Multi-scale modeling of dynamic systems for evolution

by

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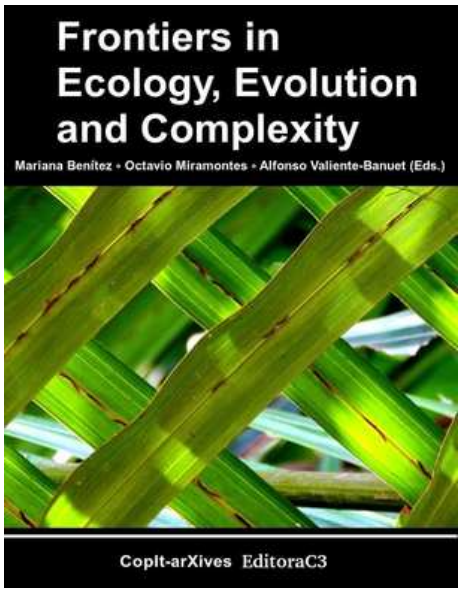

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Multi-scale modeling of dynamic systems for evolution

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1 Abstract

It has long been recognized that processes occurring at different scales of organization affect the evolution of organisms. Molecular, cellular and environmental sub-processes, among others, are involved in settling the basis where evolutionary processes will take place. Changes at the genetic level can affect gene expression patterns, protein biochemical properties, and regulatory interactions, which in turn can modify the structure and dynamic of regulatory networks. Changes at the cellular level can affect cell properties, which modify the cell microenvironment, communication and interaction with the surroundings. Finally, environmental changes modify the morphology, physiology and behavior of the organisms. Until now, most of these levels of organization have been studied as independent from each other. However, all of them interact, constraining and allowing the evolutionary possibilities at the same time. In such a scenario, the sub-processes are not just passive players during evolutionary processes, instead they help to determine the variety of possibilities. With the advent of new theoretical and technological approaches for biological research, especially from the computational and mathematical fields, multi-scale models that study the interaction of these sub-processes in evolutionary processes are starting to appear. Here we highlight some of the results obtained by these studies in order to gain a better view of their importance and utility in the areas of development, evolution and biological complexity.

2 Resumen

Desde hace mucho tiempo se sabe que procesos que ocurren en diferentes niveles de organización afectan la evolución de los organismos. Hay varios subprocesos, como los moleculares, los celulares y los ambientales, entre otros, involucrados en los procesos evolutivos. Cambios a nivel de la secuencia genética pueden afectar los patrones de expresión

genético, las propiedades bioquímicas de las proteínas, e interacciones de regulación, que a su vez pueden modificar la estructura y dinámica de las redes de regulación. Cambios a nivel celular pueden alterar propiedades celulares, modificando el microambiente celular y el modo en que la célula se comunica e interactúa con su vecindario. Finalmente, cambios ambientales modifican la morfología, fisiología y el comportamiento de los organismos. Hasta ahora, los distintos niveles de organización han sido estudiados de forma independiente. Sin embargo, todos actúan de forma conjunta, interactuando entre si, para restringir y posibilitar los procesos evolutivos. En este escenario, los subprocesos no son actores pasivos durante la evolución, sino que participan en la determinación de las posibilidades evolutivas. Con la llegada de nuevas herramientas tecnológicas y teóricas para la investigación biológica, especialmente del campo de las matemáticas y la computación, comienzan a aparecer modelos multi-escala que permiten estudiar la acción conjunta de los subprocesos durante la evolución. En este trabajo describimos algunos de los principales resultados obtenidos con estos modelos, con la finalidad de mostrar su utilidad e importancia en las áreas de desarrollo, evolución y complejidad biológica.

3 Introduction: Changing the paradigm, multi-scale modeling approaches

Most of evolutionary research has been focused on the molecular basis of evolution, as genetic changes can result in beneficial or deleterious phenotypic changes. Based on the idea that differences in genes and allele frequency can reflect and determine the evolutionary history of any organism, population genetics has flourished arguably as the most important evolutionary research field in biology. The proliferation and advances in the tools and methodologies available for population genetics research have been marvelous (e.g., [1]), but underestimate the role of development and ecological influences in evolutionary processes. For example, the genotype-phenotype mapping that occurs during development, which is fundamental to validate current assumptions and understand evolution, is just starting to be understood. Nowadays, we know that the phenotype is the result of development, which is influenced by diverse processes performed by genes, proteins and other molecules, as well as cell interactions, morphogen fluxes, environmental conditions, physical forces, among other things, and not genes alone.

Importantly, in part due to the technological improvements, during the last decades the mechanisms behind biological complexity have become more evident, including developmental and evolutionary ones. There are a large number of elements involved in such processes, all of which interact non-linearly producing non-intuitive behaviors. Therefore, these processes are difficult to predict and understand. Given this complexity, the challenge to understand biological phenomena is largely about the interpretation and integration of experimental results of a sole process studied in pieces. Because of this, modeling approaches that allow the integration of different sorts of data have become

indispensable for biological research.

Biological processes can be studied at different temporal and spatial scales. Spatially, biological research ranges from molecular, to cell, tissue, organ, organism and ecological scales. The temporal scale of biological processes also has a broad range, some processes occurring in microseconds, like the molecular interactions, while other take years, like many organisms life cycles, and other centuries or more, like evolutionary processes [2](see Figure 1).

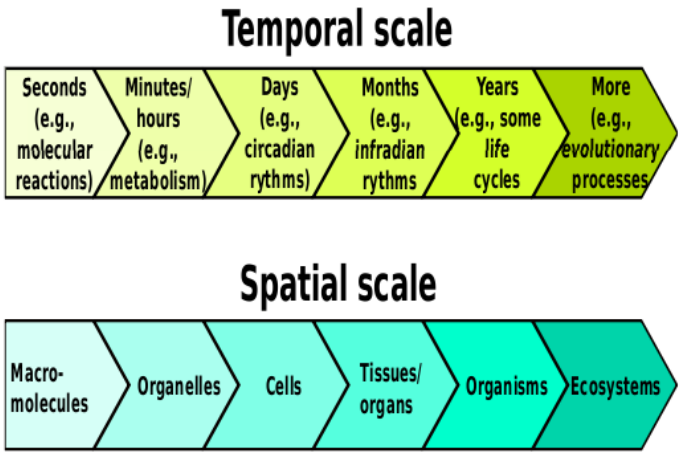

Figure 1: Different temporal and spatial scales of biological organization.

Different tools and methodologies have been developed to study processes at each scale. For example, network theory is useful to structurally and dynamically study processes at the molecular, cellular and ecological scale [3]. However, many biological processes are the product of processes acting together at different scales. For example, during developmental processes, while cells are differentiating via the action of their own gene regulatory network, they might influence the differentiation status of neighboring cells through the movement of molecules, leading to coherent cellular patterns, which will form different tissues and organs. The geometrical and mechanical properties of the tissue can influence morphogen distribution, cellular arrangement and behavior [4–6] which could modify gene activity. Thus, studying how these processes act together is fundamental for a better understanding of biological processes.

Consequently, multi-scale models are starting to appear more frequently. Similarly, software to analyze multi-scale models is being constantly developed (e.g., [7–15], see also the Supplementary Information section at the end of this chapter). In particular, multi-scale modeling has become a useful tool for the study of development.

The software for multi-scale modeling usually relies in different methodologies and formalisms that need to be coupled. For example, CompuCell3D (CC3D) is a software that implements the Cellular Potts Model (CPM) formalism and enables the user to develop

multi-scale models [7]. Such models can take into account intracellular and extracellular dynamics, that in a population of cells can lead to the formation of tissues or complex organs. In CPM cells are modeled as joint positions in a lattice with the same identifier, and their behavior with a potential energy H. We provide an example of H in the next equation:

$$H = \sum_{(i,j)} \sum_{(i',j')} J_{\tau(\sigma_{i,j}),\tau(\sigma_{i',j'})} + \sum_{\sigma} (P_\sigma - P_T)^2 \tag{1}$$

where (i, j) is a position of the lattice, J is the contact energy between cells, τ is the cell type, σ is the cell identifier and P is a certain cellular property. The first term includes two summations over the lattice positions (i, j) and over its neighboring positions (i', j'). The parameter $J_{\tau(\sigma_{i,j}),\tau(\sigma_{i',j'})}$ quantifies the contact energy between the neighboring lattice points $(i, j), (i', j')$ and serves to model adhesive and cohesive interactions between cells. Such interactions underlie the formation of cell clusters by cell-cell contacts. The second term is a summation over all cells to quantify the deviation between the actual (P_σ) and the target value (P_T) of a cellular property. Using this term, the user can define different cellular properties, such as the cell perimeter or area. A CPM simulation uses a Monte-Carlo algorithm to select cellular configurations that minimize the potential energy.

At the same time, CC3D allows the use of different modeling techniques for other biological processes not considered in Equation (1). For example, regulatory networks can be introduced through different formalisms according to the specific requirements of a model. It is possible to use Boolean and ordinary differential equations formalisms, among others. Importantly, cellular properties like the cell adhesion parameters can be defined by the state of an intracellular network. Moreover, using partial differential equations (PDE), elements of a network can move between cells leading to communication circuits that help to coordinate a population of neighboring cells. Additionally, using PDE it can be modeled environmental inputs as nutrient availability.

Therefore, with CC3D it is possible to build models of complex process encompassing dynamics at the intracellular (regulatory network), cellular (cell adhesion) and tissular (molecule gradient) scale, which altogether regulate a certain biological phenomena (see Figure 2).

Multi-scale models of morphogenesis have been used with great results to give insights into how processes are spatio-temporally coupled and which is the role of each of them in the resulting macroscopical pattern. Anyhow, the use of multi-scale models to study evolution has remained scarce. Now we review how multi-scale modeling approaches have been successful in different contexts, with an emphasis for development. Then we look at a few examples of how they have been used in evolution. Finally, we discuss their utility and necessity to extend their use for the study of evolution.

4 Multi-scale models of non-evolutionary biological processes

Multi-scale models have been used in many biological contexts with successful results. For example, due to global climate change, the demand for models that can predict and understand the response of organisms to environmental changes has become a main issue for planning conservation strategies. However, in an ever-changing world, the number of variables that can affect the organism responses is huge and come from different organizational scales. First attempts to include multiple variables from different scales, like demography, gene flow and heterogeneous environments, among others, are starting to appear. These studies have provided projections of species distribution and community structure [16].

Other studies have focused on the interaction between organisms and environment. A methodology commonly used for this kind of models is the so-called functional-structural models [8]. One of the most employed functional-structural models are L-systems [17]. For example, using L-systems, Leitner and collaborators [18], developed a model of plant root growth that integrates internal cues that in turn responded to changes in the environmental conditions. Using this model, they were able to understand the impact of root and rizhosphere on plant resource efficiency.

Developmental studies have been the focus of multi-scale modeling. For example, when nutrients are scarce and the growing conditions are not adequate, *Dyctiostelium discoideum* aggregate in a multicellular slug that will develop into a fruiting body. Its formation involves some cells periodically secreting cAMP and others periodically moving chemotactically towards a cAMP gradient. This process was studied in a two-dimensional model considering intracellular excitable cAMP dynamics, cAMP secretion and cellular migration [19]. Because the model studies a population of cells, each of them with an intracellular dynamic and a gradient of cAMP that guides cell chemotaxis, it constitutes a multi-scale model. The model was able to reproduce the cellular movements observed *in vivo*, and was useful to understand how some sub-processes are spatio-temporally coupled for the morphogenesis of the fruiting body. Moreover the model predicted that chemotactic movements produce pressure waves displacing non-responding cells downwards and responding cells upwards of the fruiting body.

Another example of multi-scale models for the study of developmental processes is one of somitogenesis proposed by Hester and collaborators [20]. The formation of somites is an important event in the embryonic development of vertebrates as they form different body segments in organisms as varied as chicken, mice, zebrafish and snakes. Hester and collaborators [20] proposed a multi-scale model of somitogenesis that takes into account an oscillatory regulatory network, a growth factor gradient, differential cell adhesion and cell proliferation. Through multi-scale modeling it was possible to describe how these different sub-processes are concerted and establish the spatio-temporal dynamic observed during somite formation. The model makes predictions about some sub-processes and the somitogenesis process as a whole. For example, it provides hints of the changes in the

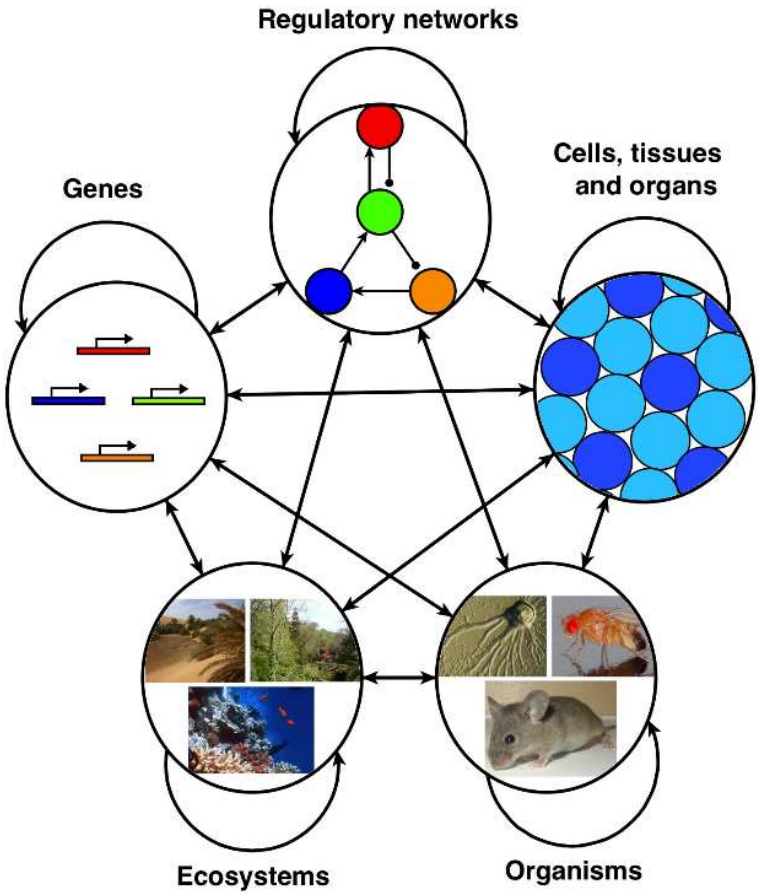

Figure 2: Scales of organization that can been considered in multi-scale models.

parameters of the model that lead to the different number and length of somites observed in different vertebrate organisms.

This is only a small sample of multi-scale modeling in biology. However, multi-scale models have been used also to study other developmental processes like gastrulation, stem cell differentiation, vasculogenesis, diseases like cancer [21] and tuberculosis [22], to combine physical and molecular processes [23, 24], among many other issues. Now, let us briefly review some of the multi-scale models of evolution published until now.

5 Multi-scale models of evolutionary processes

In one of the most interesting multi-scale models of evolution generated until now, the genotype was translated into a dynamical network in a multicellular space to study tooth

morphogenesis [25]. Depending on the dynamic of the network, specific morphologies were observed, which corresponded with observed ones in different mammalian populations. The morphology was then translated into a fitness value, which determined the individual chances of contributing to the next generation and the model reproduced actual evolutionary transitions. Thus, the model allowed the study of the complex genotype-phenotype mapping and the identification of the changes in the parameters (mutations) that give rise to a variety of morphologies actually observed in nature. This is a pioneering work that considers a genotype translated into a realistic evolving phenotype.

Hogeweg [26] proposed a multi-scale model in which cells had a gene regulatory network that defined its differentiation status and adhesion properties. Cells stretch due to their adhesion properties and proliferate whenever their volume surpassed a threshold. Evolution was incorporated in the model by allowing random mutation in the gene regulatory network. Using this model it was possible to simulate and analyze the evolution of complex morphologies as engulfing, budding and elongation, intercalation and elongation, among others. Thus, by using a multi-scale approach, Hogeweg studied the concerted action of cell growth, cell differentiation and cell biophysical properties during evolution of multicellular morphologies.

Moving forward with the evolutionary multi-scale modeling approach, Ten Tusscher and Hogeweg [27] studied how body a pattern with segments and different cell types could evolve. In order to do this, they generated a population of organisms, each one composed of a hundred cells. The identity of the cells and the appearance of segments were determined by the stable states of a gene regulatory network, which perceived the concentration of a morphogen wavefront. The network was allowed to evolve, by changing the gene interactions and update functions. Finally, organisms were able to reproduce and they were selected according to the body pattern that they generated, following a genetic algorithm approach. This work not only showed how a network able to produce segments and different cell types could evolve, but also challenged some generic network features theoretically proposed. For example, it has been proposed that organisms produce different morphological traits (segments and cell types in this case) as a consequence of the modular structure of gene networks. However, the networks produced in this study were not structurally modular, but functionally modular.

6 Discussion and conclusions

Some biological processes contain sub-processes that can be studied independently from each other. Different mathematical tools can be used to model these sub-processes according to the level of description necessary to describe them dynamically. For example, gene regulatory networks can be modeled with boolean networks, cell signaling with differential equations, transport of molecules between cells with logic rules, and diffusion of morphogens with partial differential equations, etc. As useful as it is to separate

spatio-temporal scales to simplify any research, it is extremely difficult to explain biological processes by studying independently each sub-process. Thus, it is often not possible to fully understand them if we only study their sub-processes in isolation. Consequently, multi-scale modeling is a necessary tool to understand many current questions in many different biological fields.

Evolution is not the exception. The evolution of organisms is the result of ongoing complex processes at different scales. Currently, with the advent of modeling tools and the increase in available biological data, it is expected a rise in the limited amount of work done for the study of evolution with multi-scale modeling approaches. Efforts in this direction would be important in order to understand and gain better insight about evolutionary processes. For example, it would be useful to understand the genotype-phenotype map and to consider the role of developmental processes to functionally understand how genetic mutations change the fitness of an organism. Such an approach could explain how phenotypic novelties arise and are subject to natural selection.

However, multi-scale models present some complications, constrains and limitations. For instance, as multi-scale modeling deals with spatio-temporal processes, one critical step is to carefully couple such processes in time and space, which can be methodologically challenging. Also, multi-scale modeling contain many elements and data. This complicates modeling, is computationally expensive and prevents analytical analyses of the models.

It is important to notice, that multi-scale models do not need to consider each and all sub-processes. Instead, it is an approach that opens the possibility to study how some subprocesses, important by themselves, are part of a sole process.

As briefly reviewed in this article, multi-scale modeling is a useful tool to discern the entanglement of processes regulating complex morphological traits, the environmental-organism interactions, and the effect of environmental change. Importantly, in the studies mentioned, some of the results could not be obtained without the use of multi-scale modeling since they are the outcome of the interplay between micro- and macroscale dynamics over evolutionary time. Evolutionary studies could take advantage of the great integrative and analytical capacity of the multi-scale models.

For the reasons exposed above, we think that the use of a multi-scale modeling approach could improve our predictability and understanding of evolutionary processes under an integrative framework. We hope that this article will convince the reader of the utility of multi-scale modeling for the study of biological processes, specially the evolutionary ones.

Supplemenary Information Online

For a table compiling a list with examples of software designed for multi-scale modeling, visit: http://miro.fisica.unam.mx/SI-01.html

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