

Systems Morphodynamics: understanding the development of tissue hardware

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## Summary

Systems morphodynamics describes a multi-level analysis of mechanical morphogenesis that draws on new microscopy and computational technologies and embraces a systems biology-informed scope. We present a selection of articles that illustrate and explain this rapidly progressing field.

## Background

Genes do not make tissues, cells do. In recent decades, the analysis of the physical making of tissues in normal development has taken a back seat to the analysis of gene regulatory networks. Recently, however, there has been a maturation of genetic and genomic approaches and an increasing recognition that genes alone cannot drive complex tissue shape changes, but the genes must somehow regulate the generation of forces to do so. At the same time, cell biology has historically focused on the behavior of individual cells rather than cells in a tissue context. Tissue shape changes in such a context require all varieties of cellular behaviors, such as growth, division, migration, rearrangement (which may or may not be the same thing as migration) and death. There is also increasing recognition that for tissue shape changes, cells must act coordinately in a manner very different from, and yet related to, that of single cells in vitro.

Morphogenesis, or the proximate origin of biological form, has long been one of the great problems in biology. A useful subdivision of morphogenesis was articulated by the mathematician Alan Turing in his seminal 1952 Philosophical Transactions paper [1] when he identified two types of morphogenesis: chemical and mechanical. The mechanisms, including Turing mechanisms, governing chemical morphogenesis, which we nowadays term “pattern formation”, are beginning to be well understood, with a flurry of experimental activity as well as numerous reviews [2-6]. Mechanical morphogenesis, however, is only just emerging as an exciting new area of discovery and analysis. The chemical and mechanical processes of morphogenesis are not mutually exclusive, but are often interdependent and concurrent, and this adds enormously to the complexity. A major challenge now is to straddle the chemical/mechanical subdivision and bridge the chemical with the mechanical to give a more integrated view of tissue morphogenesis. However, our mechanical understanding is still lagging and it is here where we should expect rapid progress in the near future.

Why now? Apart from the maturation of molecular biology and the recognition that cells in vivo live in 3D and often work as populations, recent technological advances are converging to tackle mechanical morphogenesis challenges. Advances in microscopy, particularly in speed and depth (rather than resolution as such) are enabling live imaging of tissues rather than individual cells cultured on plastic. Automated image analysis is making rapid progress, feeding on advances in IT generally, including raw computing power, which has created a community of “computer vision” groups bringing their tools to bear on biology. Computational modelling has likewise become increasingly accessible with parallel processing, facilitating a step change in the scales of computation that are feasible. The growth of materials science and “soft matter physics” has helped to increase the biological realism of computational models of cells in tissues.

We have entitled this theme issue “Systems Morphodynamics” not to generate some new jargon but to try and capture the ensemble of approaches involving theoretical, computational, and experimental techniques that both describe and explain the causal links between genes, molecules and anatomical development. “Mechanism” in this morphodynamics context should no longer mean a purely molecular description. Instead, mechanism should mean what it says: the direct physical and, above all, causal set of interactions that establishes a given outcome at a scale finer than that at which the outcome is defined. In other words, a mechanism of tissue morphogenesis can be defined by the mechanical behaviours of cells without direct reference to the molecules that are, of course, required. Thus, systems morphodynamics links finer scale processes with higher levels of organisation at which emergent processes occur, including cell population behaviours and the generation of long-range forces and geometries. Much has been written about the cell

being the proper level at which biology should be understood [7, 8] and we contend that systems morphodynamics embraces levels above, below and at the level of the cell, exactly as prescribed.

The contributors for this theme issue are at the forefront of these technological advances, each with their field of expertise, yet merging to integrate quantitative imaging, computational modeling, bioengineering and biophysical tools and developmental cell biology to understand tissue morphogenesis. This is an excitingly fast-developing field and consequently this selection of articles under-represents the breadth of approaches being taken.

For any significant omissions, we ask for the reader's understanding, but we hope that by highlighting this open frontier we can enthuse you, the reader, to engage with and participate in the science. For that reason, we include broad introductory articles as well as more specialist reviews and some primary research.

## **Topics in this theme issue**

### **1. Integrating cellular hardware with signaling software**

The first section in this theme issue serves as an overview of the challenges and approaches used in the field to integrate chemical signaling with cell mechanics. By using specific examples of embryogenesis, Davidson [9] highlights the need of novel biophysical tools in mechanical measurements and mechanical manipulation to integrate mechanical signaling with biochemical signaling and pattern formation. Just as gene knockout and over-expression studies are essential for understanding genetic regulation, techniques for applying and measuring mechanical forces in cells and tissues are critical for understanding mechano-regulation of morphogenesis. In their article, Abad et al. [10] use the making of a flower as a case study to highlight the power of multidisciplinary approaches in linking the complex network of regulatory genes and signaling molecules to the cellular hardware, namely the cell wall structure, in driving flower morphogenesis.

### **2. Image acquisition and analysis**

Our second set of papers is really about seeing. As the great baseball coach and aphorist Yogi Berra said "You can observe a lot just by watching" and this is certainly true in biology. While much has been written about advances in microscopy optics and in vivo labelling, the rate-limiting step for analysis of morphogenesis is often the basic set-up of the microscope stage to enable image acquisition. Practical considerations of this are reviewed here by Bell. In the end, though, an image or series of movie frames are just collections of pixels or voxels. Dufour [11] takes on the task of giving an overview of how to convert such raw materials into biologically meaningful datasets. He takes us through the steps of image processing to enhance the detectability of features, image segmentation – the rather jargon word for the assignment of image regions to particular objects such as a nucleus or a cell, and cell tracking. As he points out, quantitative imaging absolutely requires these processes and they remain aspects of the science that are at once rate limiting for research and a locus of continuing improvement. Blanchard [12] introduces us to a usefully systematic method for analysing ensemble movements of cells, namely tensors and vector fields. We encourage even slightly mathematically literate biologists to take a good look at this article (which is effectively a companion piece to Blanchard et al.'s paper on "tissue tectonics"[13] as it describes the basis for extracting simple processes, such as cell flow, cell shape change and cell rearrangement, from otherwise unintelligible seas of tissue movement. Yes, it is true that Einstein struggled with tensor mathematics, but this is tensor mathematics of a much simpler order, dating back around two hundred years, here newly applied to cells rather than nets and fluids. Veldhuis et al. [14] present original work on the inference of force from images. This brings us right up to the physics of morphogenesis and beautifully demonstrates how an engineering approach to morphogenesis can be applied to understand the causes and effects of cell behaviours. We recommend the accompanying short introductory video (link) as a welcoming way into this work.

### **3. Cell-to-tissue modelling**

As well as big datasets, what distinguishes Systems Biology from other ways of doing biological research is being quantitative. Systems morphodynamics must be quantitative not only in the descriptive data that are captured and inferred but also in the ways that it formulates and tests hypotheses. Mathematical or computational models are simply formalisations of hypotheses – even simplistic, qualitative hypotheses – into quantitatively falsifiable forms. Fletcher [15] provides an introductory overview of some approaches to modelling epithelial morphogenesis, while Salbreux [16] shows how one type of model, the vertex model, can be applied in increasingly sophisticated ways to tissues in 2D and 3D. Shvartsman [17] presents application of a vertex approach to a specific morphogenetic process in *Drosophila*, illustrating the effect of patterning – chemical morphogenesis – on the mechanical morphogenesis that follows.

A particular recognition should be made here that the articles included cover only very few of the approaches to modelling mechanical morphogenesis, and the omission of specific articles emphasising other approaches,

such as Cellular Potts, Finite element or Agent-based is simply a result of the exigencies of editing a theme issue and should by no means be taken as a preference or prejudice of the editors. The reader is directed to excellent reviews on these topics elsewhere in the literature [18-21]

#### 4. Tissue morphogenesis motifs

Returning to the more experimental aspects of Systems Morphodynamics the final three articles describe morphogenetic motifs. A morphogenetic motif is on the one hand a useful and necessary shorthand for describing the cellular behaviours underlying formation of recurrent structures in biology, and on the other a claim that there is a definite, small repertoire of ensemble behaviours conserved across species and developmental time. Pearl et al. [21] survey such a set of ensemble behaviours for epithelial invagination, while Spurlin et al. [22] cover branching mechanisms. Bentley [23] takes a more detailed look at angiogenesis – a particular example of branching morphogenesis – and explores the role of cellular timing as an underappreciated aspect of morphogenetic control.

#### Conclusions

This theme issue is intended to reflect this moment in time when a leading group of researchers is beginning to integrate multicellular data acquisition, image analysis, and various flavours of modelling to form what might be considered a new field that we suggest should be called Systems Morphodynamics. As the field is moving at such a rapid pace, it is inevitable that there are many pieces of work that we unfortunately could not include in this theme issue, particularly new advances in biophysical measurements and manipulations. There is also a collection of fascinating subcellular physical and computational work that due to limitations of space and time we could not include. We hope the reader will agree that, just as was once said (by Marc Kirschner) of systems biology as a whole, systems morphodynamics is hard to define perfectly but “we know it when we see it” [7].

#### Additional Information

##### Authors' Contributions

J.B.A.G. initiated the theme issue and drafted the prospectus; Y.M. and J.B.A.G. wrote the text together.

##### Competing Interests

We have no competing interests.

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#### References

1. Turing, A.M., *The Chemical Basis of Morphogenesis*. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 1952. 237: p. 37-72.
2. Kondo, S. and T. Miura, *Reaction-Diffusion Model as a Framework for Understanding Biological Pattern Formation*. Science, 2010. 329: p. 1616-1620.
3. Tompkins, N., et al., *Testing Turing's theory of morphogenesis in chemical cells*. Proc Natl Acad Sci U S A, 2014. 111(12): p. 4397-402.
4. Woolley, T.E., et al., *Stochastic reaction and diffusion on growing domains: understanding the breakdown of robust pattern formation*. Phys Rev E Stat Nonlin Soft Matter Phys, 2011. 84(4 Pt 2): p. 046216.
5. Painter, K.J., et al., *Towards an integrated experimental-theoretical approach for assessing the mechanistic basis of hair and feather morphogenesis*. Interface Focus, 2012. 2(4): p. 433-50.
6. Meinhardt, H., *Turing's theory of morphogenesis of 1952 and the subsequent discovery of the crucial role of local self-enhancement and long-range inhibition*. Interface Focus, 2012. 2(4): p. 407-16.
7. Nurse, P. and J. Hayles, *The cell in an era of systems biology*. Cell, 2011. 144(6): p. 850-4.
8. Brenner, S., *Sequences and consequences*. Philos Trans R Soc Lond B Biol Sci, 2010.365(1537):p. 207-12.
9. Davidson, this issue
10. Abad et al., this issue
11. Dufour, this issue
12. Blanchard, this issue

13. Blanchard, G.B., et al., *Tissue tectonics: morphogenetic strain rates, cell shape change and intercalation*, in *Nat Methods*. 2009. p. 458-64.
14. Veldhuis et al., this issue
15. Fletcher, this issue
16. Salbreaux, this issue
17. Shvartsman, this issue
18. Szabo, A. and R.M. Merks, *Cellular potts modeling of tumor growth, tumor invasion, and tumor evolution*. *Front Oncol*, 2013. 3: p. 87.
19. Brodland, G.W., *Finite element methods for developmental biology*. *Int Rev Cytol*, 1994. 150: p. 95-118.
20. Wang, Z., et al., *Simulating cancer growth with multiscale agent-based modeling*. *Semin Cancer Biol*, 2015. 30: p. 70-8.
21. Zhang, Y.T., M.S. Alber, and S.A. Newman, *Mathematical modeling of vertebrate limb development*. *Math Biosci*, 2013. 243(1): p. 1-17.
22. Pearl et al., this issue
23. Spurlin et al., this issue
24. Bentley, this issue.