

## VIII Local excitation, global inhibition model

In this lecture we will discuss one of the most frequently used theories to model biological reactions limited by diffusion. Turing was the first to formulate this problem mathematically. Gierer and Meinhardt took Turing's formalisms and applied it to biological problems. The model described below is therefore often called 'the Turing-Gierer-Meinhardt theory'. One of the first models was defined as follows:

$$\begin{aligned}\frac{\partial a}{\partial t} &= r_a + k_a \frac{a^2}{i} - \gamma_a a + D_a \frac{\partial^2 a}{\partial x^2} \\ \frac{\partial i}{\partial t} &= k_i a^2 - \gamma_i i + D_i \frac{\partial^2 i}{\partial x^2}\end{aligned}\quad \text{[VIII.1]}$$

$a$  and  $i$  are the concentrations of an activator and an inhibitor. The activator is produced at a constant rate  $r_a$  (for example, a leaky promoter) plus a rate that depends on both  $a$  and  $i$ . The activator operates as a dimer whereas the inhibitor operates as a monomer. The synthesis rate of  $a$  is proportional to the saturation function  $Y$  to reflect the probability to have an activator dimer present and an inhibitor monomer absent:

$$Y = \frac{K_a a^2}{1 + K_a a^2} \left( 1 - \frac{K_i i}{1 + K_i i} \right) = \frac{K_a a^2}{1 + K_a a^2} \frac{1}{1 + K_i i} \approx \text{const} \times \frac{a^2}{i}\quad \text{[VIII.2]}$$

The approximation above is valid for small concentrations of  $a$  and large concentrations of  $i$ .  $K_a$  and  $K_i$  are the association constants for the activator and inhibitor binding.

Both the activator and inhibitor molecules obey first order decay characterized by  $\gamma_a$  and  $\gamma_i$ , respectively. The last term in equations [VIII.1] reflects the one-dimensional diffusion. The diffusion coefficient of the activator and inhibitor are  $D_a$  and  $D_i$ . The inhibitor is synthesized at a rate proportional to  $a^2$ . Apparently the activator enhances the inhibitor synthesis according to the Hill equation with  $n_H=2$ . Note that again it is assumed that the concentration of  $a$  is small (with respect to  $K_a$ ). The system of equations [VIII.1] is an example of a reaction-diffusion system. Let us analyze [VIII.1] in more detail.

## Dimensionless variables

First we will introduce dimensionless variables to make the algebra simpler. Time will be normalized to  $(\gamma_a)^{-1}$  and the spatial coordinate  $x$  will be measured in terms of the distance that the activator will diffuse in time  $(\gamma_a)^{-1}$ :

$$\begin{aligned}\tau &\equiv \gamma_a t \\ s &\equiv \frac{x}{\sqrt{D_a / \gamma_a}}\end{aligned}\tag{VIII.3}$$

Substituting this in [VIII.1] yields:

$$\begin{aligned}\frac{\partial a}{\partial \tau} &= \frac{r_a}{\gamma_a} + \frac{k_a}{\gamma_a} \frac{a^2}{i} - a + \frac{\partial^2 a}{\partial s^2} \\ \frac{\partial i}{\partial \tau} &= \frac{k_i}{\gamma_a} a^2 - \frac{\gamma_i}{\gamma_a} i + \frac{D_i}{D_a} \frac{\partial^2 i}{\partial s^2}\end{aligned}\tag{VIII.4}$$

We still have the freedom to normalize  $a$  and  $i$ :

$$\begin{aligned}A &\equiv \frac{a}{a_o} \\ I &\equiv \frac{i}{i_o}\end{aligned}\tag{VIII.5}$$

Substituting this in [VIII.4] gives:

$$\begin{aligned}\frac{\partial A}{\partial \tau} &= \frac{r_a}{\gamma_a a_o} + \frac{k_a a_o}{\gamma_a i_o} \frac{A^2}{I} - A + \frac{\partial^2 A}{\partial s^2} \\ \frac{\partial I}{\partial \tau} &= \frac{k_i a_o^2}{\gamma_a i_o} A^2 - \frac{\gamma_i}{\gamma_a} I + \frac{D_i}{D_a} \frac{\partial^2 I}{\partial s^2}\end{aligned}\tag{VIII.6}$$

By choosing

$$\begin{aligned}\frac{r_a}{\gamma_a a_o} = 1 &\rightarrow a_o = \frac{r_a}{\gamma_a} \\ \frac{k_i a_o^2}{\gamma_a i_o} = \frac{\gamma_i}{\gamma_a} &\rightarrow i_o = \frac{k_i a_o^2}{\gamma_i} = \frac{k_i r_a^2}{\gamma_i \gamma_a^2}\end{aligned}\tag{VIII.7}$$

[VIII.6] finally reduces to:

$$\begin{aligned}\frac{\partial A}{\partial \tau} &= 1 + R \frac{A^2}{I} - A + \frac{\partial^2 A}{\partial s^2} \\ \frac{\partial I}{\partial \tau} &= Q(A^2 - I) + P \frac{\partial^2 I}{\partial s^2}\end{aligned}\tag{VIII.8}$$

where

$$\begin{aligned}
 P &= \frac{D_i}{D_a} \\
 Q &= \frac{\gamma_i}{\gamma_a} \\
 R &= \frac{k_a \gamma_i}{r_a k_i}
 \end{aligned}
 \tag{VIII.9}$$

P and Q are a measure of the diffusion coefficient and decay rate relative to the activator properties. R is the ratio of the autocatalytic activator synthesis ( $k_a$ ) and the constant synthesis ('leakyness',  $r_a$ ).

### Spatially homogeneous solutions

Version [VIII.8] only contain three parameters (P,Q,R) whereas [VIII.1] contained 9 parameters. For now let's try to find a solution to [VIII.8] that is spatially homogeneous ( $\partial/\partial s = 0$ ). In this case, the steady state solution is:

$$\begin{aligned}
 \bar{A} &= R + 1 \\
 \bar{I} &= (R + 1)^2
 \end{aligned}
 \tag{VIII.10}$$

Is this solution stable? The stability matrix evaluated at the fixed point is:

$$\begin{bmatrix} \frac{2R\bar{A}}{\bar{I}} - 1 & -\frac{R\bar{A}^2}{\bar{I}^2} \\ \frac{2\bar{A}Q}{2(R+1)Q} & -Q \end{bmatrix} = \begin{bmatrix} \frac{R-1}{R+1} & -\frac{R}{(R+1)^2} \\ 2(R+1)Q & -Q \end{bmatrix}
 \tag{VIII.11}$$

Therefore [VIII.10] represents a stable solution when the trace of this matrix is negative and the determinant is positive:

$$\begin{aligned}
 \frac{R-1}{R+1} &< Q \\
 Q &> 0
 \end{aligned}
 \tag{VIII.12}$$

As Q is positive by definition [VIII.9] the first inequality characterizes a unique constant solution that is stable against small spatially homogeneous perturbations.

## Spatially inhomogeneous solutions

Now consider the full system of equations [VIII.8] and explore stability of the system around the homogeneous solution [VIII.10]:

$$\begin{aligned} A(s, \tau) &= \bar{A} + A'(s, \tau) \\ I(s, \tau) &= \bar{I} + I'(s, \tau) \end{aligned} \quad \text{[VIII.13]}$$

Based on [VIII.8] we can write:

$$\begin{aligned} \frac{\partial A'}{\partial \tau} &= \frac{R-1}{R+1} A' - \frac{R}{(1+R)^2} I' + \frac{\partial^2 A'}{\partial s^2} \\ \frac{\partial I'}{\partial \tau} &= 2Q(1+R)A' - QI' + P \frac{\partial^2 I'}{\partial s^2} \end{aligned} \quad \text{[VIII.14]}$$

To find the solutions of [VIII.14] we start by guessing a trial function:

$$\begin{aligned} A'(s, \tau) &= \hat{A}(\tau) \cos\left(\frac{s}{\ell}\right) \\ I'(s, \tau) &= \hat{I}(\tau) \cos\left(\frac{s}{\ell}\right) \end{aligned} \quad \text{[VIII.15]}$$

This trial function makes sense since the second derivative of the cosine is the cosine itself times a constant. Substituting the trial function gives:

$$\begin{aligned} \frac{d\hat{A}}{d\tau} &= \left( \frac{R-1}{R+1} - \frac{1}{\ell^2} \right) \hat{A} - \frac{R}{(1+R)^2} \hat{I} \\ \frac{d\hat{I}}{d\tau} &= 2Q(1+R)\hat{A} - \left( Q + \frac{P}{\ell^2} \right) \hat{I} \end{aligned} \quad \text{[VIII.16]}$$

Again this is system of two linear ordinary differential equations that we can test for stability:

$$\begin{aligned} -\left( \frac{R-1}{R+1} - \frac{1}{\ell^2} \right) \left( Q + \frac{P}{\ell^2} \right) + \frac{2QR}{1+R} &> 0 \\ -\left( Q + \frac{P}{\ell^2} \right) + \left( \frac{R-1}{R+1} - \frac{1}{\ell^2} \right) &< 0 \end{aligned} \quad \text{[VIII.17]}$$

The latter inequality holds since we impose stability of the homogeneous solution (see inequality [VIII.12]). The former inequality can be written as:

$$\left( \frac{Q}{P} \right) \ell^4 + \left( \frac{Q}{P} - \frac{R+1}{R-1} \right) \ell^2 + 1 > 0 \quad \text{[VIII.18]}$$

For any wavelength  $\ell$  this is satisfied if:

$$\frac{Q}{P} > \frac{R-1}{R+1} \quad \text{[VIII.19]}$$

Both [VIII.19] and [VIII.12] will certainly hold if  $P < 1$ . In other words if the activator diffuses faster than the inhibitor. In the opposite way, spatial nonuniformity and the possibility of pattern formation requires the inhibitor to diffuse faster than the activator (long range inhibition, short range activation).

### Conditions for inhomogeneous instability

Let us explore the conditions for inhomogeneous instability. To obtain an instable system we have to obey the reverse of [VIII.19]:

$$f(\alpha) \equiv \left(\frac{Q}{P}\right)\alpha^2 + \left(\frac{Q}{P} - \frac{R+1}{R-1}\right)\alpha + 1 < 0 \quad \text{[VIII.20]}$$

where  $\alpha \equiv \ell^2$ . The function  $f(\alpha)$  is a parabola that is concave upward. For  $f(\alpha)$  to be negative the parabola should have two real roots of which at least one is positive. The roots of  $f(\alpha)$  are found by solving:

$$2\alpha \frac{Q}{P} = \frac{R+1}{R-1} - \frac{Q}{P} \pm \sqrt{\left(\frac{R+1}{R-1} - \frac{Q}{P}\right)^2 - 4\frac{Q}{P}} \quad \text{[VIII.21]}$$

The roots of [VIII.21] are therefore both real if:

$$\left(\frac{R+1}{R-1} - \frac{Q}{P}\right)^2 > 4\frac{Q}{P} \quad \text{[VIII.22]}$$

According to [VIII.19] this means that both roots are positive and therefore:

$$\frac{R-1}{R+1} > 2\sqrt{\frac{Q}{P}} + \frac{Q}{P} \quad \text{[VIII.23]}$$

This is the instability condition. So if [VIII.23] is true,  $f(\alpha)$  will be negative for certain values of  $\alpha$ . Condition [VIII.23] defines a critical value for R. For  $R > R_c$  [VIII.23] holds.

$$R_c = \frac{1 + \left(2\sqrt{\frac{Q}{P}} + \frac{Q}{P}\right)}{1 - \left(2\sqrt{\frac{Q}{P}} + \frac{Q}{P}\right)} \quad \text{[VIII.24]}$$

In the following discussion we will assume strong autocatalytic reaction ( $R \gg 1$ ). In that case [VIII.23] reduces to:

$$\frac{Q}{P} + 2\sqrt{\frac{Q}{P}} < 1 \quad \text{[VIII.25]}$$

This means that

$$\sqrt{\frac{Q}{P}} = \left( \frac{D_a / \gamma_a}{D_i / \gamma_i} \right)^{1/2} < 0.4 \quad \text{[VIII.26]}$$

The ratio  $(D_a / \gamma_a)^{1/2}$  has units of length and can be interpreted as the a typical distance that activator molecules diffusion before they decay. This distance is often called the activator range. Equation [VIII.26] tells us that it is necessary for the instability of the uniform state that the inhibition range is about 2.5 times larger than the activator range.