CHEM-E7190/2020: Exercise III

Task 1. Most of the reactions occurring within a cell are catalysed by enzymes, which are proteins. Enzymes catalyse reactions by binding the reactants, or enzyme substrates, and facilitating their conversion into reaction products. By reducing the energy barrier associated to the reaction, enzymes increase the rate at which equilibrium is reached, without affecting the equilibrium itself.

Consider the following single-substrate enzyme-catalysed reaction,

$$\underbrace{S}_{\text{Substrate}} + \underbrace{E}_{\text{Enzyme}} \rightleftarrows \underbrace{\circledcirc}_{\text{Enzyme-substrate complex}} \rightleftarrows \underbrace{\circledcirc}_{\text{Enzyme-product complex}} \rightleftarrows \underbrace{P}_{\text{Product}} + \underbrace{E}_{\text{Enzyme}}$$

Let us assume that *i*) the two complexes can be lumped together as complex C (that is, $\circledcirc \rightleftarrows \circledcirc$ is much faster than the association/dissociation reactions) and that *ii*) the product never binds the free enzyme (that is, the enzyme-catalysed reaction is irreversible). The assumptions lead to the Michaelis-Menten[1] mechanism,

$$S + E \underset{k_{-1}=1}{\overset{k_1=30}{\rightleftarrows}} C \underset{k_{-2}=0}{\overset{k_2=10}{\rightleftarrows}} P + E$$

Let us also assume that in principle all involved species can be added and removed to and from the cell. We model these fluxes using the chemical reaction methafore involving non-existing species $\emptyset$; That is, we have

$$\begin{aligned}
\emptyset &\underset{k_{-S}}{\overset{k_S}{\rightleftarrows}} S \\
\emptyset &\underset{k_{-E}}{\overset{k_E}{\rightleftarrows}} E \\
\emptyset &\underset{k_{-C}}{\overset{k_C}{\rightleftarrows}} C \\
\emptyset &\underset{k_{-P}}{\overset{k_P}{\rightleftarrows}} P
\end{aligned}$$

Write the differential equation model of the cell from the component material balances[2]. For the task, *i*) let the concentrations $[S](t)$, $[E](t)$, $[C](t)$ and $[P](t)$ be the state variables $x(t) \in \mathcal{R}^4_{\geq 0}$; *ii*) let $k_S(t)$, $k_{-S}(t)$, $k_E(t)$, $k_{-E}(t)$, $k_C(t)$, $k_{-C}(t)$, $k_P(t)$ and $k_{-P}(t)$ be the input variables $u(t) \in \mathcal{R}^8_{\geq 0}$; and, *iii*) let k_1, k_{-1}, k_2, $k_{-2}0$ be parameters. As for the measurements $y(t) \in \mathcal{R}^2_{\geq 0}$, assume that we can measure $[P](t)$ and $[E](t)$.

1. Assuming arbitrary concentration and time units, what are the (arbitrary) units of the reaction rates?
2. Consider a cell in the initial state

$$x(0) = \begin{bmatrix} [S](0) \\ [E](0) \\ [C](0) \\ [P(0)] \end{bmatrix} = \begin{cases} \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \text{ for } t = 0 \quad \text{(Case I)} \\ \\ \begin{bmatrix} 5 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \text{ for } t = 0 \quad \text{(Case II)} \end{cases}$$

[1] L. Michaelis and M. L. Menten, Kinetik der Invertinwirkung. Biochemische Zeitschrift, 49(17), pp. 335–369 (1913).

[2] As an example balance using mass-action kinetics under the perfectly stirred assumption, consider species S

$$\frac{\mathrm{d}[S](t)}{\mathrm{d}t} = k_S(t) - k_{-S}(t)[S](t) - k_1(t)[S](t)[E](t) + k_{-1}(t)[C](t).$$

For both cases, simulate the system until a final time t_f to get its force-free response; that is, when

$$u(t) = \begin{bmatrix} k_S(t) \\ k_{-S}(t) \\ k_E(t) \\ k_{-E}(t) \\ k_C(t) \\ k_{-C}(t) \\ k_P(t) \\ k_{-P}(t) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \text{for all } t \in [0, t_f].$$

Comment on the dynamic behaviour of the system. Does the system reach a steady-state configuration?

3. Consider a cell in the initial state corresponding to Case II,

$$x(0) = \begin{bmatrix} 5 & 1 & 0 & 0 \end{bmatrix}^T.$$

Simulate the system until a final time t_f to get its forced response. For the task, consider the situation in which the cell is continuously fed with one unit concentration of substrate per unit time, while one unit concentration of product per unit time is removed for it; that is, when

$$u(t) = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}^T, \quad \text{for all } t \in [0, t_f]$$

Comment on the dynamic behaviour of the system. Does the system reach a steady-state configuration?

4. Suppose that we are interested in *operating* the cell under a constant feed of substrate, to make it produce a constant amount of product. In particular, assume as steady-state condition for the inputs

$$u_{SS} = \begin{bmatrix} k_S^{SS} \\ k_{-S}^{SS} \\ k_E^{SS} \\ k_{-E}^{SS} \\ k_C^{SS} \\ k_{-C}^{SS} \\ k_P^{SS} \\ k_{-P}^{SS} \end{bmatrix} = \begin{bmatrix} 5 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}$$

and as steady-state condition for the state-variables

$$x_{SS} = \begin{bmatrix} [S]^{SS} \\ [E]^{SS} \\ [C]^{SS} \\ [P]^{SS} \end{bmatrix} = \begin{bmatrix} 0.37 \\ 0.5 \\ 0.5 \\ 5 \end{bmatrix}.$$

- Determine the matrices A, B and C that characterise the linear and time-invariant system obtained when the original system model is linearised around the given point $SS = (x_{SS}, u_{SS})$;
- Study stability, controllability and observability of (A, B, C) and comment/discuss your results.
- Suppose that you only have an instrument to measure $[P](t)$, would this system be observable?
- Suppose that all species ($[S](t)$,$[E](t)$,$[C](t)$,$[P](t)$) are measured, would it make it observable?
- Determine the force-free evolution of the linearised system when starting from $x(0) = \begin{bmatrix} 5 & 1 & 0 & 0 \end{bmatrix}^T$ and compare it to the one obtained earlier (Case II, in 2.) for the original nonlinear system.