Lateral Inhibition Models of Developmental Processes*

GEORGE F. OSTER
Departments of Biophysics, Entomology, and Zoology,
University of California, Berkeley, California 94720

Received 1 June 1987; revised 29 September 1987

ABSTRACT

Most mathematical models for embryological pattern formation depend on the phenomenon of local autocatalysis with lateral inhibition (LALI). While the underlying physical and chemical mechanisms hypothesized by the models may be quite different, they all predict very similar kinds of spatial patterns. Therefore, since the underlying mechanism cannot in general be deduced from the pattern itself, other criteria must be applied in evaluating the usefulness of pattern formation models. The author points out how LALI is implemented in neural, chemical, and mechanical models of development, and suggests some general properties of LALI models that may impose limitations on organ shapes in ontogeny and phylogeny.

1. INTRODUCTION

Although embryology is principally an experimental science, mathematical theories have heavily influenced the thinking of embryologists. Indeed, development is one of the rare fields in biology where theory has had a strong influence on experiments—at least amongst a small group of receptive biologists. However, many developmental biologists are now taking a hard look at the actual contributions pattern formation models have made to their field, and I sense some disillusionment. Moreover, the current thrust in developmental biology is toward the molecular and genetic levels of organization, and this is due, in some part, to the failure of classical embryological techniques, which take a larger view of the embryo, to provide satisfactory explanations for pattern formation phenomena.

In this paper I shall discuss one of the principle criticisms leveled at embryological models: regardless of the proposed mechanisms, they all make

---


pretty much the same predictions. The reason for this is that most pattern formation models are built around the general phenomenon of local instabilities coupled with lateral inhibition. The purpose of my discussion will be to illustrate some of the various disguises this mechanism assumes, and to point out some predictions common to all models of this type. The moral of my story will be that one usually cannot infer mechanism from pattern. A developmental biologist might then fairly ask: what use are pattern formation models? I shall propose some modest answers.

In order to make my discussion accessible to biologists, I shall relegate all of the mathematics to boxed asides and focus on the qualitative similarities amongst the models. Since I am most familiar with my own models and those of my collaborators, I will draw on these as examples—with no slight intended towards the large body of excellent work by others.

2. MODELS WITH LOCAL ACTIVATION AND LATERAL INHIBITION

Most—but not all\textsuperscript{1}—models of embryological pattern formation are based on the principle of local activation with lateral inhibition (which I will henceforth abbreviate as LALI). The principle underlying this mechanism was first enunciated by Ernst Mach more than a century ago in connection with the visual illusion now known as Mach bands \cite{5}. A variant of this illusion is shown in Figure 1. In this section I shall show how a variety of embryological models are based on the same principle that produces the illusory spots in Figure 1.

**NEURAL MODELS**

In the neural net shown in Figure 1 the local activation is simply the incident light, and lateral inhibition is "hard wired" as inhibitory neural connections. The pattern of spots in Figure 1 is not too interesting; however, neural models with LALI are capable of producing patterns of great diversity and complexity. For example, Ermentrout, Campbell, and Oster \cite{1} used a neural model to reproduce a great variety of pigment patterns found on the shells of mollusks. Their model assumed that the mantle cells that secrete the pigment are driven by stimuli from a neural net with the property of LALI; a few of these patterns are shown in Figure 2. The structure of the model is illustrated in Figure 3, and the model equations are given in Box A. An example of simulated shell patterns is given in Figure 4.

\textsuperscript{1}For example, the "clockface model" of French, Bryant, and Bryant \cite{2} for limb regeneration depends on purely topological arguments (cf. \cite{21}), and the model of Odell and Bonner \cite{14} for slime mold morphogenesis is based on fluid mechanical principles.
Fig. 1. The Hermann illusion: dark spots appear at the intersections of the white corridors. The explanation for this is shown by the schematic retinal neural net shown at the right. A retinal cell excited by light inhibits its neighbors. Thus a cell at an intersection has more of its surrounding neighbors illuminated than one in a white corridor. Thus it is inhibited more strongly than a corridor cell, creating the appearance of a darker field.

Fig. 2. The mollusk *Bankivia fasciata* exhibits such a diversity of shell patterns that malecologists first classified them into different species. All of these patterns can be reproduced by models with the property of local autocatalysis and lateral inhibition. [Photo by J. Campbell.]
FIG. 3. The neural shell model. Shell material and pigment are laid down sequentially and episodically. Sensory cells sense the pigment pattern secreted during episode $t$, which affects secretion during episode $t+1$ via a LALI neural network. $E =$ excitatory neural connections, $I =$ inhibitory neural connections.

DIFFUSION-REACTION MODELS

At about the same time as Ermentrout et al. were formulating their model, Meinhardt independently developed a model for mollusk shell patterns based on a diffusion-reaction mechanism [8, 9]. This model was able to recreate a great variety of shell patterns quite beautifully. Figure 5 shows a comparison of shell patterns produced by both the neural and the diffusion-reaction model; the model equations are given in Box B. It is clear that there is little to choose between them apart from the quality of the computer graphics.

The reason for this similarity is clear once one realizes that the diffusion-reaction model is just a disguised implementation of LALI, a fact first noticed by A. Gierer and H. Meinhardt in a landmark paper [3]. As shown in Figure 6, the structure of these models is that an autocatalytic reaction is quenched laterally by a fast-diffusing inhibitor, or by depletion of a substrate required for activator production [7]. Thus any pattern that can be created by a LALI neural model can also be produced by a diffusion-reaction model with the appropriate kinetics and relative diffusion properties [11]. Of course, the time scale involved in setting up the patterns may be
Ermentrout, Campbell, and Oster [1] assumed that the neural activity of the mantle stimulated pigment cells to secrete. The model equations they employed were of the following form (cf. Figure 3):

\[ P_{t+1}(x) = S[P_t(x)] - R_t, \]
\[ R_{t+1}(x) = \gamma P_t(x) + \delta R_t(x). \]

Here, \( P_t \) is the amount of pigment secreted during the time period \( t \), and \( R_t \) is the amount of a refractory substance produced during secretion. (Other forms of the model which incorporated pigment depletion and memory effects produce similar patterns.) The model parameters \( \gamma, \delta \) control the production and metabolism of \( R \). The neural net is connected so as to generate a lateral inhibitory field, which can be modeled by the following equations:

**Excitation:**

\[ E_{t+1}(x) = \int_{\Omega} W_E(x' - x) P_t(x') \, dx'. \]

**Inhibition:**

\[ I_{t+1}(x) = \int_{\Omega} W_I(x' - x) P_t(x') \, dx'. \]

Here the kernels \( W_E(x' - x) \) and \( W_I(x' - x) \) define the connectivity of the mantle neuron population by weighting the effect of neural contacts between cells located at position \( x' \) and a cell at \( x \). In order to achieve LALI, the inhibitory kernel \( W_I(x' - x) \) must be broader than the excitatory kernel \( W_E(x' - x) \); i.e., activation has a shorter range than inhibition. \( \Omega \) is the domain of the mantle; for most shells this is a finite interval, but it may be circular in the case of mollusks such as limpets and planar in cowries. Ermentrout et al. [1] present a linear analysis and numerical study of the patterns generated by these equations.
Fig. 4. (a) The pigment patterns are laid down episodically and sequentially as the shell grows in a linear spiral. (b) There are three basic patterns that characterize the shells of *Bankivia fasciata*: (1) the pigment-secreting cells color the shell in a continuous stripe, (2) the entire population of pigment cells across the mantle cycles in and out of the secreting state, (3) traveling waves of pigment secretion move laterally across the mantle. By adjusting the parameters to excite different types of instabilities, the neural model can generate these patterns. More complex patterns arise from composites of these and from interference patterns between waves. [Photo by J. Campbell.]
FIG. 5. (a) An example of a mollusk shell pigment pattern that can be modeled by (b) either neural equations (left panel: Ermentrout et al. [1]) or diffusion-reaction equations (right panel: Meinhardt and Klingler, [9]). These particular patterns resulted from the interaction of traveling waves of activity that propagated across the mantle. [Photo by J. Campbell.]
BOX B
A Diffusion-Reaction Model for Mollusk Shell Patterns

Meinhardt and Klingler [9] modeled the mollusk shell patterns using diffusion-reaction equations of the form

\[
\frac{\partial a}{\partial t} = D_a \nabla^2 a + A(a, h),
\]

(6)
\[
\frac{\partial h}{\partial t} = D_h \nabla^2 h + H(a, h),
\]

(7)
where \(A(a, h)\) and \(H(a, h)\) are the kinetics. The activator-inhibitor scheme they used was

\[
A(a, h) = \frac{\rho(\nabla^2 + \rho_0)}{h} - \mu_a a \quad \text{(activator)},
\]

(8)
\[
H(a, h) = \rho \partial_a^2 - \nu h + \rho_1 \quad \text{(inhibitor)}.
\]

(9)
The activator-substrate kinetics are

\[
A(a, h) = \rho h \partial_a^2 - \mu a \quad \text{(activator)},
\]

(10)
\[
H(a, h) = \sigma - \rho h \partial_a^2 - \nu h \quad \text{(substrate)},
\]

(11)
where \(\partial = a^2/(1 + \kappa a^2)\), and where all symbols but \(a\) and \(h\) are constant parameters.

Other kinetic schemes were required to mimic certain shell patterns, but all generated some kind of LALI dynamics. In order for Equations (6) and (7) to generate spatial patterns certain constraints on the kinetics and the relative diffusion rates are required. In particular, lateral inhibition requires that \(D_h > D_a\) (cf. Figure 6 and Box C). Meinhardt and Klingler [9] give an extensive intuitive discussion of the pattern-forming properties of these equations.

considerably longer for a diffusion-limited process; however, the final steady-state patterns are the same.

It is worth noting that most pattern formation models can be cast in the following form\(^2\).

\[
\text{rate of change of the morphogenetic variables} = \text{local dynamics} + \text{spatial interactions}. \quad (1)
\]

\(^2\)Not all models can be written in this explicit form. For example, the mechanochemical models we shall discuss below can only be written this way under special assumptions.
Local autocatalysis is accomplished by making the local dynamics unstable (or, for wave propagation, at least excitable). Lateral inhibition can be implemented in many ways, depending on the model. In neural models this is usually contained in the integral kernel (Box A), while in diffusion-reaction models, given in Box B, lateral inhibition depends on having the inhibitor (or substrate) diffuse more rapidly than the autocatalytic activator. Other kinetic schemes may not be so transparent, but all amount to a kinetic implementation of LALI. In mechanical systems LALI is even more disguised, as we shall see below. In all cases, the emergence of spatial patterns depends on having the right balance between autocatalysis and lateral inhibition; Box C shows how this balance is computed from the model equations.

CHEMOTACTIC MODELS

Diffusion-reaction models in embryology assume that a chemical prepattern is established prior to any morphogenetic movements. Subsequently, cells move, or differentiate, according to the chemical concentrations already established. For example, if the morphogen were a chemoattractant, then a chemical concentration pattern would trigger cell movements to mimic the chemical prepattern. This presupposes that the cell movements do not significantly distort the prepattern, or that different subpopulations of cells are involved in morphogen secretion and movement. However, if the same cells that secrete the attractant are free to move in response to the chemical gradients they set up, then spatial patterns can emerge as a consequence of
The phenomenon of local autocatalysis with lateral inhibition can create spatial patterns provided there is the right balance between the two effects. For example, if the autocatalytic reaction in Equation (7) is too strong, the inhibition will be too weak to quench it. Conversely, if the inhibitor diffuses too slowly, it will be unable to outrun the activation wavefront, and cannot arrest its progress. The standard way to evaluate the right balance between activation and inhibition to produce spatial patterns is to calculate the dispersion relation. This is a graph of the growth rate of different sized patterns as a function of their wavelength:

\[ \lambda(k) = \Lambda(k), \quad (12) \]

where \( k \) is the number of wave peaks per unit length \( (= 2\pi / \text{wavelength}) \). This formula is obtained by linearizing the dynamic equations, substituting harmonic solutions of the form \( e^{\lambda t + ikx} \), and solving for \( \lambda(k) \) (the exact procedure is given, for example, in [19]). The resulting graph of \( \lambda(k) \) has the general form shown below:

This graph shows that both small and large patterns die out, but that there is a range of patterns sizes that can grow (i.e. \( \lambda > 0 \)). For 1 dimensional models, the fastest-growing model is a good indicator of the final pattern size. In 2 and 3 dimensional models this is not always the case. Moreover, more exotic kinds of dispersion relations can also produce spatial patterns [6].
LATERAL INHIBITION MODELS

BOX D
Chemotactic Patterns

Oster and Murray [22] proposed a model for cartilage condensation patterns based on chemotactically responsive chondrocytes. This is just a variation on a theme originated by Keller and Segel [4] to describe the spatial pattern observed in bacterial populations.

Consider a population of cells migrating and secreting a chemoattractant $c$. Conservation equations for the cell density $n(x, t)$ [Equation (13)] and attractant concentration $c(x, t)$ [Equation (14)] can be written as (cf. [19])

$$\frac{\partial n}{\partial t} = M \nabla^2 n - \alpha \nabla \cdot n \nabla c,$$

(13)

$$\frac{\partial c}{\partial t} = D \nabla^2 c + \frac{bn}{n + h} - \mu c,$$

(14)

where $m > 0$ and $\alpha > 0$ are the cell motility and chemotactic parameters respectively, and $D$ is the diffusion coefficient of $c$. The secretion rate is a saturating function [e.g. $bn / (n + h)$, with $b$ and $h$ positive], and $\mu c$ is the degradation rate of $c$.

the interaction between cell movement and chemical diffusion. Mathematically, this is similar to the pure diffusion-reaction situation, except that the cell motion must be dominated not by diffusion, but by their chemotactic response. An example of equations governing this kind of pattern formation model are shown in Box D.

MECHANICAL MODELS

Spatial patterns can emerge directly from mechanical interactions between cells. This can come about in a variety of ways, all of which can be interpreted as LALI phenomena. An example of a mechanical pattern formation model is the cell traction model for feather germ formation proposed by Oster, Murray, and Harris [15]. The earliest sign of the feather pattern is an aggregation of motile dermal calls into a central column, as shown in Figure 7, which subsequently breaks up into isolated clusters of cells. Cell aggregations then spread out laterally from the initial column until a regular hexagonal array is established. The sequential aspect of this pattern appears to be an important factor in establishing the regular hexagonal geometry (see Box E).
FIG. 7. Feather germs form by the aggregation of motile dermal cells. First, a central column of cells forms, which then breaks up into isolated aggregates. Subsequent rows form sequentially by intercalation between existing foci, leading to a broad hexagonal array.

There are a number of possible mechanisms for generating these patterns, based on the properties of motile cells. For example, a diffusion-reaction mechanism can set up a chemical prepatter that attracts motile cells. The mechanical mechanism suggested by Oster, Murray, and Harris [15] depends on the ability of cell tractions to set up adhesive gradients in the extracellular matrix. The dermal cells which will form the feather germs move within an intracellular fibrous matrix by adhering to adhesive sites on the matrix fibers. The traction forces exerted by motile cells on the fibrous intercellular matrix compress the matrix, increasing the density of adhesive sites. Haptotaxis is the term given to the phenomenon by which cells will move up an adhesive gradient; mathematically, this is similar to chemotaxis. Thus cell aggregation is an autocatalytic process: a region of increasing cell density will increase its net contractile force, and so recruit more cells from the surrounding regions, thus increasing the local deformation still more. Box F gives the mathematical formulation of the model.

In mechanical models of cellular systems, local autocatalysis is accomplished in two ways. First, as contractile cells aggregate, the strength of the contractile region increases. The second mechanism depends on the mechanical properties of the actomyosin fibers which generate the cells' contractile forces. As shown in Figure 9, the stress-strain curve for actomyosin contraction has negative slope, so that as fibers shorten, they become stronger. This characteristic arises because of the nature of the "sliding filament" mechanism underlying actomyosin contraction, and results in a contractile system
LATERAL INHIBITION MODELS

BOX E

Does Pattern Formation Precede Morphogenesis?

There is an important theoretical issue in development that remains unresolved: what role do chemical prepatterns play in directing morphogenesis? Tissues undergoing morphogenesis are never homogeneous in any sense. There has always been established, prior to any morphogenetic movements, a pattern of cellular differentiations (i.e. a pattern of gene activities) which amount to a chemical prepattern. The issue is: how complex must be that prepattern? At one extreme, there are believers in total prespecification: the complete final pattern is created invisibly by cellular communication, and morphogenesis is simply the execution of these chemical "instructions." The other extreme of a completely homogeneous tissue is not supportable according to current evidence. However, there are various intermediate possibilities. As I illustrated in Section 2, the mechanical interactions that accompany morphogenetic cell movements can themselves create spatial patterns. Therefore, it is generally not necessary to invoke complete prespecification. Moreover, there is a telling stability argument against a complex chemical prepattern (this argument is due to G. Odell). If a complex pattern were prerequisite for morphogenesis, and if the subsequent cell movements were a completely "slave" process, then there would be no mechanism for the embryo to correct for the inevitable perturbations that occur during normal development. In engineering lingo, development would be an "open loop" process, with no possibility of corrective feedback. Such processes are notoriously unstable, and development would likely be an very unreliable process. In fact, embryos are quite capable of buffering their development against many disturbances, a property that argues strongly that chemical prepatterns may be no more complex than simple gradients, and that there is an ongoing dialogue between morphogenetic movements and a changing pattern of chemical inhomogeneities. This viewpoint is buttressed by the argument presented in Box G.

which is inherently unstable. Lateral inhibition in this model arises from several effects.

**Distension.** The falling stress-strain property (i.e. "shorter is stronger") means that cells which have been dilated by the contraction of their neighbors are weaker. This amounts to a lateral inhibition of their contractile capability (Fig. 8).

**Depletion.** Recruitment of cells into an aggregation center depletes the neighboring regions, thus creating a mechanically weaker zone around a contractile focus.

**Elastic attenuation.** If the cells are attached to an elastic substratum, this will attenuate the range of a contractile focus.
The mechanical model for feather germ patterns (Figure 8) consists of three equations for the cells, the extracellular matrix, and the force balance between them:

**Cells:**

$$\frac{\partial n}{\partial t} = -L \nabla^4 n + D \nabla^2 n - \nabla \cdot (an \nabla \rho)$$

random motion haptotaxis

$$- \nabla \cdot \left( n \frac{\partial u}{\partial t} \right) + rn(N-n).$$

(15)

passive displacement cell division

**Matrix:**

$$\frac{\partial \rho}{\partial t} = -\nabla \cdot \left( \rho \frac{\partial u}{\partial t} \right) + S(n, \rho).$$

(16)

secretion

**Stress Balance:**

$$0 = \nabla \cdot \left[ \begin{array}{c} \text{viscous forces} \\
\mu_1 \frac{\partial \epsilon}{\partial t} + \mu_2 \frac{\partial \theta}{\partial t} I + \frac{E}{2(1+\nu)} \left( \epsilon + \frac{\nu}{1-2\nu} \theta I \right) \end{array} \right]$$

forces exerted by matrix on cells

$$+ \tau \rho n \nabla n,$$

(17)

tractions exerted by cells

where $u = \text{displacement vector}$, $\theta = \nabla \cdot u$ is the dilatation, and the strain is defined as

$$\epsilon = \frac{1}{2} (\nabla u + \nabla u^T).$$

In Equation (15) the $\nabla^4$ term models long range cell interactions [16].
Fig. 9. The actomyosin "cytomuscles" in a cell operate by a sliding filament mechanism similar to that found in striated muscle. The stress-strain curve for such a mechanism has a negative slope. This means that the system is mechanically unstable: as a cell contracts it gets stronger, and as it is dilated by its neighbors' contractions it gets weaker. This is equivalent to a mechanically autocatalytic system, analogous to chemical autocatalysis.

**Long range elastic interactions.** Fibrous materials, such as the extracellular matrix material in which the cells crawl, have the property of transmitting stress over long distances. This gives rise to a term in the model [i.e. the $\nabla^4$ term in Equation (15)] which acts to attenuate the stress so as to produce lateral inhibition.

**MECHANOCHEMICAL MODELS**

It is unlikely that most embryological patterns come about solely by mechanical means. There is abundant evidence that cells engage in a complex chemical dialogue amongst themselves, which results in mutual inductions and restrictions on their behavior. A more realistic modeling approach is to combine the mechanical and chemical interactions between cells. Oster et al. [18] modeled the formation of bone patterns in the tetrapod limb using a model that combined chemical and mechanical interactions. This resulted in a model that was quite complex, both mathematically and physically; however, the process that created the patterns could still be understood in terms of LALI.

**All LALI Models Can Produce Similar Patterns.** The above discussion illustrates the variety of ways one can implement the phenomenon of local autocatalysis with lateral inhibition. All establish a "zone of influence" around each focus that enforces a characteristic spacing. Of course, different
local kinetics can produce different pattern behavior. For example, the two types of diffusion-reaction models shown in Figure 6 behave differently with respect to variations in boundary conditions [7]. Moreover, the regularity in the spatial distribution of foci depends not only on the boundary conditions, but on the way the system becomes unstable. This is an important feature of pattern formation models (see Box G). Nevertheless, almost always, any pattern that can be generated by one type of model can be produced by the others. Parenthetically, I should mention that most inferences about the behavior of pattern formation models are based on a linear analysis of the model equations coupled with numerical simulations. This is because nonlinear analysis is quite difficult, even for simple models [6]. Since the linearization of almost any model yields the same eigenvalue problem, it is not surprising that the predicted patterns are much the same.

So what good are models? The foregoing discussion may seem a bit depressing to theoretical biologists: all manner of models produce the same spatial patterns. Thus it is not generally possible to distinguish between models solely from the patterns they generate, and the question I raised at the beginning begs an answer: what good are models of pattern formation? A stock answer from physics is that "models create a conceptual framework for thinking about a phenomenon." While this is certainly true of biological pattern formation models, and is not a criterion to be dismissed lightly, nevertheless, experimental biologists have their own ways of thinking about their experiments, and it is frequently difficult to convince them that mathematics adds anything to their understanding. After all, mathematics is good at describing only rather simple situations, not typical of biological systems. For complex systems the best descriptive language is often our native tongue (for me, English).

My response to a skeptical biologist would not be to enlist his enthusiasm about "conceptual frameworks", but to point out that there is a more important criterion by which to judge a model: different models lead to different experiments. Two examples will illustrate my point.

Example 1. Both neural and diffusion-reaction models produce the same shell patterns. However, since they are based on quite different mechanisms, they suggest quite different experimental interventions to test their assumptions. The neural model suggests administering neuroactive drugs, for example, while the diffusion model suggests that diffusion barriers would disrupt the propagation of stripes across the mantle. In some situations, the time scale of the pattern's development can rule out a particular mechanism (e.g. diffusion processes are much slower than neural propagation). However, since the shell patterns on a time scale of months or years, one cannot distinguish between a steady, or average, neural firing pattern and a slowly propagating intercellular diffusion.
BOX G

Is Morphogenesis Sequential or Simultaneous?

An interesting property of LALI models that has a correlate in many developmental processes in the location of aggregation centers. This could be cellular aggregations, strain maxima, or morphogen peaks; for the sake of concreteness, we will consider a diffusion-reaction mechanism, operating in the rectangular domain shown in Figure 10.

When the system is triggered from one boundary, the pattern spreads sequentially over the domain, and produces a regular field of morphogen peaks. The same system, when triggered simultaneously over the entire field, will produce a field of peaks that has the same average spacing; but since the precise pattern will depend sensitively on the initial and boundary conditions, there will be variability from one trial to the next. This variability was exploited by Murray [10] in his model for animal coat patterns.

The left panel shows the pattern of morphogen peaks generated by an activator-inhibitor model when the system is triggered at $x = 0$. A wave of activity spreads from left to right, creating a field of uniformly spaced chemical peaks.

The right panel shows the pattern of morphogen peaks that results from triggering the system simultaneously, and uniformly over the entire field. The resulting pattern has the same average spacing as above, but the precise location of the peaks depends sensitively on the boundary and initial conditions. Thus sequential triggering results in a more precise, repeatable pattern, whereas simultaneous triggering creates patterns with more "random" diversity.

FIG. 10.
Example 2. Murray [11] and Meinhardt [7] proposed diffusion-reaction models for the patterns found on animal coats. The same patterns can be produced by a neural model that assumes that melanocytes deposit pigment in response to nervous stimulation, analogous to the shell model. A third possible mechanism is based on the cell migration model of Oster et al. [15, 16], wherein melanoblasts settle into a patchy aggregation pattern under the influence of strain guidance cues and/or haptotaxis. Testing each of these mechanism involves quite different experimental interventions.

Of course, such experiments are easier to propose than to perform, since it turns out that almost any intervention seems to cause the mollusk to cease its shell-depositing activity. Moreover, there is currently no experimental technique that can resolve the neural connections that underlie the mammalian dermis. Nevertheless, the point is germane: a model can bring to mind experiments that one might not otherwise consider.

There is one other aspect of theoretical models that has not been widely exploited in the biological literature: models suggest limits on what forms are possible. In particular, LALI models restrict the possible morphogenetic options open to a developing organism; not just anything can happen.

3. ARE THERE CONSTRAINTS ON FORM?

While LALI models all predict pretty much the same spatial patterns, there are restrictions on what patterns can form by this mechanism. Insofar as a morphogenetic process is governed by a LALI mechanism, ontogeny will be constrained. It follows, therefore, the phylogeny—the evolution of that organ—will be constrained to only those admissible forms. Thus natural selection cannot create arbitrary forms, but can only produce certain variations on a basic theme. This notion of a "developmental constraint" imposed by the mechanisms of morphogenesis can be used to address certain problems in comparative anatomy and evolutionary biology. In this section I shall briefly indicate the nature of the argument. For a more complete discussion, see [18].

LIMB MORPHOGENESIS

Tetrapod limbs are amazingly diverse, ranging from the bat’s wing to the whale’s fin. Yet despite this geometric diversity, there is an underlying topological similarity that has been maintained throughout millions of years of divergent evolution. That is, limbs appear to have evolved to their present diverse forms while still obeying some underlying rules of construction that maintained certain topological features. Figure 11(a) shows the forelimb of an axolotl; superficially, it appears that the skeletal pattern can be built up from a sequence of branching and segmentation events. Indeed, Shubin and
Fig. 11. (a) The pattern of bones in the forelimb of the axolotl can be built from a sequence of segmentations (S) and branchings (B), after the initial focal condensation that formed the humerus. (b) A schematic of the growing limb bud. The limb grows distally, adding most cells in the progress zone just under the apical epidermal ridge. The cellular condensations that form the bone anlagen form as they emerge from the progress zone. Surrounding each condensation is a zone of recruitment, so that there is competition between foci for cells.

Alberch [20] have shown that this is the case for all tetrapod limbs, a fact that can be understood by examining the morphogenetic process of limb development [18]. The construction rules for limb development must arise from the underlying cellular processes that lay down the earliest cartilage patterns. Figure 11(b) shows a cartoon of how these early patterns are created by cellular aggregations that form, grow distally, and branch.

There is an important feature of tetrapod limb development that constrains the possible bone patterns: the limb develops sequentially, from
proximal to distal in an approximately tubular limb bud.³ With this boundary condition, LALI models are restricted to but three types of bifurcations, as shown in Figure 12.

_Focal condensation_, wherein a uniform field of cells condenses into a denser aggregate. Aggregates grow by recruiting cells at their distal ends. The first bone anlagen form this way (i.e. the femur/humerus).

_Branching_, wherein a growing condensation divides into two distal aggregations (e.g. fibula/tibia, radius/ulna).

_Segmentation_, wherein a tubular aggregate separates into two smaller aggregations (e.g. the phalanges).

Which type of bifurcation occurs depends upon the model parameters; however, limb geometry exerts a particularly important influence. This geometry dependence is characteristic of all LALI models.⁴

---

³There is an important exception: the digital arch that forms the phalanges. How this structure fits into the general scheme is discussed in [18].

⁴The simple reason for this is that the linear bifurcation analysis results in an eigenvalue problem whose solutions depend strongly on the boundary geometry.
If chondrogenesis is the outcome of some LALI mechanism, then the impression given in Figure 11(a) is valid: after the initial focal condensation that forms the first elements, limb geometry can be built up from a sequence of branching and segmentation events. The few exceptions to this scheme can be understood in terms of size and geometry effects on the “zone of influence” of condensation foci [18]. Furthermore, this restriction is a true “developmental constraint” in that it limits the possible limb geometries that morphogenesis can produce. For example, it is quite unlikely that a “trifurcation” could occur (i.e. three elements branching from one).

It is easy to find a system where the “construction rules” are violated: the fins of fish form from a limb bud that is broad and flat. This allows many chondrogenic foci to form simultaneously, rather than sequentially as in the tetrapod limb. The result is that fins exhibit a much greater degree of geometric variability than tetrapod limbs (see Box G). Such variability is the grist of natural selection, and so one would expect that organs that develop sequentially (e.g. tetrapod limbs, somites) would be less prone to diversification than organs that form simultaneously (e.g. neural connections, animal coat patterns).

This brief discussion illustrates how the general properties of LALI models can be used to suggest some organizational principles for embryonic pattern formations. However, I do not mean to leave the impression that all embryological patterns arise from LALI effects. Indeed, this principle is most applicable where structures arise de novo from previously homogeneous tissue. In embryogenesis, organ boundaries and borders between tissue types frequently play a decisive role in establishing subsequent patterns. In such cases other pattern-forming mechanisms may play the dominant role.

The work described herein was supported by NSF Grant No. MCS-8110557. The author would like to thank Hans Meinhardt for his illuminating comments on the manuscript.

REFERENCES


