Activator-Inhibitor Systems

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Abstract

Activator-inhibitor systems are able to explain many pattern forming processes in nature. The interaction of these two substances can be described by two simple differential equations that incorporate the influence of the activator and inhibitor on each other as well as production, degradation and diffusion processes. A set of differential equations of an activator-inhibitor system is presented and the systems behaviour is described. Finally, an alternative reaction-diffusion model was used to simulate pattern forming processes.

1 Introduction

Pattern formation is a very important process in the development of all organisms. For example the colony formation of small marine animals is triggered by anactivator-inhibitor system. Furthermore, the regular spacing of leaves or the the ordering of stomata on a leaf can be explained with the help of such interacting system.
There exist different mathematical models that are able to simulate such processes. These models consist of at least two substances that influence each other. The system has to be globally stable and locally unstable to form patterns. In order to achieve theses characteristics the diffusion plays a very important role as it is shown in the following.

2 Behaviour of Activator-Inhibitor Systems

An activator-inhibitor system consists of two substances that act on each other. The activator stimulates its own production via autocatalysis as well as the production of the inhibitor. The inhibitor in turn represses the production of the activator (see figure 1). In addition, the inhibitor diffuses more rapidly than the activator such that patterns of activator and inhibitor concentrations can arise.

Figure 2 demonstrates the behavior of an activator-inhibitor system after an initial perturbation. Two cases are considered: 1) An equal activator increase at all positions of a linear array of cells. 2) A random perturbation in just a few cells of the array. Both situations will lead to different behaviours of the system.

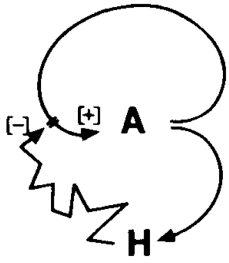


Figure 1: Activator-inhibitor system. The activator A stimulates its own production as well as the production of inhibitor H. H represses the production of A and diffuses more rapidly than A. Figure taken from Meinhardt [**?**].

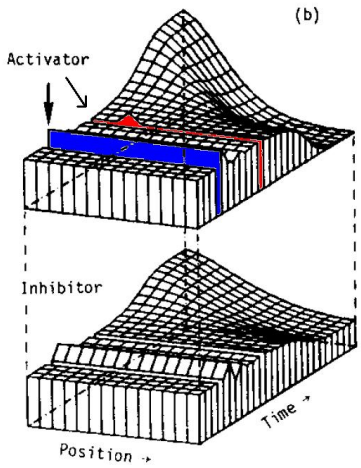


Figure 2: Concentration time profile of activator and inhibitor after some perturbation in a linear array of cells. Blue: Equal activator increase at all positions. Red: Activator increase in just a few cells. Figure taken from Meinhardt [**?**], modified.

Equal activator increase The equally increased activator concentration in all cells stimulates the further production of activator but also the production of inhibitor. Since neither activator nor inhibitor are able to diffuse into the surrounding because of the equal concentrations in all cells the inhibitor is able to overcome the activator such that after some time activator and inhibitor turn back to their steady state concentrations.

Activator increase in few cells If the activator increase occurs just in a few cells the production of activator and inhibitor is stimulated in these cells, too. Since the inhibitor diffuses more rapidly than the activator most of the inhibitor in the cells of initial perturbation is lost into the neighbourhood. Therefore the activator production is no longer repressed at this point but in the rest of the field. At the point of initial perturbation the activator can increase further and further until the gain of activator by production is equal to the loss of activator by diffusion and degradation. Finally the cloud of inhibitor around the activator maximum stabilizes the pattern.

2.1 Mathematical Example of an Activator-Inhibitor System

An example of a mathematical description of an activator-inhibitor system is given in the following:

$$\frac{da}{dt} = \frac{pa^2}{h} - \mu a + D_a \frac{d^2a}{dx^2} \tag{1}$$

$$\frac{dh}{dt} = p'a^2 - \nu h + D_h \frac{d^2h}{dx^2} \tag{2}$$

where $\frac{da}{dt}$, $\frac{dh}{dt}$ determine the change of activator and inhibitor in time. p and p' denote the respective production rates, μ and ν the degradation rates. The last terms of the above equations determine the diffusion where D_a and D_h are the diffusion constants.
To have a closer look at the systems behaviour we set all the parameters to unity and assume that no diffusion occurs. In order to analyse the change of activator in time we first assume the inhibitor concentration to be constant and equal to one. Therefore we get

$$\frac{da}{dt} = \frac{a^2}{1} - a = a^2 - a \tag{3}$$

There exists a trivial stable steady state at $a = 0$ and a second unstable steady state at $a = 1$.
The change of inhibitor in time

$$\frac{da}{dt} = a^2 - h \tag{4}$$

possesses a steady state at $h = a^2$. If we insert this result in the activators differential equation we get

$$\frac{da}{dt} = \frac{a^2}{a^2} - a = 1 - a \tag{5}$$

and the unstable steady state at $a = 1$ becomes stable.
At points where a stochastic increase of activator occurs the inhibitor concentration can be assumed to be constant because of the more rapid diffusion. In these cells the activator can increase further and further (unstable stead state). Since the inhibitor diffuses into the surrounding its concentration at these positions cannot be assumed to be constant. In contrast, the inhibitor overcomes the activator there (stable steady state in the presence of inhibitor). Since the activator cannot increase to infinity because of degradation and diffusion a globally stable pattern arises finally.

3 Role of Activator and Inhibitor Range in Pattern Formation

In nature many processes are triggered by the rise of a certain substance above a threshold concentration. This substance can be for example the activator, i.e. if the activator reaches a certain concentration the formation of a new leave or the formation of a hair is triggered. It is obvious that an organism is interested in forming multiple activator maxima in order to grow leaves or hairs.

Range of a substance The range of a substance is defined as the mean distance between production and decay of this substance, i.e. the range is a measure of how far this substance can diffuse.

Multiple activator maxima can arise if the size of the simulated field is larger than the range of inhibitor. Otherwise the inhibitor would repress the formation of a new activator maximum. In addition, a small perturbation, i.e. an increase in activator or a decrease in inhibitor, outside the inhibitor range is needed.
The influence of the range of activator and inhibitor, respectively, was studied in marine hydroids. Marine hydroids are small animals that form colonies by a branching network of stolons. These are hollow tubes which are growing until they connect in order to build the network. The signal for the formation of a new stolon is triggered by an activator maximum. It was observed that all stolons have a minimal distance to each other and that this distance corresponds to the range of the inhibitor.
Plickert [**?**] studied the influence of the inhibitor and activator range on the development of new stolons in detail (see figure 3). The formation of a new activator maximum can be stimulated by tapping the animal on its surface. If two activator maxima are induced in close proximity to each other, i.e. within the range of the activator, one activator maximum exactly in between them can arise (figure 3 a)). The activator of both induction points diffuses into the surrounding. In the middle of the two induction points the inhibitor is not able to overcome the activator. In the second case (figure 3 b)) the second induction point is outside the activator but within the inhibitor range of the first one. Therefore just one activator maximum can arise either at the position of the first or at the position of the second one because the inhibitor of one activator will overcome the other activator maximum. In figure 3 c) the case in which the two induction points are outside the inhibitor range is shown. Here both activator maxima can arise.

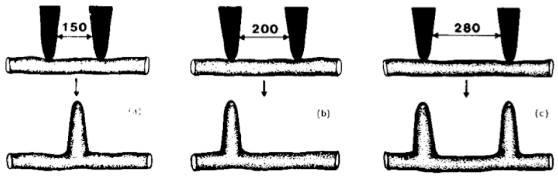


Figure 3: Formation of activator maxima in dependency of the distance of the two induction points [**?**]. (a) The second induction point lies inside the activator range of the first one. One activator maximum in the middle of the induction points will arise. (b) The second induction point lies outside the activator but inside the inhibitor range. An activator maximum either at the position of the first or at the second induction point will arise. (c) The second induction point lies outside the inhibitor range of the first one. Both activator maxima will arise. Figure taken from Meinhardt [**?**].

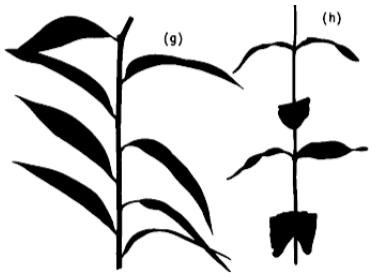


Figure 4: Regular spacing of leaves as often observed in nature. Figure taken from Meinhardt [**?**].

3.1 Regular Patterns in Phyllotaxis

The described characteristics of an activator-inhibitor system and the range of these two substances are a possible explanation how the regular spacing of leaves as shown in figure 4 is reached. In many plants a zigzag ordering of the leaves can be observed. The signal for the development of a new leave corresponds to an activator maximum. If the stipe grows an activator maximum arises and the formation of a new leave is triggered. The formation of a second maximum is prevented because of the inhibitor range. But if the stipe grows further the field size becomes larger than the range of the inhibitor. Since the stipe grows just in height the first position where a new maximum can arise is the point with the largest distance to the old activator maximum (see figure 5).

3.2 Examples of Irregluar Patterns

Examples of observed irregular patterns are shown in figure 6. For example the position of a stoma on a leaf can correspond to an activator maximum and also the position of a cilius on a frog embryo. The minimal distances between the stomata or cilia that are defined by the inhibitor range are kept. Since the leaf or the frog embryo grows further the stomata and cilia, respectively, grow apart such that the inhibitor range of the old maxima do not cover the whole field anymore. Therefore new activator maxima in between the old ones can arise

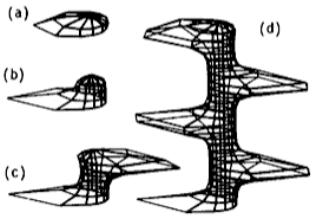
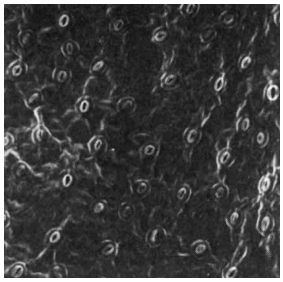
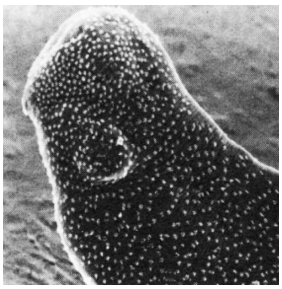


Figure 5: Development of the regular spacing of leaves. The formation of a new leave corresponds to an activator maximum. A new leave can be developed just outside the inhibitor range of the old one. Since the stipe grows in height this is the point of largest distance to the old maximum during the process of development. Figure taken from Meinhardt [**?**].



(a) Stomata on a leaf.



(b) Cilia on *Xenopus* embryo.

Figure 6: Examples of irregular patterns. Figures taken from Meinhardt [**?**].

and an irregular pattern is formed.

4 Reaction-Diffusion Model by Gray and Scott [?]

An alternative to the activator-inhibitor systems described above is a reaction-diffusion system proposed by Gray and Scott [**?**, **?**]. The model is based on the two following chemical equations:

$$\begin{aligned} U + 2V &\rightarrow 3V \\ V &\stackrel{k}{\rightarrow} P \end{aligned}$$

where U and V are two substances that influence each other. V is produced by sum kind of autocatalysis that also consumes V. V in turn is degraded with rate k. In addition, there exists a feed process that on the one hand consumes V and on the other hand regulates U back to one in arbitrary units. The corresponding differential equations are the following ones:

$$\frac{dU}{dt} = -UV^2 + F(1-U) + D_U \frac{d^2U}{dx^2} \tag{6}$$

$$\frac{dV}{dt} = +UV^2 - (F+k)V + D_V \frac{d^2V}{dx^2} \tag{7}$$

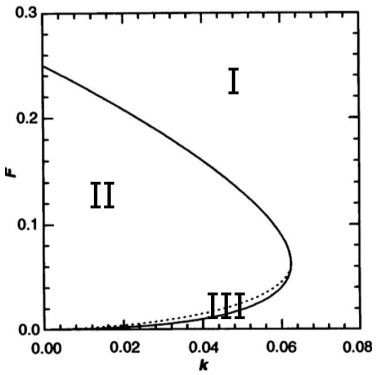
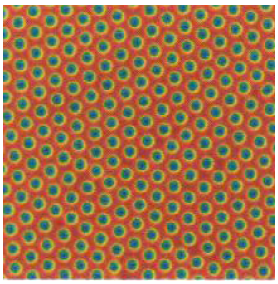


Figure 7: Phase diagram of the reaction kinetics. Part I: Trivial stable steady state at $U = 1$ and $V = 0$. Part II: In addition, two new steady states are present. One of them is stable the other one is unstable. Part III: The nontrivial stable steady states loses stability by Hopf bifurcation. Figure taken from Pearson [**?**], modified.

where F determines the feed term and D_U, D_V the diffusion constants of U and V, respectively.
The system possesses one trivial stable steady state at $U = 1$ and $V = 0$ that is globally attracting. In dependency of the parameters k and F up to three steady states can appear. The phase diagram of the reaction kinetics is given in figure 7. In part II of the phase diagram three steady states can be observed. There is the trivial steady state as well as an unstable and a stable steady state. In Part III the nontrivial stable steady state lost stability by Hopf bifurcation.

4.1 Simulations

The system was simulated using a field size of 256 by 256 grid points. The entire system was placed in the trivial steady state initially. The mid grid points were perturbed to about $U = 1/2$ and $V = 1/4$. Then the simulations with different combinations of the parameters k and F were run. The resulting pattern strongly depends on the choice of these parameters. The used parameter combinations ranges from $0.04 \leq k \leq 0.07$ and $0 < F \leq 0.06$ but always within Part I or III of the phase diagram. Two examples of the simulation results are shown in figure 8.



(a) Dots: $k = 0.066$ and $0.036 \leq F \leq 0.04$

(b) Stripes: $k = 0.064$ and $0.04 \leq F \leq 0.06$

Figure 8: Results of simulation of the Gray-Scott model [**?**, **?**] using different parameter values. Figures taken from Pearson [**?**].

A MatLab Code of the Gray-Scott Model

```
function r = gitter(time,printsteps,filename,feed,k)

sizex = 2.5;
sizey = 2.5;
gridx = 256;
gridy = 256;
pgridx = 20;
pgridy = 20;
deltat = 1;
ustart = 1;
vstart = 0;
diffusionrateu = 0.00002;
diffusionratev = 0.00001;
perturbedustart = 0.5;
perturbedvstart = 0.25;
perturbationratio = 0.01;

U = zeros(gridx,gridy);
V = zeros(gridx,gridy);
% Building grid
for i=1:gridx
  for j=1:gridy
     U(i,j) = ustart;
     V(i,j) = vstart;
  end
end
% Controlled Perturbing
for i=((gridx-pgridx+2)/2):((gridx+pgridx)/2)
  for j=((gridy-pgridy+2)/2):((gridy+pgridy)/2)
     U(i,j) = perturbedustart;
     V(i,j) = perturbedvstart;
  end
```

```
end
% Stochastic Perturbation
for i=1:gridx
  for j=1:gridy
     U(i,j) = U(i,j) + U(i,j)*(rand()*2-1)*perturbationratio;
     V(i,j) = V(i,j) + V(i,j)*(rand()*2-1)*perturbationratio;
  end
end

if(length(filename)>0)
  fig=figure;
  set(fig,'DoubleBuffer','on');
  set(gca,'xlim',[0 256],'ylim',[0 256],...
       'NextPlot','replace','Visible','off')
end

framecount = 0;
tic;
timesteps=time/deltat;
diffusion_h=sizex/gridx;
diffusion_l=sizey/gridy;
for t=1:timesteps
  Unew = zeros(gridx,gridy);
  Vnew = zeros(gridx,gridy);
  % Solve with forward Euler scheme
  for i=1:gridx
    for j=1:gridy
      thisU = U(i,j);
      thisV = V(i,j);
      % the diffusion terms
      diffU = -(2/(diffusion_h^2)+2/(diffusion_l^2))*U(i,j);
      diffV = -(2/(diffusion_h^2)+2/(diffusion_l^2))*V(i,j);
      if (i>1)
        diffU = diffU + U(i-1,j)/(diffusion_h^2);
        diffV = diffV + V(i-1,j)/(diffusion_h^2);
      end
      if (i<gridx)
        diffU = diffU + U(i+1,j)/(diffusion_h^2);
        diffV = diffV + V(i+1,j)/(diffusion_h^2);
      end
      if (j>1)
        diffU = diffU + U(i,j-1)/(diffusion_l^2);
        diffV = diffV + V(i,j-1)/(diffusion_l^2);
      end
      if (j<gridy)
        diffU = diffU + U(i,j+1)/(diffusion_l^2);
        diffV = diffV + V(i,j+1)/(diffusion_l^2);
      end
      diffU = diffU*diffusionrateu;
      diffV = diffV*diffusionratev;
```

```
      % the differential equations
      Unew(i,j)=thisU+(-thisU*thisV^2+feed-feed*thisU+diffU)*deltat;
      Vnew(i,j)=thisV+(thisU*thisV^2-feed*thisV-k*thisV+diffV)*deltat;
    end
  end
  U = Unew;
  if(mod(t,printsteps)==0)
    toc;
    tic;
    t
    if(length(filename)>0)
      h = contourf(U);
      framecount = framecount + 1;
      F(framecount) = getframe(gca,[-25 -20 470 420]);
    end
  end
  V = Vnew;
end

if(length(filename)>0)
  movie2avi(F,filename,'quality',25,'compression','None')
end

contourf(U);
```