

Turing Pattern and other Pattern Forming Mechanisms in Developmental Systems

Angela Stevens

University of Münster

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 signaling, 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.

[Edelstein-Keshet: book]

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

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

Linearizing 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

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

Calculate the 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

$$\begin{aligned}\alpha_1\sigma &= -D_1q^2\alpha_1 + a_{11}\alpha_1 + a_{12}\alpha_2 \\ \alpha_2\sigma &= -D_2q^2\alpha_2 + a_{21}\alpha_1 + a_{22}\alpha_2\end{aligned}$$

which is linear w.r.t. α_1, α_2 . Non-zero solutions only exist, if $\det M = 0$ where

$$M_{11} = \sigma + D_1q^2 - a_{11}, \quad M_{12} = -a_{12}$$

$$M_{21} = -a_{21}, \quad M_{22} = \sigma + D_2q^2 - a_{22}$$

i.e.

$$\begin{aligned}\sigma^2 + \sigma(-a_{22} + D_2q^2 - a_{11} + D_1q^2) \\ + [(a_{11} - D_1q^2)(a_{22} - D_2q^2) - a_{12}a_{21}] = 0\end{aligned}$$

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

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

$$a_{11}D_1 + a_{22}D_2 > 2\sqrt{D_1D_2}\sqrt{a_{11}a_{22} - a_{12}a_{21}} > 0 \quad (1)$$

For wavenumbers close to q_{min} the rate of growth of the perturbations is positive.

Thus suitable 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 has to be negative.

Let $a_{22} < 0$, i.e. $\partial R_2 / \partial C_2 < 0$.

Thus C_2 inhibits its own rate formation.

Due to condition $a_{11}D_2 + a_{22}D_1 > 0$ we obtain that $a_{11} > 0$, i.e. $\partial R_1 / \partial C_1 > 0$.

Thus the C_1 activates its own formation.

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

Thus 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 $a_{11} + a_{22} \cdot 1 < 0$.

So the diffusion coefficients of the two chemicals
must be dissimilar for a diffusive instability to occur.

Further, one can show, 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 cannot 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>

Selforganization of Dictyostelium discoideum, (Dd)

Chemotactic Aggregation

$$\partial_t u = -\partial_x(-\mu\partial_x u + \chi u\partial_x v)$$

$$\partial_t v = -\partial_x(-D\partial_x v) + fu - kv$$

Steady state analysis results in $f\bar{u} = k\bar{v}$.

Destabilization and Onset of Aggregation

Equations for small perturbations \hat{u}, \hat{v} :

$$\partial_t \hat{u} = \mu \partial_{xx} \hat{u} - \chi (\partial_x \hat{u} \partial_x \hat{v} + \bar{u} \partial_{xx} \hat{v} + \hat{u} \partial_{xx} \hat{v})$$

$$\partial_t \hat{v} = D \partial_{xx} \hat{v} + f \hat{u} - k \hat{v}$$

Delete quadratic terms w.r.t. the perturbations

$$\partial_t \hat{u} = \mu \partial_{xx} \hat{u} - \chi \bar{u} \partial_{xx} \hat{v}$$

$$\partial_t \hat{v} = D \partial_{xx} \hat{v} + f \hat{u} - k \hat{v}$$

Ansatz:

$$\hat{u}(t, x) = A \exp(\sigma t) \cos(qx)$$

$$\hat{v}(t, x) = C \exp(\sigma t) \cos(qx)$$

We obtain $Re(\sigma) > 0$ if

$$\mu(Dq^2 + k) < \chi \bar{u} f$$

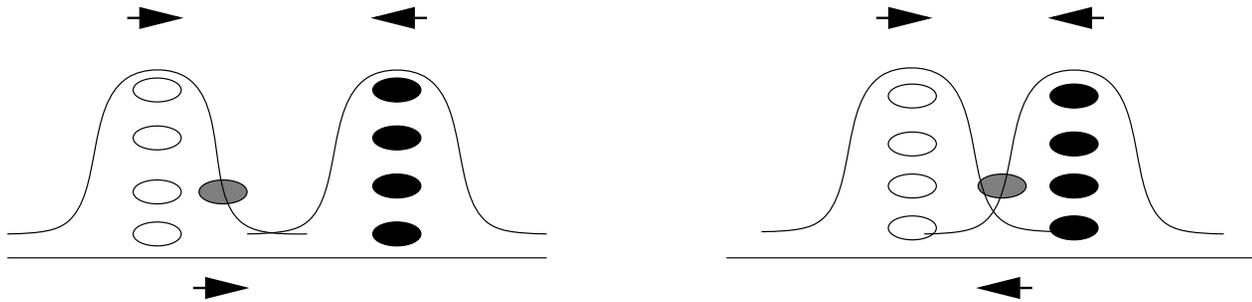
2 Orientational Selection and Aggregation in Structured Population Models

See <http://cmgm.stanford.edu/devbio/kaiserlab>

About Myxococci ...

Selforganization and rippling in populations of myxobacteria.

[Lutscher - S.]



Signaling upon Contact

Countermigrating traveling waves in myxobacteria

A simple model with symmetry

$$\begin{aligned}\partial_t u + \partial_x u &= -F(u, v)u + F(v, u)v \\ \partial_t v - \partial_x v &= F(u, v)u - F(v, u)v\end{aligned}$$

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

In this case linearization 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.

3 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.

→ 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-signaling, 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.

Alignment:

$$\begin{aligned}\partial_t f(t, \gamma) &= - \int_I T[f](\gamma, \gamma') f(t, \gamma) d\gamma' \\ &\quad + \int_I T[f](\gamma', \gamma) f(t, \gamma') d\gamma'\end{aligned}$$

where $T[f](\gamma, \gamma') = \int_I G_\sigma(\gamma' - \gamma - V(w - \gamma)) f(t, w) dw$,
 $I = [-\frac{1}{2}, \frac{1}{2}]$, V is the orientational angle,

an odd function and 1-periodic,

G_σ measures the accuracy of reorientation

and can be chosen as the standard periodic Gaussian.

Bi-Directional Alignment - Attraction and Repulsion:

If the angle between myxobacteria is small, they attract each other.

If the angle between myxobacteria is larger, they are repulsive, respectively they are attracted to the ends of their interaction partners.

Peak Solutions for the Limiting Equation:

Consider G_σ with $\sigma = 0$, the Dirac mass δ_0 , which describes deterministic turning.

Convergence of solutions of our equation for G_σ to solutions for δ_0 , for σ small enough, was proved by [E. Geigant](#).

[Kang - Perthame - S. - Velázquez]

For continuously varying initial distributions
an exchange of mass and generalized momenta takes place.

Define suitable partial masses $m_1(t), m_2(t)$ as well as
suitable means of partial first moments $\xi_1(t), \xi_2(t)$.

By showing that suitable generalized second moments are decreasing
in time it could be proved, that two oriented peaks develop
at two exactly opposite orientations $\tilde{\xi}_1, \tilde{\xi}_2$,
if initially two slightly asymmetric oriented peaks are present.
Their final masses \tilde{m}_1, \tilde{m}_2 can be different.

These initial peaks may differ in size but should both be of higher
order of magnitude in size than the rest of the initial distribution.

*So we obtained local stability
for alignment into two opposite directions,
but **NO** selection of mass.*

[Primi - S. - Velázquez]

Have a closer look at the case $\sigma > 0$.

If the orientational angle V is very small
the kinetic equation can be approximated by

$$\partial_t f = \frac{\sigma^2 m}{2} \partial_{xx} f + \partial_x \left(f(x) \int_I V(x-y) f(y) dy \right)$$

We are interested in the steady states.

An equivalent formulation for these is

$$\begin{aligned} \frac{\sigma^2}{2} \partial_x f(x) + f(x) \int_I V(x-y) f(y) dy &= 0 \\ \int_I f(x) dx &= 1 \text{ and } f(x+1) = f(x) \end{aligned}$$

Heuristics for the Selection Mechanism

Let $\sigma = 0$, then the equation reduces to

$$f(x) \int_I V(x-y)f(y)dy = 0$$

Any function of the form $f(x) = \alpha\delta_0(x) + \beta\delta_0(x - \frac{1}{2})$ is a solution, for arbitrary choice of α, β .

For $\sigma > 0$ this is not the case.

Suppose $f_\sigma \rightarrow \alpha\delta_0(x) + \beta\delta_{\frac{1}{2}}(x)$ for $\sigma \rightarrow 0$.

For $\sigma \ll 1$, f_σ can then be approximated by the solution of

$$\begin{aligned}\frac{\sigma^2}{2} \partial_x f(x) + f(x) V_{\alpha,\beta}(x) &= 0 \\ \int_I f(x) dx &= 1\end{aligned}$$

where $V_{\alpha,\beta} = \alpha V(x) + \beta V(x - \frac{1}{2})$.

This equation can be solved explicitly

$$f(x) = \frac{\exp(-\frac{2}{\sigma^2} [\alpha\phi(x) + \beta\phi(x - \frac{1}{2})])}{\int_I \exp(-\frac{2}{\sigma^2} [\alpha\phi(y) + \beta\phi(y - \frac{1}{2})]) dy}$$

with $\phi(x) = \int_0^x V(z) dz$, so $\phi(x) = \phi(-x)$.

Assume $\phi(\frac{1}{2}) \neq 0$, which is generally the case.

The condition for having two peaks concentrated at $x = 0$ and $x = \frac{1}{2}$ is that $\alpha\phi(x) + \beta\phi(x - \frac{1}{2})$ reaches its minimum at these points.

In particular $\alpha\phi(0) + \beta\phi(-\frac{1}{2}) = \alpha\phi(\frac{1}{2}) + \beta\phi(0)$.

This can only happen for $\alpha = \beta = \frac{1}{2}$.

What are the conditions on V for either one or two peaks of equal size to occur?

Suppose for $\sigma \ll 1$ exists a peak-like smooth function f , mainly concentrated at 0, which solves

$$\begin{aligned} \frac{\sigma^2}{2} \partial_x f(x) + f(x) \int_I V(x-y) f(y) dy &= 0 \\ \int_I f(x) dx &= 1 \end{aligned}$$

and converges to δ_0 for $\sigma \rightarrow 0$.

This function may be approximated by the solution of

$$\frac{\sigma^2}{2} \partial_x f(x) + f(x)V(x) = 0 , \int_I f(x)dx = 1 .$$

Therefore

$$f(x) = \frac{\exp(-\frac{2}{\sigma^2} [\int_0^x V(z)dz])}{\int_I \exp(-\frac{2}{\sigma^2} [\int_0^y V(z)dz])dy}$$

For $\int_0^{\frac{1}{2}} V(x)dx > 0$ we have a main concentration around 0.

For $\int_0^{\frac{1}{2}} V(x)dx < 0$ the peak is located at $\pm \frac{1}{2}$,
which is a contradiction.