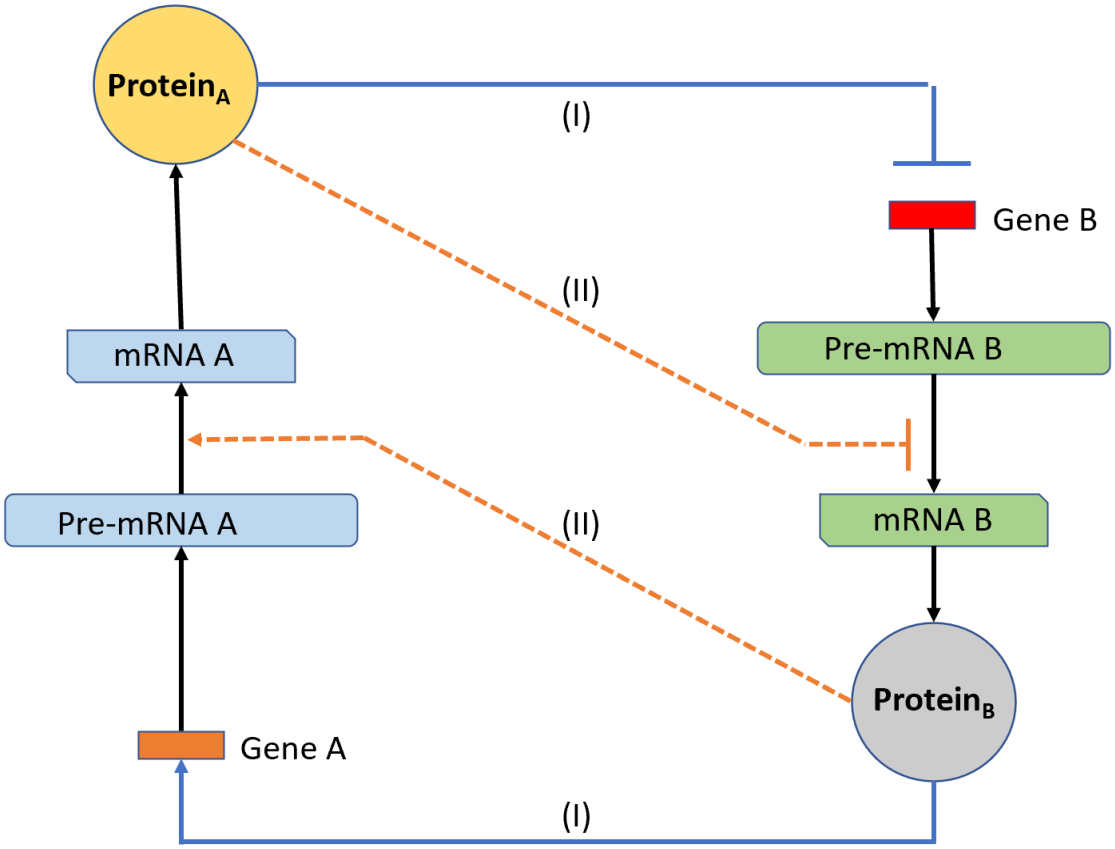

Solid blue line -Transcription Factor – influences transcription

Orange dotted lines - Splicing Factor – influences splicing

Figure 1: Gene interaction network

1. (7 points) We consider a hypothetical regulatory network (see Figure 1) where proteins A and B modulate the expression of genes A and B via two distinct interaction routes labeled (I) and (II). It is important to note that the modulation can happen either via route (I) or (II), meaning, if protein A works via route (I), protein B also works via route (I) and vice-versa.

Two total-RNA sequencing experiments have been performed to ascertain which regulatory route is active in two different cell types.

(a) The first total-RNA sequencing experiment for mRNA B generated an abundance of the sequence "**AGCGC**." Based on this sequence presented, your tasks are as follows,

(i) Identify the regulatory route (I or II) through which gene regulation occurs, inferring from the sequence presented. Hint: The classification of the total-RNA sequence data is to be carried out using the Viterbi algorithm, employing the transition probabilities, emission probabilities, and initial state probabilities specified in Tables 1, 2, and 3, respectively.

(ii) Develop a gene regulation model for the inferred route. This model should quantify the dynamic interactions between protein levels and gene expression using the appropriate model: either an ordinary differential equation (ODE) formulation or SDEVelo formulation that incorporates Hill

kinetics (hint: the choice of formulation may depend on the observed mRNA status). Parameter values for these models are given in Tables 4 and 5, respectively.

(iii) Plot the time evolution of mRNA A and mRNA B concentrations.

(iv) Generate a subspace plot of the protein dynamics (i.e., a phase-plane plot showing the dynamics of Protein A versus Protein B).

(b) The second total-RNA sequencing experiment for mRNA B yielded an abundance of the sequence "**AUUAU**." Based on this sequence presented, your tasks are as follows,

(i) Identify the regulatory route (I or II) through which gene regulation occurs, inferring from the sequence presented. Hint: The classification of the total-RNA sequence data is to be carried out using the Viterbi algorithm, employing the transition probabilities, emission probabilities, and initial state probabilities specified in Tables 1, 2, and 3, respectively.

(ii) Develop a gene regulation model for the inferred route. This model should quantify the dynamic interactions between protein levels and gene expression using the appropriate model: either an ordinary differential equation (ODE) formulation or SDEVelo formulation that incorporates Hill kinetics (hint: the choice of formulation may depend on the observed mRNA status). Parameter values for these models are given in Tables 4 and 5, respectively.

(iii) Plot the time evolution of mRNA A and mRNA B concentrations.

(iv) Generate a subspace plot of the protein dynamics (i.e., a phase-plane plot showing the dynamics of Protein A versus Protein B).

(c) Now compare the protein subspace plots from (a) and (b) and describe the dynamic behaviours observed in these plots.

Table 1:

Transition probabilities	**Exon**	**Intron**
Exon	0.9	0.1
Intron	0.2	0.8

Table 2:

Emission Probabilities	**A**	**U**	**G**	**C**
Exon	0.25	0.25	0.25	0.25
Intron	0.4	0.4	0.05	0.15

Table 3:

Initial Probabilities
∏(Exon)=0.5
∏(Intron) = 0.5

Table 4:

SDEVelo parameters
a_A = 1.0 s
a_B = 0.25 s
b_A = 0.0005
b_B = 0.0005
c_A = 2.0 Ms^{-1}
c_B = 0.5 Ms^{-1}
β_A = 2.35 s^{-1}
β_B = 2.35 s^{-1}
γ_A = 1.0 s^{-1}
γ_B = 1.0 s^{-1}
$n_A = n_B = 3$
θ_A = 0.21 M
θ_B = 0.21 M
k_{PA} = 1.0 s^{-1}
k_{PB} = 1.0 s^{-1}
m_A = 2.35 s^{-1}
m_B = 2.35 s^{-1}
δ_{PA} = 1.0 s^{-1}
δ_{PA} = 1.0 s^{-1}
σ_{1A} = 0.05 $Ms^{-1/2}$
σ_{2A} = 0.05 $Ms^{-1/2}$
σ_{1B} = 0.05 $Ms^{-1/2}$
σ_{2B} = 0.05 $Ms^{-1/2}$
Initial concentration of unspliced mRNA A (pre mRNA)= 0.8 M
Initial concentration of unspliced mRNA

B (pre mRNA) = 0.8 M
Initial concentration of protein A = 0.8 M
Initial concentration of protein B = 0.8 M
Initial concentration of spliced mRNA A = 0.8 M
Initial concentration of spliced mRNA B = 0.8 M

Table 5:

ODE parameters
m_A=2.35 s^{-1} # max Transcription rate of Gene A
m_B=2.35 s^{-1} # max Transcription rate of Gene B
γ_A = 1 s^{-1} # mRNA A deg rate
γ_B = 1 s^{-1} # mRNA B deg rate
k_{PA} = 1.0 s^{-1} # Translation rate of Protein A
k_{PB} = 1.0 s^{-1} # Translation rate of Protein B
θ_A = 0.21 M # expression threshold Protein_A binding
θ_B = 0.21 M # expression threshold for Protein_B binding
n_A = 3 # Hill coefficient for $Protein_A$ (increased for stronger nonlinearity)
n_B = 3 # Hill coefficient for $Protein_B$ (increased for stronger nonlinearity)
δ_{PA} = 1.0 s^{-1} # Degradation rate of $Protein_A$
δ_{PB} = 1.0 s^{-1} # Degradation rate of $Protein_B$
Initial concentration of mRNA A = 0.8 M
Initial concentration of mRNA B = 0.8 M
Initial concentration of protein A = 0.8 M
Initial concentration of protein B = 0.8 M

2. (3 points) Consider the system below,

$$\frac{dx}{dt} = \alpha x - \beta xy$$

$$\frac{dy}{dt} = -\gamma y + \delta xy$$

Here x is concentration of a metabolite, y is concentration of an enzyme.

a) Abstracting the underling gene regulatory dynamics what would be your explanations for the above system of equations? Hint: take each term in the equations apart and explain what they imply
b) Carry out a stability analysis for, $\alpha = 2$, $\beta = 1.1$, $\gamma = 1$ and $\delta = 0.9$, x(0) = 1, y(0) =0.5
c) Plot the stream plot with equilibrium point and nullclines