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Scale-invariance in reaction-diffusion models of spatial pattern formation

(development/regulation/morphallaxis)

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ABSTRACT **We propose a reaction-diffusion model of spatial pattern formation whose solutions can exhibit scale-invariance over any desired range for suitable choices of parameters in the model. The model does not invoke preset polarity or any other *ad hoc* distinction between cells and provides a solution to the French flag problem without sources at the boundary. Furthermore, patterns other than the polar pattern that usually arises first in a growing one-dimensional system described by Turing's model can be obtained. Evidence is given that suggests that the model may apply in the slug stage of *Dictyostelium discoideum*.**

At numerous stages in the development of a multicellular organism, an aggregate of essentially indentical cells undergoes spatially dependent differentiation or pattern formation and new types of cells emerge in the proper spatial relationship. Pattern formation is commonly viewed as the result of the response of individual cells to an underlying spatial pattern of control variables, and a major problem in developmental biology is to discover mechanisms that generate the appropriate spatial pattern of these variables in an aggregate of initially similar cells (1).

Numerous models in which the control variables are diffusible chemical species called "morphogens" have been proposed, but many invoke *ad hoc* specialization of boundary or other cells to produce nonuniform distributions of the morphogens. Such models sidestep the fundamental problem, and a more attractive hypothesis, which requires no such prior specialization, is that the pattern arises spontaneously from the interaction between chemical reactions within or on cells and some mode of spatial communication between cells. In its simplest form this idea is due to Turing (2), who assumed that cells interact via diffusible morphogens, and the standard Turing model is described by a system of reaction-diffusion equations in which kinetic and diffusion coefficients are taken to be space- and time-invariant. Many of the applications and open questions surrounding the model are discussed in refs. 3–6.

Turing's model can provide a plausible explanation for pattern formation in mosaic systems and in systems that regulate by epimorphosis. However, it is less successful in predicting the range of size- or scale-invariance observed in systems, such as *Hydra* and *Dictyostelium discoideum* slugs, that regenerate by morphallaxis under appropriate conditions. The reason for the failure is that in Turing's theory the wavelength of growing disturbances is fixed solely by the reaction and diffusion coefficients; the overall size of the system enters only in fixing the number of repetitions of the basic pattern that will fit into the system. According to linear theory, the basic structure of the pattern selected remains invariant only over a limited range of lengths, and numerical computations on model reaction mechanisms show that the same conclusion often holds for the nonlinear theory as well (5).

The assumption that the kinetic and diffusion coefficients in a reaction-diffusion model are constant is certainly only an approximation, and our purpose here is to show that any desired degree of scale-invariance can be achieved via a simple, yet plausible, mechanism by which the overall size of the system is reflected in these coefficients. We treat in detail a case in which it is assumed that the diffusion coefficients of the morphogens depend on the concentration of a diffusible regulatory species that is produced at a constant rate by all cells, and we show that the desired invariance can be obtained by adjusting the production rate and the rate at which the regulatory species leaks into the sourroundings.

There are several ways in which such concentration-dependence could arise. For instance, the permeability of the cell membrane (either junctional or ordinary) could be increased by the regulatory species; in the continuum description we adopt here, this would be reflected in an increased diffusion coefficient. Alternatively, the regulatory species could facilitate transport by increasing adsorption of the morphogens on cellular structures, thereby enhancing surface diffusion, or through the formation of specialized transport structures. Recent experimental evidence shows that the postulated effect on membrane permeability actually occurs in some developing systems. For example, the molting hormone ecdysone stimulates a period of increased epidermal communication, as measured by the degree of electrical coupling between cells, in the prepupa stage of the beetle *Tenebrio* (7), and there is evidence that gap junctions in some amphibian oocytes are hormonally controlled (8). In these examples the source of the regulatory species is extracellular, but the same effect can be achieved when the source is intracellular.

SCALE-INVARIANCE IN TURING'S MODEL

Let S denote the region of space occupied by the developing system, whose boundary is assumed to be impermeable to the morphogens but not to the regulatory species, and suppose that transport within S is solely by diffusion. Suppose that there are N morphogens whose concentration is $C = (C_1, \ldots, C_N)^T$, and let C_{N+1} denote the concentration of the regulatory species. We first consider the case in which the regulatory species affects only the morphogen diffusivities and, for simplicity, we assume that the effect is linear in C_{N+1}. Then the governing equations are

$$\frac{\partial C}{\partial t} = \nabla \cdot (\mathcal{D}_0 + \mathcal{D}_1 C_{N+1})\nabla C + R(C) \quad \text{in } S \qquad [1]$$

$$-\mathbf{n} \cdot (\mathcal{D}_0 + \mathcal{D}_1 C_{N+1})\nabla C = 0 \quad \text{on } \partial S$$

$$\frac{\partial C_{N+1}}{\partial t} = \mathcal{D}_{N+1}\nabla^2 C_{N+1} + R_{N+1} \quad \text{in } S \qquad [2]$$

$$-\mathbf{n} \cdot \mathcal{D}_{N+1}\nabla C_{N+1} = hC_{N+1} \quad \text{on } \partial S$$

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plus appropriate initial conditions. Here, $\mathcal{D}_0$ and $\mathcal{D}_1$ are constant $N \times N$ diagonal matrices, $R(C)$ is the reaction rate vector (which is independent of C_{N+1}), and R_{N+1} denotes the constant rate of production of the regulatory species. All kinetic coefficients in $R(C)$ and the mass transfer coefficient h are assumed to be constant.

In order to cast the equations into dimensionless form, let L be a measure of S, let $\overline{C}_i$ be a reference concentration for species i, let κ^{-1} be a time scale characteristic of the morphogen kinetics, and let $\delta_i = \max(\mathcal{D}_i)_{jj}; i = 0,1$. Write the spatial coordinate as $\mathbf{r} = \zeta L$, set $\tau = \kappa t$, $c_i = C_i/\overline{C}_i$, $(\overline{\mathcal{D}}_i)_{jj} = (\mathcal{D}_i)_{jj}/\delta_i$, and $\overline{\nabla} = L\nabla$; then Eqs. **1** and **2** become

$$\frac{\partial c}{\partial \tau} = \frac{1}{\kappa L^2}\overline{\nabla}\cdot(\delta_0\overline{\mathcal{D}}_0 + \delta_1\overline{C}_{N+1}\overline{\mathcal{D}}_1 c_{N+1})\overline{\nabla}c + \overline{R}(c) \quad [3]$$

$$\mathbf{n}\cdot(\delta_0\overline{\mathcal{D}} + \delta_1\overline{C}_{N+1}\overline{\mathcal{D}}_1 c_{N+1})\overline{\nabla}c_{N+1} = 0, \text{ and}$$

$$\theta_0\frac{\partial c_{N+1}}{\partial \tau} = \overline{\nabla}^2 c_{N+1} + \theta_1\theta_2 \quad [4]$$

$$\mathbf{n}\cdot\overline{\nabla}c_{N+1} = \theta_2 c_{N+1}.$$

Here, $\theta_0 \equiv \kappa L^2/\mathcal{D}_{N+1}$, $\theta_1 \equiv R_{N+1}L/h\overline{C}_{N+1}$, and $\theta_2 \equiv hL/\mathcal{D}_{N+1}$. Hereafter, the overbars will be dropped.

The unique solution of Eq. **4** can be written

$$c_{N+1}(\zeta,\tau) = \theta_1\theta_2\sum_{k=0}^{\infty}\frac{\psi_k(\zeta)}{\beta_k^2}\int_S \psi_k(\xi)d\xi + \sum_{k=0}^{\infty} e^{-\beta_k^2\tau/\theta_0}a_k\psi_k(\zeta) \quad [5]$$

where (β_k^2,ψ_k) is a solution of

$$\nabla^2\psi_k = -\beta_k^2\psi k \quad [6]$$

$$\mathbf{n}\cdot\nabla\psi_k = -\theta_2\psi_k,$$

and the ψ_k are normalized to 1. When θ_2 is small, β_0 is small and the first term of each series is dominant, and in this case the solution is nearly uniform in space and slowly varying in time. A steady-state level of c_{N+1} is reached only if $\theta_1\theta_2 \to 0$ as $\theta_2 \to 0$, but whether or not this holds, the zero-order approximation consists in setting c_{N+1} and $\delta_0\mathcal{D}_0 + \delta_1\overline{C}_{N+1}\mathcal{D}_1 c_{N+1}$ equal to a constant and a constant matrix, respectively. This leads to the standard Turing model.

A basic assumption of Turing's model is that there exists a constant, spatially uniform solution c^s of Eq. **3** that loses stability as either kinetic or diffusion coefficients cross critical loci in parameter space. Stability of the uniform solution is governed by the linearization of Eq. **3**, and the solution of the resulting linear equation is (9)

$$u(\zeta,\tau) = \sum_{n=0}^{\infty} e^{(K-\mu_n\mathcal{D})\tau}\, y_n\phi_n(\zeta). \quad [7]$$

The matrix K is the Jacobian of $R(c)$ at $c = c^s$, $u = c - c^s$, $\mu_n = \alpha_n^2\delta/\kappa L^2$ and (α_n^2,ϕ_n) is a solution of Eq. **6** with $\theta_2 = 0$, ordered by the magnitude of α^2.‡ If $K - \mu\mathcal{D}$ has exactly one real positive eigenvalue for $\mu\epsilon[\mu^-,\mu^+]$, where $\mu^- > 0$, and if all other eigenvalues have a negative real part, then the nth eigenfunction is unstable according to linear theory when

$$L\epsilon[L_n^-,L_n^+] \equiv \left[\alpha_n\sqrt{\frac{\delta}{\kappa\mu^+}}, \alpha_n\sqrt{\frac{\delta}{\kappa\mu^-}}\right].$$

The intervals of unstable "lengths" for successive modes are disjoint if and only if $L_{n-1}^+ < L_n^-$—that is, if and only if $\alpha_{n-1}/\alpha_n < \sqrt{\mu^-/\mu^+}$. For instance, in a one-dimensional system of length L, $\alpha_n = n\pi$, and therefore the intervals are disjoint for all n such that

$$n < \frac{1}{\left(1 - \sqrt{\frac{\mu^-}{\mu^+}}\right)}. \quad [8]$$

Now consider what happens as L increases, perhaps due to growth or to rearrangement of the cells. If L is sufficiently small and all $\mathcal{D}_i$ are positive, all nonuniform disturbances decay exponentially in time and the system returns to a uniform state (4, 11). The smallest length at which c^s loses stability is L_1^- and the growing mode at this point is ϕ_1, which generally has a simple spatial structure. (For example, in a one-dimensional system, $\phi_1 = \cos\pi x/L$, which decreases monotonically between +1 and −1.) The largest L for which ϕ_1 is linearly unstable is L_1^+ and if $\alpha_2 > \alpha_1\sqrt{\mu^+/\mu^-}$, the instability interval for ϕ_1 is followed by a gap $[L_1^+,L_2^-]$ in which all modes are stable according to linear theory. This succession of instability intervals separated by gaps is repeated for higher modes at larger L, but eventually the gaps disappear and the instability intervals overlap for sufficiently large values of n. When this happens several modes are simultaneously unstable and more complicated patterns can result.

If the jth interval $[L_j^-,L_j^+]$ is disjoint from other intervals, the wave number of the growing mode varies between $\sqrt{\kappa\mu^-/\delta}$ and $\sqrt{\kappa\mu^+/\delta}$ as L increases through $[L_j^-,L_j^+]$. However, the nodal structure of the growing disturbance, which captures the essence of the spatial pattern, does not change because ϕ_j is nondegenerate; it merely shifts to accommodate the increase in L. Thus, the linear system exhibits a limited degree of scale-invariance in that the spatial structure of the growing mode is essentially unchanged within an instability interval. It can certainly happen that such limited invariance suffices in particular instances but it is not adequate for all systems, and we show next that much stronger results can be obtained for larger values of θ_1 and θ_2.

RAPID LOSS OF THE REGULATORY SPECIES PRODUCES PERFECT INVARIANCE

When θ_1 and θ_2 are no longer small, c_{N+1} can vary on time and distance scales comparable to those characteristic of the morphogens, and the temporal and spatial variation of the $\mathcal{D}_i$ must be taken into account. However, when θ_2 is large, $\beta_0^2 \approx \mathcal{O}(10)$, and so if $\kappa^{-1} \gg L^2/10\,\mathcal{D}_{N+1}$, the unique steady-state distribution of the regulatory species is established rapidly compared to the time required for significant changes in the morphogens. A reasonable estimate for κ^{-1} in the present context is 2–3 hr, and if $\mathcal{D}_{N+1} \approx 10^{-5}$ cm^2/sec, then the foregoing condition is met if $L \ll 1$ cm. It is noteworthy that pattern formation typically occurs in systems whose largest dimension is of the order of 1 mm (12).

The geometry of S must be known to compute the steady-state distribution, and hereafter we restrict attention to one-dimensional systems. In addition, we only consider the special case in which $\mathcal{D}_0 = \mathcal{D}_1 \equiv \mathcal{D}$. The steady-state distribution is

$$c_{N+1}(\zeta) = \frac{\theta_1\theta_2}{2}(\theta_2^{-1} + \zeta - \zeta^2)$$

and the linear problem associated with Eq. **3** can be written

$$\frac{\partial u}{\partial \tau} = \frac{\delta}{\kappa L^2}\mathcal{D}\frac{\partial}{\partial\zeta}\left((\Delta_1 + \Delta_2(\zeta - \zeta^2))\frac{\partial u}{\partial\zeta}\right) + Ku \quad [9]$$

$$\Delta_1\frac{\partial u}{\partial\zeta} = 0 \qquad \text{at } \zeta = 0,1$$

‡ It can happen, particularly if S is symmetric, that some of the α_n^2 are degenerate (10). However, such degeneracy can be removed by a small perturbation of S and, for simplicity, we assume that the α_n^2 are simple.

where

$$\Delta_1 \equiv \left(\delta_0 + \frac{\delta_1 \bar{C}_{N+1}\theta_1}{2}\right)\Big/ \delta \qquad \Delta_2 \equiv \delta_1 \bar{C}_{N+1}\theta_1\theta_2/2\delta$$

and

$$\delta \equiv \sqrt{\left(\delta_0 + \frac{\delta_1 \bar{C}_{N+1}\theta_1}{2}\right)^2 + \left(\frac{\delta_1 \bar{C}_{N+1}\theta_1\theta_2}{2}\right)^2}.$$

The appropriate eigenvalue problem for the pattern functions is

$$\frac{d}{d\zeta}(\Delta_1 + \Delta_2(\zeta - \zeta^2))\frac{d\phi}{d\zeta} + \alpha^2\phi = 0 \qquad [10]$$

$$\Delta_1 \frac{d\phi}{d\zeta} = 0 \qquad \text{at } \zeta = 0,1,$$

for then the stability of the uniform steady state again hinges on the eigenvalues of K-$\mu_n\mathcal{D}$ where, as before, $\mu_n \equiv \alpha_n^2\delta/\kappa L^2$. The relative kinetic and diffusion coefficients fix the μ values for which there is an eigenvalue with a positive real part, but now the instability intervals for the various modes cannot be computed directly even in the one-dimensional case, because the eigenvalues α_n^2 cannot be computed analytically, except in two limiting cases.

The first occurs when $\theta_1 = \theta_2 = 0$, because then $\Delta_1 = 1$, $\Delta_2 = 0$ and we recover Turing's model with its limited invariance. In one dimension the eigenvalues and eigenfunctions are $\alpha_n^2 = (n\pi)^2$ and $\cos n\pi\zeta$, respectively. In the second case, $\Delta_1 = 0$ and $\Delta_2 = 1$, which corresponds to $\delta_0 = 0$, $\theta_2 = \infty$ and $\theta_1\theta_2 < \infty$. This case arises when $c_{N+1} = 0$ on the boundary and here Eq. **10** reduces to Legendre's equation, for which the eigenvalues are $\alpha_n^2 = n(n+1)$, $n = 0,1,\ldots$. As before, the nth mode is unstable according to linear theory if and only if $\mu_n \epsilon [\mu^-, \mu^+]$, which is true if the production rate is such that

$$\frac{2\kappa\mu^-\mathcal{D}_{N+1}}{n(n+1)\delta_1} < R_{N+1} < \frac{2\kappa\mu^+\mathcal{D}_{N+1}}{n(n+1)\delta_1}. \qquad [11]$$

It will be the only growing mode if

$$\mu_n - \mu_{n-1} > \mu^+ - \mu^-$$

and

$$\mu_{n+1} - \mu_n > \mu^+ - \mu^-,$$

and these are satisfied provided that

$$R_{N+1} > \frac{\kappa\mathcal{D}_{N+1}}{n\delta_1}(\mu^+ - \mu^-).$$

It follows that the instability intervals defined by inequality **11** are disjoint for all $n < n^*$ where

$$n^* \equiv \frac{\mu^+ + \mu^-}{\mu^+ - \mu^-}.$$

Since these intervals are independent of L, the linear problem shows complete scale invariance! Furthermore, it is clear from Eq. **3** that the same conclusion holds for the nonlinear problem as well.

The eigenfunctions in the scale-invariant case are the Legendre polynomials, the first four of which are

$$P_0(\zeta) = 1$$

$$P_1(\zeta) = 1 - 2\zeta$$

$$P_2(\zeta) = \frac{3}{2}(1 - 2\zeta)^2 - \tfrac{1}{2}$$

$$P_3(\zeta) = \frac{5}{2}(1 - 2\zeta)^3 - \frac{3}{2}(1 - 2\zeta).$$

The major qualitative difference between these and the trigonometric functions is the behavior at the endpoints. When $(\Delta_1,\Delta_2) = (0,1)$, the flux at the boundary vanishes because the diffusion coefficient vanishes, whereas for any $\Delta_1 > 0$ the boundary conditions imply that $d\phi/d\zeta = 0$. When Δ_1 is very small there is a boundary layer near $\zeta = 0$ and $\zeta = 1$ in which the derivative of the ϕ_ns changes rapidly. As Δ_2 varies between 0 and 1 the eigenfunctions vary continuously from the trigonometric functions to the Legendre polynomials.

Similarly, the eigenvalues vary continuously between $(n\pi)^2$ and $n(n+1)$ as Δ_2 varies between 0 and 1, and for small Δ_2 the eigenvalues are analytic functions of Δ_2. One finds that the first terms in the power series expansion are

$$\alpha_n^2 = (n\pi)^2\Delta_1 + \left(\frac{1}{2} + \frac{(n\pi)^2}{6}\right)\Delta_2 + \mathcal{O}(\Delta_2^2).$$

Therefore the eigenvalues increase for small Δ_2 but, since $\pi^2 > 1 + 1/n$ for $n \geq 1$, they must eventually decrease. It is known more generally that, however Δ_1 and Δ_2 vary, the eigenvalues of Eq. **10** increase (decrease) whenever $\Delta_1 + \Delta_2(\zeta - \zeta^2)$ increases (decreases) for all $\zeta\epsilon[0,1]$ (13). Consequently, by maximizing the critical point of $\sqrt{1 - \Delta_2^2} + \Delta_2(\zeta - \zeta^2)$ over ζ, one finds that $\partial\alpha_n^2/\partial\Delta_2 < 0$ whenever $\Delta_2 > \Delta_2^* = 1/\sqrt{17}$. We shall regard only h,L, and R_{N+1} as variables in Δ_2, and it follows that $\partial\Delta_2/\partial L \geq 0$, $\partial\Delta_2/\partial h \geq 0$ and that

$$\frac{\partial\Delta_2}{\partial R_{N+1}} = \begin{cases} >0 & \text{for } L \to \infty \\ <0 & \text{for } L \to 0 \\ \equiv 0 & \text{for } \delta_0 = 0 \end{cases} \qquad [12]$$

Therefore, the eigenvalues α_n^2 are decreasing functions of h and L whenever $\Delta_2 > \Delta_2^*$, which is equivalent to the condition

$$L > L^* = \frac{\mathcal{D}_{N+1}}{8h}\left[1 + \sqrt{1 + 32\delta_0 h^2/\delta_1 R_{N+1}\mathcal{D}_{N+1}}\right]. \qquad [13]$$

Because each α_n^2 depends on h, L, and R_{N+1} only through the combinations hL and $R_{N+1}L/h$, each is invariant under all transformations of the form

$$R_{N+1} \to \lambda R_{N+1},\ L \to L/\sqrt{\lambda},\ h \to \sqrt{\lambda}h \qquad [14]$$

for any positive λ, and under such a transformation

$$\mu_n = \frac{\alpha_n^2\delta}{\kappa L^2} \to \lambda\mu_n.$$

To quantify scale-invariance in Turing's model, we established the criterion that a system shows scale-invariance with respect to a given Fourier mode over the range of L for which that mode is linearly unstable. To compare the predictions of the present model with those of Turing's, the instability interval for each mode must be computed for fixed values of h and R_{N+1}. This computation requires the corresponding eigenvalue α_n^2 as a function of the parameters and these eigenvalues have been computed for the lowest modes using a finite-difference approximation to Eq. **10**. First, suppose that $\delta_0 = 0$, which means that the concentration-independent component of the diffusivities is zero, and let $\bar{C}_{N+1}\delta_1 = \mathcal{D}_{N+1} = 10^{-5}$ cm^2/sec, $R_{N+1}/\bar{C}_{N+1} = 2.5 \times 10^{-4}$ sec^{-1}, and $\kappa = 10^{-4}$ sec^{-1}. Fig. 1 shows the dependence of the first nonzero eigenvalue α_1^2 and the dimensionless wave number μ_1 on the parameters h and L, and it is apparent from the former that h has a significant effect on the transition between $\alpha_1^2 = \pi^2$ for $L \to 0$ and $\alpha_1^2 = 2.0$ for $L \to \infty$. The computations show that the turning points in Fig. 1 *Upper* are essentially equal to L^*, and since $L^* = 10^{-5}/4h$ (in cm) when $\delta_0 = 0$, this accounts for the strong influence of h.

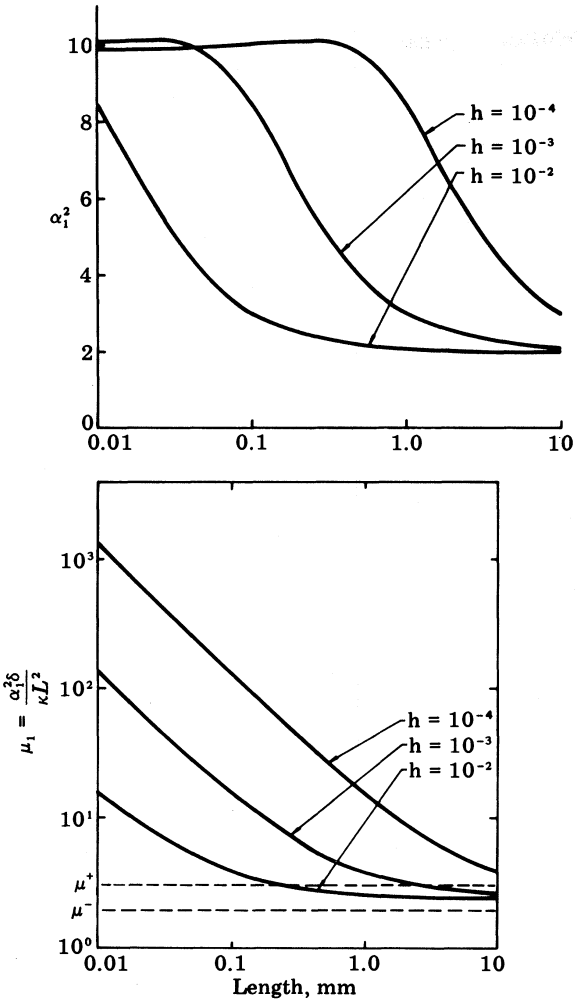

FIG. 1. The lowest nontrivial eigenvalue (*Upper*) and the reduced wave number (*Lower*) as functions of L for $\delta_0 = 0$.

The mode ϕ_1 is unstable when $\mu \in [\mu^-, \mu^+]$ and we have seen that μ^- and μ^+ are fixed solely by the relative kinetic and diffusion constants of the morphogens. To compute them requires a kinetic model and for illustrative purposes we have used a polynomial model for glycolysis (14).[§] This requires three parameters—the input flux, the rate of decay of x, and the normalized diffusivity of y—and these were fixed at 1.0, 0.001, and 0.165, respectively. For these choices $\mu^- = 1.97$ and $\mu^+ = 3.08$, which are shown as dashed lines in Fig. 1 *Lower*. When $h = 10^{-2}$, for instance, ϕ_1 is unstable for $L \in [0.25, \infty]$—i.e., for all lengths greater than about 25 cell diameters. Since α_n^2 is independent of R_{N+1} and δ is proportional to R_{N+1}, the curves are translated parallel to the μ axis by changes in R_{N+1}. For the preceding choice of h, a reduction of 25% in R_{N+1} changes the instability interval of ϕ_1 to $L \in [0.1, 1.0]$ and produces invariance over the range 10–100 cell diameters, which is precisely the range of interest in many biological systems. The fact that μ_n is proportional to R_{N+1} can also be used to adjust the curves for higher modes so that they pass through the interval $[\mu^-, \mu^+]$ for the desired range of L.

[§] It is unnecessary to choose a kinetic model if one arbitrarily chooses $\mu^{\pm}$, but it would then be difficult to match these values with a particular kinetic model, as would be required for computations of solutions of the nonlinear equations.

The effect of a small nonzero component of the diffusivities is shown in Fig. 2, wherein all parameters but δ_0 are as in Fig. 1 and the exception is set at $0.01\ \overline{C}_{N+1}\delta_1$. Comparison of Figs. 1 *Upper* and 2 *Upper* shows that this value of δ_0 is too small to affect the transition between $\alpha_1^2 = \pi^2$ and $\alpha_1^2 = 2.0$ when $h = 10^{-4}$, but it has the effect of compressing the transition region considerably when $h \geq 10^{-3}$. This effect can be predicted by comparing the relative magnitude of the two terms in Δ_1.

A similar effect is observed in the transition of μ_1 between its asymptotes at small and large L. When $\delta_0 \neq 0$, $\Delta_1 \to 1$ and $\mu_1 \to \pi^2\delta_0/\kappa L^2$ as $L \to 0$, and all curves are asymptotic to the line of slope -2 labeled "Turing's model." (By comparison, when $\delta_0 = 0$, all curves are asymptotic to lines of slope -1 as $L \to 0$, but the intercepts depend on h.) The asymptote for large L for the given parameters is $\mu_1 = 2.5$, whether or not $\delta_0 \neq 0$. Increasing h sharpens the transition between the asymptotes, as it must, given the effect of h on α_1^2. The instability interval for ϕ_1 is [0.57,0.71] according to Turing's model, while if $h = 10^{-2}$, ϕ_1 is unstable for $L > 1.75$. The latter is much larger than the lower limit of 0.25 that holds when $\delta_0 = 0$, which shows that the lower limit of instability may be quite sensitive to the choice of δ_0. Of course, whether or not $\delta_0 \neq 0$, the range of instability can be adjusted more or less at will by judicious choice of the parameters and by application of transformation **14**.

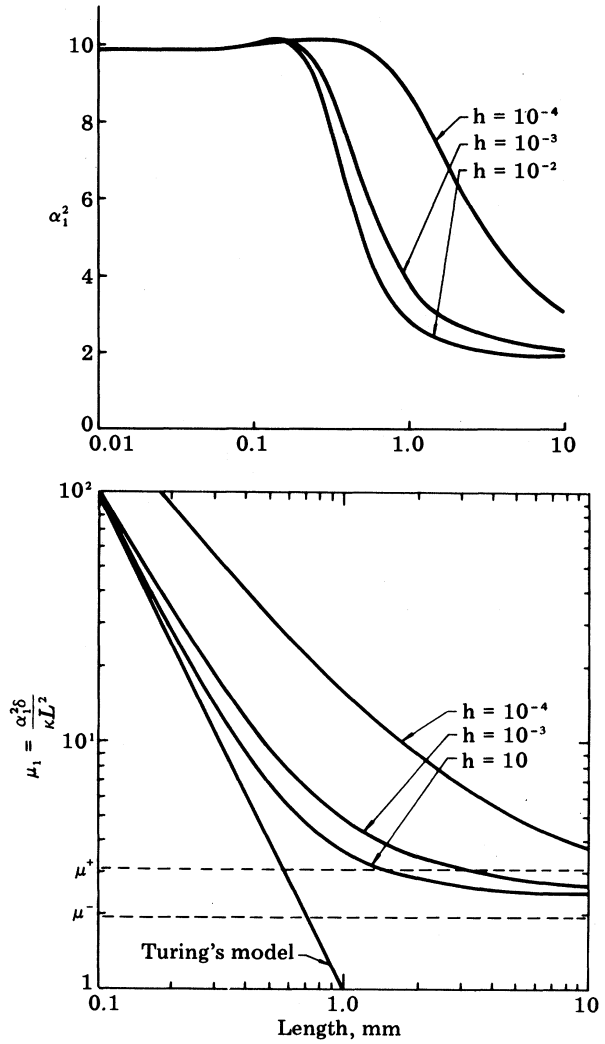

FIG. 2. The lowest nontrivial eigenvalue (*Upper*) and the reduced wave number (*Lower*) as functions of L for $\delta_0 = 0.01\ \overline{C}_{N+1}\ \delta_1$.

CONCLUSION

It is remarkable that perfect scale-invariance can be achieved by a relatively simple and biologically plausible modification of Turing's model. The key requirement is that the morphogen diffusivities be proportional to L^2, L being a measure of the size of the system, and we have shown that this can be accomplished by admitting a certain form of concentration dependence in the diffusivities. In our model the dependence is not on the morphogen concentration, but on the concentration C_{N+1} of a diffusible regulatory species produced at a constant rate by all cells. The diffusivities are assumed to be linear functions of C_{N+1}, and if the constant term $(\mathcal{D}_0)_{ii}$ vanishes and C_{N+1} is zero on the boundary of the system, then perfect scale-invariance results. Although much of our analysis dealt with one-dimensional systems, it is apparent from Eqs. **1** and **5** that perfect scale-invariance results whenever $(\mathcal{D}_0)_{ii}$ vanishes and C_{N+1} is zero on the boundary, irrespective of the number of space dimensions. When $(\mathcal{D}_0)_{ii} \neq 0$ or when the rate of loss of the regulatory species at the boundary is finite, perfect invariance no longer obtains, but we have shown on the basis of a linear analysis that the range of L over which the growing pattern is essentially unchanged can be made as large as desired by adjusting the parameters appropriately. This is certainly adequate in the biological context and if, as we expect, it holds for the nonlinear problem as well, some doubts concerning the applicability of reaction-diffusion models to pattern formation should be removed.

In the preceding section we have emphasized selection of the lowest nonconstant mode, but other modes can certainly be selected. Patterns with any desired number of extrema in the morphogen distributions can be produced and these could be used to trigger differentiation at equally spaced sites in a scale-invariant manner. Indeed, the earlier discussion on the case in which the $(\mathcal{D}_0)_{ii}$ are zero leads to the conclusion that selection of the desired mode can be accomplished simply by varying the production rate of the regulatory species, and this rate could be programmed genetically.

There are systems that are essentially one-dimensional and exhibit a scale-invariant polar pattern of differentiation. Our results may apply to at least one of these, the slug stage of *D. discoideum*. It has been proposed (15) that all cells in the slug produce a diffusible substance during normal development, and that the permeability of the surface sheath which surrounds the slug limits leakage of this substance into the environment to the anterior end. These two processes produce an axial gradient of the substance and this gradient could be used in pattern formation. Our model can be readily adapted to apply to this system, even though the properties of the boundary are variable. The simplest case results when the slug is regarded as a cylinder whose boundary is impermeable to the morphogens everywhere and is impermeable to the regulatory species except at the anterior end, where the concentration of this species vanishes. This leads to equations similar to Eqs. **3** and **4** and it can be shown that, when the $(\mathcal{D}_0)_{ii}$ are zero, the morphogen distributions are perfectly scale-invariant. The results of numerical calculations for other cases and a discussion of experimental tests of the predictions of the model for this system will be reported elsewhere.

The idea that model parameters may depend on the concentration of other species can certainly be developed further. For instance, it is equally possible that a regulatory species could affect only the kinetic coefficients or both the kinetic and diffusion coefficients. If the regulatory species functions as a pure V_{max} inhibitor for all reactions and if $c_{N+1} \propto L^2$, then all rates are proportional to $1/L^2$ and perfect invariance results. If not all of the kinetic terms are affected, detailed numerical work is required to determine the degree of invariance present. Some results along these lines are given in ref. 5. An example of an illuminated reacting system in which pattern size is related to the size of the system is given in ref. 16.

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