A Measure of Morphodynamics

By Mattia Serra and L. Mahadevan

One of the grand challenges of modern biology is understanding the way in which a complex, multicellular organism arises from a single cell via spatiotemporal patterns that are repeatable and reproducible across the tree of life. As the organism grows, its cells change their number, size, shape, and position in response to genetic, chemical, and mechanical cues (see Figure 1a). Four-dimensional microscopy (three spatial dimensions and one time) is beginning to illuminate how these cues impact the fate of cells and the geometric form of tissues and organs that constrain and enable function at multiple scales [3]. Even though individual cells might seem to move chaotically, the large-scale cellular movements within tissues resemble a choreographed ballet and raise a few natural questions:

i) How can we quantify the patterns and predict the formation of different organ systems?

ii) How can we understand these patterns from a biophysical and biochemical perspective as a function of the way in which cells divide, grow, and move in response to environmental cues?

iii) How can we control these movements to intervene and correct pathological development or guide tissue development in situations like organoid formation?

Here we focus on the property invariant quantification of large-scale cellular movements and draw inspiration from the study of objective transport barriers in hydrodynamics [2, 5]. Just as it is more meaningful to focus on the large-scale coherent structures in a complex flow rather than track individual particles, we believe that it is useful to quantify the large-scale motions that characterize tissue morphogenesis. Any framework that aims to analyze spatiotemporal trajectories in morphogenesis requires a self-consistent description of cell motion that is independent of the choice of reference frame or parameterization. This objective (frame-invariant) description of cell pattern ensures that the material response of a deforming continuum—e.g., a biological tissue—is independent of the observer [7]. One can quantify this idea mathematically by considering two reference frames that describe tissue flows and are related to each other via the transformation $\mathbf{R}(\lambda)\mathbf{Q}(\lambda) = \mathbf{Q}(\lambda)\mathbf{R}(\lambda) + \mathbf{h}(\lambda)$, where $\mathbf{Q}(\lambda)$, $\mathbf{h}(\lambda)$ are time-dependent rotation matrix and translation vector respectively. A quantity is objective (frame invariant) if the corresponding descriptions in both frames transform appropriately: scalars $c(\lambda)$ (e.g., concentration) must remain the same with $\mathbf{R}(\lambda)\mathbf{Q}(\lambda)$: vectors $\mathbf{v}(\lambda)$ (e.g., velocity field) must transform via the metric $\mathbf{B}(\lambda) = \mathbf{Q}(\lambda)\mathbf{h}(\lambda)$; second-order tensors $\mathbf{A}(\lambda)$ (e.g., strain rate) must transform via the rule $\mathbf{B}(\lambda)\mathbf{A}(\lambda)\mathbf{B}(\lambda)^{-1} = \mathbf{Q}(\lambda)\mathbf{A}(\lambda)\mathbf{Q}(\lambda)^{-1}$; and so forth [7].

Though one can technically derive a full mathematical model of a skater on ice, such a model is hardly informative for theoretical understanding. The model would have to incorporate the motion of the head, torso, and every limb—all controlled simultaneously. This challenge provokes the idea of a good candidate for modern machine learning methods, such as reinforcement learning. However, we are interested in the problem by designing the simplest realistic mechanical model as possible. We focus on the skater’s motion without the blade’s friction with ice, which is a reasonable assumption for a description of the motion on short to intermediate time scales.

During the continuous motion of a skater on ice, the skate in contact with the ice can only move in the direction of the blade. When the skate turns with respect to the ice, the direction of motion also changes. There is thus a constraint on the velocities of the skate on ice. One cannot write the skate velocity constraint in terms of coordinates only, meaning that the mechanical system

---

The image contains diagrams and figures related to the topic of figure skating and cellular flows, but the text does not directly reference them. The text focuses on the mathematical and physical understanding of cellular movements and morphogenesis.
A priori is Mathematics and Statistics Awareness Month! Each year, the Joint Policy Board for Mathematics—a collaboration between SIAM, the American Mathematical Society, the American Statistical Association, and the Mathematical Association of America—holds a month-long celebration to enhance public understanding and appreciation of mathematics and statistics. Both subjects have real-world societal impacts in nearly every imaginable field, such as medicine, biotechnology, energy, manufacturing, and business. Throughout the month of April, universities, high schools, student groups, research institutes, professional organizations, and other related organizations host math-related events. These activities often include workshops, lectures, films, exhibits, houses, festivals, lectures, art exhibits, poetry readings, and other events centered around themes related to mathematics and statistics. Due to the ongoing pandemic, participants are encouraged to celebrate virtually this year and use the hashtag #MathStatMonth on social media to share their festivities.

Mathematics and Statistics Awareness Month originated in 1986 as Mathematics Awareness Week under then-U.S. president Ronald Reagan, who noted that enrollment in U.S. mathematical programs was declining. Mathematics Awareness Week initially focused on national-level events, such as a mathematics exhibit at the Smithsonian Institution and a reception on Capitol Hill. It became Mathematics Awareness Month in 1999 and began to shift its emphasis towards local, state, and regional activities. In 2017, the name changed to Mathematics and Statistics Awareness Month to recognize important research in both fields. The inaugural celebration marked a time when these disciplines have grown throughout the years, the event has remained dedicated to increasing the visibility of mathematical and statistical research across a wide audience.

University department chairs, high school teachers, public policy representatives, and other professional leaders can access and share resources that help educators and the public about the importance of mathematics and statistics in ongoing scenarios like sustainability, internet security, disease, and climate change. Mathematical and statistical research drives technological innovation and leads to discoveries that expand the impact of broad societal importance across many scientific fields. Here, several members of the SIAM News Editorial Board detail the ways in which they utilize mathematics to solve engaging problems.

Hans Kaper (Georgetown University), editorial chair of SIAM News and a long-time applied mathematician by training, education, and profession, and my interests lie in the field of mathematical physics and non-linear field theories of mechanics and mathematical physics at the University of California, Davis): “Anyone who has tried to enter or exit a massive lecture room, music hall, or other large venue has likely been stuck in a crowd. This situation is not a pleasant abstraction; it reflects reality but should not be thought of as ‘reality.’ It reveals the essential mechanism that drives the phenomenon of interest and allows us to explore various scenarios, whether theoretically or computationally.”

Among the natural phenomena that have fascinated me in the past are reaction-diffusion fusion phenomena in combustion systems, vortex formation and transport in high-temperature superconductors, and pattern formation in magnetic materials. I have recently become interested in climate issues and modeling the effects of human activities on Earth’s climate system. Some of my current work is related to the dynamics of glacial cycles during the Pleistocene, problems that concern food systems and food security, and mathematical approaches to resilience.”

Korana Burke (University of California, Davis): “The process of entering or exiting a large crowd often involves some kind of social interaction that can be modeled and analyzed.”

Morphydynamics

By Jillian Kunze

Continued from page 1

by cell velocities. $V_{i}^{*}(x,t)$ characterizes the maximum rate of separation of points in a neighborhood of $x_{0}$—denoted by the infinitesimal vector $dx$—during the time window $[t_{0},t]$ (see Figure 2). The FTLE has a natural interpretation in continuum mechanics and is related to the largest exponent eigenvalue of the Cauchy-Green strain tensor $[7]$, therefore serving as a natural invariant measure of deformation in a continuous medium.

When deploying this approach on light-sheet microscopy data from the embryo of a normally-developing chick that involves $10^{7}$ cells (Figure 3a)[4], we see that the dynamic morphoskeleton consists of two repellers—critical boundary regions across which cells appear to flow and likely experience different fates—and one attractor (see Figure 3b). Repeller 1 marks a dynamic boundary between embryonic and extra-embryonic regions. By contrast, repeller 2 marks the anterior-posterior boundary of a characteristic feature that is known as the primitive streak (PS); a zone of strong cellular convergence (an attractor) during early embryogenesis. First, we note that repellers remain invisible to Euelerian and Lagrangian tools that researchers use in multicellular flows.3 This fact may explain why repellers appear to be undocumented in the literature, despite their relevance for cell fate assignment.

Second, we notice that just an hour after cells have barely started to move, the dynamic morphoskeleton captures the PS’s early footprint—well before it is actually visible to conventional tools (see Figure 3c). This approach can also detect preliminary signatures of abnormal developmental use. Of a drug to inhibit the presence of a critical diffusible morphogen (FGF) that is required for early gastrulation causes the PS formation to fail (see Figure 3d) and results in a lack of anterior-posterior cell differentiation, which is quantified by the loss of repeller 2 (evident in the left panels of Figure 3b and 3d). Similar analysis of a whole curved embryo of a developing fruit fly with roughly 6,000 cells allows us to visualize how narratives and repellers characterize the motions that lead to gastrulation in both normal and pathological development [6].

An animation in the online version of this article depicts the time evolution of the dynamic morphoskeleton for the FGF receptor inhibitor embryo.

The enormous amounts of data that are rapidly becoming available from large-scale imaging of biological development require proper invariant methods of analysis. The aforementioned approach—which integrates local (cell-based) and nonlocal (neighborhood/issue-based) cues—provides a step in the right direction. The dynamic morphoskeleton sets the geometric stage for uncovering the dynamic organizers of cellular movements and tissue formation. It also provides a lens for uncovering the underlying relevant mechanisms at play. When we combine the morphoskeleton with the ability to track and manipulate gene expression levels, mechanical forces, etc., perhaps we will be able to determine the biological mechanism underlying normal and pathological morphogenesis and move a little closer to answering one of the grand questions of modern biology.

References


Matti Serra is an assistant professor of physics at the University of California, San Diego. He was previously the Sheard Distinguished Science Fellow at Harvard University. L. Mahadevan is a professor of applied mathematics, mechanics, and organismic and evolutionary biology at Harvard University.