Model formulation - exercise 2021

TBMT37 / TBMT19

Question

Take the role as a systems biologist working in a project together with an experimental collaborator. Your collaborator **can indirectly measure the concentration of insulin receptors at the surface of fat cells**, i.e. all insulin receptors that are located in the plasma membrane. She is interested in how fat cells respond to the **input insulin**. She has already an hypothesis for key interactions of the underlying biological system, and made a drawing that shows this hypothesis (Figure 1). She thinks that the reaction were the insulin receptor recirculates from inside the cell to the plasma membrane is **saturated** so that is has a maximum rate. Now it is your role to interpret the drawing and formalize into equations.

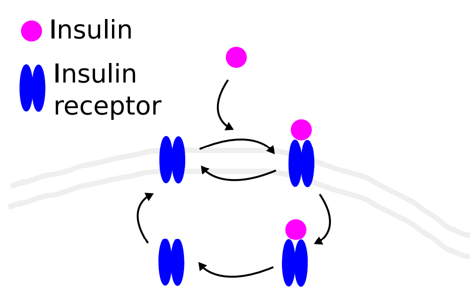

Figure 1: *The insulin receptor is located in the plasma membrane were insulin binds to the insulin receptor and forms a complex. This complex is either 1) internalized into the fat cell where insulin is released before the receptor recirculates to the plasma membrane or 2) resolved so that insulin is released and the insulin receptor is free to bind another insulin molecule.*

Use the drawing above as the interaction graph for the model. Formulate the corresponding system of ordinary differential equations! Feel free to make assumptions, and include these assumptions in your answer. Introduce parameters with values of your choice. The result should be a complete model that can be simulated.

Suggested answer

1. Identify model states:

$$x1 = InsulinReceptor_{plasmamembrane}$$
$$x2 = InsulinReceptor^{insulin}_{plasmamembrane}$$
$$x3 = InsulinReceptor^{insulin}_{internalized}$$
$$x4 = InsulinReceptor_{internalized}$$

2. Let us assume mass-action kinetics for all reactions except the saturated recirculation reaction (v5). Let us also assume that Insulin is the input $u = Insulin$. We then have the following reaction rates:

$$v1 = k1 \cdot x1 \cdot u$$
$$v2 = k2 \cdot x2$$
$$v3 = k3 \cdot x2$$
$$v4 = k4 \cdot x3$$
$$v5 = (Vmax \cdot x4)/(Km + x4)$$

where

$$v1 : x1 \rightarrow x2$$
$$v2 : x2 \rightarrow x1$$
$$v3 : x2 \rightarrow x3$$
$$v4 : x3 \rightarrow x4$$
$$v5 : x4 \rightarrow x1$$

3. Formulate ODEs:

$$d/dt(x1) = -v1 + v2 + v5$$
$$d/dt(x2) = v1 - v2 - v3$$
$$d/dt(x3) = v3 - v4$$
$$d/dt(x4) = v4 - v5$$

4. What is measured?
   Let us assume that we can measure something proportional to the sum of x1 and x2 since these states represent receptors in the plasma membrane.
   $$\hat{y} = ky \cdot (x1 + x2)$$
5. Parameters and their values:
   $k1 = 3$, $k2 = 1$, $k3 = 2$, $Vmax = 1$, $Km = 3$
   $ky = 0.5$
   $x1(0) = 10$, $x2(0) = 0$, $x3(0) = 10$, $x4(0) = 0$
   All parameter values are made up. We also assume a value for the input strength: $u = 100$.
   All of these values are needed to simulate the model.

The full system of ODEs:

$$\begin{aligned}
d/dt(x1) &= -v1 + v2 + v5 \\
d/dt(x2) &= v1 - v2 - v3 \\
d/dt(x3) &= v3 - v4 \\
d/dt(x4) &= v4 - v5 \\
v1 &= k1 \cdot x1 \cdot u \\
v2 &= k2 \cdot x2 \\
v3 &= k3 \cdot x2 \\
v4 &= k4 \cdot x3 \\
v5 &= (Vmax \cdot x4)/(Km + x4) \\
\hat{y} &= ky \cdot (x1 + x2)
\end{aligned}$$

$x1(0) = 10$, $x2(0) = 0$, $x3(0) = 10$, $x4(0) = 0$
$k1 = 3$, $k2 = 1$, $k3 = 2$, $k4 = 4$, $Vmax = 1$, $Km = 3$
$ky = 0.5$
$u = 10$