Project 2

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Some contents have been redacted from this version.

1 Physical Significance, Application, and What I've Learned

In this project, we modeled the size of a tumor within a petri dish over a span of time, subject to a certain dosage and timing of a drug with a known efficacy. This required approximating a solution to a nonlinear system of differential equations. Then, we minimized a cost function for the dosage and timing of the drug, under certain constraints, which was also dependent on the solution to the system. Plots demonstrated that the optimized parameters decreased the growth rate of the tumor, but were unable to eradicate it.

The two main components of solving this problem, solving a nonlinear system of differential equations and optimizing a multivariable cost function dependent on a unique solution of the former, would be incredibly difficult, perhaps even impossible, to solve analytically. For the first component, we were able to implement our own numerical method, but for the second, we had to call a function already defined within Matlab. In real-world applications, numerical methods which we have learned may be implemented in predefined functions like this. Nevertheless, there is still value in learning them, to better understand their behavior and limitations.

This project demonstrates a clear, albeit simplified, application of class concepts to improving cancer treatments. However, optimization of a function dependent on a nonlinear system of differential equations has a wide range of applications beyond oncology. Many real-world problems can be modeled with differential equations, because they relate to physical laws or are otherwise more intuitive to formulate. For example, fluid mechanics, dynamics, thermodynamics, and population models can all entail differential equations. Inevitably, some of these models are going to involve systems of equations, perhaps nonlinear ones, and perhaps there will be an associated cost function to be minimized or a benefit function to be maximized, on the basis of certain parameters. As in this case, such problems may be most effectively solved with numerical methods.

This problem has some degree of personal signifiance. Back in 2010, my mother was diagnosed with cancer. She received a transplant and has been

clear of cancer for the past decade. In the period between diagnosis and surgery, she underwent chemotherapy and radiation treatments. As was the case with the drug in our project, these treatments weren't enough to eliminate the tumor. Nevertheless, since transplant waiting lists can be quite long, optimizing treatments to slow down tumors is incredibly valuable.

From this project, I've learned to appreciate the value of crossing disciplines to solve problems. While, in deveoping a real-world treatment, real-world clinical trials would be necessary for effectiveness and saftey, computer models such as this one could be used as an aid to better understand the problem and develop solutions. Sych an enhancement, enabling more effective treatments to be developed sooner, would certainly have a meaningful impact, increasing both the quantity and quality of countless lives.

2 Answers to Problems 1, 2, and 3

For this project, we are given the following system of differential equations and cost functions.

$$\begin{cases} \dfrac{\mathrm{d}g}{\mathrm{d}t} = \lambda_{\mathrm{p}} g(1-g) - \lambda_{\mathrm{a}} g - \lambda_{\mathrm{k}} g f \\ \dfrac{\mathrm{d}f}{\mathrm{d}t} = -\lambda_{\mathrm{d}} f + p \\ p(t) = \displaystyle\sum_{i=1}^{N_{\mathrm{treat}}} \frac{\delta_i}{\sigma\sqrt{2\pi}} e^{-\frac{(\tau_i - t)^2}{2\sigma_2}} \end{cases}$$

$$J(\boldsymbol{\delta}) = \boldsymbol{\delta} \cdot \boldsymbol{\delta} + a g(T) + b \int_0^T g(t)\,\mathrm{d}t$$

$$J_{\mathrm{new}}(\boldsymbol{\delta}, \boldsymbol{\tau}) = \boldsymbol{\delta} \cdot \boldsymbol{\delta} + a g(T) + b \int_0^T g(t)\,\mathrm{d}t + c \int_0^T f(t)\,\mathrm{d}t$$

- g: volume fraction of cancer cells
- f: volume of drugs
- p: total rate at which drugs are introduced as a function of time
- λ_{p}: instantaneous proliferation rate of cancer cells
- λ_{a}: instantaneous apoptosis rate of cancer cells
- λ_{k}: instantaneous kill rate of cancer cells by a given volume of drug
- λ_{d}: instantaneous decay rate of drug
- $\boldsymbol{\delta}$: set of dosages of drug
- $\boldsymbol{\tau}$: time at which maximum of each dosage is added

- σ: spread of each dosage (e.g. a large σ means that the dose is administered gradually)

These equations can be interpreted. The growth rate of the cancer $\frac{\mathrm{d}g}{\mathrm{d}t}$ is logistic, slowed down by apoptosis and the drugs, which each kill it at a rate proportional to the current volume fraction. The rate of change of the drug $\frac{\mathrm{d}f}{\mathrm{d}t}$ in the petri dish is equal to the rate at which it's being added, specified by p, minus the rate at which it decays, which is proportional to its volume. Finally, the rate at which the drug is added, p, is the sum of a rate function applied to each dosage and timing. This function, when graphed for time, looks like a bell-shaped curve with a maximum amount being added at the timing τ_i. The area under this curve for all time approaches δ_i, so this value is roughly the amount of drug added throughout the trial. The spread makes the graph either narrower and taller or wider and shorter. A small σ means that the majority of the dose is administered in a shorter period. Because all of these functions are simply summed together, it can be assumed that they are either of the same drug or several drugs that behave similarly.

Each of the first three equations, $\frac{\mathrm{d}g}{\mathrm{d}t}$, $\frac{\mathrm{d}f}{\mathrm{d}t}$, and $p(t)$, are given their own function in Matlab. Then, another function `F` takes advantage of their discretization from Problem 1 (i) to solve them simultaneously, returning vectors representing approximate data points for g and f at a given t. Each t is spaced a distance Δt from its neighbors, determined from an integer k where $\Delta t = \frac{0.01T}{2^k}$. J and J_{new} also have their own Matlab functions, which call on `F` utilizing the provided $\boldsymbol{\delta}$ and $\boldsymbol{\tau}$ parameters. Integrals of f and g within the cost functions are approximated using the trapezoidal rule. Finally, anonymous functions which call the cost functions are created, only requiring $\boldsymbol{\delta}$ or both $\boldsymbol{\delta}$ and $\boldsymbol{\tau}$ to be passed, since all other values are constant. This format allows the cost to be minimized by `fmincon`. The function is called with specifications: a limited domain for the optimized value between `xmin` and `xmax`, error tolerances for the value and function output `tolx` and `tolfun`, and a maximum number of iterations `toliter`. For each of the three problems, all of these implemented functions vary slightly based on which paramaters are variable and which are held constant.

It should be noted that during the treatment, even when the dosage and timing are optimized, the tumor continues to grow logistically. This is reasonable, because in reality, many cancers are too aggressive to completely curtail without surgical removal or organ transplantation. However, if the cancer's proliferation rate λ_{p} is reduced, the models show the drug successfully eliminating the cancer.

2.1 Problem 1

(i) Using a small h, the derivative of a function can be approximated sufficiently.

$$f'(x) = \lim_{x \to 0} \frac{f(x+h) - f(x)}{h}$$
$$f'(x) \approx \frac{f(x+h) - f(x)}{h}$$
$$f(x+h) \approx f(x) + f'(x)h$$

If $h = \Delta t$, then a discretization of the given system of differential equations can be constructed, with an index n starting at 1.

$$t_{n+1} = t_n + \Delta t$$
$$g(t_{n+1}) \approx g_{n+1} = g_n + \left.\frac{\mathrm{d}g}{\mathrm{d}t}\right|_{f=f_n, g=g_n} \Delta t$$
$$f(t_{n+1}) \approx f_{n+1} = f_n + \left.\frac{\mathrm{d}f}{\mathrm{d}t}\right|_{f=f_n, t=t_n} \Delta t$$

Exceptions to this formula are at $n = 1$, where $t_1 = t_0$, $g_1 = g_0$, and $f_1 = f_0$, and potentially for the final index n_f. Because $g(T)$ and $f(T)$ are being sought, it should always be that $t_{n_f} = T$, $g_{n_f} \approx g(T)$ and $f_{n_f} \approx f(T)$. To achieve this, for that iteration of calculations, Δt should be substituted with $\Delta t_{\text{new}} = T - t_{n_f - 1}$, where $|\Delta t_{\text{new}}| \leq |\Delta t|$.

(ii) As seen in Table 1, the ideal $k = k_0$, which keeps the approximate relative error below 1%, while also minimizing the number of calculations performed, is 2. This value wil be used to calculate Δt for the rest of the problem set. Decreasing the step size past this point doesn't significantly change the solution function. From this, it can be inferred that the approximation closely follows a perfect solution.

2.2 Problem 2

(i) After executing the optimization function `fmincon`, the following optimal value was returned.

$$\boldsymbol{\delta}_{\text{opt}} = \text{REDACTED}$$

As expected, this optimized value lowers the cost.

$$J(\boldsymbol{\delta}_0) = \text{REDACTED}$$
$$J(\boldsymbol{\delta}_{\text{opt}}) = \text{REDACTED}$$

(ii) For plots, see Figure 1. The optimized parameters markedly decrease the growth of the tumor.

2.3 Problem 3

For this problem, a new $\boldsymbol{\tau}_{0,\text{new}} = (9.7955, 19.5171, 30.6384, 40.6257)$ is provided.

(i) After executing the optimization function `fmincon`, the following optimal values were returned.

$$\boldsymbol{\delta}_{\text{opt,new}} = \text{REDACTED}$$
$$\boldsymbol{\tau}_{\text{opt,new}} = \text{REDACTED}$$

As expected, these optimized values successfully lower the cost.

$$J_{\text{new}}(\boldsymbol{\delta}_0, \boldsymbol{\tau}_0) = \text{REDACTED}$$
$$J_{\text{new}}(\boldsymbol{\delta}_{\text{opt,new}}, \boldsymbol{\tau}_{\text{opt,new}}) = \text{REDACTED}$$

(ii) For plots, see Figure 2. On the graph, it is apparent that the optimized paramaters from Problem 3 allow the cancer to grow much faster than in Problem 2, while still being an improvent over the initial conditions. This seems to be because in the new cost function, the weighting $c = 0.001$ of the cost of having a higher volume of drugs in the petri dish for a longer time, $\int_0^T f(t)\,\mathrm{d}t$, is much larger than the weightings $a = 0.0005$ of the cost of having a higher volume fraction of the drug at the end of the trial, $g(T)$, and $b = 0.00005$ of the cost of having a higher volume fraction of cancerous cells in the petri dish for a longer time, $\int_0^T g(t)\,\mathrm{d}t$. Perhaps the cost associated with c could represent the undesirable, harmful, or, past a certain threshold, lethal side effects associated with common cancer treatments such as chemotherapy. Thus, while this new optimization is less effective at eliminating the tumor, perhaps it is more viable overall.

3 Project Roles

Our group did a particularly good job of collaborating this time around, despite the fact that we were unable to meet each other face-to-face. Communication took place via text messaging and Zoom calls. Matlab Drive was a particularly helpful tool for collaboration, because it allowed us to maintain centralized Matlab files that everyone could access and modify. During our Zoom calls, members would take turns working on code, sharing their screen so that the whole group could still contribute. Everyone was involved in the coding and problem-solving, but each individual also had their own unique contributions, which I noted below.

- H. B.
  - Initiated group communication
  - Recorded meetings and took notes
- Ashton Cole

  - Explained and set up Matlab Drive

- T. L.
  - Interpreted and implemented optimization

- M. N.
  - Project leader
  - Wrote down discretization

- I. Z.
  - Motivated group to complete project well in advance
  - Organized project variables and constants

4 Code Supplements

All of the coding used to answer the problems is organized into the following files.

- `Poject2_Problem1.m`
- `Poject2_Problem2.m`
- `Poject2_Problem3.m`

A Tables and Figures

Table 1: Values of $g(T)$ and Approximate Relative Percent Error based on k

k	$g^k(T)$	e^k

Figure 1: $g(t)$ and $f(t)$ when $\boldsymbol{\delta} = \boldsymbol{\delta}_0$ and $\boldsymbol{\delta} = \boldsymbol{\delta}_{\text{opt}}$

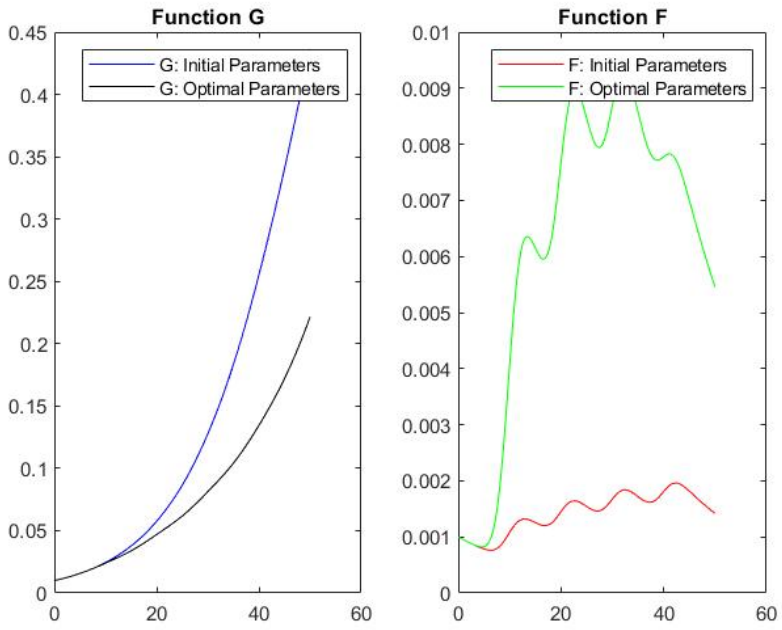

Figure 2: $g(t)$ and $f(t)$ when $\boldsymbol{\delta} = \boldsymbol{\delta}_0$ and $\boldsymbol{\tau} = \boldsymbol{\tau}_{0,\text{new}}$, $\boldsymbol{\delta} = \boldsymbol{\delta}_{\text{opt}}$ and $\boldsymbol{\tau} = \boldsymbol{\tau}_0$, and $\boldsymbol{\delta} = \boldsymbol{\delta}_{\text{opt,new}}$ and $\boldsymbol{\tau} = \boldsymbol{\tau}_{\text{opt,new}}$