BME 7410 Final Exam
December 17, 2021
100 points total

1. (20 points) **Numerical quadrature and pharmacokinetics**
In the field of pharmacokinetics, the area under the curve (AUC) is the area under the curve in a plot of concentration of drug in plasma against time. In real-world terms the AUC represents the total amount of drug absorbed by the body, irrespective of the rate of absorption. This is useful when trying to determine whether two formulations of the same dose (for example a capsule and a tablet) release the same dose of drug to the body. Another use is in the therapeutic monitoring of toxic drugs. For example, gentamicin is an antibiotic which displays nephro- and ototoxicities; measurement of gentamicin concentrations in a patient's plasma and calculation of the AUC is used to guide the dosage of this drug.

    a) Suppose you want to design an experiment to calculate the AUC in a patient over a four-hour period, using a four-point Gaussian quadrature. At what times (starting the experiment at $t = 0$) should you make the plasma measurements? Show your work.
    b) Now redesign the experiment, to obtain plasma measurements appropriate for using an eight-panel Simpson's rule quadature.
    c) Which of the two numerical integration schemes would be more appropriate for an adaptive quadrature routine? Explain.

    Weights and nodes for the Gaussian four-point rule:

x_i^*	w_i^*
±0.8611363…	0.3478548…
±0.3399810…	0.6521452…

2. (20 points) **Nonlinear regression of chemical reaction data**
In your laboratory course there is an experiment examining the reaction kinetics of an NaOH:phenolphthalein reaction. The extent of reaction is measured using a colorimeter, where the absorbance is proportional to the concentration of the phenolphthalein. The purpose is to measure the reaction rate constant K at different temperatures and NaOH concentrations to learn something about the reaction mechanism. In the experiment you measure absorbances A_i at times t_i. The absorbances should fit an exponential rate law:

$$A = C_1 + C_2 e^{-Kt}$$

    where C_1, C_2, and K are unknown constants.

    a) Write a Matlab function that can be fed into the built-in function `fminsearch` to perform a nonlinear regression for the unknown constants.
    b) Now suppose that you obtain a solution, but you suspect that the `fminsearch` routine may be getting stuck in a local minimum that is not the most accurate solution. How would you test this?

3. (35 points) **ODE integration and receptor binding kinetics**
Consider simple monovalent receptor/ligand binding on a cell surface:

$$R + L \underset{k_r}{\overset{k_f}{\rightleftarrows}} C$$

C represents the concentration of receptor (R) – ligand (L) complex, and k_f and k_r are the forward and reverse reaction rates, respectively. If we assume that the ligand concentration remains constant at L_0, the following differential equation governs the dynamics of C:

$$\frac{dC}{dt} = k_f \left[R_T - C\right] L_0 - k_r C$$

Where R_T is the total number of receptor molecules on the cell surface.

a) Determine the numerical stability of this differential equation by calculating the Jacobian. Supposing that we are interested in studying the binding of fibronectin receptor to fibronectin on fibroblast cells ($R_T = 5 \times 10^5$ sites/cell, $k_f = 7 \times 10^5$ $M^{-1}min^{-1}$, $k_r = 0.6$ min^{-1}), show the range of ligand concentrations L_0 for which this differential equation is stable.
b) For a ligand concentration of $L_0 = 10^{-4}$ sites/cell, an initial condition of $C(t=0) = 0$, and a time step of 0.1 min, perform the first two iterations of a numerical integration using a four-stage Runge-Kutta scheme. If you do not remember the Runge-Kutta rules, you may use the Euler method for partial credit.

4. (25 points) **Single factor ANOVA test of experimental cancer data**
Two experimental anti-cancer drugs (Neurohib, Mitostop) were tested against a control treatment for their ability to reduce the growth of brain tumors over a three month period. The raw data of tumor diameters (in mm) are given below:

Control	**Neurohib**	**Mitostop**
7	4	1
8	5	2
10	7	4
11	8	5

Perform a single factor ANOVA test to determine whether there is a statistically significant difference among these three groups, at the 0.05 level of significance. If you decide to reject the null hypothesis of "no difference" then perform the pairwise *t*-test comparisons to determine exactly which samples differ from each other. For your multiple comparisons after ANOVA, you should set the overall probability of making a Type I error at 0.05.