Project: Discrete Repressilator

(Reference: "A synthetic oscillatory network of transcriptional regulators", Elowitz and Leibler, *Nature* 2000.[1]) Suppose there is a gene called Y. The concentration of its product is denoted y, in units of proteins per cell, where y is measured in thousands. Suppose there are $y(i)$ proteins at minute i, and suppose that proteins are produced at a constant rate α_0 and degraded at a rate d. Then y obeys

$$y(i+1) = \alpha_0 - dy(i). \tag{1}$$

Now suppose that gene Y is repressed by the product of another gene X. Then y obeys

$$y(i+1) = \frac{\alpha}{1 + x(i-\tau)^n} + \alpha_0 - dy(i) \tag{2}$$

where α can be thought of as the repression strength, n is a coefficient[2] that controls the nonlinearity of X's effect on Y, and τ is a non-negative integer that introduces a time-delay. That is, the behavior of y at timepoint $i+1$ is sensitive to the concentration of x at some past timepoint, $i - \tau$. (This is a simplified way to account for the time required before Y "feels" the effect of X, due to processes such as transcription, translation, and gene regulatory processes).

Suppose $\alpha_0 = 1$ and $d = 0.1$. First consider only Model (1):

a. According to your intuition, what concentrations are *steady states*, meaning that if the concentration y had that value at time $i = 0$, then it would remain at that value?

b. Sketch your intuition for the population $y(t)$ from a starting population $y(0) = 0.2$.

Now consider Model (2), and suppose α=2 and $n = 4$ and $\tau = 3$:

c. Suppose (for the time being) that x is present at a constant concentration of 2. According to your intuition, what concentrations of y are steady states?

d. If x is not present ($x = 0$), according to your intuition, what concentrations of y are steady states?

Now consider the "repressilator" circuit. In this circuit, three genes X, Y, and Z are "wired" in a repressive cycle (each gene is repressed by the one upstream). Develop the equations to describe the concentrations of x, y, and z over time. Write code to solve the dynamical system, and answer the following questions:

e. Generate time series of the populations for a few starting populations $x(0), y(0), z(0)$. Does it match your intuition?

   - Hint: How to code it to deal with the time delay, especially at the beginning of the simulation?

f. Can you find a set of parameters and initial conditions that shows a damped oscillation?

g. Can you find a set of parameters and initial conditions that shows a persistent oscillation?

h. Can you find a set of parameters and initial conditions that shows no oscillation?

i. Can you find a set of parameters and initial conditions that shows the species oscillating in phase? Or, out of phase? Or any other types of behavior?

j. Choose one of the following parameters: α, τ, n. For your chosen parameter, investigate the behavior of the system for a range of parameter values. State in words the effect your parameter has on the system's oscillations. (Bonus challenge: Is there a neat and tidy way to graph your parameter's effect?)

[1] Note that the original work uses a continuous-time model.
[2] often called a *Hill coefficient*