

CS341 SYSTEMS BIOLOGY I

LECTURE 9

NEGATIVE FEEDBACK AND OSCILLATIONS

We have talked about simple signal cascades and feed-forward loops, and now it is time to get to my favorite loop - the negative feedback loop. We are going to implement one of the oldest and most important models of the circadian clock - that of Brian Goodwin.¹

This model was designed to examine oscillations in general and involves three biological entities: X, which causes Y to be produced, which causes Z to be produced, which, in turn, represses production of X.

There is a great description of by Gonze & Ruoff.²

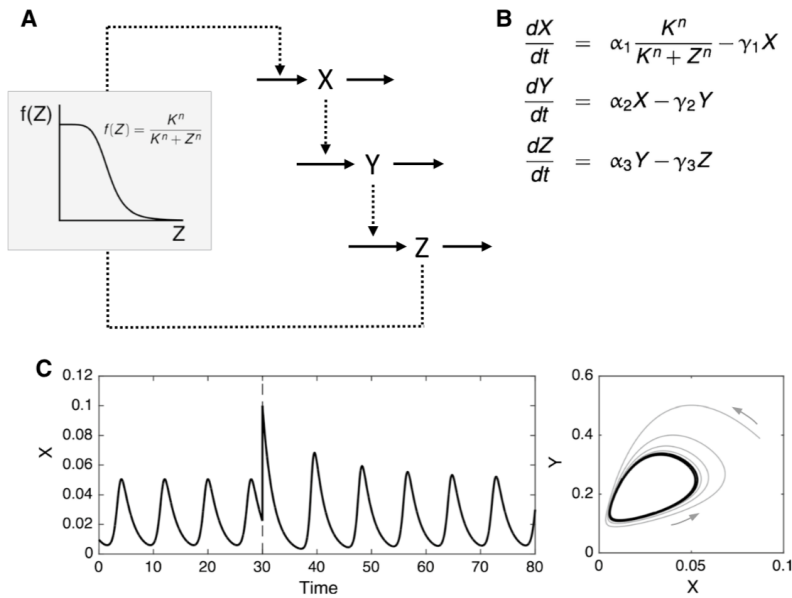


Fig. 2 (A) Scheme of the three-variable Goodwin model. (B) Equations of the Goodwin-Griffith three-variable model. (C) Limit cycle oscillations obtained by numerical integration of the model given in (B), for the following parameter values: $\alpha_1=5$, $\alpha_2=\alpha_3=5$, $\gamma_1=\gamma_2=\gamma_3=0.5$, $n=10$, $K=1$. At time $t=30$ the value of variable X is increased

¹B.C. Goodwin, Oscillatory behavior in enzymatic control processes, Adv. Enzym. Regul. 3 (1965)

²D Gonze & P Ruoff, The Goodwin Oscillator and its Legacy, Acta Biotheoretica, 2020

Goals for Today. Today, we will simulate the oscillator with two goals in mind

- Gain an intuition for how negative feedback can cause oscillations.
- Gain practical experience simulating until the limit cycle is found, so that we can analyze the stable oscillations.

Model Simulation. The dynamics can be explained like this: more X, means more Y, which means more Z, but more Z means less X. So there is a battle between X and Z. Such a battle can continue with stable oscillations (X is winning, then Z is winning, etc.) forever, if there is enough of a time delay between production of X and production of Z. For this model, it has been shown that a high Hill coefficient (> 8) is also necessary for sustained oscillations.

When this model is constructed with appropriate parameters (which basically just means the Hill coefficient is high enough), it is a limit cycle oscillator. A limit cycle oscillator is an oscillator that will approach one particular limit cycle (orbit, cycle, etc.), when a simulation begins at almost any initial condition. Circadian clock models (at least, ODE-based models) are almost always limit cycle models. Because they always return to the same cycle, even if there are temporary changes in parameters. This makes them good models for biological systems, that return to their usual behavior after a disturbance.

In the Jupyter Notebook, we implement the model, and simulate it from different initial conditions to watch it reach the same limit cycle. We also adjust the Hill coefficient to see what happens when it isn't large enough.