# Receptor signaling: crosstalk, specificity and pleiotropy

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It is not clear with what mechanism the cell probes its environment and understands the composition of the different products in its surrounding. Here, we will investigate different receptor and ligand dynamics that hopefully describe a method in which the cell can estimate different concentrations of ligands in its proximity.

For now, the idea is to go through Anton's draft and try to rederive each equation. We will describe particular signaling pathways and define their masters equations. Presently, there are 2 different modes which are described below. We will continue thinking about different pathways possible and what the cell is trying to optimize.

## I. RECEPTOR SIGNALING: THE BIOLOGY

[WORK ON]

## II. MASTERS EQUATION

### A. Mode 1

We start with the process that creates a product $n$ with rate $k_p$ when a ligand is bound to the receptor. It binds with rate $k_{on}c$ and unbinds with rate $k_off$ to the receptor.

(Need to make the figure for this)

The master equations are

$$\begin{aligned} \dot{P_0^n} &= k_{off}P_1^n - k_{on}cP_0^n \\ \dot{P_1^n} &= k_{on}cP_0^n - k_{off}P_1^n + k_pP_1^{n-1} - k_pP_1^n. \end{aligned} \tag{1}$$

What we are interested in this equation is the average and variance of the prouct $n$ within the cell as we can find what the best estimate the cell can make of the ligand concentration outside. Anton also argues that a second quantity is important, the cell needs to also estimate $k_{off}$ to know what is the identity of this ligand. There are a couple ways to solve this system: generating functions is one venue but is difficult to solve analytically. Using this method, Anton gets a certain average and standard deviation

Instead, we will try another method using the master equation. Note that we will use the solution for the probability of being bound as a function of time (derived by Anton and confirmed by us, type it out)

$$\begin{aligned} P_1(t) &= P_1^{ss}(1-e^{-rt}) + P_1(0)e^{-rt} \\ &= \frac{x}{1+x} + \Delta_1 e^{-rt} \end{aligned} \tag{2}$$

where

$$\begin{aligned} P^{ss} &= \frac{x}{1+x} \\ r &= k_{on}c + k_{off} \\ \Delta_1 &= P_1(0) - P_1^{ss}. \end{aligned}$$

We write down the time derivative of average $n$ and replace terms by the master equations to solve the equation

$$\begin{aligned} \dot{\langle n\rangle} &= \sum_{n=0} n(\dot{P_0^n} + \dot{P_1^n}) \\ &= k_p \sum_{n=0} n(P_1^{n-1} - P_1^n) \\ &= k_p \sum_{n=0} P_1^n \\ &= k_p P_1(t). \end{aligned}$$

Replacing our expression in equation 2 in this formula, we integrate to get the solution

$$\langle n\rangle = k_p\frac{x}{1+x}t + n_0 + \frac{k_p\Delta_1}{r}(1-e^{-rt}). \tag{3}$$

Assuming that the initial product number $n_0 = 0$ and that the initial probability of being bound is the same as steady state $\Delta = P_1(0) - P_1^{ss} = 0$ we find

$$\langle n\rangle = k_p\frac{x}{1+x}t.$$

For the variance, as similar approach can be taken

$$\begin{aligned} \dot{\langle n^2\rangle} &= \sum_{n=0} n^2(\dot{P_0^n} + \dot{P_1^n}) \\ &= k_p \sum_{n=0} n^2(P_1^{n-1} - P_1^n) \\ &= k_p \sum_{n=0} (n+1)^2P_1^n - n^2P_1^n \\ &= k_p \sum_{n=0} (2n+1)P_1^n \\ &= k_p(2\sum_{n=0} nP_1^n + \sum_{n=0} P_1^n) \\ &= k_p(2\langle n\rangle + P_1(t)) \end{aligned}$$

By using the expression for $\langle n\rangle$ in equation 3 we can integrate to obtain $\langle n^2\rangle$

$$\langle n^2\rangle = {k_p}^2\frac{x}{1+x}t^2 + 2k_p n_0 t + 2\frac{{k_p}^2\Delta_1}{r^2}(rt-1+e^{-rt}) + \langle n\rangle. \tag{4}$$

It is straightforward at this point to combine equations 3 and 4 to obtain the variance

$$\begin{aligned} Var(n) &= \langle n^2\rangle - \langle n\rangle^2 \\ &= k_p\frac{x}{1+x}t^2 + 2k_p n_0 t + \frac{2k_p\Delta_1}{r^2}(rt-1+e^{-rt}) + \langle n\rangle \\ &\quad - \langle n\rangle^2 \end{aligned} \tag{5}$$

If $\Delta_1 = P_1(0) - P_1^{ss} = 0$ and $n_0$=0

$$\begin{aligned} Var(n) &= {k_p}^2\frac{x}{1+x}t^2 + k_p\frac{x}{1+x}t - {k_p}^2\frac{x^2}{(1+x)^2}t^2 \\ &= {k_p}^2\frac{x}{(1+x)^2}t^2 + k_p\frac{x}{1+x}t \\ &= k_p\frac{x}{1+x}t(k_p\frac{1}{1+x}t+1) \end{aligned} \tag{6}$$

### B. Mode 2

Next, we investigate the process that releases a GPCR product $m$ upon ligand binding to the receptor. Similar to mode 1, the ligand binds with rate $k_{on}c$ and unbinds with rate $k_off$ to the receptor.

(Need to make the figure for this)

The master equations are

$$\begin{aligned} \dot{P_0^m} &= k_{off}P_1^m - k_{on}cP_0^m \\ \dot{P_1^m} &= k_{on}cP_0^{m-1} - k_{off}P_1^m. \end{aligned} \tag{7}$$

Again, what we are interested in this equation is the average and variance of the prouct $m$ within the cell as we can find what the best estimate the cell can make of the ligand concentration outside. We will later investigate the best estimate for $k_off$.

For now, we will continue along the same derivation of $\langle m\rangle$ and $\langle m^2\rangle$ as before. Note that we will use the solution for the probability of being bound as a function of time, equation 2, but with the variation

$$P_0(t) = \frac{1}{1+x} - \Delta e^{-rt} \tag{8}$$

where

$$\Delta_0 = -\Delta_1 = P_0(0) - P_0^{ss}.$$

We write down the time derivative of average $m$ and replace terms by the master equations to solve the equation

$$\begin{aligned} \dot{\langle m\rangle} &= \sum_{n=0} n(\dot{P_0^m} + \dot{P_1^m}) \\ &= k_{on}c\sum_{n=0} n(P_0^{m-1} - \dot{P_0^m}) \\ &= k_{on}c\sum_{n=0} P_0^m \\ &= k_{on}cP_0(t). \end{aligned}$$

Replacing our expression in equation 2 in this formula, we integrate to get the solution

$$\langle m\rangle = k_{on}c\frac{1}{1+x}t + m_0 - \frac{k_{on}c\Delta_0}{r}(1-e^{-rt}). \tag{9}$$

Assuming that the initial product number $m_0 = 0$ and that the initial probability of being unbound is the same as steady state $\Delta_0 = P_0(0) - P_0^{ss} = 0$ we find

$$\begin{aligned} \langle m\rangle &= k_{on}c\frac{1}{1+x}t \\ &= k_{off}\frac{x}{1+x}t \end{aligned}$$

since $x = k_{on}c/k_{off}$. For the variance, as similar approach can be taken

$$\begin{aligned} \dot{\langle m^2\rangle} &= \sum_{m=0} m^2(\dot{P_0^m} + \dot{P_1^m}) \\ &= k_{on}c\sum_{n=0} m^2(P_0^{m-1} - P_0^m) \\ &= k_{on}c\sum_{m=0} (m+1)^2(P_0^m - m^2P_0^m) \\ &= k_{on}c\sum_{m=0} (2m+1)P_0^m \\ &= k_{on}c(2\sum_{m=0} mP_1^m + \sum_{n=0} P_0^n) \\ &= k_{on}c(2\langle m\rangle + P_0(t)) \end{aligned}$$

By using the expression for $\langle m\rangle$ in equation 3 we can integrate this obtain $\langle m^2\rangle$

$$\begin{aligned} \langle m^2\rangle &= k_{on}ck_{off}\frac{x}{1+x}t^2 + 2k_{on}cm_0t - 2\frac{k_{on}c\Delta_0}{r^2}(rt+e^{-rt}) \\ &\quad + \langle m\rangle. \end{aligned} \tag{10}$$

It is straightforward at this point to combine equations 3 and 4 to obtain the variance

$$\begin{aligned} Var(m) &= \langle m^2\rangle - \langle m\rangle^2 \\ &= k_{on}ck_{off}\frac{x}{1+x}t^2 + 2k_{on}cm_0t - \\ &\quad \frac{(k_{on}c)^2\Delta_0}{r^2}(rt+e^{-rt}) + \langle m\rangle - \langle m\rangle^2. \end{aligned} \tag{11}$$

Assuming $m_0 = 0$ and $\Delta_0 = P_0(0) - P_0^{ss} = 0$ gives us

$$Var(m) = k_{on}ck_{off}\frac{x}{1+x}t^2 + k_{off}\frac{x}{1+x}t - {k_{off}}^2\frac{x^2}{(1+x)^2}t^2 \tag{12}$$

### C. Mode 1 & 2

Combining both modes we can construct a model where binding releases a GPCR product $m$ from the receptor and starts producing some other product, $n$.

(Need to make the figure for this)

The master equations are

$$\begin{aligned} \dot{P_0^{n,m}} &= k_{off}P_1^{n,m} - k_{on}cP_0^{n,m} \\ \dot{P_1^{n,m}} &= k_{on}cP_0^{n,m-1} - k_{off}P_1^{n,m} + k_pP_1^{n-1,m} - k_pP_1^{n,m}. \end{aligned} \tag{13}$$

What we are interested in this equation is the now average and variance of proucts $n$ and $m$ within the cell as we can find what the best estimate the cell can make of the ligand concentration outside. From the master equation approach

$$\begin{aligned} \dot{\langle n\rangle} &= \sum_{n,m=0} n(\dot{P_0^{n,m}} + \dot{P_1^{n,m}}) \\ &= \sum_{n,m=0} n(k_pP_1^{n-1,m} - k_pP_1^{n,m} + k_{on}cP_0^{n,m-1} - k_{on}cP_0^{n,m}) \\ &= k_p\sum_{n,m=0} n(P_1^{n-1,m} - P_1^{n,m}) \\ &= k_p\sum_{n,m=0} P_1^{n} \\ &= k_pP_1(t). \end{aligned}$$

We can relabel all $m$ in step 3 as this sum over $m$ goes from 0 to infinity and is non-sensical for $m = 0$ given that $P_1^{n,-1} = 0$. Note that we find that the $\langle n\rangle$ is exactly the same form for our calculation of $\langle n\rangle$ of mode 1 (equation X). The same goes for $\langle n^2\rangle$, $\langle m\rangle$ and $\langle m^2\rangle$ derived in previous sections.

The correlation $\langle nm\rangle$ is less straightforward. We can write

$$\begin{aligned} \dot{\langle nm\rangle} &= \sum_{n,m=0} nm(\dot{P_0^{n,m}} + \dot{P_1^{n,m}}) \\ &= \sum_{n,m=0} nm(k_pP_1^{n-1,m} - k_pP_1^{n,m} + k_{on}cP_0^{n,m-1} - k_{on}cP_0^{n,m}) \\ &= \sum_{n,m=0} k_pm((n+1)P_1^{n,m} - k_pP_1^{n,m}) \\ &\quad + k_{on}nc((m+1)P_0^{n,m} - P_0^{n,m}) \\ &= \sum_{n,m=0} mk_pP_1^{n,m} + nk_{on}cP_0^{n,m-1}.. \end{aligned}$$

Where do we go from here? Event less obvious is how to get $Var(nm)$ as this will give even more terms