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Editor

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ensemble-averaging approach [5, 8], except that the momentum exchange and mass transfer source terms are directly obtained from the NDF description of the particle phase.

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Pattern Formation and Development

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Mathematics Subject Classification

35K57; 92-00; 92BXX

Synonyms

Morphogenesis; Self-organization

Glossary

Diffusion-driven instability The mechanism via which chemical patterns are created from an initially uniform field due to the destabilizing action of diffusion.

Morphogenesis The generation of structure and form in an embryo.

Morphogen A chemical that influences the differentiation of cells during embryogenesis.

Short Definition

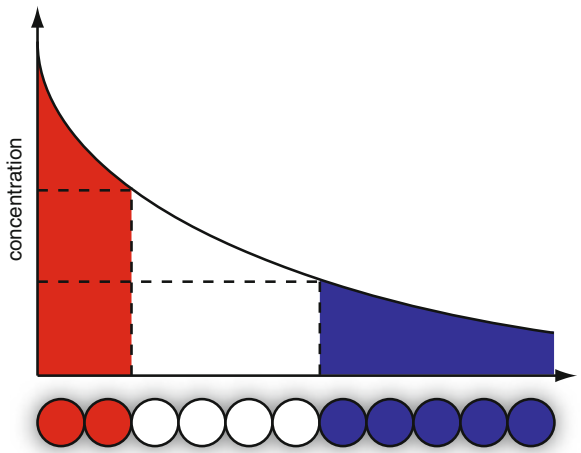
The emergence of global spatiotemporal order from local interactions during embryonic development.

Description

Development is overflowing with examples of self-organization, where local rules give rise to complex structures and patterns which, ultimately, bring about the final body structure in multicellular organisms. Understanding the mechanisms governing and regulating the emergence of structure and heterogeneity within cellular systems, such as the developing embryo, represents a multiscale challenge typifying current mathematical biology research.

Classical Models

Classical models in the field consist mainly of systems of partial differential equations (PDEs) describing concentrations of signaling molecules and densities of various cell species [8]. Spatial variation, arising from diffusion/random motion and a variety of different types of directed motion (for example, due to chemical or adhesion gradients), is represented through the use of different types of flux terms, and chemical reactions, cell proliferation and cell death through source terms which are polynomial and/or rational functions. The major advantages of using such types of models lie in the wealth of analytical and numerical tools available for the analysis of PDEs. For simple systems, exact analytical solutions may be possible and, where they are not, separation of space and time scales or the exploitation of some other small parameter enables the use of multiscale asymptotic approaches which give excellent insight into system behavior under different parameter regimes [3]. As the number of model components becomes too unwieldy or the interactions too complex for such approaches, increasingly sophisticated computational methods allow accurate numerical approximations to be calculated over a wide range of parameter space.



Pattern Formation and Development, Fig. 1 An illustration of Wolpert's "French Flag" model [15]. A concentration gradient of a morphogen induces subsequent cell differentiation according to thresholds in concentration with cells experiencing concentrations above the highest threshold becoming *red*, cells between thresholds becoming *white*, and cells below the lower threshold becoming *blue*

Morphogen Gradient Models

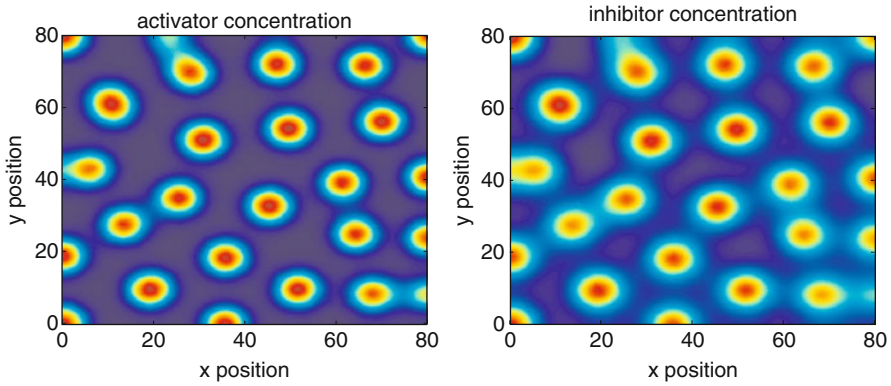
Wolpert [15] proposed one of the first mechanisms for providing positional information by a morphogen gradient with his "French Flag" model. In the model, each cell in a field has potential to be either blue, white, or red. When exposed to a concentration gradient of morphogen, arising from the combination of production at a localized source, diffusion, and decay, each cell interprets the information from the concentration profile by varying its response to different concentration thresholds of morphogen: Cells become blue, white, or red according to their interpretation of the information – see Fig. 1 for an illustration. Applications of Wolpert's model are still used in a number of fields, including whole organism scale modeling of *Drosophila* patterning [13].

Turing Reaction-Diffusion Models

Turing's seminal work [12] proposed a mechanism via which a field could organize without any external cue from the environment. Given a system consisting of two or more chemicals (morphogens), which react according to certain rules, and diffuse at different rates throughout a field, spontaneous patterns in chemical concentration may arise as diffusion destabilizes the spatially uniform steady state of the system. This is known as a diffusion-driven instability and subsequent cell differentiation is then assumed to arise much in the same way postulated by Wolpert except that here, typically, cells respond to one threshold instead of multiple thresholds. Applications of the Turing model to patterning during development abound, and potential candidates for Turing morphogens include: (1) Nodal and Lefty in the amplification of an initial signal of left–right axis formation and zebrafish mesoderm cell fates; (2) Wnt and Dkk in hair follicle formation; (3) TGF-β as the activator, plus an unknown inhibitor, in limb bud morphogenesis [1].

General, necessary and sufficient, conditions for a Turing instability on an n-dimensional spatial domain are presented in the literature for the two-component system and can be found in most textbooks, see for example [9], but the analysis for more than two chemicals is still an open question. Methods for the analysis of Turing systems on finite domains start by linearizing around a spatially homogeneous steady state and examining the behavior of the discrete spatial Fourier modes as one of the model parameters is varied. Asymptotic techniques, such as the method of multiple scales, and the Fredholm alternative are used to examine the exchange of stability of bifurcating solution branches in a small neighborhood of the bifurcation point, and may be used to distinguish the types of patterns that arise. Figure 2 illustrates the patterns that may arise in such a model in two spatial dimensions.

Turing's postulation has stimulated vast amounts of theoretical research into examining the finer detail of the Turing model for patterning, for example: (1) characterization of the amplitude equation and possible bifurcations in terms of group symmetries of the underlying problem being offered as an alternative approach to the weakly nonlinear analysis; (2) many results have been derived on the existence and uniqueness of localized patterns, such as spikes, that arise in certain Turing models; (3) the development of sophisticated numerical methods for solving Turing models on a variety of surfaces and investigating bifurcation behavior. For a comprehensive guide to the analytical and numerical methods used to investigate Turing models, see [14] and the references therein. The model has been shown to be consistent with many observed pattern formation processes and to also yield predictions that agree with experimental manipulations of the system.



Pattern Formation and Development, Fig. 2 Results from numerical simulation of a Turing reaction-diffusion model in two dimensions. Gierer–Meinhardt kinetics [9, page 77] were used with parameters $b = 0.35$ and $D = 30$ (see [2] for more details) and red (*blue*) indicates high (low) chemical concentration

However, the model can produce many more patterns than those observed in nature and this leads to the intriguing question of why patterning in biology is rather restricted. It is observed that in many cases in biology, patterning occurs behind an advancing front, either of a permissive signaling cue, or of domain growth. Analysis of the model shows that precisely these constraints are sufficient to select in a robust manner certain (observed) patterns at the expense of other (unobserved) patterns. It is important to note that such a propagating front can also serve to move a bistable system from one state to another, and this is an alternative mechanism to the Turing model for pattern formation.

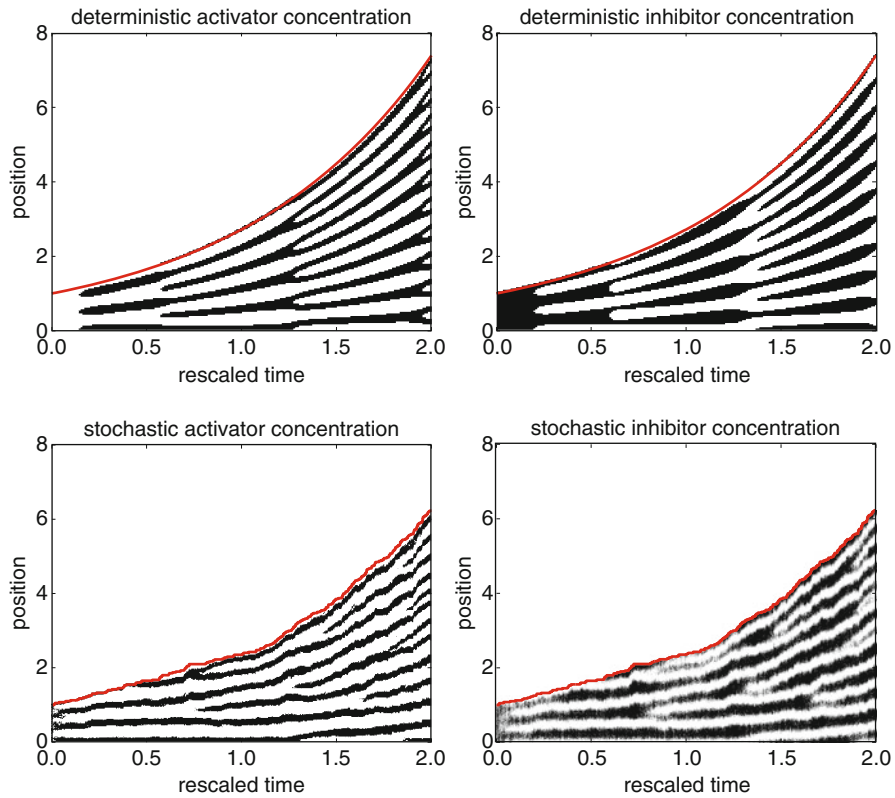
Cell Chemotaxis Models

Whereas Turing's model assumes no explicit interaction between cells underlying the field and evolution of the chemical pattern, cell chemotaxis models assume that cells move preferentially up chemical gradients, and at the same time amplify the gradient by producing the chemical themselves. Examples of chemotaxis during development include the formation of the gut (gastrulation), lung morphogenesis, and feather bud formation [1]. In addition to modeling chemotaxis in development, such models are also commonly considered for coat marking patterns and swarming microbe motility. We note that there are numerous types of "taxis" that can be observed during development, including those up/down gradients in cellular adhesion sites (haptotaxis), substrate stiffness (mechanotaxis), light (phototaxis), to name but a few [1, 11].

Whereas the Turing model gives rise to a parabolic system, taxis models can be of mixed parabolic/hyperbolic type, although the parabolic part is usually taken to dominate. Mathematically, therefore, taxis models are similar to the Turing model, with linear and nonlinear analyses demonstrating the existence of bifurcations and predicting the emergence of steady state patterns. In addition, a large body of work has been devoted to considering the potential for certain formulations of the chemotaxis model to exhibit "blow up," where solutions become infinite in finite time, and showing existence and uniqueness of solutions [5]. The unifying mechanistic theme behind many of these models – Turing, chemotaxis, and mechanochemical – is that of short-range activation and long-range inhibition [9]. From a mathematical viewpoint, the patterns exhibited by all these models at bifurcation are eigenfunctions of the Laplacian.

Growing Domains

Throughout development the embryo undergoes enormous changes in size and shape, and as a result biologically accurate patterning models must take these variations into account if they are to be capable of validating hypotheses and making predictions. The inclusion of growth in reaction-diffusion models was first considered sytematically by Crampin and coworkers [4] who derived a general formulation by considering conservation of mass and the application



Pattern Formation and Development, Fig. 3 The Turing model on a growing domain using both deterministic (PDE) and stochastic (Monte Carlo) formulations. Schnakenberg kinetics [9, page 76] were used with parameters $k_1 = 1.0$, $k_2 = 0.02$, $k_3 = 10^{-6}$, $k_4 = 3.0$, $D_A = 10^{-5}$, $D_B = 10^{-3}$, and uniform growth rate $r = 10^{-4}$. (See [4] for more details of the growing domain formulation.) *Black shading* indicates where the system is above the spatially uniform steady state, and the *red line* the edge of the domain

of Reynold's transport theorem. The extra terms arising in the reaction-diffusion system as a result of growth occur as material is both transported around the domain and diluted during growth. Key to applications of Turing's model to development was the discovery that domain growth increases the reliability of pattern selection, giving rise to consistent patterns without such tight control of the reaction parameters and, more recently, to the discovery that patterns may form in systems that do not satisfy Turing conditions under certain types of domain growth [7]. Figure 3 shows the results of numerical simulation of the Turing model on a growing domain, and illustrates the changing patterns that arise as the domain grows.

More Recent Developments

However, one should be aware of the limitations of these classical models. The flux and/or production terms in the conservation formulation generally employed are often phenomenological, without derivation from universal or fundamental principles. In addition, as the material density becomes low, stochastic effects can become significant. (Compare, for example, the results of stochastic and deterministic simulations of patterning on a growing domain in Fig. 3.) Finally, tortuous cellular level geometry complicates the investigation of spatial fluctuations at the cellular scale and the possibility of large variations among neighboring cells prevents straightforward use of a continuum limit. Moreover, the parameters within the kinetic terms themselves arise due to dynamics at a lower scale level. As such, many of the recent developments in modeling pattern formation have explored the derivation of these classical models from individual considerations where cell-level behavior may be taken into account [10] and the

role of noise explicitly studied. However, with careful consideration of these pitfalls and awareness of when and where techniques can successfully be applied, PDEs remain one of the most useful and insightful tools for modeling self-organization in developmental biology [1].

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Petrov-Galerkin Methods

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Mathematics Subject Classification

65N30

Petrov-Galerkin Methods for Variational Problems

For the solution of partial differential equations, a corresponding variational problem can be derived, and the variational solution can be approximated by → Galerkin methods. Petrov-Galerkin methods extend the Galerkin idea using different spaces for the approximate solution and the test functions.

This is now introduced for abstract variational problems. Let U and V be Hilbert spaces, let $a: U \times V \longrightarrow \mathbb{R}$ be a bilinear form, and for a given functional $f \in V'$ let $u \in U$ be the solution of the variational problem $a(u, v) = \langle f, v \rangle$ for all $v \in V$.

Let $U_N \subset U$ and $V_N \subset V$ be discrete subspaces of finite dimension $N = \dim U_N = \dim V_N$. The Petrov-Galerkin approximation $u_N \in U_N$ is a solution of the discrete variational problem $a(u_N, v_N) = \langle f, v_N \rangle$ for all $v_N \in V_N$.

It is not a priori clear that the continuous and the discrete variational problems have unique solutions. For the well-posedness of the continuous problem, we assume that positive constants $C \geq \alpha > 0$ exist such that

$$|a(u, v)| \leq C \|u\|_U \|v\|_V$$

and

$$\sup_{v \in V \setminus \{0\}} \frac{a(u, v)}{\|v\|_V} \geq \alpha \|u\|_U ,$$

and that for every $v \in V \setminus \{0\}$ some $u_v \in U$ exists such that $a(u_v, v) \neq 0$. The variational problem corresponds to the equation $Au = f$, where $A \in \mathcal{L}(U, V')$ is the