



## Introduction

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This Special Issue consists of contributions from participants of three workshops with similar focus held in 2016–17:

“Modelling of Tissue Growth and Form” held from March 6 to March 10, 2017, at the NSF Mathematical Biology Institute (MBI), Columbus, OH, USA,

“Multi-scale Modeling of Complex Systems in Developmental and Plant Biology” held on December 15, 2017, at the Interdisciplinary Center for Quantitative Modeling in Biology, University of California, Riverside, CA, USA,

“Computing a Tissue: Modeling Multicellular Systems” at the 15th European Conference on Computational Biology held from September 3 to September 7, 2016, at The Hague, Netherlands.

This Special Issue combines papers on recent advances in the field with review articles discussing in detail some open problems. Contributors were asked to describe the recent results on the application of the very latest mathematical and

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computational modeling and experimental approaches used for studying problems in morphogenesis and growth of plants and animals.

Modeling in developmental biology differs from many other fields of mathematical biology in that the background topology and geometry on which the dynamics of patterning and information processing play out are themselves dynamic. This Special Issue focuses on multi-scale models in developmental biology rooted in the cellular level, i.e., models making links between cellular processes such as cellular growth and division, cell movement and interaction with the extracellular matrix (ECM) and mechanical or chemical signaling between cells and organ shape development at more integrated scales.

Understanding the mechanisms underlying the patterns of behavior arising from cell–cell and cell–substrate interactions is a highly important area of research for basic science (embryology) as well as regeneration (e.g., wound healing) and disease (e.g., cancer). The paper by Hassan et al. develops a novel computational model to study cell migration on a 2D non-deformable substrate. It is shown how different assumptions on lamellipodial dynamics can give rise to several well-known cell behaviors, such as a persistent random walk for an individual cell, and contact inhibition of locomotion (CIL) in a collection of cells, the latter being dependent also on cell density. In this framework, CIL is shown to be an emergent phenomenon arising through indirect cell–cell interactions via the substrate, rather than the commonly imposed direct cell–cell interaction rules. Jiang et al. use a phase-field formulation, based on a free energy density, to study how the deformability of cells affects cell growth, division and packing. The resultant model is numerically implemented, and the effects of different physiological mechanisms on the resultant dynamics of cell growth, division and compaction in multicellular aggregates are investigated.

This Special Issue also provides examples of how mathematical modeling helps to understand pattern formation during plant development. Julien et al. analyze recent extensions of mathematical models for accumulation of the phytohormone auxin in shoot apical meristem development. While initial models (Jönsson et al. 2006; Smith et al. 2006) proposed that biochemical mechanisms were responsible for polarizing auxin fluxes during meristem development, later studies (Heisler et al. 2010; Sassi et al. 2014) suggested that mechanical signals must be responsible: Auxin softens the cell wall, leading to an increased strain, and thus an increased mechanical stress in the surrounding cell walls. It is still unclear if plant cells are more likely to respond to strain (i.e., deformation) or to stress (i.e., force buildup). Using careful sensitivity analysis of a model based on strain sensing and another model based on stress sensing, followed by comparison with published experimental observation, Julien et al. argue in detail that strain sensing mechanisms are more probable.

In a similar spirit, Banwarth-Kuhn et al. introduce a multi-scale combined mechanical and chemical signaling model of the shoot apical meristem based on the subcellular element (SCE) approach, to analyze how expression of WUSCHEL (WUS) directs the curvature of the shoot apical meristem (SAM) in *Arabidopsis*. Using microscopic imaging, they showed that expression of WUS in the SAM inhibits cell division and expression. They then used the observed expression patterns of WUS to set the growth rates of the cells in their model and assumed that superficial

cells expanded parallel to the surface of the SAM, whereas deeper cells expanded in a direction perpendicular to the SAM surface. Interestingly, the empirically obtained expression pattern of WUS, combined with the assumed expansion directions of the cells, was sufficient to predict the progressive bulging of the SAM and its shape as well as its maintenance. The model was validated using genetic lines that allowed the researchers to enlarge the expression domain of WUS and the simulations correctly predicted the observed shape and enlargement of the SAM.

Beyond simulation of growth, computational models are also used to quantitatively explore the complex response to various physical or molecular processes of multicellular structures, whose geometries are reconstructed with precision from 3D microscope images. Ali et al., for instance, study how turgor-induced stresses provide geometry-related mechanisms of growth. In order to model and simulate plant morphogenesis, one needs to understand how this transduction from tissue geometry to mechanical stress works. The authors use a computational model to determine how the number and shapes of cells, the depth of the tissues considered and the rheological properties of tissues can influence stress fields and, therefore, the mechanical homeostasis of meristematic tissues, including both realistic young flower buds and purely virtual structures. The authors were able to demonstrate a strong influence of the inner walls on the epidermis mechanical stress pattern, especially in negatively curved regions. They also demonstrated correlations between stress intensity and cell size, as well as differential responses to loading between epidermal and inner cells.

Altogether, these papers showcase a prominent new approach in developmental biology in which modeling and experiments go hand in hand to analyze the mechanisms of development. These new methods are driven by technical developments in experimental biology, such as advanced imaging and inducible promoter lines, as well as by novel mathematical and advanced computational techniques. There exist many approaches to modeling cell growth and rearrangement in tissue during morphogenesis and plant growth. The purely continuum approach describes tissue as a viscoelastic–plastic deformable material satisfying the laws of continuum mechanics. This approach has the advantage of generating a small system of (albeit highly nonlinear) coupled partial differential equations with a limited number of parameters. The disadvantages are that they are too coarse-grained to account for changes in cell shape or for cell-level properties and to allow comparison between model and experiment at cellular and molecular level. To alleviate these difficulties, discrete and hybrid multi-scale cell-based models have been developed (e.g., subcellular elements models, vertex-based models and cellular Potts models (CPM)). These models allow for extraction of detailed metrics on cell size and shape that, in principle, can be compared with experimental data. The disadvantages are that there are many more free parameters in such models and there is no widely accepted mathematical theory underlying them. There is the common challenge for all these multi-scale models of calibration, identifiability and validation.

Issues of multi-scale mathematical formulation are dealt with in characteristically different, but interrelated ways, by the authors in this Special Issue. For example, Hassan et al. consider force and torque balance and lamellipodia and cell–substrate interactions at the microscopic scale to derive a “persistent random

walk” formulation of cell migration at the mesoscopic scale. This leads to the collective nematic spatial order at the macroscopic scale. Jiang et al. use level set and phase field methods to model closely packed multi-cell aggregates with soft cellular boundaries, evolving due to cell growth, cell division and mechanical contact, governed by free energy models. Alternatives to the level set/phase field representation of curved boundaries in biomechanics include the parametric spatial embeddings used to study dynamical stability in tubular biological macrostructures by Erlich et al.

Another approach is proposed by Wolff et al., who introduce a new variation in the vertex-based model which can be viewed as an off-lattice generalization of the CPM, a popular lattice-based model used extensively in developmental biology. This provides an extension of the open source package VirtualLeaf, initially developed for simulating plant tissue morphogenesis, by allowing cells to move with respect to each other by introducing a new rule for cell–cell shear or sliding. This new “sliding operator” is incorporated in simulating node displacements using a Metropolis-based energy minimization approach from the CPM. This yields new applications of VirtualLeaf to problems in animal development. Simulations of the newly extended VirtualLeaf are compared with the results obtained using traditional vertex-based models on describing differential adhesion-driven cell sorting as well as neighborhood topology of soft cellular networks. The extended version of VirtualLeaf is also demonstrated by simulating epithelial cell packing.

If one wishes to represent dynamic cytoskeleton as well as cell-level networks, the dynamical graph grammars of Mjolsness, with spatially embedded graph specializations such as graded and stratified graphs, and a universal operator algebra formulation of the dynamics for such structures, may provide a common geometric/topological framework; this paper also introduces a machine learning method for creating coarse-scale models. The dynamics of cell–cell adjacency and pattern formation in plant stem cell niches, such as root and shoot meristems, are also addressed briefly there, and in considerably more detail in the papers by Ali et al., Banwarth-Kuhn et al., and Julien et al.. The paper concludes with a conceptual “meta-hierarchy” for mathematical modeling languages, by which diverse multi-scale biological models and modeling methods could be integrated.

A fuller understanding of the basic biology of development with the help of mathematical modeling approaches will significantly enhance our understanding of how organisms regulate and regenerate structures. This, in turn, could translate into potentially significant advances in medicine in, for example, wound healing, and tissue engineering, as well as in the treatment of many cancers, which can be thought of as unconstrained development. Similarly, it could translate into advances in plant breeding and yield improvement, for example, through better control of shoot and root branching, to optimize light and water capture.

The recent advances in imaging, coupled with those in computation, now mean that we are at a very exciting stage where mathematical and computational modeling of spatiotemporal phenomena can be used to quantitatively test *in silico* hypotheses about organism development and can provide direct feedback for experimental studies. To do so will require new advances in areas such as mechanical modeling of growing multicellular structures, multi-scale integration of multiphysics models,

computational and discrete differential geometry, non-conventional programming languages, parameter identifiability and sensitivity analysis, spatial statistics and machine learning. In this way, the mathematical and computational biology community will progressively be able to set up the foundations for a new theory of living and active matter that is linked with experimentation in a way never done before and allowing a new kind of insight into the fundamental biology of development and disease in animal and plant organisms.

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