Content: The cellular slime mold model and Turing instability
chapter 11.1-11.3

**Biology background**
The dynamics is shown in the diagram below

1. In its native state a slime mold population consists of a large number of unicellular amoeboid cells, which moves independently and feeds on bacteria, and are uniformly distributed.
2. When food becomes scarce centers of organisation (called aggregation sites) appear towards which cells are attracted.
3. Contacts begin to form between neighbours, and streams of cells converge on a single site, eventually forming a shapeless multicellular mass.
4. The aggregate undergoes curious contortions in which its shape changes several times: for a while it looks like a miniature slug that moves about in a characteristic way.
5. Cells differentiate into two types of cells which will have different fates: anterior cells turn into stalk cells while posterior cells become spores.
6. The sluglike collection of cells executes a crawling motion followed by a sequence of shapes. As a culmination of this amazing sequence of events, cellular streaming resembling a “reverse fountain” brings all prestalk cells around the outside and down through the center of the mass. The result is a slender, beautifully sculptured stalk bearing a spore-filled capsule at its top. In order to provide a rigid structural basis, the stalk cells harden and eventually die.
7. The spore cells are thereby provided with an opportunity to survive the harsh conditions, to be dispersed by air currents, and to thus propagate the species into more favorable environments.

A starved slime mold amoebae secrete cAMP together with an enzyme that degrades it. cAMP secretion is autocatalytic in the sense that free extracellular cAMP promotes further cAMP secretion by a chain of enzymatic reactions.

**Modelling the aggregation phase**
To build a model we start with the following assumptions/observations

1. Individual cells undergo a combination of random motion and chemotaxis towards cAMP
2. Cells neither die nor divide during aggregation
3. The attractant cAMP is produced at a constant rate by each cell
4. The rate of degradation of cAMP depends linearly on its concentration
5. cAMP diffuses passively over the aggregation field.

Introducing
\[ a(x,t) = \text{density of cellular slime mold amoebae per unit area} \]
\[ c(x,t) = \text{concentration of cAMP per unit area} \]

this turns into the equations
\[
\frac{\partial a}{\partial t} = -\frac{\partial}{\partial x} \left( \mu \frac{\partial a}{\partial x} + \chi \frac{\partial c}{\partial x} \right)
\]
\[
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + fa - kc
\]

where \( \mu = \text{amoeboid motility} \), \( \chi = \text{chemotactic coefficient} \), \( D = \text{diffusion rate of cAMP} \), \( f = \text{rate of cAMP secretion per unit density of amoebae} \) and \( k = \text{rate of degradation of cAMP in environment} \).

In addition we will assume that we are in an interval \([0, l]\) and that at the boundaries the space derivatives are zero (Neumann-condition).

**Steady state and its stability**
A constant solution \((a, c)\) to the system must be such that \(fa = kc\), which means that in every location the amount of cAMP degraded per unit time matches the amount secreted by cells per unit time.

To look at its stability replace \(a\) by \(\bar{a} + a\) and the same for \(c\) and eliminate all nonlinear terms. That gives us the linear system
\[
\frac{\partial a}{\partial t} = \mu \frac{\partial^2 a}{\partial x^2} - \chi \frac{\partial^2 c}{\partial x^2} \\
\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} + fa - kc
\]

To investigate stability we try for a (nonzero) solution of the form
\[ a(x,t) = A\phi(t)\bar{v}(x) \]
\[ c(x,t) = B\phi(t)\bar{v}(x) \]

The equations are now
\[
A\phi'(t)\bar{v}(x) = (\mu A - \chi A)\phi(t)\bar{v}'(x) \\
B\phi'(t)\bar{v}(x) = (fA - kB)\phi(t)\bar{v}(x)
\]

From the first equation follows that \(\phi'(t) = c\phi(t)\) for some constant \(c\). From this we get
\[ A\sigma\bar{v}(x) = (\mu A - \chi A)\bar{v}(x) \]
\[ B\sigma\bar{v}(x) = (fA - kB)\bar{v}(x) \]

Looking at the first equation again, we find that \(\bar{v}'(x) = -\lambda \bar{v}(x)\) for some \(\lambda > 0\) (we want a localised solution, i.e. \(v_0(0) = v_0(l) = 0\) for some \(l > 0\)), and we end up with the relations
\[
\begin{cases}
A\sigma = -(\mu A - \chi A)B \\
B\sigma = -(fA - kB)B
\end{cases} \quad \Rightarrow \quad \begin{cases}
-(\lambda + \sigma)A + \chi AB = 0 \\
-(DA + \sigma + k)B + fA = 0
\end{cases}
\]

This is a linear system in \((A, B)\), which has a nonzero solution only if the determinant is zero, i.e.
\[
(\lambda + \sigma)(DA + \sigma + k) - f\chi A = 0.
\]

This is a quadratic equation in \(v: v'^2 + av + \beta = 0\), where
\[
a = \Lambda(\mu + D) + k > 0, \quad \beta = \Lambda(\mu(\mu + D) - f\chi B).
\]

\footnote{We have that \(\int_0^l \bar{v}(x)^2 dx = \int_0^l \bar{v}'(x)^2 \bar{v}(x) dx = -\int_0^l \bar{v}'(x)^2 \bar{v}'(x) dx = \int_0^l \bar{v}'(x)^2 dx > 0\)}
We note also that where now \( u \sigma \) published a paper which became extremely interesting as a concept gate this we consider a solution of the form is stable if it is certain that a small perturbation will die out. To investi-
the space dimension is one. Incoorporating this into the model we get

\[
\begin{align*}
\frac{\partial u}{\partial t} &= D \frac{\partial^2 u}{\partial x^2} + f(u, v) \\
\frac{\partial v}{\partial t} &= D \frac{\partial^2 v}{\partial x^2} + g(u, v)
\end{align*}
\]

We assume that this system has an equilibrium \((u^*, v^*)\). Stability is inferred from the linearized system around \((u^*, v^*)\), which we write \( u' = Au \). The stability condition is that \( \text{Tr}(A) < 0 \) and \( \det A > 0 \).

We next assume that the chemicals diffuses around, introducing space dependency. For the sake of simplicity we assume for now that the space dimension is one. Incorporating this into the model we get a reaction-diffusion equation

\[
\begin{align*}
u_t &= u_{xx} + f(u, v) \\
v_t &= Dv_{xx} + g(u, v)
\end{align*}
\]

We have assumed that the diffusions coefficients are not necessarily the same, and we choose our units so that the first chemical has diffusion coefficient one. We now want to see if this affects the stability of the equilibrium \((u^*, v^*)\).

For this we consider the linearized system

\[
\begin{align*}
u_t &= u_{xx} + a_{12} u + a_{22} v \\
 v_t &= Dv_{xx} + a_{21} u + a_{22} v
\end{align*}
\]

where now \( u, v \) are deviations from the equilibrium. The equilibrium is stable if it is certain that a small perturbation will die out. To investigate this we consider a solution of the form \( u(x, t) = e^{\lambda t} \cos(\mu x) \).

Inserting that into the system and rearranging gives us the system in \( A_1, A_2 \):

\[
\begin{pmatrix}
\lambda - a_{11} - \mu^2 & -a_{12} \\
-a_{21} & \lambda - a_{22} + D\mu^2
\end{pmatrix}
\begin{pmatrix}
A_1 \\
A_2
\end{pmatrix} = \begin{pmatrix}
0 \\
0
\end{pmatrix}.
\]

This has a nontrivial solution iff \( \sigma \) is an eigenvalue to the matrix

\[
\begin{pmatrix}
a_{11} + \mu^2 & a_{12} \\
a_{21} & a_{22} + D\mu^2
\end{pmatrix}.
\]

The real part of \( \sigma \) is negative, i.e. the equilibrium stable, precisely if the trace is negative and the determinant positive. This means that it becomes unstable if any of the following two criteria is violated:

\[
a_{11} + a_{22} - (1 + D)\mu^2 < 0, \quad (a_{11} - \mu^2)(a_{22} - D\mu^2) - a_{12} a_{21} > 0.
\]

The first of these will automatically be true if the equilibrium is stable without diffusion. The left hand side of the second criteria is a quadratic in \( \lambda = \mu^2 \):

\[
D\lambda^2 - K\lambda + \det A = D(\lambda - \frac{K}{2D})^2 + \det A - \frac{K^2}{4D^2},
\]

where \( K = a_{22} + D a_{11} \). If therefore \( 2\sqrt{D\det A} < K \) we have diffusive instability.

These results have some important interpretations, where we must remember the meaning of the different \( a_{ij} \). Since \((u^*, v^*)\) is stable, we must have \( a_{11} + a_{22} < 0 \), and it is no restriction to assume that \( a_{11} > 0 \). This means that \( \frac{\partial u}{\partial \mu}(u^*, v^*) < 0 \), which means that chemical 2 inhibits its own rate of formation. We call this substance an inhibitor. But we also have that \( a_{22} + D a_{11} > 0 \), from which it follows that \( a_{11} > 0 \) (and also that \( D > 1 \)) and therefore that \( \frac{\partial u}{\partial \mu}(u^*, v^*) < 0 \), which means that chemical 1 promotes its own formation. We call this substance an activator. Since the determinant is positive and \( a_{11} a_{22} < 0 \) we must have also that \( a_{12} a_{21} < 0 \). This gives us two choices:

**activator-inhibitor system:** \( a_{12} < 0, a_{21} > 0 \),

**positive-feedback system:** \( a_{12} > 0, a_{21} < 0 \).

**Example** Consider the simplified model for glycolysis which we considered in an exercise:

\[
\begin{align*}
\tau_1 &= u_{xx} + \gamma(a - u + u^2 v) \\
\tau_2 &= Dv_{xx} + \gamma(b - u^2 v)
\end{align*}
\]

In the exercise we then saw that if \( b - a > (b + a)^2 \) the equilibrium \((a + b, \frac{b}{a + b})\) is unstable (without diffusion) and that in that case the system exhibit a limit cycle behaviour. Now we want to see when it exhibits diffusive instability. We have

\[
\begin{align*}
a_{11} &= f_u''(u^*, v^*) = \frac{b - a}{b + a}, \quad a_{12} = f_v'(u^*, v^*) = (a + b)^2 > 0, \\
 a_{21} &= g_u'(u^*, v^*) = -\frac{b}{a + b} < 0, \quad a_{22} = g_v'(u^*, v^*) = -(a + b)^2 < 0.
\end{align*}
\]

We see here that \( a_{12} > 0 \) and \( a_{21} < 0 \) if \( b > a \), in which case this is a positive-feedback system. For diffusive instability we need that

\[
K = a_{22} + D a_{11} = \frac{D(b - a) - (a + b)^3}{a + b} > 0
\]

and that

\[
K^2 - 4(D\det A) = \left(\frac{D(b - a) - (a + b)^3}{a + b}\right)^2 - 4D(a + b)^2 > 0.
\]

The inequalities

\[
\begin{align*}
0 < b - a < (a + b)^3, \\
D(b - a) > (a + b)^3, \\
(D(b - a) - (a + b)^3)^2 > 4D(a + b)^4
\end{align*}
\]

therefore defines a domain in the \((a, b, D)\)-space, called the Turing space, within which the mechanism is unstable to certain spatial disturbances of wavenumbers \( \mu \), namely those that satisfies

\[
(\mu^2 - \frac{K}{2D})^2 < \frac{K^2 - 4D\det A}{4D^2}.
\]
A system constrained to a region

We now want to consider the reaction-diffusion system in a region of a size we want to vary. Assume that the equation is valid for $0 < x < L$ and that $u_t(a,t) = v_x(a,t) = 0$, $a = 0, L$. If we introduce $\gamma = L^2$, new time $t/\gamma$ and new space variable $x/L$ the system we want to solve is

$$\begin{align*}
\frac{u_t}{\gamma} &= u_{xx} + \gamma f(u,v), \quad u_x(0,t) = u_x(1,t) = 0 \\
\frac{v_t}{\gamma} &= Dv_{xx} + \gamma g(u,v), \quad v_x(0,t) = v_x(1,t) = 0
\end{align*}.$$  

The linearized system then has solutions of the form above with $\mu = \pi k$ for some integer $k$. Comparing to the above only the wavenumbers such that

$$\left(\frac{\pi^2 k^2}{\gamma} - \frac{K^2}{2D}\right)^2 < \frac{K^2 - 4D \det A}{4D^2}$$

will be unstable. When $\gamma$ (i.e. $L$) is very small, only $k = 0$ fulfills the criteria. As it increases these will be $\pm \pi$ and 0, so a first pattern will appear. As the size growths further this pattern will be replaced by other, obtained from more wavenumbers.