Pattern Formation and Turing Pattern in Developmental Cell Systems

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Analysis and Mathematical Modelling

in the Life-Sciences

Cells can detect chemical and mechanical information
by signal specific receptors on the cell surface.

Cells signal to interact with their environment
and with neighboring cells, for instance by

- diffusive signals

- spatially localised signals, e.g. bound
  to the extra cellular matrix (ECM)

- cell surface bound signals

The reaction of cells to external signals often result in macroscopic structure formation on the population level.

The understanding of pattern formation
in wildtype populations and mutant populations
can thus reveal basic underlying principles
of cellular signalling, motion, and growth.

1 Turing Pattern, Diffusion Driven Instabilities

- two or more chemicals,

- with different rates of diffusion

- chemical interaction of activator-inhibitor type

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis.

A. M. Turing (1952): The chemical basis for morphogenesis. Phil. Trans. Roy. Soc. Lond., 237, 37–72.

[*Compare the book by Edelstein-Keshet*]

Consider two morphogens C_1, C_2

$$
\begin{aligned}
\partial_t C_1 &= D_1 \Delta C_1 + R_1(C_1, C_2) \\
\partial_t C_2 &= D_2 \Delta C_2 + R_2(C_1, C_2)
\end{aligned}
$$

For constant steady states $\bar{C}_1, \bar{C}_2$ we have
$$
R_1(\bar{C}_1, \bar{C}_2) = 0 = R_2(\bar{C}_1, \bar{C}_2).
$$
To study the effects of small inhomogeneous perturbations $\hat{C}_1(t, x), \hat{C}_2(t, x)$ of these constant states let

$$
\hat{C}_1(t, x) = C_1(t, x) - \bar{C}_1 \quad \text{and} \quad \hat{C}_2(t, x) = C_2(t, x) - \bar{C}_2
$$

Linearising around $\bar{C}_1, \bar{C}_2$ we obtain

$$
\begin{aligned}
\partial_t \hat{C}_1 &= D_1 \partial_{xx} \hat{C}_1 + a_{11} \hat{C}_1 + a_{12} \hat{C}_2 \\
\partial_t \hat{C}_2 &= D_2 \partial_{xx} \hat{C}_2 + a_{21} \hat{C}_1 + a_{22} \hat{C}_2
\end{aligned}
$$

where

$$
a_{ij} = \frac{\partial R_i}{C_j}(\bar{C}_1, \bar{C}_2) \ .
$$

Calculate the so-called characteristic equation with the ansatz

$$
\hat{C}_1(t,x) = \alpha_1 \cos(qx) \exp(\sigma t) \quad , \quad \hat{C}_2(t,x) = \alpha_2 \cos(qx) \exp(\sigma t)
$$

Then

$$\begin{aligned}
\alpha_1 \sigma &= -D_1 q^2 \alpha_1 + a_{11}\alpha_1 + a_{12}\alpha_2 \\
\alpha_2 \sigma &= -D_2 q^2 \alpha_2 + a_{21}\alpha_1 + a_{22}\alpha_2
\end{aligned}$$

This equation is linear in α_1, α_2. Non-zero solutions only exist, if the determinant of the matrix M with coefficients
$M_{11} = \sigma + D_1 q^2 - a_{11}$, $M_{12} = -a_{12}$
$M_{21} = -a_{21}$, $M_{22} = \sigma + D_2 q^2 - a_{22}$
equals zero, i.e.

$$\sigma^2 + \sigma(-a_{22} + D_2 q^2 - a_{11} + D_1 q^2)$$
$$+[(a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12}a_{21}] = 0$$

For $D_1 = D_2 = 0$ we have

$$\sigma_{1,2} = \frac{a_{11} + a_{22}}{2} \pm \sqrt{\frac{(a_{11} + a_{22})^2}{4} - (a_{11}a_{22} - a_{12}a_{21})}$$

The system is stable $(Re(\sigma) < 0)$ when

$$a_{11} + a_{22} < 0$$
$$a_{11}a_{22} - a_{12}a_{21} > 0$$

Consider the analogous conditions for $D_1, D_2 \neq 0$,
to see how diffusion can destabilise the system

$$
\begin{aligned}
a_{11} + a_{22} - D_2 q^2 - D_1 q^2 &< 0 \\
(a_{11} - D_1 q^2)(a_{22} - D_2 q^2) - a_{12} a_{21} &> 0
\end{aligned}
$$

The violation of any of these inequalities
leads to diffusion driven instabilities.
Since $D_1, D_2 > 0$, only the second inequality can be violated.
For $z = q^2$ its left hand side can be written as

$$
H(z) = D_1 D_2 z^2 - (D_1 a_{22} + D_2 a_{11}) z + (a_{11} a_{22} - a_{12} a_{21})
$$

where $H(z)$ is a parabola with minimum in

$$
z_{min} = \frac{1}{2} \left(\frac{a_{22}}{D_2} + \frac{a_{11}}{D_1} \right)
$$

A minimal condition for $H(z)$ to have negative values is, that

$$H(z_{min}) < 0 \quad \text{or}$$

$$a_{11}D_1 + a_{22}D_2 > 2\sqrt{D_1 D_2}\sqrt{a_{11}a_{22} - a_{12}a_{21}} > 0 \qquad (1)$$

For wavenumbers close to q_{min}^2 the rate of growth
of the perturbations, i.e. σ, is positive.

Thus necessary and sufficient conditions
for diffusion driven instabilities are:
the stability conditions for the ordinary differential equations
and (1).

Interpretation

Due to condition $a_{11} + a_{22} < 0$ at least
one of the two coefficients a_{11} and a_{22} has to be negative.
Suppose a_{22} is negative, i.e. $\partial R_2 / \partial C_2 < 0$.
This means, that the second chemical inhibits its own rate formation
and thus is called inhibitor.

Due to condition $a_{11} D_2 + a_{22} D_1 > 0$ we obtain
that a_{11} has to be positive, i.e. $\partial R_1 / \partial C_1 > 0$.
This means, that the first chemical promotes or activates
its own formation and thus is called activator.

Thus $a_{11}a_{22} < 0$.

Therefore condition $a_{11}a_{22} - a_{12}a_{21} > 0$
can only be met, if $a_{12}a_{21} < 0$.

We also have $a_{11} + a_{22}D_1/D_2 < 0$. Thus $D_1 \neq D_2$,
since otherwise $a_{11} + a_{22} \cdot 1 < 0$.

This means, that the diffusion coefficients of the two chemicals
must be dissimilar for a diffusive instability to occur.

Further calculations reveal that the range of inhibition
is larger than the range of activation and that $D_2 > D_1$.

So due to a random perturbation of the constant steady states
a small peak concentration of the activator is created
at some location.

This causes an enhanced production of the inhibitor.

Since the inhibitor diffuses away more rapidly than the activator,
it can not control the local activator production
and the initial peak will grow.

The region near this peak contains sufficient levels of inhibition
to prevent further peaks of activation close by.

See

http://www.ncbi.nlm.nih.gov/projects/genome/guide/img/

dictyEM.jpg

Selforganisation of *Dictyostelium discoideum*, (Dd)

See

http://cmgm.stanford.edu/devbio/kaiserlab/

About Myxococci ...

Selforganization and rippling in populations of myxobacteria.

Turings Idea for Direct Cell-Cell Interaction

Countermigrating traveling waves in myxobacteria

A simple model with symmetry [Lutscher-S.]

$$\partial_t u + \partial_x u = -F(u,v)u + F(v,u)v$$
$$\partial_t v - \partial_x v = F(u,v)u - F(v,u)v$$

The turning rates are assumed to be general and depend on both, the left and right moving part of the population.

In this case linearisation does not show patterns.

[Primi-S.-Velázquez]

Without the above given symmetry, 3 equations of this type are sufficient to obtain patterns with a defined wavelength.

Systems with symmetry

$$\partial_t u_1 + \partial_x u_1 \;=\; -T_1(u_1, u_2, v_1, v_2) + T_2(v_1, v_2, u_1, u_2)$$

$$\partial_t u_2 \;=\; T_1(u_1, u_2, v_1, v_2) - T_2(u_1, u_2, v_1, v_2)$$

$$\partial_t v_1 - \partial_x v_1 \;=\; T_2(u_1, u_2, v_1, v_2) - T_1(v_1, v_2, u_1, u_2)$$

$$\partial_t v_2 \;=\; T_1(v_1, v_2, u_1, u_2) - T_2(v_1, v_2, u_1, u_2)$$

Example with a defined wavelength:

$$T_1 \;=\; F_1(u_1 + u_2 + v_1 + v_2, u_1, v_1, v_2)$$

$$T_2 \;=\; F_2(u_1 + u_2 + v_1 + v_2, u_2)$$

u_1 can become u_2 in dependence of the total population, its own kind and the countermigrating part of the population.

u_2 can turn its direction, in dependence of the total population.

If u_2, v_2 move, but with a different speed than u_1, v_1,
then inhibiting effects are needed
in order to obtain a defined wavelength.

For the given situation inhibition is not a reasonable mechanism.

2 Test Experiment for the Model

Mix wildtype with mutants, which do not produce
the surface bound C-signal.
Upon contact of a wildtype with a countermigrating mutant,
the wildtype does not change direction, whereas the mutant does.
$\rightarrow$ The more mutants, the larger the wavelength.
Too many mutants make the pattern disappear.

$u_1 \rightarrow u_2 \rightarrow u_3 \rightarrow v_1 \rightarrow v_2 \rightarrow v_3$, all move with the same speed.

$\lambda = u_1 + u_2 + u_3 + v_1 + v_2 + v_3 + \bar{u}_1 + \bar{u}_2 + \bar{u}_3 + \bar{v}_1 + \bar{v}_2 + \bar{v}_3$,
where $\bar{u}_j, \bar{v}_j$ describe the respective mutant populations.

$$T_1 = F_1(\lambda, u_1) \ , \ T_2 = u_2 F_2(v_1 + v_2 + v_3) \ , \ T_3 = f_3 u_3$$
$$\bar{T}_1 = F_1(\lambda, \bar{u}_1) \ , \ \bar{T}_2 = \bar{u}_2 F_2(v_1 + v_2 + v_3) \ , \ \bar{T}_3 = f_3 \bar{u}_3$$

$$T_1 = F_1(\lambda, u_1) \ , \ T_2 = u_2 F_2(v_1 + v_2 + v_3) \ , \ T_3 = f_3 u_3$$

$$\bar{T}_1 = F_1(\lambda, \bar{u}_1) \ , \ \bar{T}_2 = \bar{u}_2 F_2(v_1 + v_2 + v_3) \ , \ \bar{T}_3 = f_3 \bar{u}_3$$

Interpretation:

u_1 needs a minimal total population density to start C-signalling, i.e. to become excited and able to turn.

The excited bacteria u_2 receive the C-signal
upon contact with countermigrating wildtype cells.

u_3 turns with a certain probability.

The mutants $\bar{u}_2$ need contact with the countermigrating
wildtypes v_1, v_2, v_3 in order to be able to turn.