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Cells as strain-cued automata

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ABSTRACT

We argue in favor of representing living cells as automata and review demonstrations that autonomous cells can form patterns by responding to local variations in the strain fields that arise from their individual or collective motions. An autonomous cell's response to strain stimuli is assumed to be effected by internally-generated, internally-powered forces, which generally move the cell in directions other than those implied by external energy gradients. Evidence of cells acting as strain-cued automata have been inferred from patterns observed in nature and from experiments conducted *in vitro*. Simulations that mimic particular cases of pattern forming share the idealization that cells are assumed to pass information among themselves solely via mechanical boundary conditions, i.e., the tractions and displacements present at their membranes. This assumption opens three mechanisms for pattern formation in large cell populations: wavelike behavior, kinematic feedback in cell motility that can lead to sliding and rotational patterns, and directed migration during invasions. Wavelike behavior among ameloblast cells during amelogenesis (the formation of dental enamel) has been inferred from enamel microstructure, while strain waves in populations of epithelial cells have been observed *in vitro*. One hypothesized kinematic feedback mechanism, "enhanced shear motility", accounts successfully for the spontaneous formation of layered patterns during amelogenesis in the mouse incisor. Directed migration is exemplified by a theory of invader cells that sense and respond to the strains they themselves create in the host population as they invade it: analysis shows that the strain fields contain positional information that could aid the formation of cell network structures, stabilizing the slender geometry of branches and helping govern the frequency of branch bifurcation and branch coalescence (the formation of closed networks). In simulations of pattern formation in homogeneous populations and network formation by invaders, morphological outcomes are governed by the ratio of the rates of two competing time dependent processes, one a migration velocity and the other a relaxation velocity related to the propagation of strain information. Relaxation velocities are approximately constant for different species and organs, whereas cell migration rates vary by three orders of magnitude. We conjecture that developmental processes use rapid cell migration to achieve certain outcomes, and slow migration to achieve others. We infer from analysis of host relaxation during network formation that a transition exists in the mechanical response of a host cell from animate to inanimate behavior when its strain changes at a rate that exceeds 10^{-4}–$10^{-3}\,s^{-1}$. The transition has previously been observed in experiments conducted *in vitro*.

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1. Introduction

The depiction of a cell as a "strain-cued automaton" is defined for the purposes of this article by the multi-scale paradigm of Fig. 1. All the chemical and physical actions that occur within a single cell (cell-scale phenomena) are subsumed in an elementary response function for the cell (the "single-cell response function") (Cox, 2010). The response function prescribes the next action of an individual cell given only the mechanical boundary conditions (tractions and displacements) acting on its surface, which serve as stimuli for the cell's next migratory action. The mechanical boundary conditions are computed as functions of time by simulating the behavior of a large population of cells (population-scale phenomena), with each cell governed by a common single-cell response function; the mechanical boundary conditions for one cell are determined from the relative motions of all its neighboring cells in the population-scale simulation.

The multi-scale paradigm has the virtue that it couples intra-cell and population-scale phenomena, both of which may be extremely complex, via a response function that can be very simple. In several of the examples reviewed in the following, the single-cell response function is controlled by just one or two scalar parameters. The plausibility of such a simple coupling between scales is rooted in the integral nature of cells.

In the strain-cue theories discussed in this work, chemical factors are absent from the variable set (boundary conditions) used to define the current state of a cell via the single-cell response function. Nevertheless, they are always present implicitly in the multi-scale paradigm. For example, at the population scale, a chemical factor might uniformly permeate a population of cells at some time, causing either the single-cell response function or the constraints on cell motions (e.g., the resistance to motion or history effects) to change for all cells. However, such a chemical effect need not in itself generate a pattern in the population; we will show in the following that cells can form patterns when guided by a single-cell response function that refers to each cell's mechanical boundary conditions alone, is common to all cells that actively participate in forming the pattern, and is time-invariant over the duration of the pattern forming process. Further remarks on the role of chemical factors in a system of cells acting as strain-cued automata in the paradigm of Fig. 1 can be found in the document "soldiers.pdf", a thought experiment, published online as Supplementary Material.

This article can be regarded as addressing two ideas. The first is the proposition that:

For certain time intervals and over certain spatial domains, individual cells act as strain–cued automata. (1a)

The second is the conditional statement:

If each cell in a large population of cells acts as a strain–cued automaton, governed by a common, time–invariant response function, then the population can develop spatial patterns similar to a number of patterns observed in nature. (1b)

The conditional statement Eq. (1b) can be proven by deductive reasoning: computer simulations of the development of patterns constitute a mathematical proof, executed by numerical methods. On the other hand, the proposition Eq. (1a), that cells do indeed act as strain-cued automata during development or in disease, is not easily proven. However, considerable credence can be found in the extent to which simulations of strain-cued automata match details of morphological development in the cases studied. Furthermore, at the intuitive level, one might foresee that a system known to be as rich in its behavioral potential as the living cell should be capable of acting as a strain-cued automaton, if that were to offer an advantage.

In the proposition Eq. (1a), the phrase "for certain time intervals and over certain spatial domains" is key. Generally, cells are known to respond to chemical, strain, and electromagnetic stimuli, not strain stimuli alone. But in this work, we hypothesize that, during the formation of patterns by certain types of migrating cell, a cell might determine its next migratory choice using only (or predominantly) the information contained in the local strain, or the time rate of change of the local strain, that it senses.

1.1. The breaking of symmetry

In the most widely cited depiction of pattern forming in biological systems, symmetry is broken in a cell population when a spatial pattern arises in some chemical factor: the concentration c_1 of chemical species 1 changes from being uniform in space to being some function $c_1(\boldsymbol{x})$ of the spatial variable $\boldsymbol{x}$. The seminal theory for this transition is the reaction–diffusion model of Turing: two or more species, 1 and 2, diffuse through space while simultaneously reacting with each other in reactions that modify their concentrations, c_1 and c_2 (Turing, 1952). Turing's model needs consider only the concentrations of the chemical species, independently of other factors, to break symmetry and form templates for a wide range of patterns.

In recent theoretical work (Cox, 2010, 2013, 2011; Serra-Picamal et al., 2012), a fundamentally different mechanism for symmetry breaking is demonstrated: if cells in a population migrate by responding to variations in the strain fields $\varepsilon(\boldsymbol{x})$ that arise around them, with each cell governed by the same rule for choosing the direction of its migration given its local strain environment, then the population can spontaneously develop either wavelike disturbances (Cox, 2010; Serra-Picamal et al., 2012), sliding layered patterns (Cox, 2013), or branched, network patterns (Cox, 2011). In these theories, symmetry breaking