Gradients in Pattern Formation (based on [1])

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Abstract

Pattern formation occurs in different stages of the development of all organisms. Processes like the determination of the tissue to which an embryo cell will differentiate can easily be explained by simple mathematical models. In order to explain spatial correlation in different pattern forming systems, gradients are supposed to serve as an initial disturbance for other activator/inhibitor systems. Gradients which are themselves build by activator/inhibitor systems have certain features giving them structural stability. Finally these gradients can not only explain simple patterns in other systems but also the stripe-like segmentation of embryos.

1 Introduction

All of the currently known mathematical models for pattern forming systems require an initial disturbance in order to break down the homogeneous distribution of a substance across the simulated field. After such an effect the system will drive itself further away from the initial unstable steady state and a pattern can arise in the simulated field. For most purposes it is sufficient to assume the initial disturbance to be of stochastic nature. But when a mathematical model is supposed to explain spatially correlated patterns in different activator/inhibitor systems, a different level of spatial information has to be incorporated.

A very simple kind of spatial information is a gradient of a substance x across a cell or a small tissue (as shown in figure 1). This substance x can now serve as an initial disturbance for different activator/inhibitor systems, e.g. by enhancing activator production. Different systems induced by x will now be able to form spatially correlated patterns even though they do not have any further chemical relation.

2 Gradient formation

In order to explain how a gradient is build up different theories have been propounded. The first theory supposes that the field in which the gradient is build up contains a source and a sink. At the source the substance x is constantly produced, from there it diffuses across the field and is finally consumed at the sink at the opposite end. While this theory is quite simple it also has some problems. A general source-and-sink model is heavily dependend on its parameters,

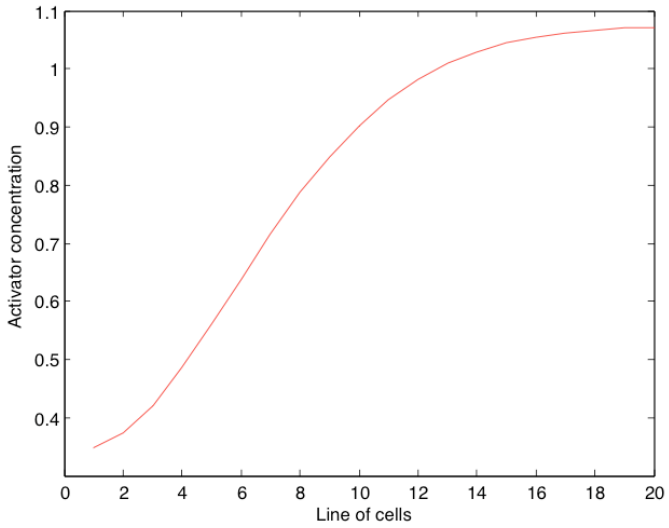


Figure 1: A gradient across a field of cells.

so the shape of the gradient changes with the field size or the diffusion rates. Another problem is that in order to build up a source and a sink a different process like another gradient would have to determine their location. So, the polarity determination is not solved by this simple model.

A more plausible theory is that the gradient substance x is the activator in a different activator/inhibitor system. By using this theory two properties of the gradient pattern can easily be explained. At first, a gradient has only one concentration maximum along the whole field. In case the inhibitor range is larger than the field size, one activator/inhibitor maximum prevents the formation of other maxima. At second, the only maximum has to appear on the edge of the simulated field. This will also happen in a simple activator/inhibitor system in case the activator range is also a bit larger than the field size. An explaination for this phenomenon is fairly simple. In the beginning, at the place of the initial stochastic disturbance an activator maximum will arise. From this place the activator will diffuse into the surrounding and also into the direction of the nearest field boundary. Since its range is larger than the field size a significant amount of activator will arrive at the boundary and accumulate there. Furthermore, it will help to form a new activator maximum here which will finally overcome the initial maximum (as shown in figure 2).

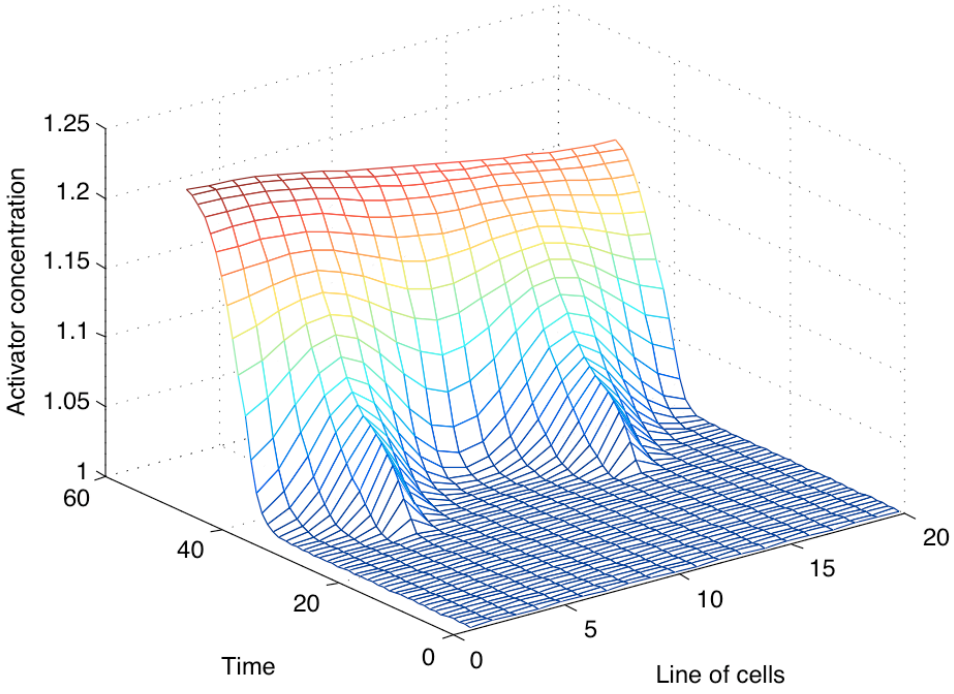
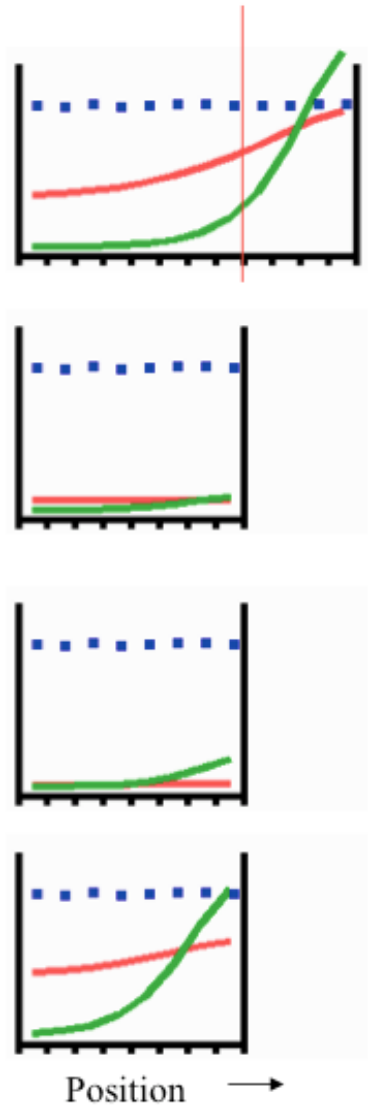


Figure 2: Formation of a gradient pattern in an activator/inhibitor system with two initial disturbances. The left activator maximum overcomes the right one and is drawn to the left boundary of the field. This behaviour is highly dependent on the ranges of the two substances. The picture looks completely different for bisected ranges. In this case two maxima arise at the same point at which they have been induced.

3 Gradient recovery



Gradient recovery, taken from Meinhardt's presentation at FEBS meeting, Gosau (2007). Activator (green) and inhibitor (red) concentration from tail (left) to head after the loss of the head.

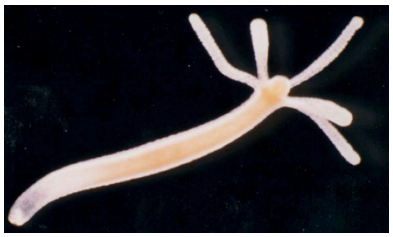


Figure: Hydra, taken from Meinhardt's presentation at FEBS meeting, Gosau (2007)

An organism in which a gradient is used as positional information is the Hydra. Here an activator/inhibitor system is used to determine the region in which the cells are supposed to grow a head.
Very interesting about this organism is that it is able to regrow its head very fast once it has been cut off. Before the Hydra can regrow its head it has to restore the positional information of the gradient which was disturbed by the loss of the head. As seen on the left hand side, the gradient easily recovers itself.
With the loss of the head also the site at which most of the inhibitor is produced gets lost. Since the inhibitor is degraded more rapidly than the activator at some point in time it will drop below a critical threshold. This will happen at the same side at which the head has been since the activator concentration is highest here. Afterwards, at this place a new activator maximum will arise and the gradient will be restored. Finally the Hydra will regrow a head and gain in size again.
By making use of the gradient, the Hydra is able to specifically restore the lost tissue. This is very important for the survival of the organism since it is not able to consume any food, hence to produce new energy, during the time without its head.

4 Segmentation

A gradient is not only able to determine a certain region in which something is happening but also to determine segments along an axis. This is made use of during the development of all higher organisms, e.g. in *Drosophila m.*, in order to determine the part of the body the cells later will develop to. In insects these

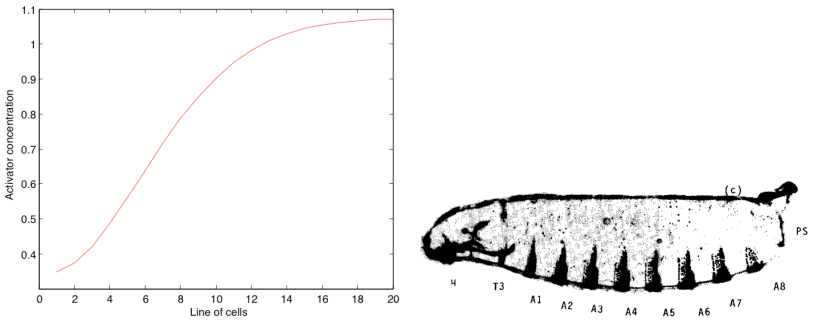


Figure 3: Normal development of *Drosophila m.*, right side taken from Menhardt: Models of ...

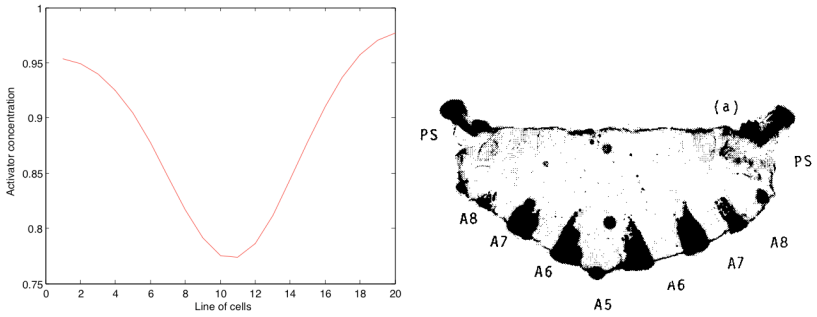


Figure 4: Double abdomen development of *Drosophila m.*, right side taken from Menhardt: Models of ...

regions are later visible as segments.

The genetic reason for the segmentation is the expression of different Hox genes. The cells in the developing insect can switch between two states and every time they change to the second state the next Hox gene is activated. Whether a cell changes its state depends on the concentration of the gradient substance and in case the threshold for the switching increases every time a stripe-like pattern evolves along the gradient.

In case the gradient is disturbed the sequence of the segments will change (as shown in figure 4) and a completely disordered organism will develop.

5 Conclusion

Gradients are very important in pattern formation. Once a gradient has build up induced by a stochastic disturbance, the cell can reuse this positional information to ensure the position of the activator maxima of further patterns. It is also important to notice that the organism does not have to spend much energy on keeping the gradient up since in most cases very shallow gradients are sufficient to serve as an initial disturbance for the induction of further maxima.

A simple model for the formation of a gradient is an activator/inhibitor system. Using this model the recovery of a gradient of a disturbance can easily be explained. Finally, gradients are also used in segmentation, which makes

them an important factor in the development of all higher organisms.

References

[1] Meinhardt, H: Models of biological pattern formation (1982)

[2] Meinhardt, H: Elementary networks for pattern formation in early development (Presentation at FEBS meeting, Gosau 2007)

A Matlab code for figure 2

```
function r = solve_muster(tend)
% Function for simulating Turing's ring of cells
% written by Sabine Pilari
% modified to simulate a cell line with an
% activator/inhibitor system by Marvin Schulz
global N
N = 20;
init = [ones(1,40) 0];
init(5) = 2;
init(15)= 1.9;
options = odeset('MaxStep',0.1,'InitialStep',10^(-20));
[t,c] = ode23s(@muster,[0 tend],init,options);
y = c(:,N+1:2*N);
figure(1)
mesh(y)
xlabel('Line of cells')
ylabel('Time')
zlabel('Activator concentration')
figure(2)
timesteps = length(t);
firsty = y(1,:);
lasty = y(timesteps,:);
axis([1 N 0 2.5])
plot(lasty,'r')
xlabel('Line of cells')
ylabel('Activator concentration')

function dcdt = muster(t,c)
global N
% diffusion constants 16/8=single_maximum 4/2=dual_maxima
mu = 4;
nu = 2;
% vector c, first N elements = x, then N elements = y, last = gamma
gamma = c(2*N+1);
for r=1:N
    fxy(r) = c(r)*c(r)/c(r+N) - c(r);
    gxy(r) = c(r)*c(r) - c(r+N);
    if (r==1)
```

```
        dcdt(r) = fxy(r) + mu*(c(r+1)-c(r));
        dcdt(r+N) = gxy(r) + nu*(c(r+1+N)-c(r+N));
    elseif (r==N)
        dcdt(r) = fxy(r) + mu*(-c(r)+c(r-1));
        dcdt(r+N) = gxy(r) + nu*(-c(r+N)+c(r-1+N));
    else
        dcdt(r) = fxy(r) + mu*(c(r+1)-2*c(r)+c(r-1));
        dcdt(r+N) = gxy(r) + nu*(c(r+1+N)-2*c(r+N)+c(r-1+N));
    end
end
dcdt(2*N+1) = 2^(-7);
dcdt = dcdt';
```