Notes: For all problem sets in this course, you are encouraged to work in groups, but you must turn in your own assignment. Note any assumptions you make, and include all code and figures. Keep in mind that these assignments are designed to help you learn the mathematical sides of the course material. For any homework related questions, please email Honesty (honestyk@stanford.edu).

Problem 1: Short answers (10 pts)

a) How does varying the value n affect the Hill Equation?

b) We discussed in class how delays can cause oscillations in some genetic circuits. What are some potential sources of delays in biological systems?

c) What is one way to describe the synchrony of a group of phase oscillators?

d) Name at least four requirements for multicellularity. If you have more than four, or have requirements that weren't discussed in lecture, argue for their inclusion in your list.

e) What is a repressilator?

Problem 2: 1D dynamics (20 pts)

Consider a system where two oscillators which influence each other, such as the *her1,7* oscillators in the zebrafish tail. A simplified model is as follows, where θ_i are the phases of the two oscillators, ω_i are the natural frequencies, and α is the coupling strength:

$$\dot{\theta}_1 = \omega_1 + \alpha \sin(\theta_2 - \theta_1)$$
$$\dot{\theta}_2 = \omega_2 + \alpha \sin(\theta_1 - \theta_2)$$

a) Combine these two equations into one for the phase difference, $\phi = \theta_2 - \theta_1$. By rearranging the parameters, and *nondimensionalizing* time (i.e. rescaling time t into a dimensionless variable T), you can come up the following equation: $\frac{d\phi}{dT} = 1 - \mu \sin(\phi)$ where $\mu = \frac{2\alpha}{(\omega_2 - \omega_1)}$. Show the derivation and give an intuitive explanation for the meaning of μ. 3 pts.

b) Since we are considering ϕ as a phase, we now restrict our attention to just the interval $[0, 2\pi]$. Define $f(\phi) = \frac{d\phi}{dT}(\phi)$. In Matlab, plot graphs of $f(\phi)$ for $\mu = 0, 0 < \mu < 1$, and $\mu > 1$. Mark stable fixed points with a closed circle and unstable fixed points with an open circle. Give an intuitive explanation for what is happening in each case. Plot the fixed points on the vertical axis as a function of μ. Curves corresponding to unstable fixed points should be plotted as a dashed line. This is the *bifurcation diagram.* A Matlab template has been provided. 5 pts.

c) Linear stability analysis is a mathematical method (rather than graphical) to determine fixed point stability. By Taylor expanding $f(\phi)$ around a fixed point ϕ^*, one can show that a deviation $\delta\phi$ from the fixed point (i.e. $\phi = \phi^* + \delta\phi$) has a time-derivative $\frac{d\delta\phi}{dT}$ proportional to $\frac{df}{d\phi}|_{\phi^*}$.

(i) Prove this, and state what one can conclude about stability based on the sign of $\frac{df}{d\phi}|_{\phi^*}$. 4 pts.

(ii) Use this method to show which fixed points from part (b) (left or right) for ϕ are stable and which are unstable. 4 pts.

d) Using Matlab (template provided), plot θ_1 and θ_2 on the same axes for the four qualitatively different cases (ie. 4 figures – corresponding to $\mu = 0, 0 < \mu < 1, \mu > 1, \mu = \infty$ – with 2 curves each). Assume reasonable initial conditions and parameter values that satisfy the chosen value of μ. Referencing the original parameters, explain why the behavior of the system changes as it does when $\mu > 1$. 5 pts.

Problem 3: Numerical integration and Delay Equations (15 pts)

Consider a mechanical system, with a mass connected horizontally to the wall by a spring with constant κ. The entire system is submersed in fluid, so that there is a drag coefficient γ and a constant external force F. The equation for this system is:

$$m\ddot{x} + \gamma\dot{x} + \kappa x = F$$

a) Rewrite this system as a set of two equations by setting $\dot{x} = y$. 1 pts.

b) Using the starter code provided, numerically integrate the system using (i) Euler's method, (ii) 4th-order Runge-Kutta, and (iii) Matlab's ode45 function. Include plots of $x(t)$ and of y vs. x (phase space). See Numerical Recipes (Press et al.), chapter 17, for details on the Euler and Runge-Kutta methods. The constants are set as $F = 1, m = 2, g = 1, k = 3$. Note the initial conditions chosen. 5 pts.

c) Play around with the values of the parameters (use ode45). What qualitatively different types of behavior can you obtain? See *Nonlinear Dynamics and Chaos* (Strogatz), chapter 5, for a more in-depth discussion of two-dimensional linear systems. 4 pts.

d) Delay differential equations (DDEs), $\dot{x}(t) = f(x) + f(x(t - \tau))$, come up frequently in biological systems, but are significantly more difficult to analyze than standard ODEs. Matlab has a function `dde23` which numerically integrates such equations. For a single constant delay, the function call is:

```
dde23(xdot, tau, x0, [ti tf])
```

where `tau` is the delay time, `xdot` is a function handle for the derivative of x, `x0` is the value of x between $-\tau$ and 0, `[ti tf]` are the first and last time values to consider. **Note:** Unlike `ode45`, `dde23` takes a function handle that has **three** arguments:

```
xdot = @(t,y,z) some function...;
```

where `z` is the value $x(t-\tau)$. Use `dde23` to numerically integrate the function: $\dot{x} = \alpha x(t-\tau)$ Plot your results for $\tau = 1$ with values $\alpha = -\pi/8, -\pi/2, -3\pi/4, -\pi/4$. Note: no starter code is provided! 5 pts.

Problem 4: Synchrony and the segmentation clock (35 pts)

In the first problem set we analyzed two coupled phase oscillators, and determined under what conditions the two were phase-locked, or "synchronized." As we discussed in class, the situation becomes more complicated when there is a collection of many coupled oscillators in the presence of noise. A model governing equation for globally coupled oscillators can be written as:

$$\dot{\theta}_i = \omega_i + \alpha \sin(\langle\theta\rangle - \theta_i) + \zeta_i \tag{1}$$

a) Setting all ω_i equal, simulate $N = 100$ phase oscillators, specified in MATLAB as a vector $\vec{\theta}$, initialized to a uniform random distribution. Be sure to calculate the average $\langle\theta\rangle$ using the circular average. Plot the circular variance (synchrony) over time. Also plot the sine of the phases of all oscillators together on one plot. Describe what you see. Use $\alpha = .1$, and ζ a Gaussian distribution with mean $\mu = .1$ and standard deviation $\sigma = .1$ added to θ every time step (use $dt = .1$). (It is strongly recommended to write your solver for this problem – eg. using Euler's method – rather than using ode45. Note: no starter code is provided for Problem 4.) 10 pts.

b) Switch the sign of α to be negative, repeat the simulation, and generate the same types of graphs. What happens? Why? What happens if $N = 2$? Why? 5 pts.

c) For positive α, vary the mean and variance of ζ. Describe some of the behaviors you see, include some plots, and give an intuitive explanation of how the noise relates to synchrony. 5 pts.

d) We are now prepared to model the spatio-temporal production of zebrafish somites via travelling waves. To do so, consider the 100 oscillators not as randomly positioned in space, but rather along the anterior-posterior axis of a growing tail. Modify your simulation from earlier as follows:

1) Instead of being globally coupled, each oscillator is now coupled to its two neighbors: $\dot{\theta}_i = \omega_i + \alpha \sin(\theta_{i+1} - \theta_i) + \alpha \sin(\theta_{i-1} - \theta_i)$.

2) Instead of all ω_i being equal, they now have a global frequency profile (biologically determined by a gradient): $\omega_i = 1 - \exp(-i/\lambda)$, and set $\lambda = 20$.

3) Add a new oscillator with phase equal to the last to the end of the vector about 10 times per oscillation (does not have to be exact). When you do this, shift the ω gradient over by one to include the new oscillator, and stop simulating the anterior-most oscillators. Alternatively, this can be thought of as having a 100-oscillator 'active' simulation region with new oscillators being added at the posterior end which causes old oscillators to be pushed out of the 'active' region at the anterior end (i.e. frozen). The new oscillator phase can be set to the same phase as the previously posterior-most oscillator. Choose reasonable parameters as needed.

Plot the sine of the oscillators over space (not over time as was done earlier) for several time values to show the travelling waves and "freezing" of the anterior "segments." It may help to animate your simulation by re-plotting $\sin\theta$ every time step. The commands `drawnow` and `pause` may come in handy if you choose to do this. Include in your submission a few (eg. 5 – 10) such plots at various time points during the progress of your simulation. 15 pts.