

### 1) Consider the following model

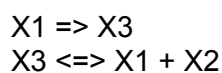
$$\begin{aligned}d/dt([A]) &= -k_1*[A] \\d/dt([B]) &= k_1*[A] - k_2*[B] \\yhat &= k_y*[B] \\[A](0) &= 1 \\[B](0) &= 0.5 \\k_1 &= 1, k_2 = 3, k_y = 2\end{aligned}$$

- a) What are the underlying reactions?
- b) Make the  $k_1$ -reaction reversible and update the equations
- c) What is the simulated measurement at time  $t = 0$ ?
- d) What is the value of  $[B]$  at time  $t = 0.1$ , if you take one step with an Euler forward? (use the original equations)
- e) Update the measurement part to be saturated with respect to  $[B]$

#### Answers:

- a)  $A \Rightarrow B \Rightarrow$
- b) The ODEs turns into (NOTE: UPDATED ANSWER)  
 $d/dt([A]) = -k_{1f}[A] + k_{1b}[B]$   
 $d/dt([B]) = k_{1f}[A] - k_{1b}[B] - k_2[B]$   
and therefore you also need to update the parameter values:  
 $k_1 = 1$  is replaced by  $k_{1f} = 2$ ,  $k_{1b} = 0.5$  (made up values)
- c)  $yhat(0) = k_y*[B](0) = 2*0.5 = 1$
- d)  $B(0.1) = B(0) + 0.1*d/dt(B) = 0.5 + 0.1*(1*1 - 3*0.5) = 0.5 + 0.1*(-0.5) = 0.45$
- e)  $yhat = V_{max2}*[B]/(K_{m2} + [B])$ ,  
 $V_{max2} = 3.5$ ,  $K_{m2} = 55$  (made up values)

### 2) Consider the following reactions



- a) Assume that the first reaction is described by Michaelis-Menten kinetics, and the second by mass action. What are the differential equations?

- b) Assume that you can measure the sum of the concentrations of X1 and X2, and that everything is located in the X1 state at time 0. Write the initial conditions and the measurement equation.
- c) What are the states in the model?
- d) What are the parameters?
- e) Assume that X2 is controlled by the user, i.e. it is an input. What would change?

**Answers:**

- a)
- $$v1 = Vmax*[X1]/(Km + [X1]), v2f = k2f*[X3], v2b = k2b*[X1]*[X2], v2 = v2f-v2b$$
- $$d/dt([X1]) = -v1 + v2$$
- $$d/dt([X2]) = v2$$
- $$d/dt([X3]) = v1 - v2$$
- b)
- $$[X1](0) = 10 \text{ (made up value)}, [X2](0) = [X3](0) = 0$$
- $$yhat = [X1] + [X2]$$
- c) [X1], [X2], and [X3]
- d) Vmax, Km, k2f, k2b (note: no measurement parameters in this model)
- e)
- You could write  $u = [X2]$ , remove the differential equation for  $d/dt([X2])$ , and replace the  $v2b$  with  $v2b = -k2b*[X1]*u$

**3) Consider the following model:**

$$d/dt(x1) = -k1*x1 + Vmax*x2/(Km + x2)$$

$$d/dt(x2) = k1*x1 - Vmax*x2/(Km + x2) - k3*x2$$

$$yhat = kmeas*(x1 + x2)$$

- a) What are the underlying reactions making up the interaction graph of this model?
- b) Assume that the k1-reaction is saturated. What changes?
- c) Assume that on top of the change in b), the original Vmax-reaction no longer is saturated; what happens?
- d) Assume that on top of the change in c), there appears a new reaction that creates x1, with a constant rate k0. What changes?
- e) Assume that on top of the change in d), the k3-reaction is saturated with respect to x2, and that it creates the substance X3. What changes?
- f) Assume that we obtain a new measurement that is proportional to the concentration of X3. What changes?

Answers:

a)

Say that  $x_1 = [X_1]$ ,  $x_2 = [X_2]$ . Then:

R1:  $X_1 \Rightarrow X_2$  (mass-action, constant  $k_1$ )

R2:  $X_2 \Rightarrow X_1$  (Michaelis-Menten,  $V_{\max}$ ,  $K_m$ )

R3:  $X_2 \Rightarrow$  (mass-action, constant  $k_3$ )

(Note that we here differentiate between the state  $x_1$ , and the protein/substance whose concentration  $x_1$  is describing,  $X_1$ . This is the correct way to do things, but you would pass this dugga even if you write e.g.  $x_1 \Rightarrow x_2$  as the first reaction).

b)

$$d/dt(x_1) = -V_{\max 1} * x_1 / (K_{m1} + x_1) + V_{\max} * x_2 / (K_m + x_2)$$

$$d/dt(x_2) = V_{\max 1} * x_1 / (K_{m1} + x_1) - V_{\max} * x_2 / (K_m + x_2) - k_3 * x_2$$

(if there would have been parameter equations as well, these would have to be updated)

c)

$$d/dt(x_1) = -V_{\max 1} * x_1 / (K_{m1} + x_1) + k_2 * x_2$$

$$d/dt(x_2) = V_{\max 1} * x_1 / (K_{m1} + x_1) - k_2 * x_2 - k_3 * x_2$$

(if there would have been parameter equations as well, these would have to be updated; this holds for all similar changes below)

d)

$$d/dt(x_1) = -V_{\max 1} * x_1 / (K_{m1} + x_1) + k_2 * x_2 + k_0$$

$$d/dt(x_2) = V_{\max 1} * x_1 / (K_{m1} + x_1) - k_2 * x_2 - k_3 * x_2$$

e)

$$d/dt(x_1) = -V_{\max 1} * x_1 / (K_{m1} + x_1) + k_2 * x_2 + k_0$$

$$d/dt(x_2) = V_{\max 1} * x_1 / (K_{m1} + x_1) - k_2 * x_2 - V_{\max 3} * x_2 / (K_{m3} + x_2)$$

$$d/dt(x_3) = V_{\max 3} * x_2 / (K_{m3} + x_2)$$

where  $x_3 = [X_3]$

f) We get a new measurement equation  $\hat{y}_2 = k_{y2} * x_3$