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Review

# Using cell deformation and motion to predict forces and collective behavior in morphogenesis

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ABSTRACT

In multi-cellular organisms, morphogenesis translates processes at the cellular scale into tissue deformation at the scale of organs and organisms. To understand how biochemical signaling regulates tissue form and function, we must understand the mechanical forces that shape cells and tissues. Recent progress in developing mechanical models for tissues has led to quantitative predictions for how cell shape changes and polarized cell motility generate forces and collective behavior on the tissue scale. In particular, much insight has been gained by thinking about biological tissues as physical materials composed of cells. Here we review these advances and discuss how they might help shape future experiments in developmental biology.



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## 1. Introduction

Morphogenesis is a fundamental example of a biological process that must involve both biochemical signaling processes and mechanical forces. This convergence makes morphogenesis an exciting and fruitful research area that requires close and interactive collaborations between mechanical modelers and developmental and cell biologists.

One of the goals of morphogenesis research is to understand how forces alter cell and tissue shape to generate functional organs and body plans. Similar questions are studied in the physical sciences and engineering, where researchers have developed rules that characterize how forces affect the shape of an object. Depending on the field, these are called “constitutive” or “rheological” equations.

These rules are different for different types of materials. For example, the force required to push on a fluid is proportional to how *fast* you push, while the force required to push on a solid is proportional to how *far* you push. More interesting materials like silly putty or mayonnaise exhibit aspects of both solid-like and fluid-like behavior, and a significant fraction of current research in materials science is devoted to organizing and quantifying rules for these types of materials.

Importantly, all modeling of morphogenetic processes must involve some assumptions about the underlying constitutive law for the material properties of cells and/or tissues [1]. Of course, in biological tissues these laws are much more interesting because they are under the direct control of signaling molecules (e.g. morphogens) that can alter mechanical properties during a developmental process. In addition, there are complex feedback

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mechanisms such as mechanosensitive signaling pathways that allow cells to change their behavior depending on their local microenvironment. Furthermore, cells can grow, divide, extrude, and die, allowing a much greater range of behavior than could possibly be found in non-biological materials.

Because of these novel features specific to biology, one might despair of ever developing a correct constitutive law for cells and tissues. It is true that new techniques are needed to handle new twists on how a material composed of cells behaves in response to forces. However, there are some remarkably simple ways of categorizing the material properties of tissues, and we will show in this review that simple mechanical models can make quantitative predictions about tissue behavior.

For example, one important question is whether cells inside a tissue intercalate or exchange neighbors. Neighbor exchange is a primary hallmark of a fluid, and the number of neighbor exchanges can be used to determine a *diffusion constant* that quantifies how likely an individual cell is to move through a dense tissue. In developmental processes associated with large-scale flow or deformation (such as convergent extension in Drosophila or the shield stage involving mesendoderm/ectoderm sorting in zebrafish) cells diffuse over large distances and the tissue behaves as a fluid. In contrast, when cells do not exchange neighbors the tissue often behaves more like a solid, supporting stresses and buckling or folding to form functional shapes. Of course, there are some unique features of biological tissues that can alter this simple picture. For example, cell divisions may fluidize [2] or solidify [3] a tissue.

So far, we have discussed constitutive laws for cells and tissues somewhat interchangeably. However, the type of constitutive law that is most useful depends on the scale at which one images and quantifies the system. For example, very large scale structures such as spinal cords or limbs have been successfully modeled using continuum or finite element models that approximate the structure using a single, simple equation, such as that for an elastic solid [4,5]. At the much smaller intracellular scale, the dynamics of the actomyosin cytoskeleton during processes such as blebbing and cell division have been remarkably well-described by active gel models that exhibit both fluid-like and solid-like properties [6–8]. In this review, we focus on constitutive models at the intermediate scale of cellular morphogenesis that predict how cell-level shape changes, movements, and rearrangements give rise to tissue-scale behavior.

It is important to note that the constitutive law for a material (such as a tissue) can be very different from the constitutive laws for the underlying constituents (such as cells), depending on how those constituents interact with one another. For example, an individual grain of sand behaves as an elastic solid, but a pile of sand can flow like a fluid or anchor a sand castle depending on the magnitude of water-based adhesion between the grains.

Another insight is that complex, large-scale patterns in groups of cells or tissues do not necessarily require complex, large-scale control mechanisms. Specifically, local rules, such as alignment interactions between the migration direction of pairs of cells, can give rise to collective migration patterns where large groups of hundreds of cells move in the same direction. One can also find other patterns such as hexagonal lattices [9] or spiral waves [10]. Taken together, these observations suggest that minimal models may be able to capture some of the complicated features seen in developmental biology.

There are many excellent models that try to explain and predict features of tissues at a wide variety of scales, and this review cannot be comprehensive. Instead, we will focus on reviewing a class of recent techniques that model features at the cellular (but not intracellular) scale and then make prediction for collective, more global properties of tissues. Although some results are explicitly from embryonic model organisms, we will also review discoveries made in non-developmental tissues and discuss how they might be used to generate new hypotheses about morphogenesis. Importantly, recent advances in imaging, force measurement, and mutant analysis have made it possible to test these quantitative theories.

In the remainder of this review article, we focus on three recent advances that we believe are directly relevant for cellular morphogenesis: Section 2 focuses on establishing how small-scale cell deformation generates large-scale tissue deformation, Section 3 discusses new predictions about how forces are related to cell deformation by casting the problem in terms of a fluid-to-solid transition, and Section 4 focuses on how polarized cell motility leads to collective motion in groups of cells.

## 2. Connecting cellular deformation processes to global tissue deformation

Before studying the cellular forces that drive morphogenesis, much can already be learned by quantifying the cellular processes that underlie tissue deformation. Such cellular processes could be cell shape changes, cell neighbor exchanges, cell divisions, and cell extrusions (Fig. 1A). For instance, the elongation of a piece of tissue could equally be accounted for by cell shape changes or by oriented cell neighbor exchanges (Fig. 1B).

To identify the cellular processes at work in a deforming piece of tissue, time-lapse imaging of fluorescently labeled cell membranes has turned out to be a useful tool. Recent techniques allow imaging of developing organs or even entire embryos *in vivo*, as well as automated tracking of the motion and deformation of each individual cell [11–17]. From such data, tissue deformation can be quantified in a straightforward manner using particle image velocimetry [18,13]. However, if one is interested in systematically characterizing the cellular processes that underlie this large-scale tissue deformation, segmentation of the image data is required, including tracking of cell identities across subsequent images [13,15,19–24]. Moreover, just counting how often a cellular process occurs is in general not enough to know how much it actually contributes to tissue deformation. For instance many randomly oriented T1 transitions will not contribute to overall tissue deformation.

To precisely quantify the contribution of each cellular event to the overall deformation based on segmented image data, two classes of methods have been developed [11,15,17,25–31]. The first class focuses on the shape of cell outlines and their deformation [25,11,12,27,28]. For example, Blanchard et al. define cell shape by fitting an ellipse to the cell outline (Fig. 2A) [11]. Cellular shape change is thus measured by a change of aspect ratio and angle

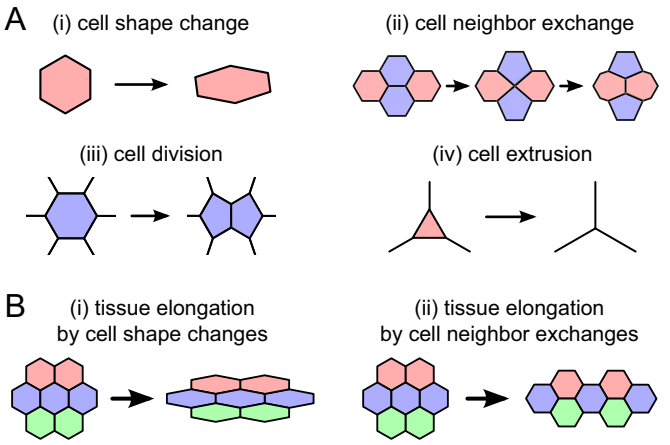


**Fig. 1.** (A) Cellular processes underlying large-scale tissue deformation. (B) Large-scale elongation of a piece of tissue could be accounted for by (i) cell shape changes or (ii) cell neighbor exchanges.

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