
Mathematics for Systems Biology and Bioinformatics

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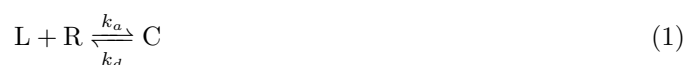
Exercise sheet no. 12

Submission until 30.1.2013 10:00 am in the tutorials

Homework 18: Receptor Modelling (10 Points)

Receptors are most commonly found at the cell surface, where extracellular signaling molecules, the ligand, can bind to them. Signaling proteins include cytokineses, insulin, hormones or growth factors, which could for example be transported through the blood stream. The binding process leads to a transmission of the signal into the cell where it can affect various processes, including the transcription of genes, which in turn can control various important cell functions.

Here we focus at a basic model for cell surface receptor binding, using the reversible bimolecular reaction



where R and L denote the free receptor of a cell and ligand molecules, respectively and C denotes the LR complex, i.e., receptors that are 'occupied'. k_a is the velocity at which ligands bind to receptors and k_d describes the dissociation rate. We refer to receptor and ligand as monovalent to assume that at any time only one ligand and one receptor molecule form a complex. For a single cell, the mass action model that describes temporal changes in the number of LR complexes is

$$\frac{dC(t)}{dt} = k_a R(t) L_f(t) - k_d C(t) \quad (2)$$

where L_{free} gives the free ligand concentration of the medium; R is the concentration of free receptors, C the concentration of receptor-ligand complexes.

a) Make use of the conserved entity of total receptors $R_{\text{Total}} = R(t) + C(t)$ and assume that the ligand depletion is negligible ($L_f(t) \approx L_0$) and rewrite Eq. (2).

b) *Steady State:*

Calculate the steady state ($\frac{dC(t)}{dt} = 0$). What is the number of receptor-ligand complexes at equilibrium (at equilibrium the reaction rates are equal).

c) *Integration:*

Linear, inhomogeneous, first-order ODEs (i.e. Eq.(4)) can be solved by defining an *integrating factor*:

$$\rho(t) = \exp\left(\int_0^t P(t') dt'\right) \quad (3)$$

One can multiply the ODE with this factor (Eq.(4)), applying the product rule of differentiation backwards Eq.(7) and integrating both sides of the equation (Eq.(8)) in order to get a form of the ODE from which the solution $C(t)$ can be directly computed.

$$\frac{dC(t)}{dt} + P(t)C(t) = Q(t) \quad (4)$$

$$\Leftrightarrow \frac{dC(t)}{dt}\rho(t) + \underbrace{P(t)\rho(t)}_{\frac{d\rho(t)}{dt}}C(t) = Q(t)\rho(t) \quad (5)$$

$$\Leftrightarrow \frac{dC(t)}{dt}\rho(t) + \frac{d\rho(t)}{dt}C(t) = Q(t)\rho(t) \quad (6)$$

$$\Leftrightarrow \frac{d}{dt}(\rho(t)C(t)) = Q(t)\rho(t) \quad (7)$$

$$\Leftrightarrow \int \frac{d}{dt}(\rho(t)C(t)) dt = \int Q(t)\rho(t) dt \quad (8)$$

$$\Leftrightarrow \rho(t)C(t) + c = \int Q(t)\rho(t) dt \quad (9)$$

c is some arbitrary integration constant.

Task:

- i.) Bring the ODE (result of a)) in a comparable form with Eq. (4) and identify $P(t)$ and $Q(t)$.
- ii.) Knowing $P(t)$, calculate $\rho(t)$ (Eq. 3) and using $Q(t)$ evaluate the right-hand side of Eq. (9):

$$\text{Eq. (9)} \Rightarrow \rho(t)C(t) = \int_0^t Q(t')\rho(t')dt' + c \quad (10)$$

- iii.) Solve Eq. (10) for $C(t)$ and insert the above results. This is the solution of the ODE!
- iv.) Use the initial condition, $C(t=0) = C_0$ and replace the integration constant c .