

Thus, for P2,  $a = b = 0$ . It's unstable.

[3] for P3(0, 0, 0, 0), same as P2,  $a = b = 0$  and it's unstable.

## 3.2 HMC dynamics

In the second part here, with regard to the detailed behavior of mRNA and protein dynamics, we look into their momentum and numbers with 6 status(only the first 2(a)-2(c) and the last 2(d)-2(f) transition examples of the origin 3groups\*5transition statuses figures ) in all are studied detailedly while the whole data based on 15 status. As we only investigated the positive direction, the red ones(top left) the application on clinical data while green one(top right) in the larger scaled simulation with more transition status(blue dashed line is the predicted dynamics).Note that the persisters and normals are the roles they take in the whole process(considering from bifurcation to catastrophe and extinction) where here they can be all considered as promoters as their numbers both grows in this process until the last status as their interaction in constant environment is of our main interest as we mentioned before. Generally, with small change studied in one status, the trend is more significant than the larger scale transition. For instance, the green simulation are always more sensitive to the momentum change and shows them more significantly on the cell trajectory comparing to the red clinical transition(we manually break one clinical status into sub-status in simulations.)

Specifically, in the  $1 \rightarrow 2$  transition, the production of the  $HS_1$  is slightly faster than  $hax1$  with the accelerate from faster to slower as well as the  $hax1$ 's momentum decreases from fast to slow while  $HS_1$ 's momentum increases from fast to slow similarly. The larger scaled simulation show the trend similarly but with larger momentum difference and thus gives out the curve trajectory instead of straight line in the top left figure; On contrary, in  $2 \rightarrow 3$  transition,both the clinical application and larger simulation give totally the same behavior according to the dynamics , where proteins products faster than mRNA but with similar acceleration. Other transition can be similarly analysis. Note that from the  $4 \rightarrow 5$  of the larger scale simulation, there starts to show the switching where the protein changes into persisters with degradation instead of production which can be both detected from cell numbers figure in the top left and momentum figures in the right bottom although the fewer status contained clinical data does not show this behavior yet. In the last transition status, the switching of proteins becoming into persister is detected in both clinical process and simulation, where in the clinical data, the momentum change of proteins and mRNA are both linear process while in simulation, the momentum of the mRNA grows slightly from faster to slower and proteins degrade slightly from faster to slower as well and in the last short time, proteins go back to normals again which according to the rising number change in the top left and increase in the momentum both relatively to mRNA(left bottom) and absolutely (right bottom.))

In the second series of figures 2(c), 2(f), we compute the mean time to switch approximation with the solution based on mapping to their difference space where we choose the object as 1) single population of mRNA to the end of the transition(top left); 2) single population of proteins to the end of the transition (top right); 3) mRNA population to the end status of protein(left bottom) and 4) proteins population to the end status of mRNA.(right bottom.) There gives some different patterns, as in the  $1 \rightarrow 2$ , both the mRNA and proteins has the mean time to switch increase linearly with their number change while there exists one significantly longer time at 0.4 for the proteins compare to the final status of mRNA and one totally unstable transition recorded; In the  $2 \rightarrow 3$ , all the MTS increase linearly with the cell number growth; In the  $4 \rightarrow 5$ , as there exists the decrease of proteins thus there exists one negative MTS stands for the status; And in  $5 \rightarrow 6$ , the last status for the proteins again, compared to the final status where the number back to increase, the previous degradation status also leads to the minus MTS but positive to the mRNA as they both grow in the end.

In the last part, **Further application using the transition matrix of the model**, we compute some basic markov chain quantities based on the stochastic process as following with the pre-computation result(in availability):

## 3.3 Conclusion

In general, Hamiltonian markov chain advantage over the markov

The first step of the further computation of rewards of continuous Markov Chain is to prepare the matrix as follows: use conversion rate computed as transition rate in matrix R:  $R =$

$$\begin{bmatrix} 0 & ConvertRate1 & 0 & 0 & ConvertRate5 \\ ConvertRate1 & 0 & ConvertRate2 & 0 & 0 \\ 0 & ConvertRate2 & A & 0 & 0 \\ 0 & 0 & ConvertRate3 & 0 & 0 \\ 0 & 0 & 0 & ConvertRate4 & 0 \\ 0 & 0 & 0 & 0 & ConvertRate5 \end{bmatrix}$$

where  $A = ConvertRate1:5$ ;  $B = ConvertRate1:5$ ; we have:  $R =$

Then, we get the approximated marginal distribution by summation of R:  $E = sum(R)$ , and the embedded probability:  $Pemb = -\frac{R}{repmat(E', 6, 1)^T} + diag([E']) =$

$$\begin{bmatrix} 0.0095 & -0.9999 & 0 & 0 & -0.0001 & 0 \\ -0.9985 & 0.9649 & 0.0015 & 0 & 0 & 0 \\ 0 & -0.0658 & 0.0006 & -0.8680 & 0 & 0 \\ 0 & 0 & -0.0002 & 0.8680 & -0.9998 & 0 \\ 0 & 0 & 0 & -0.2309 & 0.1570 & -0.7691 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$Q = R + diag([E']) = \begin{bmatrix} 0.0095 & 0.0095 & 0 & 0 & 0 & 0 \\ 0.9634 & 0.9649 & 0.0015 & 0 & 0 & 0 \\ 0 & 0.0001 & 0.0006 & 0.0005 & 0 & 0 \\ 0 & 0 & 0.0002 & 0.8680 & 0.8678 & 0 \\ 0 & 0 & 0 & 0.0362 & 0.1570 & 0.1207 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$P_{unif} = eye(size(Q)) + \frac{Q}{max(E)} = \begin{bmatrix} 1.0095 & 0.0095 & 0 & 0 & 0 & 0 \\ 0.9634 & 1.9649 & 0.0015 & 0 & 0 & 0 \\ 0 & 0.0001 & 1.0006 & 0.0005 & 0 & 0 \\ 0 & 0 & 0.0002 & 1.8680 & 0.8678 & 0 \\ 0 & 0 & 0 & 0.0362 & 1.1570 & 0.1207 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

1) taking J0 = [0, 2], froms0tos4 :

$$Prob = P_{emb}(1, 5) * (exp^{(-E(1)*0)} - exp^{(-E(1)*4)}) = [0.0095, 0.9649, 0.0006, 0.8680, 0.1570, 1];$$

2) Prob(trueU[0, 2], 84) : stat = max(E) \* 2

n = 4;

ProbC = 0

FOR : i = 1 : n

$$ProbC = ProbC + exp(\frac{(-stat)*stat^i}{factorial(i)})$$

END

$$ProbC = ProbC * [0, 0, 0, 0, 1, 0]' = [0, 0, 0, 0, 0.8120, 0];$$

3) The number of cells expected after 6 time units have inactivated can be given by

$$Exp^C(s, X_c <= t) = \frac{1}{q} * \sum_{i=0}^{\infty} \exp^{(-qt)} * \frac{(qt)^i}{factorial(i)} * (P_{unif})^i * (q * P_{unif} * [1, 1, 1, 1, 1, 1]')$$

$$ProbC2 = 1.0e + 03 * \begin{bmatrix} 0.0487 & 0.0024 & 0 & 0 & 0 & 0 \\ 0.2475 & 0.2941 & 0.0094 & 0 & 0 & 0 \\ 0 & 0.0000 & 0.0464 & 0.000 & 0 & 0.0001 \\ 0 & 0.0001 & 0.0000 & 0.2555 & 0.2258 & 0.0393 \\ 0 & 0 & 0 & 0.0094 & 0.0704 & 0.0827 \\ 0 & 0 & 0 & 0 & 0 & 1.3212 \end{bmatrix}$$

$$ProbC2 = 1.0e+03 * [0.0526, 0.6184, 0.0471, 0.6051, 0.1983, 1.8000];$$

Thus, if we want to know:the status when after 6 unit times products mRNA cells over 1000 the only satisfied status is the last one which might product 1800 mRNAs.

chain random walk with its faster convergence. As in 2(g) and 2(h), the convergence(variation to mean) of the markov chain hamilton is in blue line and the red line for clinical data and simulation on more possible transition status, giving different convergence but similar phase interval(according to 2(i)), interestingly. The last status transition converge the worst followed by the fist transition. And the result simulated with more markov chain status converges better than the clinical results. And according to the convert rate, the mRNA to Protein transfer ratio should be the highest when starting, and goes especially lower in the last two status which is in assistance to the protein binding as we cut off the process around the convergence point where the two population has reached metastability  $F_M$ [5]. According to the simulation result, the protein has gone through the switching process changing from normals to persisters and back to normals(bursts in optimal time in 2(h) might also due to the switch.). Mean while, as the second population providing food(protein) to the other's binding site and either activate or deactivate it, it works as the extrinsic noise induced the excitability or inhibition of the other gene. Here, as we choose  $hax1$  and  $HS_1$ , they work as promoters for each others. One noticeable computation is the reward computation based on stochastic model selection which is useful in predict the possible status of the cell numbers easily with precomputation. And we can consider correct the transition matrix with simulated clinical tested results to improve the prediction as well. On the other hand, the most important calculation action potential is easier to be achieved through Hamilton as we proved with geometric minimum action and stochastic approximation. Other methods can cover