1. Type 1 or juvenile diabetes is a very dangerous disease caused by an autoimmune response to the β-cells in the pancreas. The earlier the diagnosis of the disease, the better the chances of controlling it with insulin and helping the subject live longer. One simple test for diagnosis is the glucose tolerance test (GTT), where the subject ingests a large amount of glucose (1.75 mg/kg body wt) then has his or her blood monitored for about 6 hours following the glucose administration. Ackerman *et al* [1] created a simple mathematical model for glucose and insulin regulation that was described in class and simplified to the equation

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + \omega_0^2 g = F(t), \tag{1}$$

where $g(t)$ is the variation in the blood glucose level (in mg/dl of blood) around the equilibrium value, α and $\omega_0 = \sqrt{\omega^2 + \alpha^2}$ are key parameters that are determined from the blood monitoring, and $F(t)$ is basically a δ function representing the large dose of glucose given initially in the GTT after the subject has fasted. In class, we showed the blood glucose level could be given by the equation

$$G(t) = G_0 + Ae^{-\alpha t}\cos(\omega(t-\delta)).$$

Experimental testing of this model showed that the parameter α varied from subject to subject, so was not a good predictor of diabetes. However, the parameter ω_0 was quite robust and proved a good indicator of diabetes. In particular, healthy individuals satisfied $2\pi/\omega_0 < 4$, while the reverse inequality indicated diabetes. Consider the data below from a couple of patients. Find the best fitting parameters in the equation for $G(t)$, then determine if the data came from a normal or a diabetic patient. Write the sum of square errors between the data and the model.

t (hr)	$G_1(t)$ mg/dl	$G_2(t)$ mg/dl
0	75	105
0.5	160	190
0.75	180	205
1	155	225
1.5	95	200
2	75	185
2.5	65	110
3	80	100
4	85	85
5	80	90

2. According to a famous diabetologist, the blood glucose concentration of a nondiabetic who has just absorbed a large amount of glucose will be at or below fasting level in 2 hours or less.

a. The deviation $g(t)$ of a patient's blood glucose concentration from its optimal concentration satisfies:

$$\frac{d^2g}{dt^2} + 2\alpha\frac{dg}{dt} + \alpha^2 g = 0,$$

immediately following absorbtion of a large amount of glucose, where t is in minutes. Show that this patient is normal according to Ackerman *et al*, if $\alpha > \pi/120$ (min), and that this patient is normal according to the famous diabetologist if

$$g'(0) < -\left(\frac{1}{120} + \alpha\right) g(0).$$

b. Suppose that a patient's blood glucose concentration $G(t)$ satisfies the initial value problem:

$$\frac{d^2G}{dt^2} + 0.05\frac{dG}{dt} + 0.0004G = 0.03,$$

$$\begin{aligned} G(0) &= 150(\text{mg glucose}/100 \text{ ml blood}) \\ G'(0) &= -\alpha G(0)/(\text{min}); \qquad \alpha > 0.02042 \end{aligned}$$

immediately after fully absorbing a large amount of glucose. Is this patient diabetic according to Ackerman *et al*? Explain. Is this patient diabetic according to the diabetologist? Explain.

3. Consider the reduced 3-D model for diabetes in NOD mice by Mahaffy and Edelstein-Keshet [2].

$$\begin{aligned} \frac{dA}{dt} &= (\sigma + \alpha_1 M)f_1(p) - (\beta + \delta_A)A - \epsilon A^2, \\ \frac{dM}{dt} &= \beta 2^{m_1} f_2(p)A - f_1(p)\alpha_2 M - \delta_M M, \\ \frac{dE}{dt} &= \beta 2^{m_2}(1 - f_2(p))A - \delta_E E, \end{aligned}$$

where

$$p \approx (RB/\delta_p)E,$$

and

$$\begin{aligned} f_1(p) &= \frac{p^n}{k_1^n + p^n}, \\ f_2(p) &= \frac{a{k_2}^m}{k_2^m + p^m}. \end{aligned}$$

You are given the following parameter values:

$$\sigma = 0.02 \quad \alpha = 20 \quad \beta + \delta_A = 1 \quad \epsilon = 1 \quad k_1 = 2 \quad n = 2$$

and

$$\beta 2^{m_1} = 1 \quad a = 0.7 \quad k_2 = 1 \quad m = 3 \quad \alpha_2 = 2 \quad \delta_M = 0.01 \quad \beta 2^{m_2} = 0.1 \quad \delta_E = 0.3.$$

Also, let

$$R = 50 \quad B = 1 \quad \delta_p = 1.$$

a. Find all equilibria for this system of differential equations. Find all eigenvalues at each of the equilibria. Discuss the stability of the equilibria.

b. Simulate this system showing trajectories starting near each of the equilibria.

c. Perform a crude sensitivity analysis by examining the changes in behavior by changing each of the following parameters by $\pm 10\%$.

$$n, \qquad a, \qquad \text{and} \qquad \delta_p.$$

See how these changes affect your trajectories in the simulation and how the eigenvalues change at your equilibria.

[1] Ackerman, E., Rosevear, J. W., and McGuckin, W. F. (1964). A mathematical model of the glucose tolerance test, *Phys. Med. Biol.*, **9**, 202-213.

[2] Mahaffy, J. M. and Edelstein-Keshet, L., Modeling cyclic waves of circulating T cells in autoimmune diabetes, *SIAM J. Appl. Math.*, **67**, 915-937 (2007).