A generative principle of pattern formation based on lateral inhibition, local instability and global stability

Alfred Gierer and Hans Meinhardt, see http://www.eb.tuebingen.mpg.de/dept4/meinhardt/home.html

The proposed mechanism is based on a generative principle that allows in a straightforward manner to check whether an interaction will lead to a stable pattern or not (Gierer and Meinhardt, 1972; Gierer, 1981). Our mostly used activator-inhibitor equation

$$\frac{\partial a}{\partial t} = \frac{\rho a^2}{h} - \mu a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_0 \qquad (1a)$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \nu h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (1b)$$

is only one example. The crucial condition is that the system is locally unstable but globally stable. If a and h changes according to the equations

$$\frac{\partial a}{\partial t} = f(a,h); \quad \frac{\partial h}{\partial t} = g(a,h) \qquad (2ab)$$

and h equilibrates rapidly over a large area by diffusion or convection, h can be approximated as a function of the concentration of a averaged over a region from which the inhibitor is derived. The change of the activator concentration can then be written as function of the local concentration of a and the spatially averaged concentration $\bar{a}$:

$$\frac{\partial a}{\partial t} = f(a, h(\bar{a})) \qquad (2c)$$

This may have a uniform steady state solution at $a_0 = \bar{a}$ at which $\partial a/\partial t = 0$. Patterns are formed if a slight local increase over this steady state concentration grows further, i.e. if

$$\left(\frac{\partial f}{\partial a}\right)_{a_0} > 0 \qquad (2d)$$

The inhibitor will lead to a globally stable pattern if

$$\left(\frac{\partial f}{\partial a}\right)_{a_0} + \left(\frac{\partial f}{\partial h}\,\frac{\partial h}{\partial \bar{a}}\right)_{a_0} < 0 \qquad (2e)$$

This principle now allows to derive a general criterion for the power laws in pattern-forming interactions, assuming the decay of substances proceeds in the normal (linear) way:

$$\frac{\partial a}{\partial t} = \rho \frac{a^k}{h^l} - \mu a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (3a)$$

$$\frac{\partial h}{\partial t} = \rho' \frac{a^m}{h^n} - \nu h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (3b)$$

The condition given in equations 2d and 2e is satisfied if

$$\frac{l\,m}{n+1} > k - 1 > 0$$

The second term states that the autocatalysis has to be nonlinear ($k > 1$) to overcome the normal decay that is proportional to the activator concentration. The first term denotes that effects of the inhibitory components have to be stronger than those of the activating components to make the system globally stable. In our standard equation we used $k = 2$, $l = 1$, $m = 2$ and $n = 0$, which clearly satisfies this condition. Another example would be that the inhibitor acts on the activation production in a nonlinear way. In this case, the inhibitor could be a decay product of the activator (conversion model)

$$\frac{\partial a}{\partial t} = \rho \frac{a^2}{h^2} - \mu a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (4a)$$

$$\frac{\partial h}{\partial t} = \mu a - \nu h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (4b)$$

The inhibitor need not to slow down the activator production. An alternative possibility is that it accelerates the activator destruction.

$$\frac{\partial a}{\partial t} = \rho a^2 - \mu h a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (5a)$$

$$\frac{\partial h}{\partial t} = \mu a - \nu h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (5b)$$

Such an enhanced degradation is assumed in the interaction proposed by Turing (1952). One problem of such an interaction is that with increasing peak hight, the half life of the activator becomes shorter and shorter. If it becomes shorter than the half life of the inhibitor, the system tends to oscillate.

The antagonistic effect can also result from the depletion of a substrate or co-factor $s(x)$ which is derived from a larger surrounding and which is consumed during the autocatalytic activator production.

$$\frac{\partial a}{\partial t} = \rho s a^2 - \mu a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (6a)$$

$$\frac{\partial s}{\partial t} = \sigma - \rho s a^2 - \nu s + D_s \frac{\partial^2 s}{\partial x^2} \qquad (6b)$$

This reaction has similarities with the so-called Brusselator reaction (Prigogine and Lefever, 1968) but is somewhat simpler.

Depletion mechanisms differ in some properties from direct activator-inhibitor mechanisms. The activator production reaches an upper limit when the substrate concentration drops to a low level. Such saturation leads to broader peaks that can more easily shift and that can split in growing fields.

Pattern formation does not require a molecule with direct autocatalytic regulation. The autocatalysis can be a property of the system as a whole. In the interaction described

in Eq. 7a-c, two substances, a and c, mutually repress each other. Such an *inhibition of an inhibition* is in fact equivalent to a self-enhancement since a small increase of a above an equilibrium leads to a stronger repression of the c-production by a. This, in turn, leads to a further increase of a, in the same way as if a would be autocatalytic. If a has won the $a - c$ competition in a particular region, c must win in the surroundings. A possible realization would be that the a molecules control the production of h which, in turn, either inhibits the a or promotes c production. These modes are equivalent since in competing systems a self-limitation is equivalent with a support of the competitor. An example is given in Eq. 7a-c in which h, a decay product of a, undermines the c-inhibition by a:

$$\frac{\partial a}{\partial t} = \frac{\rho_a}{\kappa + c^2} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_0 \qquad (7a)$$

$$\frac{\partial c}{\partial t} = \frac{\rho_c}{\kappa + a^2/h^2} - \mu_c c + D_c \frac{\partial^2 c}{\partial x^2} \qquad (7b)$$

$$\frac{\partial h}{\partial t} = \mu_a a - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} \qquad (7c)$$

The restriction of the self-amplification may not proceed by a long-ranging self-inhibition but by the activation of a second state that locally excludes the first (Meinhardt and Gierer, 1980). This type of interaction is important for segmentation. The mutual activation of *engrailed* and *wingless* by diffusible components is of this type. In this case there is not an activated and a non-activated region. Only regions with different activations exist. Due to the symmetry of the system, the region in which the one or the other activation occurs can have the same extension. Stripe-like patterns are preferred. This is in contrast to sharp activator maxima surrounded by large non-activated region generated by a direct activator-inhibitor interaction. A possible interaction is given in Eq. 8:

$$\frac{\partial a}{\partial t} = \rho_a \frac{a^2}{a^2 + c^2/d^2)} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} \qquad (8a)$$

$$\frac{\partial b}{\partial t} = \mu_a a - \mu_b b + D_b \frac{\partial^2 b}{\partial x^2} \qquad (8b)$$

$$\frac{\partial c}{\partial t} = \rho_c \frac{c^2}{a^2/d^2 + c^2} - \mu_c c + D_c \frac{\partial^2 a}{\partial x^2} \qquad (8c)$$

$$\frac{\partial d}{\partial t} = \mu_c a - \mu_d d + D_d \frac{\partial^2 d}{\partial x^2} \qquad (8d)$$

A simple calculation provides some intuition for the condition for local instability and global stability

For sake of simplicity let us first assume in Eq. 1 all constants scaled as to 1. In a first step we take the inhibitor concentration as constant and we disregard diffusion. Equation 1a would read:

$$\frac{da}{dt} = a^2 - a$$

The activator has a steady state ($da/dt = 0$) at $a = 1$. However, this steady state is unstable since for any concentration of a larger than 1, $a^2 - a$ will be positive and the concentration of a will further increase and vice versa. The reason for this instability lies in the over-exponential autocatalytic production in conjunction with a normal exponential decay.

Now let us include in a second step the change of the inhibitor concentration. Equation 1b would read:

$$\frac{dh}{dt} = a^2 - h$$

which has a steady state at $h = a^2$.

If we assume that the h equilibrates rapidly in response to a changed activator concentration, we can express the change of activator concentration as function of the activator concentration alone:

$$\frac{da}{dt} = \frac{a^2}{h} - a \approx \frac{a^2}{a^2} - a \; = \; 1 - a$$

Thus, if we include the action of the inhibitor, we also obtain a steady state at $a = 1$. This, however, is stable since if a is larger than 1, $1 - a$ is negative and the concentration will return to the steady state at $a = 1$.

To see why an interaction according to (1a,b) can generate a pattern we now include in a third step the principle of lateral inhibition, namely the effect of diffusion or other forms of spatial spreading of the inhibitory effect. The inhibitor is assumed to diffuse much faster and to have a wider range than the activator. Let us assume an array of cells; all cells are at the steady state concentrations of a and h, except one cell which should have a slightly increased activator concentration. It will produce also more of the inhibitor but since the inhibitor diffuses rapidly into the surroundings, the inhibitor can be regarded in first approximation as constant. It is the *average* activator concentration that is decisive for the inhibitor production. As mentioned, if the inhibitor remains constant, any deviation from the activator steady state will grow further, i.e., the steady state is unstable. However, after a substantial increase of the activator maximum, the inhibitor concentration can no longer be regarded as constant. As shown above, the action of the inhibitor leads to the stabilization of the autocatalysis. A new stable patterned steady state will be reached. Thus, the formation of a stable pattern depends on a local instability and a global stability.

Gierer A. and Meinhardt H. (1972). A theory of biological pattern formation. Kybernetik 12,30-39.

Gierer A. (1981). Generation of biological patterns and form: Some physical, mathematical, and logical aspects. Prog. Biophys. molec. Biol. 37,1-47.

Meinhardt H. and Gierer A. (1980). Generation and regeneration of sequences of structures during morphogenesis. J. theor. Biol. 85,429-450.

Prigogine I. and Lefever R. (1968). Symmetry breaking instabilities in dissipative systems. II. J. chem. Phys. 48,1695-1700.

Turing A. (1952). The chemical basis of morphogenesis. Phil. Trans. B. 237,37-72.