

## Assignment 2: Model development and equations

### Viterbi algorithm

The Viterbi algorithm has the following steps:

1. *Initialization:*

$$\delta_1(s) = \Pi(s) \times B(O_1|s)$$

where  $\Pi(s)$  is the initial probability of being in state  $s$  and  $B(O_1|s)$  is the emission probability of observing  $O_1$  given state  $s$ .

and

$$\psi_1(s) = \text{none}$$

2. *Recursion:*

$$\delta_t(s) = \max_{r \in s} [\delta_{t-1}(r) \times A(r, s), B(O_t|s)]$$

where  $A(r, s)$  is the transition probability from state  $r$  to state  $s$ .

and

$$\psi_t(s) = \operatorname{argmax} [\delta_t(r) \times A(r, s)]$$

3. *Termination:*

$$P_t = \max [\delta_t(s)]$$

4. *Backtracking:* Trace back through the states to determine the most likely sequence of states.

where above,  $\delta_t(s)$  is the maximum probability of being in state  $s$  at time  $t$  given the observed sequence up to time  $t$ ,  $B(O_t|s)$  is the emission probability of observing  $O_t$  given state  $s$ , and  $\psi_t(s)$  is the state at time  $t-1$  that maximizes the probability of being in state  $s$  at time  $t$ .

### Question 1

#### ODEs - Mechanism I: Transcriptional Hijack

$$\begin{aligned} \frac{dr_a}{dt} &= m_a \times h^+(P_b, \theta_b, n_b) + \gamma_a \times r_a \\ \frac{dr_b}{dt} &= m_b \times h^-(P_a, \theta_a, n_a) + \gamma_b \times r_b \\ \frac{dP_a}{dt} &= k_{P_a} \times r_a - \delta_{P_a} \times P_a \\ \frac{dP_b}{dt} &= k_{P_b} \times r_b - \delta_{P_b} \times P_b \end{aligned}$$

When transcriptional hijack,  $h^-(P_a, \theta_a, n_a) = 1$

Table 1: Definitions of the parameters used in the ODEs

Parameter	Definition
$r_i$	Concentration of transcribed mRNA A or B (M, mol L <sup>-1</sup> ).
$\frac{dr_i}{dt}$	Time-derivative / change in concentration of transcribed mRNA (M s <sup>-1</sup> ).
$m_i$	Maximum transcription rate coefficient for mRNA (M s <sup>-1</sup> ).
$h^+(P, \theta, n)$	Hill activation function (dimensionless).
$h^-(P, \theta, n)$	Hill inhibition function (dimensionless).

Parameter	Definition
$\theta_i$	Expression threshold for protein binding (M, mol L <sup>-1</sup> ).
$n_i$	Hill coefficient representing regulatory nonlinearity (dimensionless, unitless).
$\gamma_i$	Degradation rate of mRNA (s <sup>-1</sup> ).
$P_i$	Concentration of Protein (M, mol L <sup>-1</sup> ).
$\frac{dP_i}{dt}$	Time-derivative / change in protein concentration (M s <sup>-1</sup> ).
$k_{Pi}$	Effective translation rate (s <sup>-1</sup> ) converting mRNA concentration to protein production rate.
$\delta_{Pi}$	Degradation rate of Protein A or Protein B (s <sup>-1</sup> ).
$t$	Time (s, seconds).

### SDEVelo - Mechanism II: Splicing Sabotage

$$\begin{aligned}
\alpha_A(t) &= \frac{c_A}{1 + \exp b_A(t - a_A)} \\
\beta_A^* &= \beta_A h^+(P_B, \theta_B, n_B) \\
dU_A &= (\alpha_A(t) - \beta_A^* U_A(t))dt + \sigma_{1A} dW_{1A} \\
dS_A &= (\beta_A^* U_A(t) - \gamma_A S_A(t))dt + \sigma_{2A} dW_{2A} \\
dP_A &= (k_{PA} S_A(t) - \delta_{PA} P_A(t))dt \\
\\ 
\alpha_B(t) &= \frac{c_B}{1 + \exp b_B(t - a_B)} \\
\beta_B^* &= \beta_B h^-(P_A, \theta_A, n_A) \\
dU_B &= (\alpha_B(t) - \beta_B^* U_B(t))dt + \sigma_{1B} dW_{1B} \\
dS_B &= (\beta_B^* U_B(t) - \gamma_B S_B(t))dt + \sigma_{2B} dW_{2B} \\
dP_B &= (k_{PB} S_B(t) - \delta_{PB} P_B(t))dt
\end{aligned}$$

Table 2: Definitions of the parameters used in the SDEVelo equations

Parameter	Definition
$\alpha_i(t)$	Time-dependent transcription rate of unspliced mRNA (pre-mRNA) (M s <sup>-1</sup> ).
$c_i$	Maximum transcription rate coefficient for pre-mRNA (M s <sup>-1</sup> ).
$b_i$	Steepness parameter of the transcription rate sigmoid function (s <sup>-1</sup> ).
$t$	Time (s).
$a_i$	Time shift or activation delay for transcription (s).
$\beta_i^*$	Regulated splicing rate influenced by protein interactions (s <sup>-1</sup> ).
$\beta_i$	Base splicing rate parameter (s <sup>-1</sup> ).
$h^+(P, \theta, n)$	Hill activation function (dimensionless).
$h^-(P, \theta, n)$	Hill inhibition function (dimensionless).
$P_i$	Concentration of Protein (M).
$\theta_i$	Expression threshold for protein binding (M).
$n_i$	Hill coefficient (dimensionless).

Parameter	Definition
$U_i(t)$	Concentration of unspliced mRNA (pre-mRNA) at time $t$ (M).
$dU_i$	Change in unspliced mRNA concentration (M s <sup>-1</sup> ).
$S_i(t)$	Concentration of spliced mRNA at time $t$ (M).
$dS_i$	Change in spliced mRNA concentration (M s <sup>-1</sup> ).
$\gamma_i$	Degradation rate of spliced mRNA (s <sup>-1</sup> ).
$\sigma_{1i}$	Noise intensity parameter for pre-mRNA transcription (M s <sup>-1/2</sup> ).
$\sigma_{2i}$	Noise intensity parameter for the splicing process (M s <sup>-1/2</sup> ).
$dW_{1i}, dW_{2i}$	Differentials of the Wiener process (units of s <sup>1/2</sup> ); stochastic increments scale as $\sqrt{\Delta t}$ .
$k_{Pi}$	Translation rate (s <sup>-1</sup> ).
$\delta_{Pi}$	Protein degradation rate (s <sup>-1</sup> ).
$dt$	Time differential (s).

## Downstream metabolic effects

$$\begin{aligned}\frac{dR}{dt} &= \alpha R - \beta RE \\ \frac{dE}{dt} &= -\gamma E + \delta RE\end{aligned}$$

Where:

- $\alpha R$ : represents the natural growth or replenishment of the resource in the absence of any interactions with the enzyme E.
- $-\beta RE$ : represents the rate at which the enzyme E utilizes the resource R.
- $-\gamma E$ : represents the rate at which the enzyme E is lost or deactivated over time, independent of its interaction with the resource R.
- $\delta RE$ : represents the rate at which the enzyme E is generated or activated in response to the presence of the resource R.

with  $\alpha = 2$  [T<sup>-1</sup>],  $\beta = 1.1$  [M<sup>-1</sup>L<sup>3</sup>T<sup>-1</sup>],  $\gamma = 1$  [T<sup>-1</sup>],  $\delta = 0.9$  [M<sup>-1</sup>L<sup>3</sup>T<sup>-1</sup>],  $R(0) = 1$  [M<sup>1</sup>L<sup>-3</sup>] and  $E(0) = 0.5$  [M<sup>1</sup>L<sup>-3</sup>]

The fixed points of this system can be found by setting the derivatives to zero:

$$\begin{aligned}0 &= \alpha R - \beta RE \\ 0 &= -\gamma E + \delta ER\end{aligned}$$

and solving for R and E. This yields the fixed points: 1.  $(R^*, E^*) = (0, 0)$  2.  $(R^*, E^*) = \left(\frac{\gamma}{\delta}, \frac{\alpha}{\beta}\right)$

The jacobian matrix for this system is given by:

$$J = \begin{pmatrix} \frac{\partial \dot{R}}{\partial R} & \frac{\partial \dot{R}}{\partial E} \\ \frac{\partial \dot{E}}{\partial R} & \frac{\partial \dot{E}}{\partial E} \end{pmatrix} = \begin{bmatrix} \alpha - \beta E & -\beta R \\ \delta E & -\gamma + \delta R \end{bmatrix}$$

The stability of the fixed points can be determined by evaluating the eigenvalues of the jacobian matrix at each fixed point.

The eigenvalues at the first fixed point  $(0, 0)$  are:

$$\det(J - \lambda I) = 0 \implies (\alpha - \lambda)(-\gamma - \lambda) = 0$$

$$\implies \lambda_1 = \alpha = 2, \quad \lambda_2 = -\gamma = -1$$

This indicates that the first fixed point is a saddle point, which is unstable.

The eigenvalues at the second fixed point  $\left(\frac{\gamma}{\delta}, \frac{\alpha}{\beta}\right)$  are:

$$\begin{aligned} \det(J - \lambda I) = 0 &\implies \left(\alpha - \beta \frac{\alpha}{\beta} - \lambda\right)\left(-\gamma + \delta \frac{\gamma}{\delta} - \lambda\right) - \left(-\beta \frac{\gamma}{\delta}\right)\left(\delta \frac{\alpha}{\beta}\right) = 0 \\ &\implies (-\lambda)(-\lambda) - \left(-\beta \frac{\gamma}{\delta}\right)\left(\delta \frac{\alpha}{\beta}\right) = 0 \\ &\implies \lambda^2 + \alpha\gamma = 0 \\ &\implies \lambda = \pm i\sqrt{\alpha\gamma} = \pm i\sqrt{2} \end{aligned}$$

Since the eigenvalues are purely imaginary, the second fixed point is a center, which is stable but not asymptotically stable. This means that the system will exhibit oscillatory behavior around this fixed point.