Turing theory and activator – inhibitor models

Lecture 25
Stability of ODE’s stationary states revisited

Let us first consider the stability of an arbitrary stationary state for a 2D system of ordinary differential equations:
\[
\begin{align*}
\frac{du}{dt} &= f(u,v) \\
\frac{dv}{dt} &= g(u,v) \\
(u,v) &= (u^0, v^0)
\end{align*}
\]
To explore the stability of this stationary state we will introduce new variables:
\[
\tilde{u} = u - u^0, \quad \tilde{v} = v - v^0
\]
and linearize the original system in the vicinity of the stationary state. Then we will look for the solutions of the linearized system in the form of simple exponentials:
\[
\tilde{u}, \tilde{v} = \exp(\lambda t)
\]
Then as usually we will find \( \lambda \) from the characteristic equation:
\[
\begin{vmatrix}
f_u - \lambda & f_v \\
g_u & g_v - \lambda
\end{vmatrix} = 0
\]
This naturally develops into the quadratic equation:
\[
\lambda^2 - (f_u + g_v)\lambda + (f_u g_v - f_v g_u) = 0
\]
If \( A \) is a Jacobean (or linearization) matrix then:
\[
\lambda^2 - TrA \cdot \lambda + \det A = 0
\]
Finally to ascertain the stability of the stationary state in study we need to request that:
\[
\Re \lambda < 0
\]
From the properties of the roots of the quadratic equation we get the necessary and sufficient conditions:
\[
\begin{align*}
TrA &= f_u + g_v < 0 \\
\det A &= f_v g_u - f_u g_v > 0
\end{align*}
\]
Unlike many of the previous lectures, this one does not start with the introduction of biological phenomena. Instead we plunge straight into the math without much ado. Once we introduce enough mathematical formalism we can start building on it and finally will consider more and more biologically meaningful material. This approach appears to be more productive in this particular case as historically the idea first came from a mathematician and not from biologists or even physical chemists. In fact, we are going to talk about the theory proposed by Alan Turing in his famous 1952 paper for the explanation of biological morphogenesis. Although it was one and the only paper he wrote on a biological theme, the remarkable idea expressed in it was destined to introduce a new scientific paradigm. Surprisingly, the new phenomenon predicted in this paper, now known under the semi-popular name “Turing patterns” and in more technically correct terms “diffusion-driven instability”, happened to be very general and found across many disciplines.

Let us first look at the problem of stability of stationary states as it is central for the material of this lecture. To refresh the memory and to introduce some notations we are going to use later, we even start as early as stability of the stationary states in the ordinary differential equations. As the material of this slide is a recap of any elementary course in differential equations, no additional comments are necessary.
Stability in reaction-diffusion equations

Now we can proceed to partial differential equations by adding the diffusion terms:
\[
\begin{align*}
\frac{du}{dt} &= f(u,v) + D_u \Delta u \\
\frac{dv}{dt} &= g(u,v) + D_v \Delta v \\
(u,v) &= (u_0,v_0)
\end{align*}
\]

Here we again can introduce variables describing small perturbation of the state and then linearize the equations. However the solution should be sought in the form of plane waves:
\[
u \tilde{v} - \exp(\lambda t + ikr)
\]

Here \( k \)'s have dimension of inverse length and are known as wavenumbers.

After substitution of these perturbation variables into the linearized system we will get a new characteristic equation:
\[
\begin{vmatrix}
f_u - \lambda - k^2 D_u & f_v \\
g_u & g_v - \lambda - k^2 D_v
\end{vmatrix} = 0
\]

The solutions of this quadratic equation are:
\[
\lambda(k^2) = -\frac{B}{2} \pm \sqrt{\frac{B^2}{4} - 4C}
\]

where
\[
B = k^2 (D_u + D_v) - TrA \\
C = \det A + k^2 D_u D_v - k^2 (f_u D_v + g_v D_u)
\]

Now we need to identify conditions under which real parts of lambda are < 0. If this condition is satisfied for all \( k \), the stationary homogeneous state of the RDEs is stable to all perturbations.

Note that since \( TrA < 0 \), \( B \) is always positive.

Surprisingly, transition from the ordinary to partial differential equations changes very little in the method of the analysis. The only substantial difference is the form of the elementary perturbations. Also, while in the context of ODE we were more concerned with finding the domain of stability for the stationary state, in the case of RDEs, we are looking for a nontrivial behavior, that is the parameter region where the spatially homogeneous state is NOT stable. In summary, we seek the parameter domain(s) where adjunct ODE system has a stable stationary state and the full RDE system is unstable. Obviously, the two requirements are compatible only if RDE is unstable for \( k=0 \) (\( k=0 \) corresponds to an ODE case!) The characteristic equation that we obtain is quadratic for lambda and quartic for \( k \). In fact it only contains even powers of \( k \) and from now on we assume that lambda depends only on \( k^2 \) and not on \( k \) per se. The relationship connecting lambda and \( k^2 \) has a special name “dispersion relationship” in analogy to physics of waves. Just like in physics, the dispersion relationship describes the properties of the medium, in this particular case on the properties of the model.
The roots of the dispersion relation

Now we are, however, interested to find the conditions under which stationary state is *not stable* to spatial perturbations with \( k \neq 0 \).

Consider two roots \( \lambda_1, \lambda_2 \) of the dispersion relation \( \lambda = \lambda(k^2) \). They are defined by:

\[
-(\lambda_1 + \lambda_2) = B = k^2(D_u + D_v) - \text{Tr} A
\]

\[
\lambda_1 \cdot \lambda_2 = C = \det A + k^2 D_u D_v - k^2 (f_u D_v + g_v D_u)
\]

Note that since \( \text{Tr} A < 0 \), \( B \) is positive for all \( k \) and the roots cannot be both positive. Therefore, the instability can be only achieved in case of different signs:

\[
\lambda_1 > 0, \lambda_2 < 0 \quad \text{or} \quad \lambda_1 < 0, \lambda_2 > 0
\]

This can happen only if \( C(k^2) < 0 \).

Consider again the expression for \( C \):

\[
C = k^4 D_u D_v - k^2 (f_u D_v + g_v D_u) + \det A
\]

To satisfy the condition \( C(k^2) < 0 \), the coefficient at \( k^2 \) must be positive:

\[
f_u D_v + g_v D_u > 0
\]

This is a necessary but however is not a sufficient condition and we must request that the minimum of \( C(k^2) \) is below 0. After some algebra we will find that this condition implies:

\[
\frac{(f_u D_v + g_v D_u)^2}{4 D_u D_v} > \det A
\]

Here we assume that the stationary state of the adjunct ODE system is indeed stable so that the determinant of the Jacobean matrix is positive while its trace is negative. To achieve the instability, we need that one lambda is nonnegative for at least one value of \( k \). Indeed we quickly find that for this to work out, we need coefficient \( C \) to be negative. In tern, \( C \) is a “nose down” parabola and its lowest point has to be below zero for \( C \) to be negative. This condition is easy to express mathematically. We first find the minimum (“nose”) of the parabola by equating its derivative to 0 and then plug this value into \( C \). As a result, from the consideration of the dispersion relation we find two more conditions that have to be satisfied for lambda to be positive. Compare the two conditions we found. Is the first one redundant? Not really. Note that the second condition only requires that the absolute value of the combination of derivatives and diffusion coefficients exceeds the product of determinant of \( A \) and four times the diffusion coefficients. The first condition gives us a requirement on the sign.
Turing’s diffusion-driven instability

Finally, we can assemble all the obtained throughout the analysis inequalities:

\[ \text{Tr} A = f_u + g_v < 0 \]
\[ \det A = f_u g_v - f_v g_u > 0 \]
\[ f_u D_v + g_v D_u > 0 \]
\[ \frac{(f_u D_v + g_v D_u)^2}{4D_u D_v} > \det A \]

Satisfaction of all four of them guarantees that the spatially homogeneous state corresponding to a stable state \((u_0, v_0)\) becomes unstable to perturbations with wavenumbers \(k\) from a finite range:

\[ k_1^2 < k^2 < k_2^2 \]

The boundary wavenumbers can be found as the roots of the equation:

\[ k_{1,2}^2 = \frac{f_u D_v + g_v D_u}{2D_u D_v} \pm \sqrt{\left(\frac{f_u D_v + g_v D_u}{2D_u D_v}\right)^2 - \frac{4D_u D_v \det A}{2D_u D_v}} \]

The four identified conditions (two from ODE and two from RDE) have to be satisfied for the spatially homogenous state of the RDE system to be unstable. The instability means that any microscopic noise with the right wavelength (inverse of the wavenumber) will be amplified by the system and seemingly out of nowhere will emerge spatial pattern with the matching wavelength (periodicity, see pictures below).

The most common type of the dependence of \(\lambda\) on \(k^2\) is shown in the figure. What follows from the shape of the function, is that there exists a window of \(k^2\) values for which the system is unstable. If the initial perturbation has only wavenumbers below the left limit of the window, the perturbation will die out without disturbing the homogeneity of the system. Below we will discuss in detail the importance of the width and position of the “unstable wavenumbers” for the formation of patterns in the system.
Let us now again consider the conditions of existence of Turing instability:
\[ TrA = f_u + g_v < 0 \]
\[ f_v D_v + g_v D_v > 0 \]
Both conditions can only be satisfied together if the diagonal elements of the Jacobean matrix have opposite signs. For concreteness let us assume:
\[ f_u > 0, \quad g_v < 0 \]
This implies that \( u \) activates its own production while \( v \) inhibits its own production. For this reason it is a custom to call \( u \) “activator” and \( v \) “inhibitor” variables.

For further analysis let us note that both diagonal Jacobean elements have dimension \([s^{-1}]\).

Therefore the inequality can be rewritten in the more informative form:
\[ \tau_u D_u < \tau_v D_v \]
Variables \( \tau \)’s represent characteristic times of the variables. Thus the inequality can be interpreted as follows. For the existence of Turing instability it is necessary that:
1. inhibitor must diffuse faster than activator (if they have ~ equal characteristic times)
2. activator must have a shorter life time (if they have ~ equal diffusion coefficients)

Now we are eventually in the position to interpret the obtained results and match abstract mathematical inequalities to observable phenomena. As it follows from the four conditions, the variables \( u \) and \( v \) have the following properties. Variable \( u \) induces its own production while variable \( v \) inhibits its own production. This observation is responsible for the introduction of “activator-inhibitor” term describing models able to display Turing instability.

Very important is the interpretation of the condition that couples the diffusion coefficients and the characteristic times of the activator and inhibitor. This is often misinterpreted and put in the form “inhibitor must diffuse faster than activator”. More correctly however is the interpretation given on the slide. In the biologically realistic situations it is rather the second condition (activator has shorter life-time) that can be satisfied. If however we stick for now with the “classical” interpretation of different diffusion coefficients, when the fact that diffusion coefficient of the inhibitor is large results in the fact that it diffuses farther. Therefore, it is also common to interpret Turing conditions as “short range activation – long range inhibition”.
In most practically interesting cases, formation of patterns occurs on finite domains with no-flux boundary conditions. In this case the spectrum of allowed wavelengths become discrete:

\[ k_n = \frac{n\pi}{L}, \quad n = 1, 2, \ldots \]

\[ \omega_n = 2\pi / k_n = 2L / n \]

Only final number of discrete wavenumbers satisfying the dispersion relation is contributing to the Turing pattern. The number with largest lambda will eventually win.

Dispersion relation operates as a filter of spatial frequencies \( \omega_n \).

In all morphogenetic contexts, the patterns forming due to the Turing instability are always formed on the finite size domains corresponding to the whole embryo or its parts.

As in quantum mechanics the attempt to fit periodic function into a finite size box results in the fact that only discrete values of wavenumber satisfy the boundary conditions. The corresponding waveforms are called modes. In this case we assume that chemicals forming morphological gradients cannot diffuse out of the bounding box which corresponds to so-called “no-flux” boundary conditions. Mathematically this means that the spatial derivatives of the concentration distribution on the boundary must be equal to zero. Provided suitable system parameters, the instability window will fit only small number of wavenumbers which explains the patterns we will observe. If several \( k^2 \) numbers fit in the window, there will be so-called competition of modes represented by distinct wavenumbers and the mode with largest lambda will eventually win occupying the domain. Therefore, it is often said that the Turing system works as a filter of spatial frequencies (wavenumbers) or modes.
Evolution of patterns driven by the domain growth

Change in the size of the domain results in the alteration of patterns:

\[
\begin{align*}
du/dt &= \gamma \cdot f(u,v) + D_u \Delta u \\
dv/dt &= \gamma \cdot g(u,v) + D_v \Delta v
\end{align*}
\]

Parameter gamma regulates contribution of reaction relative to diffusion. Changing gamma effectively rescales diffusion coefficients or the size of the domain:

Parameter gamma modulates the position and the width of the unstable values of wavenumber:

\[ k_{1,2} = \gamma \cdot \left[ \frac{f_1D_1 + g_1D_v}{2D_uD_v} \pm \sqrt{\left(\frac{f_1D_1 + g_1D_v}{2D_uD_v}\right)^2 - \frac{4D_lD_i \det A}{2D_uD_v}} \right] \]

In the biological context, it is interesting to ask the question how the observed pattern will change with the growth of the biological system (see more on that in the next lecture).

Fortunately, reaction-diffusion equations permit very simple apparatus to tackle this problem. We only need to assume that diffusion coefficients are scaled. The smaller the D, the bigger is the spatial domain we look at. Following Murray, we introduce here parameter gamma which scales relative contribution of the reaction. As follows from the formulae, gamma simply multiplies the roots of the equation for k2. Therefore, the width and the position of the window of unstable k2 changes resulting in the substitution of observed spatial patterns. Moreover, there might be periods of growth then not a single wavenumber fits through the window (red line) and then no pattern is visible!

Shown on the figure is the result of an experiment in chemical pattern formation. All three pictures display the same physical domain of a gel reactor. What appears as a difference in magnification is a change in diffusion coefficient of the diffusing substance achieved by changing physical parameters of the gel.
What to take home

• Diffusion-driven instability is a phenomenon where diffusion plays destabilizing rather than smoothing over function.

• As a result of a diffusion-driven instability, stochastic noise with particular characteristic wavelengths is amplified to the macroscopic scales which results in the formation of stationary spatial patterns.

• For the existence of Turing instability a number of conditions on the properties of reaction and diffusion have to be satisfied.

• In the case of two variables, one of them should be “activator” (autocatalysis, positive feedback) and the other “inhibitor” (self-suppression, negative feedback).

• The size of the domain defines together with the reaction-diffusion equations which patterns are permitted.

• The phenomenon of Turing instability is found in all branches of physical sciences, such as nonlinear optics, plasma physics, surface physics, etc.