Modeling recurrent epidemics

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So far, we've analyzed a simple SIR model that is useful for thinking about single epidemics. However, many of the infectious diseases that we are interested in persist at steady levels or generate recurrent epidemics in the population. What causes persistent disease, what causes recurrent epidemics? To answer these questions, let's think back to why an epidemic dies out in the simple model. Why does the number of infectious individuals start to decline? Because the number of susceptible individuals drops below a certain threshold. Therefore, for an infectious disease to persist beyond a single epidemic, the susceptible class needs to be replenished. How can this occur? Via births, immigration, loss of immunity or no immunity.

No immunity

Let's assume that we have a closed population but recovery from infection does not lead to immunity (e.g. rotaviruses), so an individual can be infected multiple times during their lifetime. We can write down the following simple model for the rate of change of the number of susceptible individuals (S) and the number of infectious individuals (I):

$$\frac{dS}{dt} = -\beta\frac{I}{N}S + \gamma I \tag{1}$$

$$\frac{dI}{dt} = \beta\frac{I}{N}S - \gamma I\ . \tag{2}$$

Notice that the transmission term is proportional to $\frac{I}{N}S$ and not IS. This assumption - that the rate at which susceptibles become infectious is proportional to the fraction infectious rather than the absolute number infectious - is known as *frequency-dependent* transmission. In the models we've looked at previously, this can be thought of as just a rescaling of the parameter $a(=\frac{\beta}{N})$, because N is assumed

constant. However, for most human infectious diseases this assumption is biologically motivated. For example, consider two populations of different sizes: say 1000 and 100,000. If one infectious individual is introduced to each population would you expect the rate at which a susceptible individual in each population becomes infected to be the same? Not unless contact rate scales with population size. If contact rate is independent of population size - no matter where I live, on average, I experience the same number of contacts per unit time - then frequency-dependent transmission is the appropriate term.

Also notice that we can simplify these equations even further! The total population size, N, is just the sum of S and I. Therefore, $S = N - I$, and after substitution, we obtain

$$\frac{dI}{dt} = \beta \frac{I}{N}(N - I) - \gamma I = \beta I(1 - \frac{\gamma}{\beta} - \frac{I}{N}) \, . \tag{3}$$

This equation is equivalent to the equation for logistic growth that describes density-dependent population growth in ecology. You can actually solve this equation analytically (it's the only relevant model of infectious disease where this is possible)! But we don't have to solve it directly to understand the dynamics.

What are the possible equilibria? $I_1^* = 0$ (disease-free state) and $I_2^* = N(1 - \frac{\gamma}{\beta})$ (endemic state). We would like to know the conditions under which the disease persists? First, let's ask when the second equilibrium is positive (because if it's negative, it's not a biologically-feasible state): if $1 > \frac{\gamma}{\beta}$ or $R_0 = \frac{\beta}{\gamma} > 1$. Assuming $R_0 > 1$, let's sketch $\frac{dI}{dt}$ as a function of I (see Figure 1). The equilibria are just the zeros of this equation (i.e. solutions of $\frac{dI}{dt} = 0$). To find out whether the solution moves toward or away from these points, let's consider where $\frac{dI}{dt}$ is positive and negative. If $\frac{dI}{dt} > 0$, then I is increasing so the solution moves to the right, if $\frac{dI}{dt} < 0$, then I is decreasing so the solution moves to the left. Inspecting the graph, if $I > 0$ initially, $I \to N(1 - \frac{1}{R_0})$ as $t \to \infty$. Importantly, what do you notice about the slope of $\frac{dI}{dt}$ at a stable equilibrium? At an unstable equilibrium? It turns out that we can determine local stability of an equilibrium by determining the slope of the rate of change at that point. Moreover, this generalizes to systems of equations, as we shall see later.

Try This Check these qualitative results by finding the exact solution for any non-zero initial condition I_0. This model explains what might cause persistent levels of disease but does not give us any insight into recurrent epidemics...

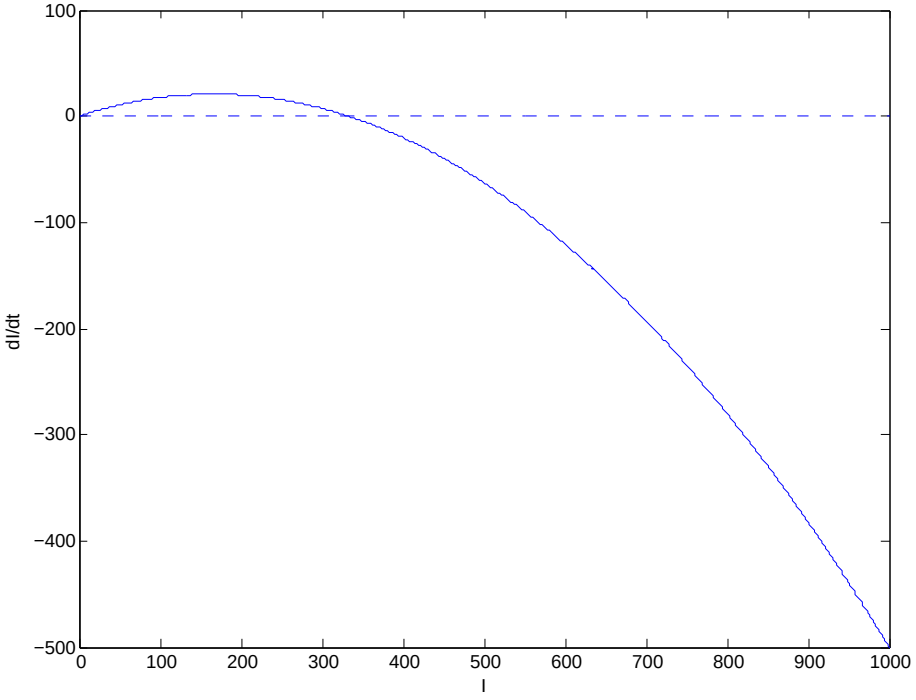

Figure 1: $\frac{dI}{dt}$ as a function of I, with $\beta = 0.75$ day^{-1} and $\gamma = 0.5$ day^{-1}.

Adding demography

Let's go back to the simple SIR model, and consider how disease can persist when infection confers permanent immunity (e.g. measles). We'll still consider a closed population but now take into account births and deaths:

$$\frac{dS}{dt} = \nu N - \beta S\frac{I}{N} - \mu I \tag{4}$$

$$\frac{dI}{dt} = \beta S\frac{I}{N} - \gamma I - \mu I \tag{5}$$

$$\frac{dR}{dt} = \gamma I - \mu R\,, \tag{6}$$

where ν is the per capita birth rate and μ is the per capita death rate. For many developed nations, births are approximately equal to deaths. For the purposes of our analysis we'll assume that $\nu = \mu$, so that $N = S + I + R$ remains constant and the dynamics are determined entirely by the equations for S and I. In fact, for frequency-dependent transmission, even if $\nu > \mu$, we can show that the proportion in each class is exactly determined by the same dynamics (where μ would be interpreted as the birth rate). To explore the dynamics of this model, we'll begin by finding the equilibria, and then investigate their stability using phase plane and linear stability analysis. Again there are two equilibria: one disease-free and one where disease persists. These are

$$S_1^* = N,\ I_1^* = 0 \quad \text{and} \quad S_2^* = N\frac{1}{R_0},\ I_2^* = N\frac{\mu}{\gamma+\mu}\left(1 - \frac{1}{R_0}\right)$$

where $R_0 = \frac{\beta}{\gamma+\mu}$. Note that the endemic equilibrium only exists if $R_0 > 1$, otherwise $I_2^* < 0$. Before we consider the general case, let's graph the direction field and a phase plane trajectory for a specific set of parameter values (see Figure 2). We notice that trajectories spiral into the endemic state. Is the endemic state always stable? We can extend the ideas that we motivated with the SIS model above to determine the stability of equilibria in systems of equations. We present the theory for n-dimensional systems and then demonstrate the theory for the SIR model given above.

Let's assume we have n variables of interest, x_i $(i = 1, 2, \ldots, n)$, the dynamics of which are governed by n coupled ordinary differential equations:

$$\frac{dx_i}{dt} = f_i(x_1, x_2, \ldots, x_n) \quad i = 1, 2, \ldots, n\,. \tag{7}$$

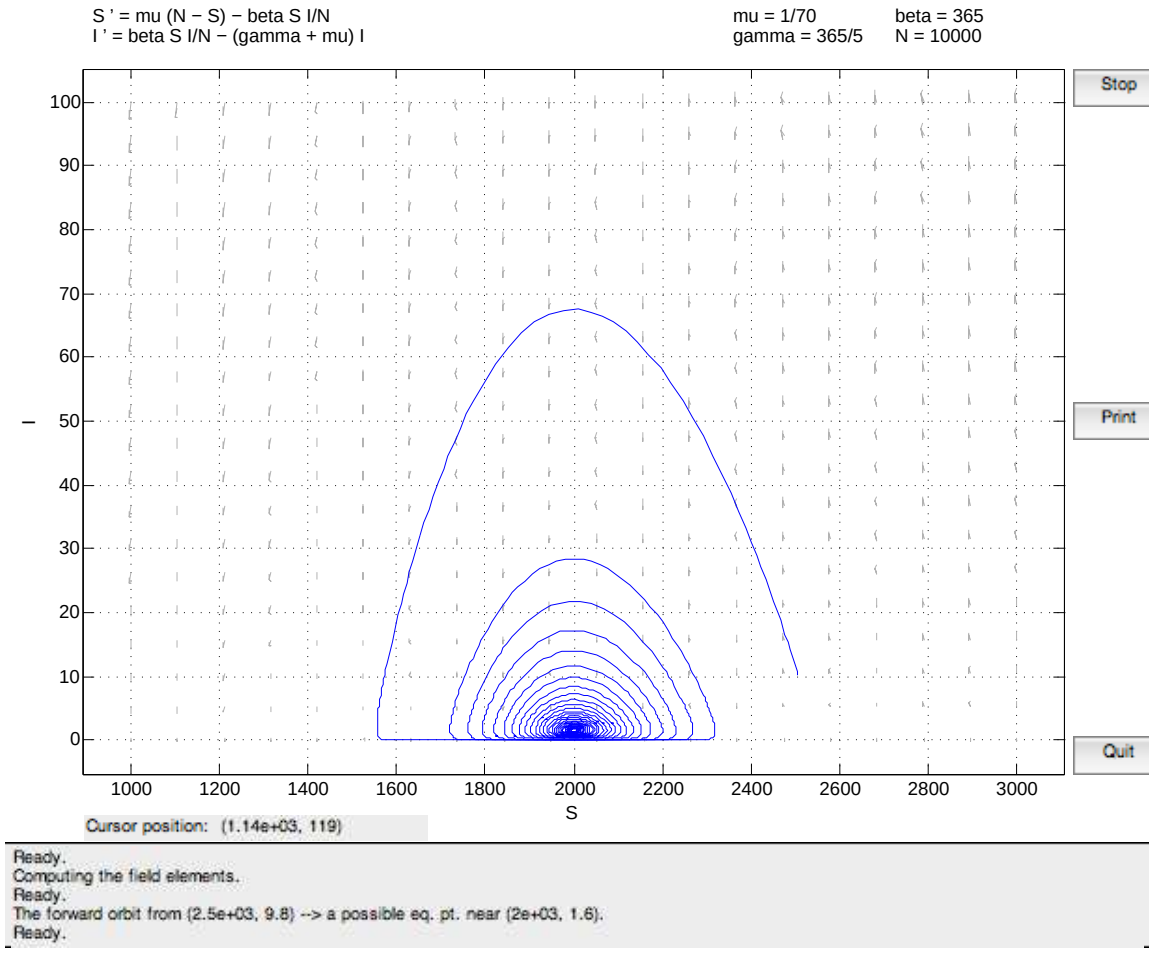

Figure 2: Phase portrait of the SIR model with demography using `pplane8.m`. The parameter values are $\beta = 365$ year^{-1}, $\gamma = 365/5$ year^{-1}, $\mu = 1/70$ year^{-1} and $N = 10000$.

Equilibria of this system satisfy

$$\frac{dx_i}{dt} = f_i(x_1^*, x_2^*, \ldots, x_n^*) = 0 \; . \tag{8}$$

We know that if the system is at equilibrium, then it will remain at equilibrium (by definition). But what happens if we apply a small perturbation? Does the system move toward or away from equilibrium? We're asking whether this small perturbation grows or decays with time. To investigate this we make the substitutions $x_i = x_i^* + \epsilon_i$ in equation 7 and explore the dynamics of ϵ_i over time:

$$\frac{d\epsilon_i}{dt} = f_i(x_1^* + \epsilon_1, x_2^* + \epsilon_2, \ldots, x_n^* + \epsilon_n) \quad i = 1, 2, \ldots, n \; . \tag{9}$$

Approximating f_i using Taylor series, noticing that $f_i(x_1^*, x_2^*, \ldots, x_n^*) = 0$ by definition, and neglecting terms above order 1 (because ϵ is small), we arrive at the following system of *linear* differential equations, which are valid close to the equilibrium point:

$$\frac{d\epsilon_i}{dt} = \left.\frac{\partial f_i}{\partial x_1}\right|_{\boldsymbol{x^*}} \epsilon_1 + \left.\frac{\partial f_i}{\partial x_2}\right|_{\boldsymbol{x^*}} \epsilon_2 + \cdots + \left.\frac{\partial f_i}{\partial x_n}\right|_{\boldsymbol{x^*}} \epsilon_n \quad i = 1, 2, \ldots, n \; . \tag{10}$$

In matrix notation this can be re-written as

$$\frac{d\boldsymbol{\epsilon}}{dt} = \boldsymbol{J}(\boldsymbol{x^*})\boldsymbol{\epsilon} \tag{11}$$

where $\boldsymbol{\epsilon} = (\epsilon_1, \epsilon_2, \ldots, \epsilon_n)^T$, $\boldsymbol{x^*} = (x_1^*, x_2^*, \ldots, x_n^*)$, and $\boldsymbol{J}$ is a matrix known as the *Jacobian* with (i, j)th element equal to $\frac{\partial f_i}{\partial x_j}$. If we can solve this system of equations, we can determine whether the perturbation grows or decays, and consequently whether the equilibrium is unstable or stable. It turns out that we can exactly solve these equations, and the solution is related to the eigenproblem that you may have met in linear algebra. The general form of these solutions (assuming n distinct eigenvalues) can be written as

$$\boldsymbol{\epsilon} = c_1\boldsymbol{v_1}\exp(\lambda_1 t) + c_2\boldsymbol{v_2}\exp(\lambda_2 t) + \cdots + c_n\boldsymbol{v_n}\exp(\lambda_n t)$$

where the c_i are constants (determined by initial conditions) and λ_i and $\boldsymbol{v_i}$ are the eigenvalues and corresponding eigenvectors of the Jacobian matrix evaluated at the equilibrium. Under what conditions does $\boldsymbol{\epsilon} \to 0$ as $t \to \infty$, which implies that the equilibrium is stable? If the real parts of *all* the eigenvalues are negative. Therefore, what matters for stability analysis is calculation of the eigenvalues of $\boldsymbol{J}$.

Let's demonstrate these ideas by applying them to the SIR system of equations (4,5). We've already calculated the equilibria, so we now need to construct the Jacobian:

$$\boldsymbol{J} = \begin{pmatrix} -\beta\frac{I}{N} - \mu & -\beta\frac{S}{N} \\ \beta\frac{I}{N} & \beta\frac{S}{N} - \gamma - \mu \end{pmatrix} . \tag{12}$$

First, let's investigate the equilibrium ($S_1^* = N$, $I_1^* = 0$). We evaluate the Jacobian at this point:

$$\boldsymbol{J}(N,0) = \begin{pmatrix} -\mu & -\beta \\ 0 & \beta - \gamma - \mu \end{pmatrix} . \tag{13}$$

To find the eigenvalues of this matrix, we need to solve

$$\det(\boldsymbol{J}(N,0) - \lambda\boldsymbol{I}) = 0 .$$

This leads to a quadratic equation in λ:

$$(-\mu - \lambda)(\beta - \gamma - \mu - \lambda) = 0$$

which has two solutions, $\lambda = -\mu < 0$, and $\lambda = \beta - (\gamma + \mu)$. For this equilibrium to be stable, we need to ensure both eigenvalues are negative, so the stability criterion becomes $\beta < \gamma + \mu$, which is equivalent to $R_0 < 1$. Conversely, the disease-free equilibrium is unstable if $R_0 > 1$.

So how does the model behave if $R_0 > 1$?

Try this

1. Solve the system of equations numerically using Matlab's Runge-Kutta ODE solver (with adaptive time steps) `ode45` for different values of $R_0(> 1)$ and γ. How do these two parameters impact the period of the damped oscillations?

2. Carry out the linear stability analysis for the endemic equilibrium. You should find that the eigenvalues are given by

$$\lambda = \frac{1}{2}\left(-\mu R_0 \pm \sqrt{(\mu R_0)^2 - \frac{4}{AG}}\right)$$

where $A = \frac{1}{\mu(R_0-1)}$ denotes the average age at infection and $G = \frac{1}{\gamma+\mu}$ determines the average realized duration of infectiousness. Often $(\mu R_0)^2$ is small enough to ignore and so

$$\lambda \approx -\frac{\mu R_0}{2} \pm \frac{i}{\sqrt{AG}} .$$

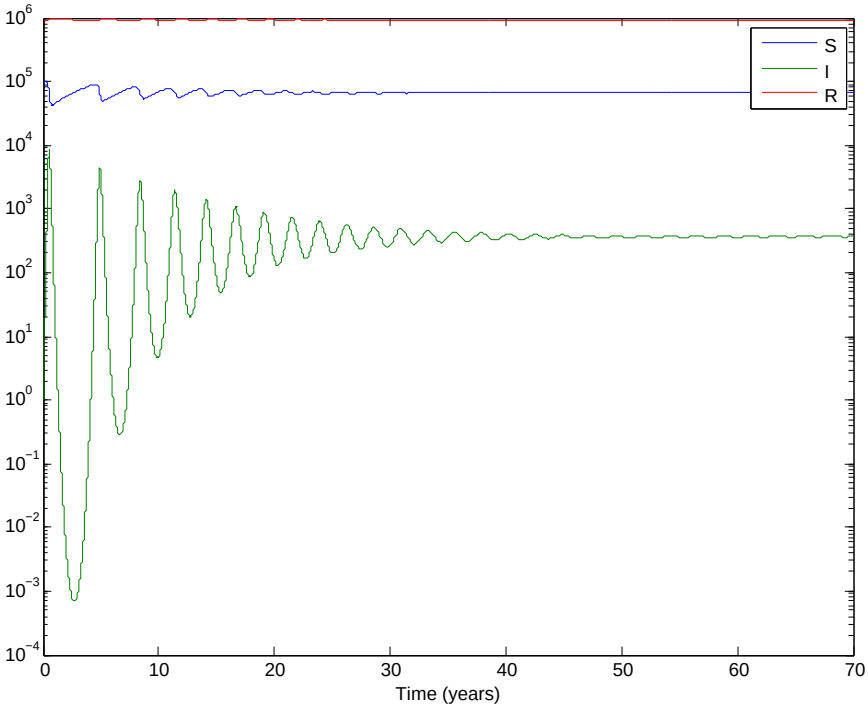

Figure 3: Numerical solution of the SIR model with demography using `ode45`. The parameter values are $R_0 = 17$, $\gamma = 365/10$ year^{-1}, $\mu = 1/70$ year^{-1}, $\beta = R_0(\gamma + \mu)$, and $N = 1000000$. Initial values are $S(0) = 100000$, $I(0) = 1$ and $R(0) = N - S(0) - I(0)$.

The fact that these are complex eigenvalues, tells us that the equilibrium is approached via oscillatory dynamics. The period, T, of these damped oscillations is determined by the inverse of the complex part multiplied by 2π, so $T \approx 2\pi\sqrt{AG}$. Does this agree with what you found numerically?

In summary, if $R_0 > 1$, the disease can persist, and although it undergoes transient oscillations, these eventually dampen out.

This model cannot fully explain recurrent epidemics because it does not generate sustained oscillations. We are going to explore two modifications that can generate sustained oscillations. First, we are going to consider a simple modification to the deterministic model proposed here, and later we will consider a stochastic model.

Seasonality

To motivate this section, let's consider the transmission rate β in more detail. This parameter is actually a product of contact rate and the probability of transmission if an infectious individual comes into direct contact with a susceptible individual. In the simple models that we've looked at, these processes are assumed constant in time, but there is good evidence that either of these processes might vary seasonally. What are some causes of seasonality in transmission rate? Aggregation of children during the school term, environmental effects on pathogen transmission, etc.

We will consider the behavior of the simple SIR model with demography when β varies seasonally. For convenience, we will assume that β is described by a cosine function, but if we have data on, for example, school terms, we could easily use a function that mimics the opening and closing of schools. Our model now looks like the following

$$\frac{dS}{dt} = \mu N - \beta(t) S \frac{I}{N} - \mu I \tag{14}$$

$$\frac{dI}{dt} = \beta(t) S \frac{I}{N} - \gamma I - \mu I \ , \tag{15}$$

where $\beta(t) = \beta_0(1 + \beta_1 \cos(2\pi t))$. If $\beta_1 = 0$ then we are back to our non-seasonally forced model. However, if $\beta_1 \neq 0$ then there are no equilibria because the parameter β varies with time.

Try this

1. Numerically integrate this model (using `ode45`) to investigate the behavior of solutions as you vary β_1 from 0 to 0.25. Use the same parameters and initial conditions as in Figure 3. Choose $\beta_0 = \beta$.

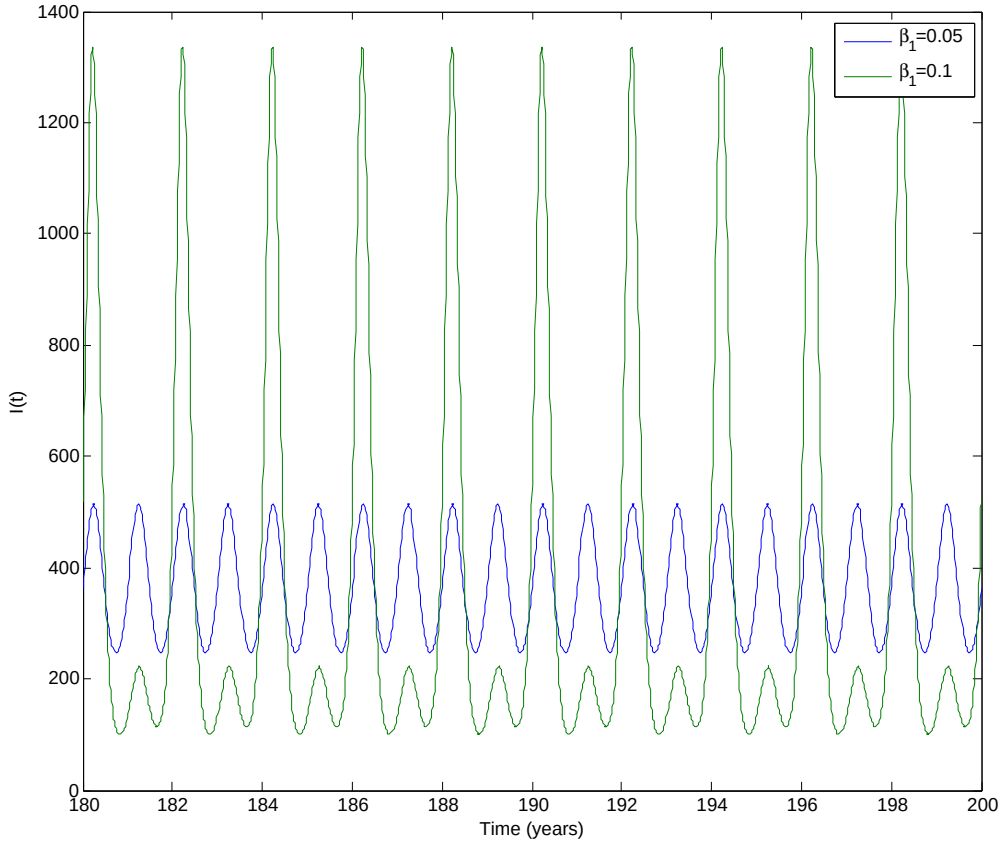

Figure 4: Numerical solution of the SIR model with demography and seasonal transmission using `ode45` for two different values of β_1. The parameter values are $R_0 = 17$, $\gamma = 365/10$ year^{-1}, $\mu = 1/70$ year^{-1}, $\beta_0 = R_0(\gamma + \mu)$, and $N = 1000000$. Initial values are $S(0) = 100000$, $I(0) = 1$ and $R(0) = N - S(0) - I(0)$.

2. **Challenge!** You should find that the period of the sustained oscillations changes as the amplitude of the forcing increases. Now, let's look at this systematically by constructing a *bifurcation diagram* for β_1. A bifurcation diagram summarizes qualitative changes in model behavior (in this case, cycle period) as a parameter is varied. How might you (crudely) measure the approximate periodicity of the oscillations? Think about how to sample the output at a yearly interval. Then plot this output against β_1, for multiple values of β_1 from 0 to 0.25.