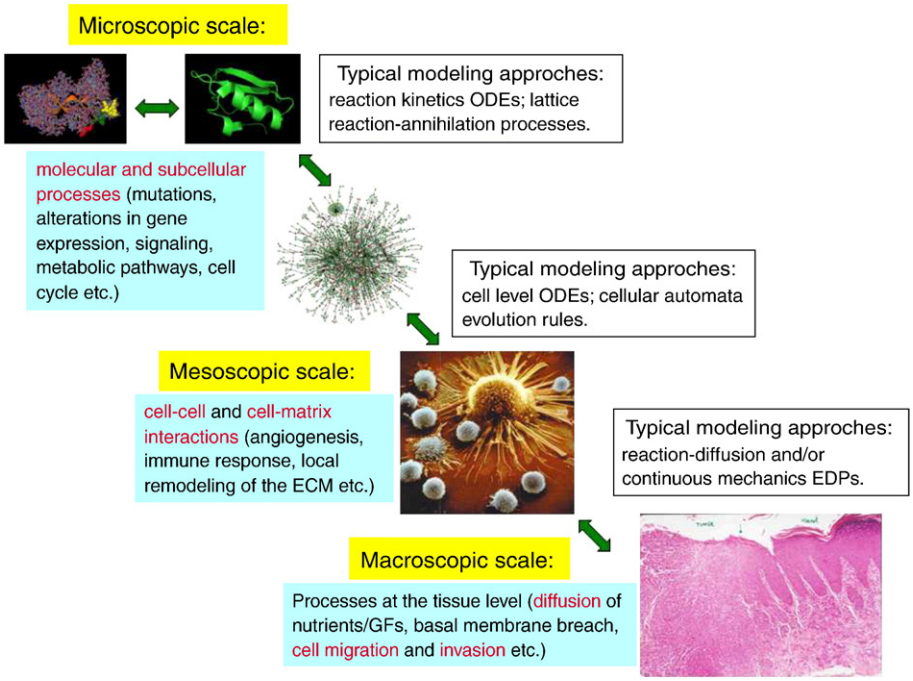

Fig. 2. Hierarchy of scales and the related mechanisms and modeling approaches. The arrows indicate the mutual interdependence between the levels in multiscale modeling of cancer growth, implying that models/subsystems at a given scale use information from another scales.

The tumor growth is intrinsically multiscale in nature. It involves phenomena occurring over a variety of spatial scales ranging from tissue (for instance, tissue invasion and angiogenesis) to molecular length scales (for example, mutations and gene silencing), while the timescales vary from seconds for signaling to months for tumor doubling times. Moreover, all those processes are strongly coupled. Indeed, an oncogene activation may confer a proliferative advantage to a given cell, promoting its clonal expansion and the depletion of the nutrient and oxygen supply which, in turn, affect the growth of cell clones. To survive in a hypoxic (low level of oxygen) environment, the transformed cells may acquire new traits such as resistance to apoptosis by a tumor suppressor gene inactivation or activated synthesis of growth factors that stimulate angiogenesis [43]. Thus, information flows not only from the finer to coarser scales, but between any pair of scales [44•], as shown schematically in Fig. 2.

A model, proposed by the authors [45], integrates the cellular (mesoscopic) and tissue (macroscopic) scales in avascular cancer growth. Furthermore, it introduces an effective stochastic cell kinetics controlled by local probabilities as a strategy to connect the macroscopic diffusion equations for nutrients and/or growth factors to cell response and interactions at the microscopic scale, a central challenge in developing multiscale models. Essentially, the tissue is represented by a regular lattice in which normal and tumor cells compete for nutrients supplied by a single capillary vessel localized at the top of the lattice. These nutrients diffuse through the tissue towards individual cells and their concentration fields follow linear,

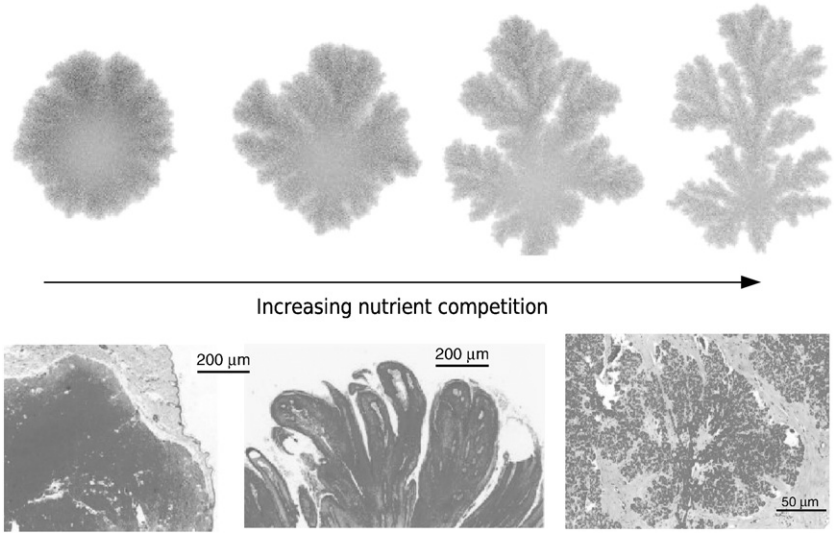

Fig. 3. Simulated patterns generated by the nutrient-limited cancer growth model of reference [45]. They change from compact to papillary or finger-like patterns as the competition for nutrients increases. Bottom: common morphologies observed in cancer. From left to right, a compact solid basocellular carcinoma, a papillary pattern of a squamous papyloma, and the characteristic ramified morphology of trichoblastomas. All these histological patterns were obtained from dogs.

continuous reaction-diffusion equations. Chemotactic interactions among cancer cells mediated by diffusive growth factors (again, governed by linear macroscopic equations) can be added to the competition for nutrients. The cells are discrete individual agents constrained to the lattice sites, and any site is occupied by only one of the cell types (normal, cancer and tumor necrotic cells).

The tumor grows from a single cancer cell, introduced at the center of the normal tissue, according to a stochastic dynamics involving three complex cellular processes: division, migration and death of cancer cells whose probabilities are dependent on the local concentration fields of nutrients and growth factors. Their functional forms are chosen in order to take into account some general features of the cancer biology. Finally, the model parameters characterizing the cancer cell response to nutrient concentrations and growth factors embody complex genetic and metabolic processes. Their values should be determined in terms of the underlying biochemistry and molecular biology, still an open problem. The other model parameters associated with the consumption of essential and non-essential nutrients for cell proliferation by the normal and cancer cells, are more easily determined from biological experiments.

Typical patterns generated by the model vary from compact to papillary-like shapes, as shown in Fig. 3. The tumor morphology is determined primarily by nutrient consumption rates and chemotactic signaling among cancer cells. All the simulated growth patterns, with and without growth factors, reproduce a main feature of avascular tumors, namely, the formation of a necrotic core of dead cancer cells due to nutrient starvation, of an outer rim of nutrient-rich, proliferating tumor cells and, in between these two layers, an intermediate region of quiescent cells. Such multilayered structure was observed in multicellular spheroids of cancer cells formed in culture essays [46,47].

This model [48] and other multiscale approaches [49] were used to analyze the effects on cancer growth of chemotherapy, radiotherapy [50], anti-angiogenic [51], and macrophage-based treatments [52]. Some recent applications of multiscale modeling have focused on oncolytic virotherapy, one of the most promising strategies to treat cancer [53]. It consists in the use of programmed viruses to specifically target, replicate in and ultimately kill cancer cells.

Extensive simulations of a multiscale virotherapy model proposed by Ferreira et al. [54,55••] revealed predictions that are in qualitative agreement with results from clinical reports. From a therapeutic point of view, their findings indicate that a successful, single agent virotherapy requires a strong inhibition of the host immune response and the use of potent virus species with a intratumoral high mobility. Moreover, due to the discrete and stochastic nature of cells and their responses, an optimal range for viral cytotoxicity is predicted since the virotherapy fails if the oncolytic virus demands either a too short or a very large time for killing the tumor cell. This finding suggests that the virus which kills cancer cells most rapidly is not necessarily the more effective agent to eradicate the tumor. The implications of such a result for the design of new replication-competent viruses are clear.

Again, new features underlying cancer growth and invasion as, for instance, the immune response, angiogenesis, tumor–stroma interactions, metabolic and signal transduction pathways, need to be incorporated in these models before significant progress can be made in deducing how distinct mechanisms interact in cancer and predicting the global response of the system to therapeutic interventions. Such mechanistic models can provide real insights into critical parameters that control cancer progression, guide the design of new essays by indicating relevant physiological processes for further clinical investigation, and prevent excessive experimentation needed to develop effective treatments.

6. Conclusions and perspectives

The complexity and diversity of biological phenomena, the range of spatial and temporal scales over which they act, extending from the molecular to the organism levels, and the intricate way in which they are interwoven, make practically unfeasible the understanding of living systems through intuition alone. Therefore, theoretical multiscale approaches are essential tools in the quest for a quantitative, "*ab initio*" physiology and pathophysiology of whole organs and systems beginning at the level of genes.

Today, the quantitative success of multiscale modeling is limited whereas the unresolved scientific problems are widespread. However, the increasing computer power, the development of inherently multiscale modeling and theoretical ideas, and a growing interest from physicists, mathematicians and biologists on this type of multidisciplinary approach, will certainly accelerate the progress and the broad applicability of the multiscale program in biological sciences. Hence, we can confidently predict a major role for multiscale models in future medical and pharmaceutical research, transforming biology in a highly computer-intensive science. The hard calculations and extended simulations necessary for the solution of multiscale mathematical models can be closer to the patient's bed as physicians never dreamed before.

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