Separation of timescales simplifies the analysis of signaling and regulatory networks. Consider a 3-stage signaling cascade coupled to transcription and translation of a target gene. The dynamics are

$$
\begin{aligned}
\beta(t) &= \beta_0 u(t) \\
\dot{x}_1(t) &= b\beta(t) - \alpha x_1(t) \\
\dot{x}_2(t) &= bx_1(t) - \alpha x_2(t) \\
\dot{x}_3(t) &= bx_2(t) - \alpha x_3(t) \\
\dot{G}^*(t) &= k_f[G_T - G^*(t)][x_3(t)]^4 - k_b G^*(t) \\
\dot{M}(t) &= \beta_M G^*(t) - \alpha_M M(t) \\
\dot{P}(t) &= \beta_P M(t) - \alpha_P P(t).
\end{aligned}
$$

The input $\beta(t)$ is proportional to the unit step function $u(t)$, and all system variables are 0 at $t = 0$.
   Parameter values are as follows:

$$
\begin{aligned}
\beta_0 &= 1 \text{ molec/cell} \\
b &= 5/\text{sec} \\
\alpha &= 1/\text{sec} \\
k_f &= 10^{-4}/[(\text{molec/cell})^4 \text{sec}] \\
k_b &= 1/\text{sec} \\
G_T &= 1 \text{ molec/cell} \\
\beta_M &= 1/(2 \text{ min}) \\
\alpha_M &= 1/(10 \text{ min}) \\
\beta_P &= 1/(10 \text{ min}) \\
\alpha_P &= 1/(600 \text{ min}).
\end{aligned}
$$

   Questions that ask for symbolic results should provide answers with symbols β_0, β_M, β_P, b, α, α_M, α_P, k_f, k_b, G_T. Questions that ask for numerical results should provide answers with numbers and units. Concentration units are molecules/cell. Time units are provided according to the timescale of the system component.

1. Provide symbolic analytical results for $x_1(t)$, termed $x_1'(t)$.

2. Calculate numerical results for $x_1(t)$, termed $x_1''(t)$, using a standard ODE solver for $t = 0$ to 1 min with a spacing of 1 second.

3. Calculate the root-mean-square (RMS) relative error, σ_r^2, of the numerical results to the exact

analytical results,

$$\sigma_r^2 = \sqrt{\sum_{j=1}^{N} [x'(t_j) - x''(t_j)]^2 \Big/ \sum_{j=1}^{N} x'(t_j)^2},$$

where the numerical trajectory is provided at N discrete times $t_j = j\Delta t$. Check that the RMS relative error is appropriate for single-precision arithmetic, about 1×10^{-6}, and that your ODE solver is working properly.

4. At steady-state , $\dot{G}^*(t) = 0$. Use this condition to express the steady-state value of $G^*(t)$ in terms of Hill function involving $x_3(t)/K$, where K depends on k_f and k_b.

5. Signaling response is usually fast relative to mRNA and protein synthesis. In this case, transcriptionally active $G^*(t)$ can be represented as $G^*(t) = G_T\Theta[\beta(t) > \beta_c]$, where β_c is a critical input value and $\Theta(\cdot)$ is 1 for a true argument and 0 for a false argument. Provide β_c in terms of model parameters, and calculate β_0/β_c.

6. Suppose that we use the approximation that $G^*(t) = G_T\Theta[\beta(t) > \beta_c]$. Use this approximation to provide symbolic results for $M(t)$ and $P(t)$.

7. Calculate numerical results for $M(t)$ and $P(t)$ for 1 day with a spacing of 1 minute.

8. Calculate the root-mean-square relative error of exact numerical results to approximate analytical results for $M(t)$ and $P(t)$.

9. A final approximation is that translation is slow compared to transcription. In this case we approximate $M(t) = M_T\Theta[\beta(t) > \beta_c]$, and $\dot{P}(t) = \beta_P M_T\Theta[\beta(t) > \beta_c] - \alpha_P P(t)$. Provide symbolic expressions for M_T and $\beta_P' = \beta_P M_T$. Provide analytical symbolic results for $P(t)$ with these approximations.

10. Calculate the root-mean-square relative error of exact numerical results to this final approximation for $P(t)$, again over 1 day with a 1 minute spacing. Plot the numerical versus approximate analytical $P(t)$.