

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 $x'_1(t)$.

$$x'_1(t) = \frac{b\beta_0}{\alpha} (1 - e^{-\alpha t})$$

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.

clear ;

B0 = 1; % mol/cell

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b = 5; % /sec
a = 1; % /sec
GT = 1; % mol / cell
Bm = 1/2; % /min
am = 1/10; % /min
Bp = 1/10; % /min
ap = 1/600; % /min

options = odeset('RelTol', 1e-8);

dx = @(t,x) b * B0 - a * x(1) ;

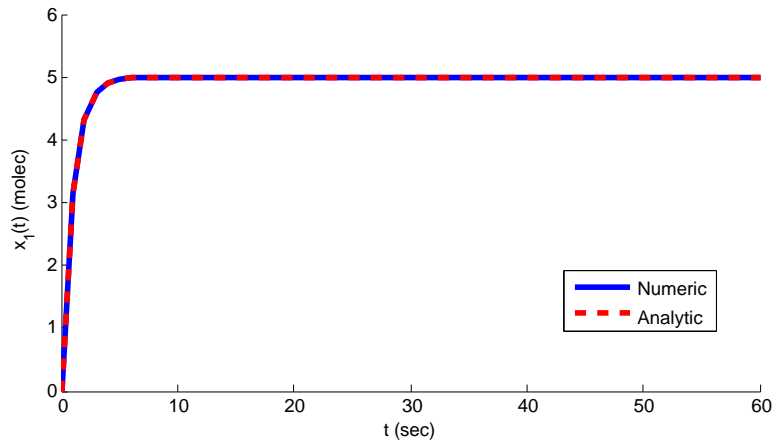
time=[0:60]';

[T, X_numeric] = ode45(dx, time, [0], options);

figure(1); clf; hold on;
plot(T, X_numeric, 'LineWidth', 3);

X_analytic = B0 * b / a * (1 - exp(- a * time));
plot(T, X_analytic, 'r--', 'LineWidth', 3);
legend('Numeric', 'Analytic');
xlabel('t (sec)');
ylabel('x_1(t) (molec)');

```



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

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

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.

$$\text{RMS}_{x1} = \text{sqrt}(\text{sum}((X_{\text{analytic}} - X_{\text{numeric}}).^2) / \text{sum}(X_{\text{analytic}}.^2))$$

$$\text{RMS}_{x1} =$$

$$5.7622\text{e-}08$$

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 .

$$\begin{aligned} \dot{G}^*(t) &= k_f[G_T - G^*(t)][x_3(t)]^4 - k_b G^*(t) \\ 0 &= k_f[G_T - G^*(t)][x_3(t)]^4 - k_b G^*(t) \\ G^*(t)(k_f[x_3(t)]^4 + k_b) &= G_T k_f [x_3(t)]^4 \\ G^*(t) &= \frac{G_T k_f [x_3(t)]^4}{k_b + k_f [x_3(t)]^4} \\ &= \frac{G_T \frac{k_f}{k_b} [x_3(t)]^4}{1 + \frac{k_f}{k_b} [x_3(t)]^4} \\ &= \frac{G_T (x_3(t)/K)^4}{1 + (x_3(t)/K)^4} \end{aligned}$$

$$\text{With } K = \sqrt[4]{k_b/k_f} = 10$$

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 .

At steady state, $x_3(t) = \beta \left(\frac{b}{\alpha}\right)^3$, where β is the amplitude of the input. In order to find where

$$\beta = \beta_c,$$

$$\begin{aligned} \frac{G^*(t)}{G_T} &> 1/2 \\ \frac{(x_3(t)/K)^4}{1 + (x_3(t)/K)^4} &> 1/2 \\ \left(\frac{x_3(t)}{K}\right)^4 &> 1 \\ \frac{x_3(t)}{K} &> 1 \\ x_3(t) &> \sqrt[4]{k_b/k_f} \\ \beta \left(\frac{b}{\alpha}\right)^3 &> \sqrt[4]{k_b/k_f} \\ \beta_c &= \frac{\sqrt[4]{k_b/k_f}}{\left(\frac{b}{\alpha}\right)^3} \\ \frac{\beta_0}{\beta_c} &= \frac{\beta_0 \left(\frac{b}{\alpha}\right)^3}{\sqrt[4]{k_b/k_f}} = 12.5 \end{aligned}$$

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 $P(t)$.

$$\begin{aligned} M(t) &= \frac{\beta_M G_T}{\alpha_M} (1 - e^{-\alpha_M t}) \\ P(t) &= \frac{\beta_P \beta_M G_T}{\alpha_P \alpha_M} + \frac{\beta_P \beta_M G_T}{\alpha_M (\alpha_M - \alpha_P)} e^{-\alpha_M t} - \frac{\beta_P \beta_M G_T}{\alpha_P (\alpha_M - \alpha_P)} e^{-\alpha_P t} \end{aligned}$$

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

```
dMP = @(t , x) [Bm * GT - am * x(1); ...
               Bp * x(1) - ap * x(2)];

time = [0:(60*24)]';
[T,MP_numeric] = ode45(dMP, time, [0 0], options);
figure(2); clf; hold on;
plot(T/60, MP_numeric(:,1), 'k', 'LineWidth', 2);
plot(T/60, MP_numeric(:,2), 'b', 'LineWidth', 2);

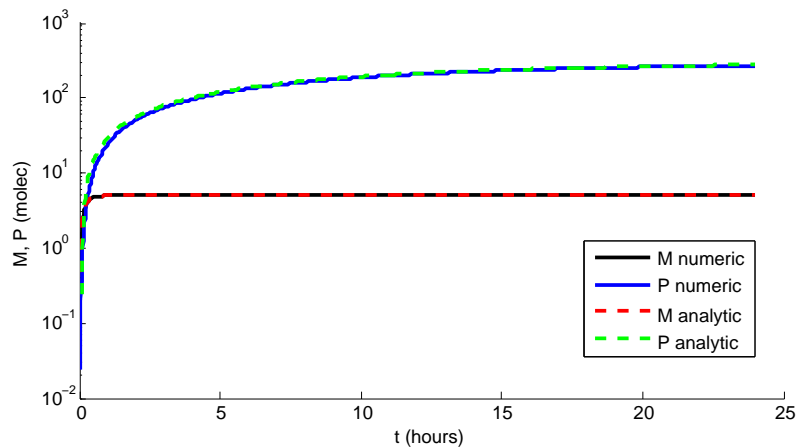
M_analytic = Bm * GT / am * (1 - exp(-am * time));
P_analytic = Bp * Bm * GT / (ap * (am - ap)) * (1 - exp(-ap * time)) + ...
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Bp * Bm * GT / (am * (ap - am)) * exp(-am * time);

plot(time/60, M_analytic, 'r--', 'LineWidth', 2);
plot(time/60, P_analytic, 'g--', 'LineWidth', 2);
legend('M_numeric', 'P_numeric', 'M_analytic', 'P_analytic');
set(gca, 'YScale', 'log');
xlabel('t (hours)');
ylabel('M, P (molec)');

```



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

```

RMS_M = sqrt( sum( ( M_analytic - MP_numeric(:,1) ).^2 ) / ...
              sum( M_analytic.^2 ) )
RMS_P = sqrt( sum( ( P_analytic - MP_numeric(:,2) ).^2 ) / ...
              sum( P_analytic.^2 ) )

```

RMS_M =
6.7773e-08

RMS_P =
0.0247

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.

$$M_T = \frac{\beta_M G_T}{\alpha_M}$$

$$\beta'_P = \frac{\beta_P \beta_M G_T}{\alpha_M}$$

$$P(t) = \frac{\beta_P \beta_M G_T}{\alpha_M \alpha_P} (1 - e^{-\alpha_P t})$$

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 $P(t)$.

```
dP = @(t,x) Bp * Bm * GT / am - ap * x(1);
[T,P_numeric] = ode45(dP, time, 0, options);
P_analytic = Bp * Bm * GT / (am * ap) * (1 - exp(-ap * time));
figure(3); clf; hold on;
plot(time/60, P_numeric, 'b', 'LineWidth', 2);
plot(time/60, P_analytic, 'g--', 'LineWidth', 2);
legend('P_numeric', 'P_analytic')
xlabel('t (hours)');
ylabel('P (molec)');
```

```
RMS_P2 = sqrt( sum( ( P_analytic - P_numeric ).^2 ) / sum( P_analytic.^2 ) )
```

