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A circuit basis for morphogenesis

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ABSTRACT

Morphogenesis is the generation of structural patterns through a dynamic process. The mathematical basis of morphogenesis has long been studied with the key initial work by Alan Turing. This paper explores the consequences of a circuit basis for reaction–diffusion systems on morphogenesis, including the reachability of patterns and the logical basis of pattern stability. We consider how morphological patterns can arise through iterative computation and produce robust forms. Through an exhaustive analysis of reaction–diffusion dynamics in a minimal model of morphogenesis, we show how the stability and reachability of morphologies are influenced by their circuit basis. We show that this model exhibits similar behavior to the recently experimentally observed dynamics not accounted for by Turing's original model. We conclude by presenting an additional class of metastable patterns exhibited in this model.

1. Introduction

Patterns displayed by organisms serve a number of roles, such as camouflage from predators and animal communication, which are commonly studied within biological disciplines. The study of pattern formation has enjoyed some attention in theoretical computer science and physics [3,4,11,1,6,18], ranging from patterns of particles to robots. In this work we focus on a minimal model of morphogenesis based upon boolean circuits. This model both captures and extends ideas originally developed by Turing [16] that describe classes of patterns produced by morphogenic processes. The significance of a circuit model for morphogenesis is underscored by recent advances in synthetic biology.

Techniques for the physical synthesis of genetic circuits [8] and DNA computers [13] have now reached the point where some classes of reaction dynamics can be expressed in the same bases as electronic circuits and computer programs. The relative simplicity of engineering with circuits and their implementation with synthetic biology motivate the extension of Turing's mathematical framework from the original linearized analysis of differential equations to studies of circuit bases. Kauffman pioneered the study of arbitrary genetic circuits by studying boolean networks with random topologies, finding that networks can be stable and generally exhibit short cycles [9]. Evidence was later provided to support the mapping between discrete genetic networks and continuous systems [7]. Edwards et al. extend computational theory to genetic networks in terms of symbolic dynamics [5]. These advances in computational and dynamical systems theory have provided some of the initial foundation for extending theoretical computer science to the design of circuits in synthetic biology.

While genetic circuits are a powerful mechanism for defining reaction systems, in the context of morphogenesis we must also address the need for spatial propagation of information. Information propagation is accomplished via diffusion in Turing's framework. One of the most pervasive techniques for spatial propagation of information in discrete computational models is cellular automata (CA) [17]. CAs are expressed as local update rules that specify the state of an element in a

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discrete space as a function of its neighborhood, such as a cell and its nearest neighbors. In our work a simple CA is used to spatially propagate information. Morphogenesis is achieved by coupling circuit-based reaction networks with a diffusion-like CA. We begin by revisiting Turing's model, the corresponding predictions, and recent experimental investigations into Turing's work. We then show that our proposed model produces the same classes of patterns as Turing's model, a class of recently experimentally discovered dynamics not be accounted for in the original Turing model, and an additional class of metastable patterns.

1.1. Morphogenesis

In Turing's Chemical Basis of Morphogenesis [16], he presents a mathematical framework for describing the dynamics of morphogenesis as a reaction–diffusion (RD) system. One of the critical contributions of this theory was the identification of spatiotemporal patterns that can arise under a simplified RD model. The model describes the RD of morphogens using differential equations. The two-morphogen model can be expressed as

$$\frac{dX(r)}{dt} = f(X(r), Y_{(}r)) + \mu(X(r+1) - 2X(r) + X(r-1)) \tag{1}$$

$$\frac{dY(r)}{dt} = g(Y(r), X_{(}r)) + \nu(Y(r+1) - 2Y(r) + Y(r-1)), \tag{2}$$

where X, Y are the two morphogens, r is position in 1D, f, g are reaction functions specifying the change in concentration of X and Y respectively, and μ, ν are the diffusion rates for each morphogen. If the system is assumed to be near equilibrium then a locally linear approximation can be used

$$\frac{dx(r)}{dt} = ax(r) + by(r) + \mu(x(r+1) - 2x(r) + x(r-1)) \tag{3}$$

$$\frac{dy(r)}{dt} = cx(r) + dy(r) + \nu(y(r+1) - 2y(r) + y(r-1)), \tag{4}$$

where x and y are the morphogens in the linearized system, and a, b, c, d are "marginal reaction rates" as termed by Turing. The diffusion rates and marginal reaction rates determine the types of patterns that may emerge from such RD systems. This theory has recently been experimentally verified in a system of synthetic chemical cells, and related to the corresponding linear stability analysis [15].

The linearized model exhibits asymptotic behavior which leads to stationary or temporally-oscillatory patterns. Turing further described the asymptotic behaviors as 6 subclasses, defined by the dynamics and wavelength of the pattern. The stationary case with long wavelength is observed when all cells fixate into the same state. The oscillatory case with long wavelength is observed when all cells oscillate between the same states in synchrony. The stationary case with short wavelength is observed when cells have different states from their nearest neighbors, but matching states to their next nearest neighbors. The corresponding oscillatory case with short wavelength is observed when next nearest neighbors oscillate in synchrony, but maintain differing states to their nearest neighbors. The remaining 2 subclasses describe finite wavelength patterns intermediate between short and long wavelengths, either stationary or oscillatory. We will return to these behaviors when discussing their computational bases.

Of great significance is the finding by Tompkins et al that in their physical system there is an additional behavioral subclass that arises [15]. This behavior is observed as a mixture between oscillatory and stationary states. In this case, a subset of cells in the system enter a stationary state, while the remaining cells oscillate with, in the Tompkins et al. findings, a short wavelength. These cells have a regular spatial organization. While this behavior was observed experimentally, it was not reproducible with a linearized model such as the one used to predict the original asymptotic dynamics, or through nonlinear simulations on homogeneous cells. Li et al have shown that heterogeneous distributions of cells can adopt this pattern in nonlinear simulations; however, simulations were not capable of replicating the mixed behavior observed by Tompkins et al. when using experimentally matched heterogeneity [10]. In the following section we introduce our extension of Turing's model and explain this recently discovered behavior, previously unbeknownst to Turing, in terms of its circuit basis.

2. Model

Our extension of Turing's mathematical framework for chemical morphogenesis to its circuit basis is an anticipation of the continued advancement of engineered molecular systems to behave as computational circuits. The model utilizes logic gates as reactions, and spatial dynamics are implemented in a diffusion-like system similar to CA. The system is defined over a 2D space with periodic boundary conditions. We conduct an exhaustive search over all possible reactions for 2-morphogen systems at a range of diffusion rates, reporting on the stability and reachability of structural patterns as a function of the corresponding RD systems.

The system is defined as a square lattice. Each grid site in the lattice may contain N boolean morphogens, where the state of each grid site is a boolean state vector $\vec{x}$ of length N. Diffusion is defined over the von Neumann neighborhood,