IX Models for eukaryotic gradient sensing

The first model on gradient sensing we discussed was developed by Narang *et al.*:

A. Narang, K. K. Subramanian, and D. L. Lauffenburger. A mathematical model for chemoattractant gradient sensing based on receptor-regulated membrane phospholipid signaling dynamics. *Ann. of Biomed. Eng.* **29**, 677-691 (2001).

Let use the reduced scheme in Fig. 2b of Narang's paper as a starting point. The model describes the time evolution of four concentrations: the active receptors (r_{10}), the membrane phosphoinositides (p), the cytosolic inositol (i), and the phosphoinositides in the endoplasmic reticulum (p_s). For the receptors Narang et al. use a very similar approach as discussed for bacterial chemotaxis (Fig. 3, Narang's paper). For Dictyostelium chemotaxis it is assumed that only the non-phosphorylated receptors are involved in the pathway. The total concentration of sensitive (non-phosphorylated) receptors is therefore:

$$r_s \equiv r_{00} + r_{10} + r_{10}^* \qquad \textbf{[IX.1]}$$

The first subscript indicates if a ligand is bound (1) or not bound (0) to the receptor. The second subscript reflects the phosphorylation state: phosphorylated (1) or not phosphorylated (0). The asterix indicates that the receptor is complexed to the deactivating (E_d) or activating enzyme (E_a).

The kinetic equation for r_s is:

$$\frac{\partial r_s}{\partial t} = (k_{01} r_{01}^* + k_{11} r_{11}^*) - k_{10} r_{10}^* + \frac{D_r}{R^2} \frac{\partial^2 r_s}{\partial \theta^2} \qquad \textbf{[IX.2]}$$

where D_r is diffusion coefficient of the receptor in the membrane and R is the cell radius. In this model any chemical gradients in the cell's cytoplasm are ignored and only gradients in the membrane are considered. In the model it is assumed that dephosphorylation is independent of ligand concentration ($k_{01}=k_{11}$). Note that this is conceptually identical to Barkai's model for perfect adaptation (demethylation is independent of ligand concentration, k_{eff4} is independent of ligand). It is also assumed

that the system reaches a quasi-steady state for the ligand binding, and the enzymes E_a and E_d that remove and add the phosphates. E_a activates the receptor by phosphorylation and E_d deactivates the receptor by dephosphorylation. Only activate receptors are involved in the signaling pathway. Therefore:

$$r_{00} = \frac{K_l}{l} r_{10}$$
$$r_{10}^* = \frac{e_d}{K_{10}} r_{10} \qquad \textbf{[IX.3]}$$

K_l and K_{10} are dissociation constants for the ligand-receptor binding and E_d-receptor binding. E_a is binding its substrates with a high affinity (K_{01},K_{11} << 1) and E_a is assumed to operate at saturation. Again this is conceptually identical to the assumption that CheR is operating at saturation for bacterial chemotaxis. Therefore:

$$r_{01}^* + r_{11}^* \approx e_{a,t} \qquad \textbf{[IX.4]}$$

$e_{a,t}$ is the total concentration of E_a. Substituting [IX.1], [IX.3] and [IX.4] in [IX.2] gives:

$$\left(1 + \frac{l}{K_l} + \frac{e_d}{K_{10}}\right)\frac{\partial r_{10}}{\partial t} = k_{01} e_{a,t} - k_{10}\left(e_d / K_{10}\right) r_{10} + \frac{D_r}{R^2}\frac{\partial^2 r_s}{\partial \theta^2}$$
$$\Rightarrow \frac{\partial r_{10}}{\partial t} = \frac{1}{1 + l/K_l + e_d K_{10}}\left[k_{01} e_{a,t} - k_{10}\left(e_d / K_{10}\right) r_{10}\right] + \frac{D_r}{R^2}\frac{\partial^2 r_{10}}{\partial \theta^2} \qquad \textbf{[IX.5]}$$

This is equation (1) in Narang's paper. Equations (2)-(4) describe the time evolution of the three other variables:

$$\frac{\partial p}{\partial t} = k_f r_{10} p^2 p_s - k_r p i + c_p - k_p p + \frac{D_p}{R^2}\frac{\partial^2 p}{\partial \theta^2}$$
$$\frac{\partial p_s}{\partial t} = -\left(k_f r_{10} p^2 p_s - k_r p i + c_p - k_p p\right) + \frac{D_{p_s}}{R^2}\frac{\partial^2 p_s}{\partial \theta^2} \qquad \textbf{[IX.6]}$$
$$\frac{\partial i}{\partial t} = s\left(k_f r_{10} p^2 p_s - k_r p i\right) + c_i - k_i i + \frac{D_i}{R^2}\frac{\partial^2 i}{\partial \theta^2}$$

c_p and c_i are basal synthesis rates of P and I synthesis respectively. P and I decay according to first order kinetics with rate constants k_p and k_i. The receptor mediated synthesis of P is cooperative (n_H=2) and autocatalytic. Note that the approximation $k_f r_{10} p^2 p_s$ is only valid for low concentrations of p and p_s. P is removed from the membrane at a rate $k_r$pi. It is clear from [IX.6] that the total amount of phosphoinositides ($p+p_s$) is conserved. The factor s in the last equation of [IX.6] denotes the membrane

length per area. This factor is required since the synthesis and removal of P is based on the length of the plasma membrane. The system of equations [IX.5]-[IX.6] are reaction-diffusion equations similar to the equations discussed in Section XIII. The role of activator is played by P whereas I acts as an inhibitor. Note that the inhibitor diffuses much faster than the membrane bound activators ($D_p << D_i$).

Narang uses periodic boundary conditions for all four variables of the form:

$$x(0,t) = x(2\pi,t)$$
$$\frac{\partial x(0,t)}{\partial \theta} = \frac{\partial x(2\pi,t)}{\partial \theta} \qquad \textbf{[IX.7]}$$

where $x=\{r_{10},p,p_s,i\}$. The homogeneous solutions are depicted with the superscript -. For a uniform simulation with ligand concentration l^-, the steady-state values for the homogeneous solutions are:

$$r_{10}^- = \frac{k_{01}e_{a,t}}{k_{10}e_d / K_{10}} \qquad \textbf{[IX.8]}$$
$$p^- + p_s^- = p_t$$

Assuming the cell has reach steady state for a uniform stimulus l^-, now the ligand profile is instantaneously changed to $l(\theta)$. We assume that immediately after this change r_{00}, r_{10}, and r^*_{10} equilibrate but r_s, p, p_s and i remain unchanged since these reaction are much slower. The total amount of active receptors is:

$$r_s = \left(1 + K_l / l^- + e_d / K_{10}\right) r_{10}^- \qquad \textbf{[IX.9]}$$

Therefore, immediately after the change from uniform the gradient stimulation r_{10} changes to:

$$r_{10} = \frac{1 + K_l / l^- + e_d / K_{10}}{1 + K_l / l(\theta) + e_d / K_{10}} r_{10}^- \qquad \textbf{[IX.10]}$$

The initial conditions are therefore:

$$r_{10}(\theta,0) = \frac{1 + K_l / l^- + e_d / K_{10}}{1 + K_l / l(\theta) + e_d / K_{10}} r_{10}^-$$
$$p(\theta,0) = p^- \qquad \textbf{[IX.11]}$$
$$p_s(\theta,0) = p_s^- = p_t - p^-$$
$$i(\theta,0) = i^-$$

This is basically all we have to know to solve the model. Narang adds one more step to obtain dimensionless equations.