Derangement model of ligand-receptor binding

Using combinatorics to study how a system with many copies of many types of ligands can have all of those ligands bind to their optimal receptor sites

1 Introduction

Ligands outside a cell bind to receptor sites on the cell's surface in order to initiate cell-to-cell signal pathways. Often a ligand of a particular type can bind to many types of receptors, even when there is only one type of receptor to which it binds optimally. Consequently, it is often much more likely that ligands will bind to sub-optimal receptors than to optimal receptors unless binding energies can overcome the entropic unfavorability of such bindings. This leads to "combinatorial competition" amongst the many types of ligands in the extracellular environment as they seek their optimal receptor sites.

In this work we derive a partition function and then the associated equilibrium conditions that define when all ligands bind to their optimal receptor sites.

2 Main Result

Say we have a system with ligands R types of ligands and R types of receptors. The ligand of type i has n_i copies in the system (with i running from 1 to R), and within this system, each ligand can either be bound to a receptor or is free to move in the space surrounding the receptor sites. There are $n_1 + \cdots + n_R$ receptors and each ligand can bind to any one of them, but for each ligand of type i there are n_i receptors to which it binds most strongly with a relative binding energy of $-\Delta_i$ with $\Delta_i \geq 0$. We call such latter bindings "optimal". Using these premises, we find that the partition function for this system is

$$\mathcal{Z}_{\boldsymbol{n}}(\boldsymbol{\delta}, \boldsymbol{\gamma}) = \frac{1}{2\pi i} \oint_{\Gamma} \frac{dz}{z} \int_0^{\infty} dx \, \exp\left[\mathcal{F}_{\boldsymbol{n}}(z, x; \boldsymbol{\delta}, \boldsymbol{\gamma})\right], \tag{1}$$

where Γ is a closed contour in the complex plane about the origin and

$$\mathcal{F}_{\boldsymbol{n}}(z, x; \boldsymbol{\delta}, \boldsymbol{\gamma}) = z - x + \sum_{i=1}^{R} \ln\left[(\gamma_i(\delta_i - 1))^{n_i} L_{n_i}\left(\frac{x(z\gamma_i + 1)}{z\gamma_i(1 - \delta_i)}\right)\right], \tag{2}$$

and we defined $\delta_i \equiv e^{\beta\Delta_i}$, and $\gamma_i = Q_i^B / Q_i^F$

From Eq.(1), we can show that the average number of optimally bound receptors is equal to

$$\langle m \rangle = \sum_{j=1}^{R} n_j \gamma_j \delta_j \frac{\mathcal{Z}_{\boldsymbol{n}_j}(\boldsymbol{\delta}, \boldsymbol{\gamma})}{\mathcal{Z}_{\boldsymbol{n}}(\boldsymbol{\delta}, \boldsymbol{\gamma})}, \tag{3}$$

where $\boldsymbol{n}_j$ is $\boldsymbol{n}$ with 1 subtracted from the jth component: $\boldsymbol{n}_j = (n_1, \ldots, n_j - 1, \ldots, n_R)$.

3 Implications

By approximating Eq.(1) for the case where $n_i \gg 1$, we can derive an approximate expression for the number of optimally bound ligands Eq.(3). Given thermal dependences for γ_i and δ_i, we can use this expression to predict the critical temperature at which all ligands in a system bind to their corresponding optimal receptor sites. Thus in real biophysical systems we can determine when optimal ligand-receptor binding is dominant in the system contingent on system parameters. Non-equilibrium simulations of this system reveal that in order to avoid kinetic traps, γ_i must be must satisfy $\gamma_i \ll \delta_i$. Thus we argue that biophysical systems where optimal binding is functionally important reside in this parameter regime.