CS341 SYSTEMS BIOLOGY I

FINAL PROJECT

Recall the 7-state model of the mammalian circadian clock published by Becker-Weimann et al. (2004). The paper investigates the relative contributions of positive and negative feedback to oscillator performance. We will be using the model presented in this paper for our final investigation.

Your goal is to demonstrate your mastery of the topics in this course by understanding and analyzing this model. Each question relates to one topic.

1. The Project

(1) Kinetics and Motifs: Describe the kinetics used in this model. Be detailed. Be sure to include a discussion of gates (i.e. AND or OR gates). What is the basic network motif used in this model?

(2) Numerical Solvers: Write code to simulate the model using the published parameters. Follow the same coding conventions used for previous projects. Simulate the model and recreate Figure 3A of the paper.

(3) Numerical Solvers: Using the **tic/toc** operators, compare the time it takes to simulate the model using **ode23**, **ode45**, **ode23s**, and **ode15s**. Use a relative tolerance of 10^{-6}, an absolute tolerance of 10^{-8}, and an end "time" of at least 1000 hours. You should know that **ode23** is a low-order non-stiff (read "explicit") solver, **ode45** is a high-order non-stiff solver, **ode23s** is a low-order stiff (read "implicit") solver, and **ode15s** is a high-order stiff solver. Do your run-times makes sense given these descriptions? Explain your answer. From the relative differences in time, what can you conclude about the stiffness of the system?

(4) Sensitivity Analysis: Perform a sensitivity analysis of the model. You may decide what you want to find the sensitivity to (the state trajectories, the period, the amplitude of a given state, etc.). Discuss any clear similarities or stark contrasts with the results from Leloup & Goldbeter's 2004 JTB paper.

2. Extensions

To receive a grade higher than a B+, you will want to include at least one extension. Here are a few possible extensions:

- Apply the sensitivity analysis of Stelling et al (2004) to the mammalian model:
  - Consolidate the sensitivity information using the vector 2-norm. In other words, from your three-dimensional matrix, extract the information for a given parameter, reshape it into a vector, and call Matlab's **norm** function on it. That gives each parameter a scalar sensitivity measure.
  - Rank the parameters from most to least sensitive. In keeping with the analysis of Stelling et al. the rank should be 0 for the most sensitive and 1 for the least sensitive. In other words, if parameter i is the least sensitive, then its "raw rank" is 1 and if parameter j is the most sensitive, then its raw rank is N_p (where N_p is the number of parameters). To convert from raw rank to rank, use

    ```
    rank = (NP - raw_rank)/(NP-1);
    ```
  - Can you come to the same conclusions about this model as Stelling et al. came to regarding the fly clock models?
- Solve the sensitivity ODEs. If you choose to do this, you may request instructions and the Jacobian code from Stephanie.
- Sample parameter space and perform sensitivity analysis at each of the new parameter sets (but only for those parameter sets that cause the system to oscillate). Compute the sensitivity rankings for each parameter set. Use them to produce a figure like Figure 2 by Stelling et al. (2004).
- Reproduce figures from Becker-Weimann et al (2004). Be sure to include a discussion of your approach and the meaning of the figure.

References

S Becker-Weimann, J Wolf, H Herzel, and A Kramer, "Modeling Feedback Loops of the Mammalian Circadian Oscillator", *Biophys. J.*, 2004

J Stelling, ED Gilles, and FJ Doyle III, "Robustness properties of circadian clock architectures", *Proc. Natl. Acad. Sci*, 2004

J-C Leloup and A Goldbeter, "Modeling the mammalian circadian clock: Sensitivity analysis and multiplicity of oscillatory mechanisms", *J. theor. Biol.*, 2004.