

## 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

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

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

$$h^+(P_i, \theta_i, n_i) = \frac{P_i^n}{\theta_i^n + P_i^n} \quad (1)$$

$$h^-(P_i, \theta_i, n_i) = 1 - h^+(P_i, \theta_i, n_i) \quad (2)$$

$$= \frac{\theta_i^n}{\theta_i^n + P_i^n} \quad (3)$$

### ODEs - Mechanism I: Transcriptional Hijack

$$\frac{dr_a}{dt} = m_a \times h^+(P_b, \theta_b, n_b) - \gamma_a \times r_a \quad (4)$$

$$\frac{dr_b}{dt} = m_b \times h^-(P_a, \theta_a, n_a) - \gamma_b \times r_b \quad (5)$$

$$\frac{dP_a}{dt} = k_{Pa} \times r_a - \delta_{Pa} \times P_a \quad (6)$$

$$\frac{dP_b}{dt} = k_{Pb} \times r_b - \delta_{Pb} \times P_b \quad (7)$$

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).
$\theta_i$	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

$$\alpha_A(t) = \frac{c_A}{1 + \exp b_A(t - a_A)} \quad (8)$$

$$\beta_A^* = \beta_A h^+(P_B, \theta_B, n_B) \quad (9)$$

$$dU_A = (\alpha_A(t) - \beta_A^* U_A(t))dt + \sigma_{1A} dW_{1A} \quad (10)$$

$$dS_A = (\beta_A^* U_A(t) - \gamma_A S_A(t))dt + \sigma_{2A} dW_{2A} \quad (11)$$

$$dP_A = (k_{PA} S_A(t) - \delta_{PA} P_A(t))dt \quad (12)$$

$$(13)$$

$$\alpha_B(t) = \frac{c_B}{1 + \exp b_B(t - a_B)} \quad (14)$$

$$\beta_B^* = \beta_B h^-(P_A, \theta_A, n_A) \quad (15)$$

$$dU_B = (\alpha_B(t) - \beta_B^* U_B(t))dt + \sigma_{1B} dW_{1B} \quad (16)$$

$$dS_B = (\beta_B^* U_B(t) - \gamma_B S_B(t))dt + \sigma_{2B} dW_{2B} \quad (17)$$

$$dP_B = (k_{PB} S_B(t) - \delta_{PB} P_B(t))dt \quad (18)$$

$$(19)$$

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) ( $M s^{-1}$ ).
$c_i$	Maximum transcription rate coefficient for pre-mRNA ( $M s^{-1}$ ).
$b_i$	Steepness parameter of the transcription rate sigmoid function ( $s^{-1}$ ).
$t$	Time (s).
$a_i$	Time shift or activation delay for transcription (s).
$\beta_i^*$	Regulated splicing rate influenced by protein interactions ( $s^{-1}$ ).
$\beta_i$	Base splicing rate parameter ( $s^{-1}$ ).
$h^+(P, \theta, n)$	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).
$U_i(t)$	Concentration of unspliced mRNA (pre-mRNA) at time $t$ (M).
$dU_i$	Change in unspliced mRNA concentration ( $M s^{-1}$ ).
$S_i(t)$	Concentration of spliced mRNA at time $t$ (M).
$dS_i$	Change in spliced mRNA concentration ( $M s^{-1}$ ).
$\gamma_i$	Degradation rate of spliced mRNA ( $s^{-1}$ ).
$\sigma_{1i}$	Noise intensity parameter for pre-mRNA transcription ( $M s^{-1/2}$ ).
$\sigma_{2i}$	Noise intensity parameter for the splicing process ( $M s^{-1/2}$ ).
$dW_{1i}, dW_{2i}$	Differentials of the Wiener process (units of $s^{1/2}$ ); stochastic increments scale as $\sqrt{\Delta t}$ .
$k_{Pi}$	Translation rate ( $s^{-1}$ ).
$\delta_{Pi}$	Protein degradation rate ( $s^{-1}$ ).
$dt$	Time differential (s).

## Downstream metabolic effects

$$\frac{dR}{dt} = \alpha R - \beta RE \quad (20)$$

$$\frac{dE}{dt} = -\gamma E + \delta RE \quad (21)$$

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  $\alpha = 2 \text{ [T}^{-1}\text{]}, \beta = 1.1 \text{ [M}^{-1}\text{L}^3\text{T}^{-1}\text{]}, \gamma = 1 \text{ [T}^{-1}\text{]}, \delta = 0.9 \text{ [M}^{-1}\text{L}^3\text{T}^{-1}\text{]}, R(0) = 1 \text{ [M}^1\text{L}^{-3}\text{]} \text{ and } E(0) = 0.5 \text{ [M}^1\text{L}^{-3}\text{]}$

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

$$0 = \alpha R - \beta RE \quad (22)$$

$$0 = -\gamma E + \delta ER \quad (23)$$

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:

$$J = \begin{pmatrix} \frac{\partial \dot{R}}{\partial R} & \frac{\partial \dot{R}}{\partial E} \\ \frac{\partial \dot{E}}{\partial R} & \frac{\partial \dot{E}}{\partial E} \end{pmatrix} = \begin{bmatrix} \alpha - \beta E & -\beta R \\ \delta E & -\gamma + \delta R \end{bmatrix} \quad (24)$$

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:

$$\begin{aligned} \det(J - \lambda I) = 0 &\implies (\alpha - \lambda)(-\gamma - \lambda) = 0 \\ &\implies \lambda_1 = \alpha = 2, \quad \lambda_2 = -\gamma = -1 \end{aligned}$$

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:

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

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.