Gierer-Meinhardt model

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The **Gierer-Meinhardt model**

$$\frac{\partial a}{\partial t} = \rho \frac{a^2}{h} - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_a$$

$$\frac{\partial h}{\partial t} = \rho a^2 - \mu_h h + D_h \frac{\partial^2 h}{\partial x^2} + \rho_h$$

is a reaction-diffusion system of the **activator-inhibitor** type that appears to account for many important types of pattern formation and morphogenesis observed in development. (Proof requires identification of the purported morphogens, measurement of their spatiotemporal concentrations and kinetics, and demonstration by knockouts or other genetic manipulations that they are essential components of the observed pattern formation.) Here,

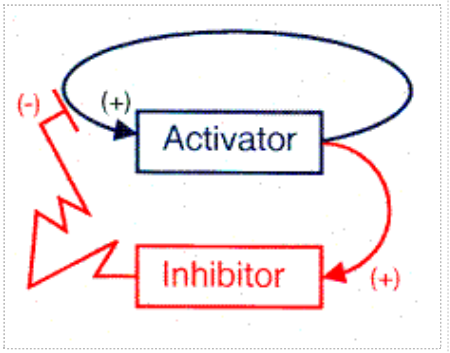

Figure 1: Short-range activator and long-range inhibitor in Gierer-Meinhardt model

- a is a short-range autocatalytic substance, i.e., *activator*, and
- h is its long-range antagonist, i.e., *inhibitor*.

$\partial a/\partial t$ describes the change of activator concentration a per time unit. The first term on the right describes the production rate which depends in a non-linear way on the activator concentration (a^2) and is slowed down by the inhibitor ($1/h$). The number of molecules that decay per time unit is proportional to the decay rate μ_a and to the number of a - molecules present (like the number of people dieing in a city depends on the number of inhabitants). The exchange of molecules is assumed to occur by diffusion ($D_a \partial^2 a/\partial x^2$), but other modes of spreading are possible as well. The second equation describes in analogous terms the change of the inhibitor concentration. ρ_a is a small activator-independent production rate of the activator and is required to initiate the activator autocatalysis at very low activator concentration, e.g. in the case of regeneration (as shown below). A low baseline production of the inhibitor, ρ_h, leads to a stable non-patterned steady state; the system can be asleep until an external trigger occurs by an elevation of the activator concentration above a threshold.

The model was formulated by Alfred Gierer and Hans Meinhardt in 1972.

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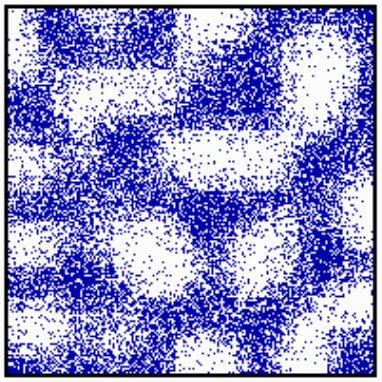

Figure 2: An example of pattern formation in the Gierer-Meinhardt model. Stripe formation occurs if the autocatalysis saturates (see blow). In equation 1 this occurs if the autocatalytic production a^2 is replaced by $a^2/(1+\kappa a^2)$.

Pattern Formation

The development of a higher organism out of a single fertilised egg is one of the most fascinating aspects of biology. A central question is how the cells, which carry identical genetic code, become different from each other. Spontaneous pattern formation in initially almost homogeneous systems is also common in inorganic systems. Large sand dunes are formed despite the fact that the wind permanently redistributes the sand. Sharply contoured and branching river systems (which are in fact quite similar to the branching patterns of a nerve) are formed due to erosion despite the fact that the rain falls more or less homogeneously over the ground.

Activator-Inhibitor Systems

Common in these pattern-forming systems is that a deviation from homogeneity has a strong positive feedback on its further increase. Erosion proceeds faster at an initial small depression since more water collects there, deepening further the depression. In the case of sand dunes, a small elevation resembles a wind shelter behind which more sand becomes deposited.

However, self-enhancement is not sufficient. On its own, it would lead to an unlimited increase and spreading. Pattern formation requires in addition a longer ranging confinement of the locally self-enhancing process. This limitation can either result from a long-ranging inhibitory signalling that spreads rapidly from such a region. Alternatively the antagonistic effect can result from a depletion of material required for the self-enhancement that is obtained from the surrounding region.

The Model

Alfred Gierer and Hans Meinhardt formalised this observation and proposed a molecularly plausible model for pattern formation, consisting of two partial differential equations (see above) of reaction-diffusion type. The model describes the concentration of a short-range autocatalytic substance, the activator, that regulates the production of its long-range antagonist, the inhibitor (Gierer and Meinhardt, 1972, Gierer, 1981; Meinhardt, 1982). It is certainly a minimal model, but it provides a theoretical bridge between observations on the one hand and the deduction of the underlying molecular-genetic mechanisms on the other hand.

The possibility to generate patterns by the reaction of two substances that diffuse with different rates has been discovered by Turing (1952). Gierer and Meingardt have shown that even if this condition is satisfied, only a very special class of reactions is able to form patterns if and only if local autocatalysis and long-ranging inhibition is involved. Different implementations are possible: The inhibition can result from a depletion or the autocatalysis can be based on an inhibition of an inhibition. Turing's equation satisfies this condition. In the term of Gierer-Meinhardt mechanism, the inhibition results from an activator removal by the rapidly diffusing substance (for details see [1] (http://www.eb.tuebingen.mpg.de/dept4/meinhardt/Details/Turing.html) or Turing Instability).

Formation of organising regions, polar patterns and primary gradients

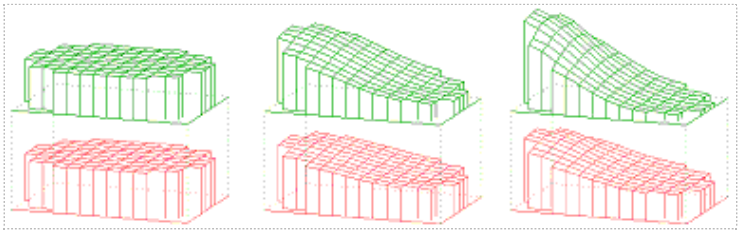

Figure 3: Primary gradients

If the range of the inhibitory substance covers the whole field, only a single maximum is possible, resulting in a simple pattern. Moreover, if the range of the activator is comparable with the total extension only a marginal activation is possible. Such an interaction is appropriate to generate a polar pattern within a field of cells. Activated regions are assumed to act as "organizing regions", i.e., as signaling centers that determine the fate of the surrounding region. Examples of such organizing regions are the opening of the gastric column in hydra and the Spemann organizer in amphibians. Upon transplantation, such organizing regions can induce secondary embryonic axes in the new surrounding. In hydra, this is a new ring of tentacles, in the frog this is a new midline (notochord and central nervous system).

Pattern regulation

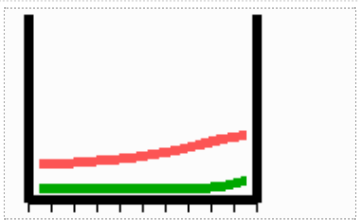

Figure 4: Pattern regulation.

Classical experiments have revealed hat in many systems tissue can be removed and development proceeds still normal. Therefore, any theory of biological pattern formation should be able to describe pattern regulation after an experimental interference. In the simulation (right) the maximum is removed. With this, also the region in which the inhibitor is produced is removed. After the decay of the remnant inhibitor, the autocatalysis triggers from a base-line activator production and the gradient becomes restored.

The ability to regulate is usually lost at later stages of development. Since in the proposed mechanism pattern formation depends on diffusion, the mechanism can only work as long as the tissue to be patterned is small. Patterning of larger fields would require too much time. Thus, in the course of development, the competence to form patterns is lost; the determination of the cells depends no longer at the signalling and is fixed. Thus, it is very important that during development the cells are competent only in a certain time window to generate primary organizing regions; otherwise multiple maxima (see below) and secondary axes would appear that would abolish any predictable axis formation.

Periodic patterns

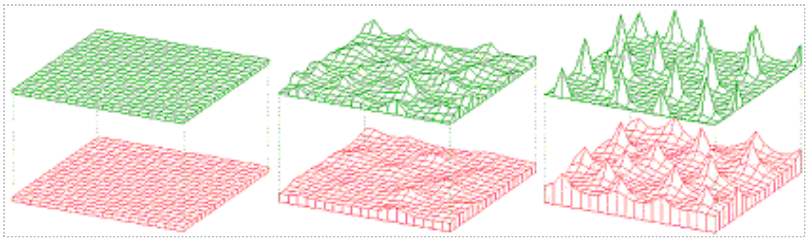

Figure 5: Periodic patterns.

Periodic patterns are very common in development. The initiation of leaves behind a growing shoot, the formation of leaf hairs, feathers in birds or hairs in mammals are examples. According to the model, periodic structures emerge if the range of the inhibitory substance is smaller than the size of the field in which the reaction takes place. If initiated by random fluctuations, the pattern will have some irregularity (as in leaf hairs). A maximum and minimum distance, however, is maintained. Very regular patterns are formed if the pattering occurs during growth. The initiation of leaves behind a growing shoots is an example. An example in which the underlying molecular reaction is very close to the proposed mechanism is the initiation of nitrogen-fixating cells in the blue-green algae Anabaena. This alga consists of a linear chain of cells. About every ninth cell differentiate into a so-called heterocyst cell. In agreement with the theory, this pattern formation is based on a transcription factor HetR that has a direct positive feedback on the transcription of its own gene (Huang et al., 2004, PNAS 101, 4848 – 4853). Only dimers of HetR can bind to the DNA, i.e., the self-

enhancement is non-linear, as theoretically expected. This HetR also activates the production of a short peptide, PatS, which can bind to the transcription factor. Binding of the peptide to the transcription factor abolishes its ability to bind to DNA. The peptide acts, therefore, as inhibitor. The peptide can be diffuse between the cells through special channels, the so-called desmosomes.

Stripe-like patterns

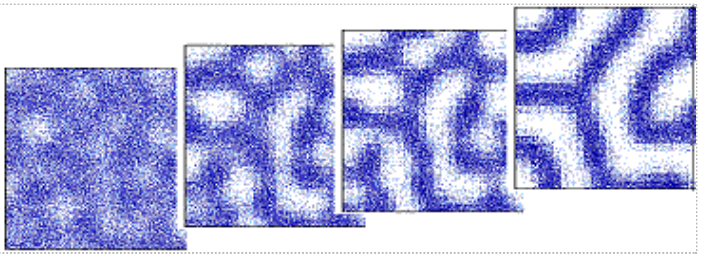
Figure 6: Stripe-like patterns.

Embryos are full of structures that have a long extension in one direction and a short extension in the other. Stripe-like patterns are formed if the autocatalysis saturates at high activator concentration. Due to this upper bound in the activator concentration, the peak height can no longer increase. Instead the spatial extension of a region carrying a high activator concentration will increase. Since the mechanism is based on lateral inhibition, a stripe-like distribution is preferred since in this case each activated cell has an activated neighbour but also non-activated neighbours are in the vicinity to dump the inhibitor.

Activated and non-activated cells in a particular ratio

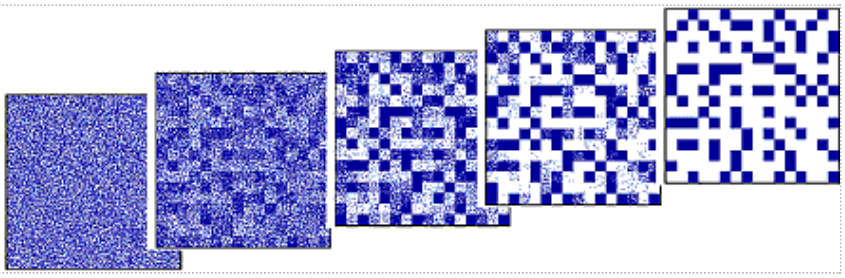
Figure 7: Cell patterns.

Stripe formation requires some diffusion of the activator. A limited diffusion is necessary for activated cells to have activated neighbours. Without diffusion but with saturation, activated cells emerge in a salt-and-pepper distribution. This is appropriate if cells with a particular differentiation have to be formed that have a certain ratio to the non-differentiated cells. The formation of prespore and prestalk cells in the slime mould *Dictyostelium discoideum* is an example.

Alternative molecular realizations: the activator-depleted substrate scheme

The long-ranging inhibition does not necessarily require an inhibitor. The antagonistic effect can also result, for instance, from the depletion of the substrate s that is consumed during the production of the autocatalytic activator a . A possible interaction is given in the following equation:

$$\frac{\partial a}{\partial t} = \rho s a^2 - \mu_a a + D_a \frac{\partial^2 a}{\partial x^2} + \rho_0$$

$$\frac{\partial s}{\partial t} = \delta - \rho s a^2 - \mu_s s + D_s \frac{\partial^2 s}{\partial x^2}$$


Figure 8: Pattern formation via activator-depletion mechanism.

In this interaction the substrate s is produced everywhere with the same rate. Again the diffusion of the substrate must be much higher than that of the activator. As can be seen in the simulation, the substrate distribution will have a minimum at the position of an activator maximum. Most inorganic pattern-forming processes mentioned above depend on such a mechanism.

The activator-depletion mechanism has an inherent limit of maximum activator production since the activator production halts if sufficient substrate is no longer available. Therefore, patterns generated by this mechanism show relatively broad maxima that tend to shift into regions in which high substrate concentrations are still available. Therefore, the spacing is generally more regular but the maxima are less sharp. Peak width and the spacing of the peaks is of the same order. Such systems behave similarly to activator-inhibitor systems with saturation.

An interesting application of the activator-depleted substrate model is the pattern formation within a cell. If the activation consists, for instance, of a self-enhancing process that takes place at the cell membrane and proceeds at the expense of precursor molecules that diffuse freely within the cytoplasm (red), the activation (green) becomes restricted to a part of the membrane. In other words, the cell becomes polar. Since diffusion processes within the membrane are expected to be much slower than those in the cytoplasm, the condition for the different diffusion rates is naturally satisfied.

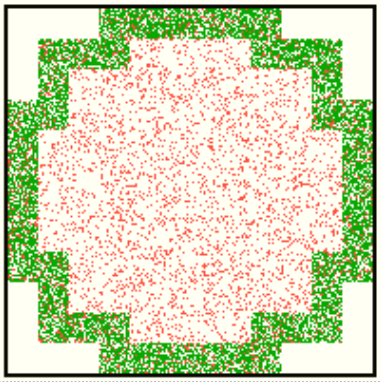

Figure 9: Pattern formation within a cell.

Autocatalysis can consist of an inhibition of an inhibition

Pattern formation does not require a molecule with direct autocatalytic regulation. Autocatalysis can be a property of the system as a whole. For instance, if two substances inhibit each other mutually, a slight increase of one the substance would lead to a stronger inhibition of the other, which would lead to a further increase of the first as if this substance would be autocatalytic. The formation of the famous Spemann-organizer in amphibians can be interpreted in this way.

If the antagonistic reaction has a longer time constant: Oscillations

The patterns mentioned above lead to stable patterned steady states if the antagonistic reaction has a shorter time constant then the self-enhancing reaction, i.e., if the inhibitor concentration reacts rapidly to a change in the activator concentration. Longer time constants of the antagonistic reaction may result in oscillations. A burst-like activation occurs that breaks down after the inhibitor has obtained a substantial concentration. After decay of the remnant inhibitor, the next burst is triggered from baseline inhibitor production. If one of the components spreads rapidly by diffusion, the oscillations in an extended region will synchronize.

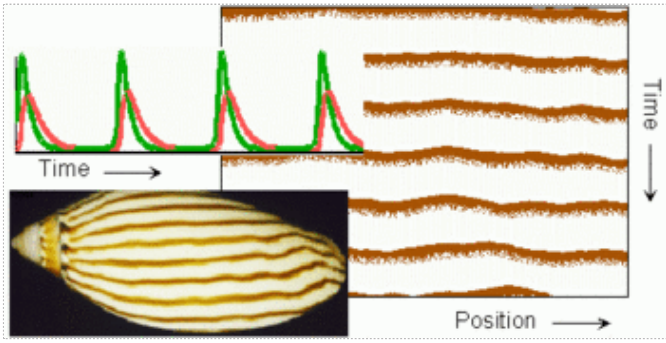

Figure 10: Parallel stripes on shells caused by a near synchronous oscillation.

The pigmentation patterns on some tropical molluscs are very instructive for such mechanisms. A mollusc can enlarge its shell only at the growing edge. As the rule, new pigment is incorporated only in this growth process at this growing edge. Therefore, these patterns are time records of a one-dimensional patterning process that took place at the margin. Parallel stripes on a shell are a time record of a synchronized oscillation.

If the activation spreads only moderately and the inhibitor is non-diffusible, travelling waves can result. Per se, such oscillators would not desynchronize. Therefore, wave initiation requires a local pacemaker or a local spontaneous trigger. Two such waves annihilate upon collision since the waves cannot enter into the regions that are refractory due to the counter-running wave. Records of such annihilation also can be seen on some shell pattern (V-like pattern, red arrows in the figure). In contrast, a spontaneous trigger can lead to two diverging waves (/\-like pattern; green arrows.)

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Figure 11: Collision and annihilation of two waves.

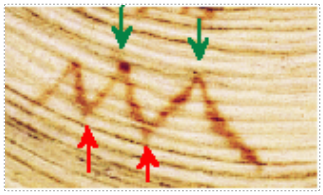

Figure 12: Oblique lines on shells that may be caused by travelling waves.

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External Links

Author's website (http://www.eb.tuebingen.mpg.de/meinhardt)

See also

Morphogenesis, Neural Fields, Pattern Formation, Reaction-Diffusion Systems, Self-Organization, Symmetry Breaking, Synergetics, Turing Instability

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