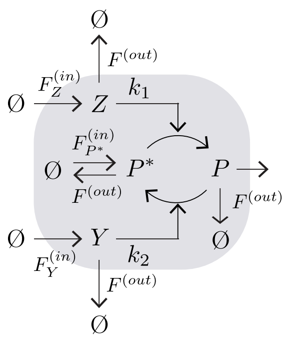
CHEM-E7225/2022: Exercise 01

Task 1 (Explicit integration methods).
Consider a phosphorylation-dephosphorylation cycle[1] (see diagram) in which the inactive state P^* (unphosphorylated) a target protein is converted into its active state P (phosphorylated) in the presence of a kinase Z. A phosphatase Y can reverse this process, thus producing P^*. The target protein P^* is produced at a constant rate $F_{P^*}^{(in)}$, and all species are subject to a first-order degradation with constant rate $F^{(out)}$. The process can be controlled by manipulating the production rates of kinase ($F_Z^{(in)}$) and phosphatase ($F_Y^{(in)}$)



$$\emptyset \xrightarrow{F_Z^{(in)}} Z, \qquad \emptyset \xrightarrow{F_Y^{(in)}} Y, \qquad \emptyset \xrightarrow{F_{P^*}^{(in)}} P^*,$$
$$Z, Y, C_1, C_2, P^*, P \xrightarrow{F(out)} \emptyset,$$
$$Z + P^* \underset{d_1}{\overset{a_1}{\rightleftharpoons}} C_1 \xrightarrow{k_1} P + Z,$$
$$Y + P \underset{d_2}{\overset{a_2}{\rightleftharpoons}} C_2 \xrightarrow{k_2} P^* + Y.$$

The mass balances for the individual components lead to the following nonlinear dynamics

$$\frac{d[Z]}{dt} = F_Z^{(in)} - F^{(out)}[Z] - a_1[Z][P^*] + (d_1 + k_1)[C_1]; \tag{1a}$$
$$\frac{d[Y]}{dt} = F_Y^{(in)} - F^{(out)}[Y] - a_2[Y][P] + (d_2 + k_2)[C_2]; \tag{1b}$$
$$\frac{d[C_1]}{dt} = -F^{(out)}[C_1] + a_1[Z][P^*] - (d_1 + k_1)[C_1]; \tag{1c}$$
$$\frac{d[C_2]}{dt} = -F^{(out)}[C_2] + a_2[Y][P] - (d_2 + k_2)[C_2]; \tag{1d}$$
$$\frac{d[P^*]}{dt} = F_{P^*}^{(in)} - F^{(out)}[P^*] - a_1[Z][P^*] + d_1[C_1] + k_2[C_2]; \tag{1e}$$
$$\frac{d[P]}{dt} = -F^{(out)}[P] - a_2[Y][P] + d_2[C_2] + k_1[C_1]; \tag{1f}$$

The state vector is $x(t) = ([Z](t), [Y](t), [C_1](t), [C_2](t), [P^*](t), [P](t))$ and the controls are $u(t) = \big(F_Z^{(in)}(t), F_Y^{(in)}(t)\big)$. The vector of model parameters in nominal operating conditions is the following

$$\theta_x = \begin{bmatrix} F_{P^*}^{(in)} \\ F^{(out)} \\ a_1 \\ a_2 \\ d_1 \\ d_2 \\ k_1 \\ k_2 \end{bmatrix} = \begin{bmatrix} 2 \\ 1 \\ 2 \\ 4 \\ 1.5 \\ 2 \\ 10 \\ 10 \end{bmatrix}$$

[1] For more details, see *C. Cuba Samaniego, A. Moorman, G. Giordano, E. Franco*, Signaling-based neural networks for cellular computation, *bioRxiv 2020.11.10.377077, 2020*

Re-write the dynamic model in Eq. (1) using the control notation to get it in the form $\dot{x}(t) = f(x(t), u(t)|\theta_x)$, then adapt the starting code in the archive `E1_code.zip` and use it to compare different integration schemes.

- Adapt the main script and the functions to simulate the system above using all the schemes included in the main script. To verify the correctness of the implementation, plot the obtained trajectories of the system variables when the system is subjected to varying control signals. We suggest the signals

$$u_1(t) = \begin{cases} u_Z & \text{for } t \leq t_Z \\ 0 & \text{otherwise} \end{cases}, \qquad u_2(t) = \begin{cases} u_Y & \text{for } t \geq t_Z \\ 0 & \text{otherwise} \end{cases},$$

  for different values of (t_Z, t_Y, u_Z, u_Y) satisfying $0 \leq t_Z, t_Y \leq 20$ and $u_Z, u_Y \geq 0$.

- Implement the RK4 scheme as a CasADi function and use it to perform the simulation. Again, verify the correctness of the implementation when the system is subjected to varying control signals.

Consider a simulation time T_f of 20 units-of-time (with $K = 500$ time-nodes k, or more) and compare the accuracy of the solutions against what obtained using `ode15s`. A valid initial state is $x(0) = (0, 0, 0, 0, 0, 0)$.

Errata

- Error in the dynamical equations in Eq. (1c) and Eq. (1d), the sign of some terms should be flipped. The correct equations are:

$$\frac{d[C_1]}{dt} = -F^{(out)}[C_1] + a_1[Z][P^*] - (d_1 + k_1)[C_1];$$
$$\frac{d[C_2]}{dt} = -F^{(out)}[C_2] + a_2[Y][P] - (d_2 + k_2)[C_2];$$