Optimizing Cancer Drug Treatment Models Using Process Dynamics

by
Alexander Russell Jones

A THESIS

submitted to

Oregon State University

Honors College

in partial fulfillment of
the requirements for the
degree of

Honors Baccalaureate of Science in Chemical Engineering
(Honors Scholar)

Presented May 28, 2020
Commencement June 2020

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Alexander Russell Jones for the degree of Honors Baccalaureate of Science in Chemical Engineering presented on May 28, 2020. Title: Optimizing Cancer Drug Treatment Models Using Process Dynamics.

Abstract approved:_____

Líney Árnadóttir

Cancer is currently the second leading cause of death in the United States and the sixth leading cause of death worldwide. Due to cancer's variability in type, location, growth rates, and patient physiology, treatment models are based off of previous experimental and clinical work. This variability, however, can lead to inconsistencies in the efficacy of a certain cancer treatments. The project objective was then to develop an overarching model that can be highly tuned to a patient's individual physiology and cancer type. It was derived from basic pharmacokinetic principles and mass transfer, and tied together using process dynamics to relate a treatment input to a cancer reduction output. The model was simulated using current clinical treatment standards for a common cancer (Non-Small-Cell Lung Carcinoma), and was further optimized against chemotherapy dosing frequency and dosage amount to obtain a more efficient dosing schedule.

Key Words: Cancer, Pharmacokinetics, Model, Process Dynamics, Optimization

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I understand that my project will become part of the permanent collection of Oregon State University, Honors College. My signature below authorizes release of my project to any reader upon request.

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Alexander Russell Jones, Author

Introduction

1. Cancer Biology

Cancer is a group of diseases characterized by unchecked malignant cell growth that can attack all tissue types and affect any person. It currently accounts for the second most common cause of death within the United States, and various types of cancer occupy the sixth leading cause of death worldwide, and the fourth, ninth, and tenth leading causes of death in middle and high income countries in 2013 [1, 2]. Cancer is a significant disease in that it can be caused by a variety of factors, including infectious disease, diet, the environment, and conspicuously, one's own genetics.

The hallmark of cancer is the presence of rapidly growing masses of cells known as tumors. These tumors form as amorphous masses capable of influencing the local microenvironment in order to siphon off nutrients and divert the blood supply. As malignant tumors' metabolic demands begin to outpace the local microenvironment, the cancer begins to spread to other portions of the body. A stage 0 cancer is *in situ* with minimal growth; a stage I cancer is relegated to its original tissue type that is small; a stage II and III cancer is determined by the deeper ingrowth of the tumor into the original tissue, and the possibility to have spread to surrounding lymph nodes; finally, a stage IV cancer is one that has traveled to a separate organ, with the worst types having crossed the horizontal midline of the body i.e. the diaphragm [3].

2. Cancer Treatment

Current cancer treatments fall under three major categories: surgical, chemotherapy, and radiotherapy. Each of the three present significant pros and cons to treatment. Depending on the area, early stage cancers can be easily treated and set into remission through a full excision of the tumor. However, as malignant tumors begin to increase in size, or are nestled in difficult to access areas, introduction of chemotherapy or radiation provides clinicians an avenue to decrease the size to operable levels, or kill the mass completely [4].

3. Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics (abbreviated PK/PD) is the branch of pharmacology and physiology dedicated to mathematical modeling of the elimination and uptake of drugs in biological systems. In design drugs, drug schedules, and drug dosing guidelines, PK/PD analysis can provide an invaluable source as the expected outcomes associated with dosage parameters. Typically PK/PD studies begin with administration of a drug to a mouse model or patient, collecting blood samples, analyzing drug concentrations, and fitting the data to standard curves [5]. For example, a bolus (instantaneous) administration of drug is considered to follow the following equations describing the blood concentration [6, 7].

$$C(t) = C_0 e^{-k_b t} \qquad \textbf{\textit{Equation 1}}$$

Equation 1 above describes the drug concentration in blood, c(t) at time *t*, after a single dose; the term C_0 denotes the amount of drug administered, and k_e denotes the drug's elimination rate within the body. While informative for general systems, PK/PD models fall short in describing the outcomes of the drug treatment. Therefore, they can be expanded upon to not only investigate how the body will react to the drug, but on the efficacy and ability to meet treatment goals.

4. Research Question

Current cancer treatments are lengthy and take a significant physical toll on a patient's body. The combination of surgery, chemotherapy and radiation all pose substantial risks to a patient, from the

financial burden of paying for multiple rounds of treatments, to the physical as adverse side-effects, loss of physical abilities, and possible death. Chemotherapeutic treatments are highly regulated by the FDA and tuned to be effective, yet conservative, by drug manufacturers and clinicians. Using mathematical models, cancer treatment can be optimized to decrease the total time of treatment, or limit the amount of drug administered, all without overstepping guidelines or deadly levels.

5. Research Objective

The overarching objective of this project is to investigate the efficacy of an optimized drug schedule to treat a vascularized tumor. This is accomplished by taking the complex mathematics associated with tumor growth and chemotherapeutic treatment, and modeling it with a highly tunable transfer function.

Mathematical Model

1. Process Dynamics

It is difficult to obtain concise, analytical solutions for typical models in mathematical oncology. Cancers are dynamic systems; to be treated as such, steps should be taken to limit the boundedness imparted by initial conditions, and increase the freedom of using a model as a simulation. It was therefore chosen to express the cancer dynamics model outlined below, as a series of transfer functions, each taking the output of a previous process as the input to a new process. A simplified model was derived that related an injection chemotherapeutic drug to the resulting blood sera drug concentration, sera concentration to drug concentration within a tumor, and ultimately drug-tumor concentration to number of cells killed; simply, an overarching transfer function would relate a dose of drug to the number of cells killed, with highly tunable parameters unique to the drug used, cancer being treated, and the patient's own physiological processes.

2. Physical System and Parameters

A. General

There is a hope that the mathematical model to be described below can be applied to all forms of vascularized tumors. For this model, despite tumors being amorphous in shape and integrated within tissues that then integrate in a robust vasculature, it is assumed that the tumor is spherical in shape and fully immersed within the body blood streams. The reason for this assumption is two-fold: firstly, setting the system as a spherical tumor increases the ability to produce a solution to the diffusion of drug from the sera into the tumor. As for the second assumption, the tumor is placed as a free floating sphere within the blood. A fully vascularized tumor has essentially the same structure, but in the assumptive case, the effect of capillaries being wound around the tumor can be neglected.

B. Drug Specific

For this simulation, all parameters used will be for treating a Non-Small Cell Lung Cancer (NSCLC) with the common therapeutic agent, paclitaxel. Given that tissue is predominantly water, it was assumed that the diffusion of paclitaxel through water would serve as the appropriate scheme for convective diffusion into the tumor cell. Experiment has shown that the diffusion coefficient of paclitaxel through water is 2.56×10^{-4} cm^2/min, or 0.01536 cm^2/hr [8]. Paclitaxel is a taxane derivative that in standard dosing schedules, has a half-life of 13.1 hours on average, with the inverse representing a total body elimination rate of 0.529 hr^{-1} [9, 10].

The cancer in this simulation is set to be a singular NSCLC tumor, and volume of 12.37 cm^3, as this provides an average size between the bounds presented by Hosokawa and Xia [11, 12]. The patient is assumed to be a 75 inches tall (6 ft. 3 inches) and 200 lbs. male, giving him a body area of 2.2 m^2. Current recommendations for NSCLC treatment with paclitaxel is a 3 hour infusion once a week at a dosage of 135 mg/m^2 [10, 13-15]. Drugs diffuse within blood plasma, of which constitutes 55% of an adult human's total blood volume of 5L. Assuming that the bolus injection rapidly and evenly distributes within the body post injection, the average drug concentration equates to $1.26x10^{-4}$ mmol/mL. Given that 1 hour constitutes just over 1% of the total treatment time (one week), the assumption of it being a bolus injection within the simulation is viable.

3. Injection Phase

Chemotherapy treatments range in application, from daily pills, weekly injections in 1, 2, 4, etc. hour duration, or a continuous drip/implant. For the purpose of this model, it was assumed that drug delivery would be weekly intravenous treatment, and due to the time scale of roughly 7 days between treatments, can be modeled as an bolus injection. In process dynamics, a bolus injection would be modeled as an impulse input.

$$\frac{dp}{dt} = I$$

Several body systems contain the mechanisms necessary to purge and eliminate foreign chemicals. These system functions are often lumped into a first order elimination equation, with a first order elimination rate constant as the inverse of the half-life of the drug within the body.

$$\frac{dp}{dt} = I - k_e * p \qquad \textbf{\textit{Equation 2}}$$

Equation 2 above is an example of an ordinary differential equation, that can be further characterized as an unsteady state mass balance of drug plasma concentration as a function of time. Performing a Laplace transform on the above differential equation yields:

$$sP = \mathrm{I} - k_e P$$

The above can now be rearranged, and the transfer function solved for:

$$G_1 = \frac{P}{\mathrm{I}} = \frac{1}{s + k_e} \qquad \textbf{\textit{Equation 3}}$$

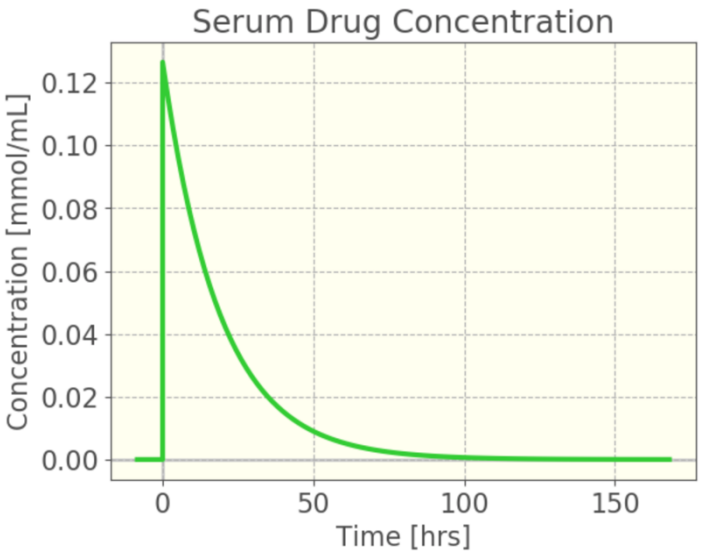

Figure 1. Pharmacokinetic plot describing the drug concentration in blood plasma after a bolus injection, as described by equations 3 and 4. As the body is assumed to remove drugs and toxins following first order kinetics, the drug concentration experiences an exponential decay proportional to the elimination rate, k_b. This model is also represented by the time-domain equation set forth in Equation 1. Values used to produce plot are found in the section "Variables/Parameters".

4. Diffusitory Phase

A typical diffusitory model does not contain all the necessary components to properly model this system. This system has a non-constant source of drug diffusing into the cell, as shown by equations 3 and 4 and by Figure 1 above. Drug diffuses into a finite medium and does so at an unsteady state, and, with less an impact, flow of blood and nutrients around the tumor must also be considered. Therefore, the typical Fickian diffusion equation will not be considered. Instead, we consider the convective mass transfer equation in which the diffusion of drug into the tumor mass is assumed to be spatially uniform; equation 4 contains an important distinction to account for an unsteady state, finite media, non-constant source:

$$N_A = k_c\left(C_{A,\infty} - C_A\right) = k_c(p - c) \qquad \textit{Equation 4}$$

By substituting the average outside concentration $C_{A,\infty}$ term for p, and the surface concentration for the concentration inside of the tumor for c, the issues arising from a non-constant source sink have been accounted for and integrated so the tumor concentration can be modeled. Both are functions of time, with blood concentration derived in equations 2 and 3 above, and drug concentration inside the tumor implicitly defined in equation 4 and solved for in equation 8. It is also important to take note of the boundary layer; convective mass transfer serves its purpose in modeling the mass transfer of species A from a moving fluid through a much more stagnant boundary layer towards the mass sink. This boundary layer was assumed to be the entire tumor mass, with the mass sink effectively being the center of the spherical tumor, thus allowing for a spatially uniform diffusion assumption.

By using a process dynamics approach, p can be left as a time-dependent function as it is the result of simulating the transfer function in equation 4; when the soon to be derived diffusitory model transfer function is combined with that of blood plasma transfer function in equation 4, the result is a tumor-drug concentration profile dependent on a time-dependent plasma concentration, integrated within the overall transfer function. The diffusion scheme was modified to fit these assumptions.

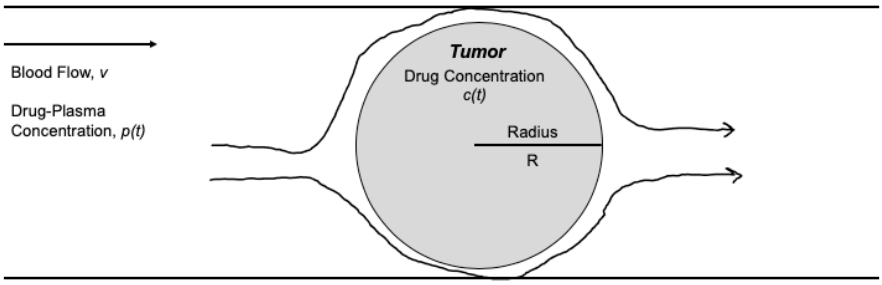

Figure 2. Schematic of the diffusive environment around the tumor mass. The tumor is assumed to be a perfect sphere; in the body, a tumor mass would be extravascular with a dynamic system of capillaries supplying necessary nutrients and oxygen to the tissue. The simulation relies on the assumption that a fully vascularized tumor can be modeled as a sphere within a flow channel with the same properties, velocity, viscosity, etc. as blood flowing in the capillary system.

The dynamics of diffusion are now modeled by the k_c term, as a sort of velocity of diffusion, which is dependent on the properties of the external flow (blood), flow geometry (assumed sphere), and diffusion parameters (diffusion coefficient, D_{AB}). For a convective flow system, k_c is modeled by calculating the Sherwood (*Sh*) number around a sphere, as a function of the Peclet number (*Pe*), one of two ways [16, 17]:

$$Sh = \frac{k_c D}{D_{AB}} = \left(4.0 + 1.21 Pe^{\frac{2}{3}}\right)^{1/2} \quad for\ Pe < 10{,}000 \qquad \textit{Equation 5}$$

$$Sh = \frac{k_c D}{D_{AB}} = 1.01 * Pe^{\frac{1}{3}} \quad for\ Pe > 10{,}000 \qquad \textit{Equation 6}$$

For mass transfer systems, the Peclet number serves as the ratio between the advective and diffusive mass transfer rates, or more simply the product of the Reynold's number over the flow geometry and the Schmidt number [17]:

$$Pe = Re_D * Sc = \frac{\rho v D}{\mu} * \frac{\mu}{\rho D_{AB}} = \frac{vD}{D_{AB}} \qquad \textit{Equation 7}$$

Using a general mass balance approach, the amount of drug within the tumor can be determined. The inlet is the amount diffusing through as described by equations 3 and 4. However, certain factors must be applied to N_A, which has units of $\left[\frac{mmol}{cm^2 * s}\right]$ to that of $\frac{dm}{dt}$ with units of $\left[\frac{mmol}{s}\right]$. Multiplying the variable diffusive flux, N_A, by the surface area of the tumor subject to diffusion, S_A, yields the variable molar flow into the tumor. Further dividing by the volume of the tumor, *V*, yields the desired time-derivative of the tumor concentration. The flux, N_A, can be expanded using equation 4 to give the influx of drug into the tumor:

$$\frac{dc}{dt} = \frac{S_A}{V} k_c (p - c)$$

The tumor cell has two ways of removing drug from its system, excretion and metabolism. Both forms are not counted as the amount of drug needed to induce cell death. Like all physiological environments, tumor masses contain the necessary infrastructure to expel a toxin from itself, modeled by a first order elimination rate, similar to that of the body. Metabolism of drug is highly variable, and minimal compared to excretion, therefore it is not included [18].

$$\frac{dc}{dt} = \frac{S_A}{V} k_c (p - c) - k_e c \qquad \textit{Equation 8}$$

From this point forth, the diffusitory factors on the concentration difference will be represented by α.

$$\alpha = \frac{S_A}{V} k_c$$

$$\frac{dc}{dt} = \alpha p - \alpha c - k_e c$$

The Laplace can now be taken of above equation.

$$sC + \alpha C + k_e C = \alpha P$$

$$sC + \beta C = \alpha s P \quad with\ \beta = \alpha + k_e$$

Solving for the transfer function yields:

$$G_2 = \frac{C}{P} = \frac{\alpha}{s + \beta}$$ ***Equation 9***

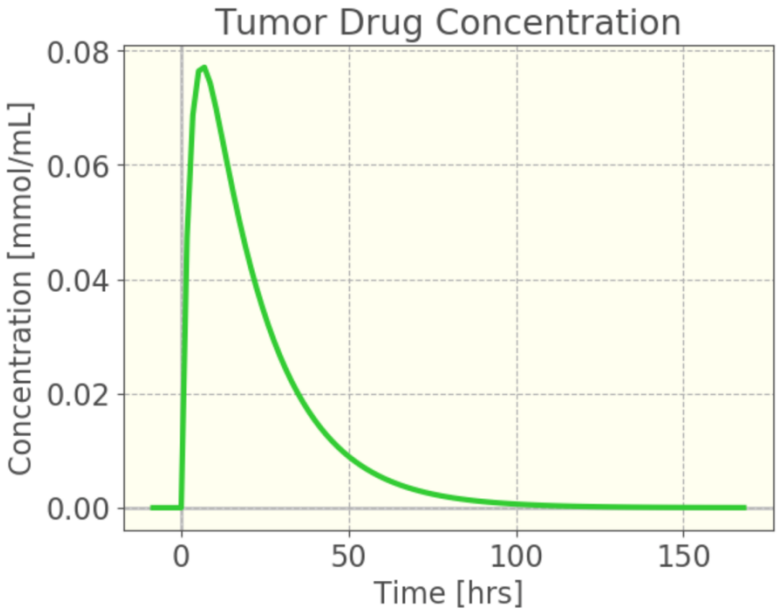

Figure 3. Pharmacodynamic plot describing the intratumoral concentration of drug after a bolus injection. Resulting drug concentration in the tumor was found by simulating an injection, I, against the product of equations 4 and 10. Values used to produce plot are found in the section "Variables/Parameters".

5. Cell Death Phase

Now that the drug concentration within the cell has been described, its effect on the tumor's overall growth and death can be determined. Using the general mass balance equation for the number of cells:

$$\frac{dn}{dt} = Growth - Death$$

Using an exposure-dependent death equation, the amount of cells killed off can be modeled. Exposure is typically modeled with Hill's equation, but for simplicity, the exposure will be defined as the concentration present within in the cell. Given that the cell has been previously modeled in equation 8 to

be able to remove some of the drug, it is assumed that any remaining drug does do cytotoxic damage to the tumor cells via an exposure-dependent treatment effect [19-21][Yin].

$$\frac{dn}{dt} = Growth - k_d nc$$

Tumor growth has been experimentally modeled to closely follow the Gompertz model [19, 22, 23]. Sigmoidal in nature, Gompertz growth allows for exponential growth at low cell numbers and forces cell amount to level off as it reaches the carrying capacity, *K* [19, 24, 25]. This model fits typical physical systems as the tumor can only become so large before it exhaust its ability to siphon oxygen and nutrients from the patient.

$$\frac{dn}{dt} = nk_g \ln\left(\frac{K}{n}\right) - k_d nc \qquad \textit{Equation 10}$$

This equation must now be linearized before it can be used in a transfer function. Linearization of this differential equation would follow the form:

$$\frac{dn}{dt} \approx f(\bar{n}, \bar{c}) + \frac{df}{dn}[at\ \bar{n}, \bar{c}] * (n - \bar{n}) + \frac{df}{dn}[at\ \bar{n}, \bar{c}] * (c - \bar{c})$$

The initial term $f(\bar{n}, \bar{c})$ can be equated to zero because at steady state, neither the number of cells, nor the cellular drug concentration is changing. The fact that at steady state the number of cells, $\bar{n}$, is not zero is accounted for once the transfer function is solved for a various input. Linearizing equation 11 yields:

$$\frac{df}{dn} = \left[k_g \ln\left(\frac{K}{\bar{n}}\right) - k_g - k_d \bar{c}\right] * n = \varphi n$$

$$\frac{df}{dc} = -k_d \bar{n} * c$$

$$\frac{dn}{dt} = \varphi n - k_d \bar{n} c \qquad \textit{Equation 11}$$

Taking the Laplace transform of equation 11 and solving for the transfer function yields:

$$sN = \varphi N - k_d \bar{n} C$$

$$G_3 = \frac{N}{C} = \frac{-k_d \bar{n}}{s - \varphi} \qquad \textit{Equation 12}$$

6. Model Solution

Finally, a model can be determined to relate the bolus injection to the number of tumor cells remaining. Before solution is possible, it must be clarified that all input and output variables at this point are in deviation form; that is the steady state variable, $\bar{x}$, subtracted from the time dependent variable, *x(t)*, to produce a deviation from steady state variable, $x^*(t)$. The stars used to denote the deviation variables were omitted in the final collection of equations for clarity. The three derived transfer functions act in series, allowing for their multiplication against one another to find an overall system transfer function.

$$G_{overall} = G_1 G_2 G_3 = \frac{P}{I} * \frac{C}{P} * \frac{N}{C} = \frac{N}{I}$$

$$G_{overall} = \frac{1}{s + k_e} * \frac{\alpha}{s + \beta} * \frac{-k_d \bar{n}}{s - \varphi} \qquad \textit{Equation 13}$$

Using a process dynamics package within the Julia programming language created by Dr. Cory Simon at Oregon State University, the above transfer function can be simulated for any bolus injection of drug, *I*, to produce a change in cell number after a dose.

The number of tumor cells at the end of simulation time, T = 168 hours [13, 26], will then be used as the starting point of the next week of treatment. The simulation was repeated 24 times, to represent a possible chemotherapy treatment scheme of 6 months [10]. The new volume was calculated as a ratio of cell number of the previous week to the cell number of the present week multiplied by the previous week volume before treatment.

$$\frac{cell_j}{cell_i} * V_j = V_i \qquad where \begin{matrix} i = current\ week \\ j = previous\ week \end{matrix} \qquad \textit{Equation 14}$$

Running the simulation showed that over a 6 month period shows a linear decrease in tumor cells at a constant dosage once every week. The volume, steady state drug concentration and steady state number for cancer cells change with each treatment. Those values after each treatment are recorded and fed back into the simulation as new parameters regarding their effects cancer treatment, where, for example, in equation 12, the ability of cancer drug in the tumor to kill cells is directly dependent on this steady state number of cells before subsequent treatments.

Optimization

1. Need for Optimization

Chemotherapy as a cancer treatment wreaks havoc on the body's systems, and the timing and dosing schedules in treatment is often the parameters most likely to be optimized. If treatment timing can be optimized, a patient does not have to undergo long duration and as many cycles to eradicate their tumor, however they may be at risk of developing drug toxicity. Similarly, as the tumor shrinks, the amount of drug administered can be optimized for each dose to limit the amount adverse effects brought on by high drug concentrations. Conversely, if not enough drug is present, its influence on the exposure-dependent death rate may not be great enough to overcome the tumors natural growth rate.

One of the obvious scenarios to optimize is to administer the maximum amount of drug with no separation between doses. There exists some unique concentration within the body, C_{max}, that provokes LD_{50} concentration within the individual. This LC50 concentration (C_{max}), is the concentration that is required to kill 50% of the population, and for most chemotherapy drugs, reaching the C_{max} induces renal and liver failure, bone marrow suppression, and peripheral neurotoxicity [27, 28]. It is therefore necessary to impede the drug concentration from becoming large enough to reach this C_{max} [18, 20].

$$p(t) \leq C_{max} \qquad \textit{Equation 15}$$

As the chemotherapeutic effect of reaching the Cmax occurs at the systemic level, only the drug concentrations within the sera described by equations 3 and 4 need to be considered. For any bolus injection *I*:

$$P = I * \frac{1}{s + k_b}$$

The above can then be solved into the time domain, producing a drug concentration curve within the plasma.

$$p(t) = I * e^{-k_b t} \qquad \textbf{Equation 16}$$

It is important to also remember that the bolus injection, *I*, is itself a conditional function where at the prescribed dosing interval, τ, the injection equals the amount of drug given, *m*.

$$I(t) = \begin{cases} m, & t = n * T \\ 0, & t \neq n * T \end{cases} \quad where\ n = 0, 1, 2, \dots$$

However, trying to optimize a conditional piece-wise function is not suitable for determine an effective dosing schedule. By setting the injection function to the form of a trigonometric function, a continuous function is developed where the intervals between doses, τ, can be highly tuned. The general form follows:

$$I(t) = m * \cos^n\left(\frac{\pi t}{\tau}\right) \qquad \textbf{Equation 17}$$

Where if the exponent, *n*, on the cosine function taken towards infinity, the resulting injection, *I(t)*, tends toward a set of continuous Delta-Dirac functions, also known as the Dirac comb, with a height of *m* and interval of τ hours. Equation 19 can now be substituted into equation 18 to yield:

$$p(t) = m * \cos^n\left(\frac{\pi t}{\tau}\right) * e^{-k_b t} \qquad \textbf{Equation 18}$$

Equation 18 will now serve as the base equation for the subsequent optimizations.

2. Frequency of Treatment

    A. Maximum Drug Concentration

The simplest optimizable parameter is to vary or lower the frequency of dosages to a point where the decrease in tumor cells reaches a maximum while still maintaining the criteria set by equations 15. This can be performed using equation 18, and solving for when the time, *t*, equals the frequency dosage, τ.

$$C_{max} \geq m * \cos^n\left(\frac{\pi t}{\tau}\right) * e^{-k_e t} \Big|_{t=\tau}$$

A precaution must be taken before evaluation – when solving for the inverse of a cosine function, the function raised to the *n*-th power when *n* is even yields a positive value, whereas an odd *n* yields a negative solution; taking the absolute value of the inverse removes this variability. This assumption is viable as *n* is desired to tend towards infinity to obtain the set of continuous Delta-Dirac functions. Evaluating time, *t*, at the interval frequency, τ, yields equation 19.

$$\tau \geq \left|\frac{1}{k_e}\ln\left(\frac{m}{C_{max}}\right)\right| \qquad \textbf{Equation 19}$$

Equation 19 also shows another peculiarity. Dosing amount never approaches the maximum possible concentration, meaning the ratio between dose and C_{max} is less than 1, the argument of which provokes a negative result. This again is mitigated through taking the absolute value to remove the variability from the *n*-th power.

B. Maximum Cell Death

As shown in part A above, there exists some dosing interval, τ, where drug concentration is below the maximum possible (C_{max}). Furthermore, there must exist some interval where rate of cell death reaches some negative maximum. This interval τ can be found by evaluating equation 13 with some dosage input, *m*. This dosage amount is assumed to represent an instantaneous, bolus injection for a single treatment (i.e. a Delta-Dirac input), which in the Laplace domain is represented by *M*. Evaluation necessitates that the resulting number of cells, *N(s)*, be brought into the time domain via an inverse Laplace transform. In this solution, the input dosage, *I*, is considered to be a single administration and instantaneous.

$$N = M * G_{overall} = \frac{1}{s+k_e} * \frac{\alpha}{s+\beta} * \frac{-k_d\bar{n}}{s-\varphi} * I$$

This equation was solved using partial fraction decomposition:

$$N = \frac{1}{s+A} * \frac{1}{s+B} * \frac{D}{s-C} = \frac{X}{s+A} + \frac{Y}{s+B} + \frac{Z}{s-C}$$

$$where\ X+Y+Z = D$$

Solutions to equation 23 yielded:

$$X = \frac{m*D}{u+v-2w}; \quad Y = \frac{m*D*R}{u+v-2w}; \quad Z = \frac{m*D}{w} * \frac{v(1+R)-2w}{w+v-2w}$$

The variables expressed above were used for simplicity in calculating the partial fraction decomposition, and are in previously defined terms:

$$A = k_e; \quad B = \beta; \quad C = \varphi; \quad D = -k_d\alpha\bar{n}$$
$$u = BC; \quad v = AC; \quad w = AB; \quad R = \frac{C-A}{B-C}$$

Taking the inverse Laplace yields:

$$n(t) = \bar{n} + Xe^{-At} + Ye^{-Bt} + Ze^{-Ct} \qquad \textbf{Equation 20}$$

Subsequently, taking the derivative of equation 20 will describe the overall effect that the dosing interval will have on the number of cells, or effectively what interval is necessary for greatest reduction in the number of cells. If the derivative is positive, cell growth dominates the killing effect of the drug at that interval, whereas if the derivative is negative, cell death dominates.

$$\frac{dn}{dt}\Big|_{t=\tau} = AXe^{-A\tau} + BYe^{-B\tau} + CZe^{-C\tau} \qquad \textit{Equation 21}$$

Results and Discussion

A. Normal Model

Simulation results of the normal model showed an insignificant 0.008% decrease in cell number and volume 1 mm^3 decrease after 24 week-long treatments. The resulting tumor shrinkage was low for typical NSCLC outcomes [12]. Research into the efficacy of paclitaxel on NSCLC by Xia showed a 50 to 63% volume decrease of tumors in advanced staged cancers, however the chemotherapy also included the adjuvant Carboplatin, as well as the patient group receiving radiation therapy [12]. As a single drug therapy, paclitaxel's efficacy resulted in roughly a 30% reduction in volume for mid-stage breast cancers (stage II and III) [29].

It is important to rectify the discrepancies in treatment models presented, as the efficacy of treatment is highly dependent on the size of tumor(s); type, number, stage, and location of tumor(s); and the prescribed therapy or therapies. In the simulation, it was a single chemotherapy prescribed to an average sized tumor of 12.38 cm^3 whereas the summation of volume across all present tumors presented by Cheung ranged in volume from 28 to 424 cm^3 [12]. Given the assumption made in the diffusive model, the increased size of the aggregate tumor allows for more drug diffusion and consequently a greater size reduction. As the aggregate volume of a tumor approaches the cleared level, ideally a volume of 0 cm^3, it will experience the leveling of drug action and lower shrinkage rates [30].

B. Optimized Dosing Frequency Model

Paclitaxel is a heavily studied and regulated drug with FDA reports detailing its elimination rates and maximum allowable concentration for a range of injectable doses. For the assumed dose of 135 mg/m^2 at the shortest infusion duration, the elimination rate is 0.0529 hr^{-1}, and the C_{max} to induce LD_{50} equates to a dose of 160 mg/kg at $6.18x10^{-3}$ mmol/mL [31], equating to 6.596 mg/m^2. With the parameters properly defined, equations 19 and 21 can be solved to find the optimal dosing frequencies. Solutions provide that $\tau \geq 73.6\ hr$ to remain below C_{max}. Figure 4 shows the optimization against equation 21; it shows a maximum decrease in cell number at a dosing interval of 0 hours, and local minima within the optimization function at 20 hours. Both are less than the stipulation to avoid reaching the C_{max}, so were not considered in the final simulations.

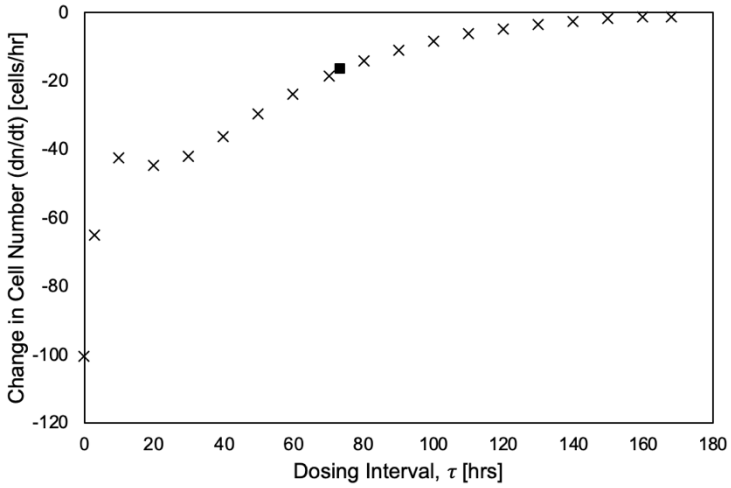

Figure 4. Resulting optimization curve from evaluating equation 21 at a time equal to the dosing interval, τ. The x's represent the cell number decreasing rate at a range of dosing intervals. The black square represents the optimized interval of 73.6 hrs, with a cell number decrease rate of 16.82 cells per hour, as compared to the maximum cell number decrease rate of -100.57 cells per hour at a dosing interval of 0 hours.

Dosing parameters are not based on frequency alone. Due to the clearance of the drug from the body being enough to eradicate it within 1 week (as shown in figure 1), it is feasible to give the simulation patient the maximum possible dose – that concentration that would induce LD50 – to provide the greatest anti-tumor activity.

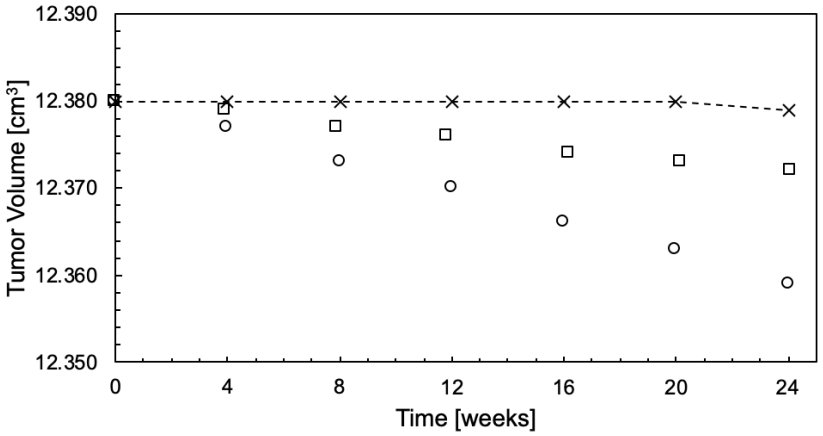

Figure 5. Simulation results of decreasing tumor volume when comparing a control case versus two optimized parameters. The "x"s and dashed line represent the nonexistent volume shrinkage under control conditions of a dosing frequency of 168 hours and dosing amount of 135 mg/m^2. The squares represent the optimized parameter of a 73.6 hour dosing interval; total volume decrease was 0.331 mm^3 per week, for a 0.068% decrease. The circles represent the optimized parameter of maximal dose of 6.596 g/m^2 at a frequency of 168 hours, for a decrease of 0.875 mm^3 per week, or a 0.168% volume decrease overall.

Optimization of both the frequency and amount of drug given provided better treatment results than that of the control simulation. Where the tumor volume and cell number remained near constant after 24 weeks of treatment of typical dosing [13], a shorter dosing frequency to avoid reaching the C_{max}, and providing the C_{max} dose at a normal frequency provided marginally better results. A normal dosing amount of 135 mg/m^2 every 73.6 hours saw a 0.068% decrease in tumor volume. The extreme dose of 6.596 g/m^2 at an interval of 168 hours (1 week) saw an improved volume decrease of 0.168%.

Optimization of the dosing interval still failed to produce the same effect as described by Perez and Xia [12, 32]. However, it must be reiterated that typical cancer treatment is combination of several chemo and radiotherapies, not a single drug as described in the simulation.

Conclusion

Simulations provide excellent models for the complex processes found in cancer biology and clinical pharmacology. Current methods, while accurate and conclusive for their purpose, have yet to integrate in a way to predict clinical outcomes and therefore, they were used in conjunction with treatment models to predict how well a drug could reduce the size of a typical tumor. The process was further applied through a different method of analysis in taking a process dynamics approach. The current model predicted a nonexistent tumor size decrease when following standard dosing schedules; when the model was optimized against dosing interval, it found that in the same 6 month treatment window, the tumor volume decreased by 0.068% when optimizing for frequency and decreased by 0.168% when optimizing for dosage amount, which were not even comparable to experimental results in less resistant cancers. However, both comparisons, (1) NSCLC cancer treated with adjuvant chemotherapies and radiation, and (2) breast cancer treated with simulation drug, are different enough from the model an accurate comparison of a single chemotherapy treatment's efficacy would be difficult to achieve. Future models should seek to integrate the effects of multiple treatment types, along with empirical correlations derived from accurate clinical data, as that is commonplace is today's medical practice.

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Variables/Parameters

Symbol	Name	Value	Units
$t_{1/2}$	Half-Life of Paclitaxel in Body	13.1	hr
k_e	Body-Drug Elimination Constant	0.0529	hr^{-1}
Vb	Total Plasma Volume	2750	mL
dose	Drug Dose	0.347	mmol
M	Average Drug Conc. at Injection	1.26E-04	mmol/mL
P	Drug Concentration in Plasma	varies	mmol/mL
D	Tumor Diameter	2.87	cm
R	Tumor Radius	1.435	cm
Sa	Surface Area of Tumor	25.88	cm^2
V	Volume of Tumor	12.38	cm^3
Dab	Drug Diffusion Coefficient	3.74E-05	cm^2/s
v	Capillary Blood Flow Velocity	108	cm/hr
Pe	Peclet Number	8.279E+06	*unitless*
kc	Convective Mass Transfer Coefficient	2.648E-03	cm/hr
T	Simulation Time Span	24	weeks
C_t	Drug Concentration in Tumor	varies	mmol/cm3
K	Tumor Carrying Capacity	1.00E+11	cells
n	Number of Cells	1.00E+08	cells
k_g	Tumor Growth Rate Constant	5.208E-03	hr^{-1}
k_d	Tumor-Drug Death Constant	0.044	cm^3/mmol-hr
τ	Dosing Frequency	168	hr

In [2]:
```
using Controlz # this *might* take a few min to compile
using PyPlot # for plotting via matplotlib
using Printf
using PyCall

# (optional) hipster plot theme
PyPlot.matplotlib.style.use(normpath(joinpath(pathof(Controlz), "..",
"hipster.mplstyle")))
```

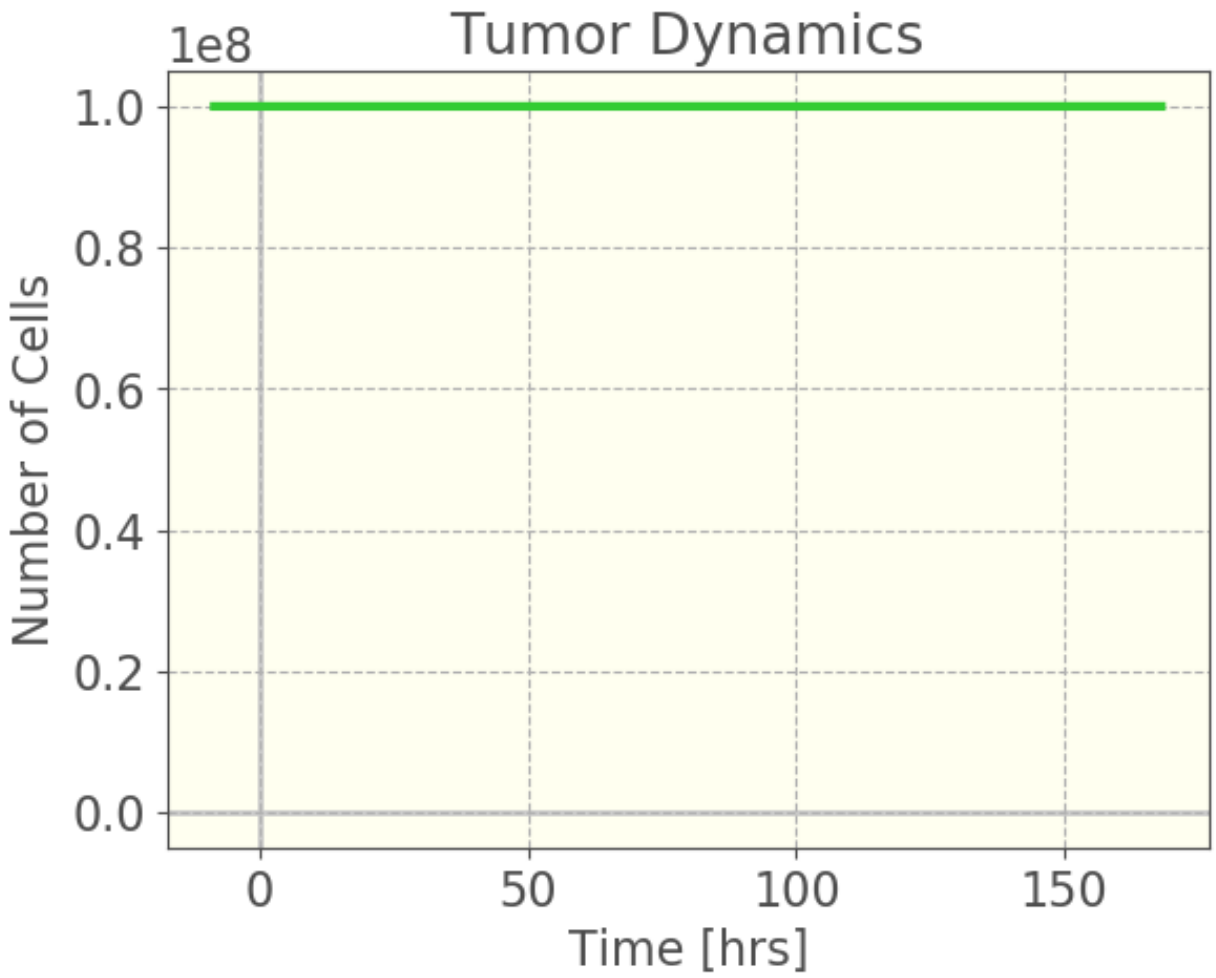
This code simulates the treatmen of a Non-Small Cell Lung Cancer (NSCLC) using Paclitaxel at the current clinical standards of a dosage (m) of 135 mg/m2 and at a dosing frequency (tau) of once per week, or 168 hours.

The simulation is ran by giving a bolus injection of drug to the patient, simulating the plasma concentration of drug, then simulating the drug concentration within the tumor cell, and finally simulating the number of cells remaining after drug treatment. The final number of cells is then re-entered as the new steady state cell number (n_bar), and the simulation re-ran until the tumor radius reaches 0.00 cm.

In [9]:
```
# Simulation Parameters
D = 2.87 # cm, diameter of tumor cell
n̄ = 1*10^8 # cells, steady state - initial number of cells
τ = 168.0 # [hrs], total time for possible diffusion, Dosing Frequency
dose = 135 # mg/m2
m = dose/853.906 #mmol/m2

# Tumor Parameters
R = D/2 # cm, radius of tumor cell
Sa = 4*π*R^2 #cm^2, surface area of tumor cell
V = (4/3)*π*R^3 #cm^3, volume of tumor cell
K = 10^11 # cells, carrying capacity
kg = (1/8)*(1/24) #hr^-1, growth rate
c̄ = 0.0 # mmol/cm^3, steady state concentration of drug in tumor cell

# Drug (Paclitaxel) Parameters
t_half = 13.1 #hours
ke = log(2)/t_half #hr^-1
Dab = 0.01536 #cm2/hr
kd = 0.044 # cm^3/mmol-hr, death rate constant

# Patient Physiology Paramters
A = 2.2 #m2, Body Area for dosing
Vb = 5*1000*0.55 #cm^3,  total blood volume (5L), times 55% as the amo
unt of plasma
v = 0.03*3600 # cm/hr, bulk blood velocity in capillaries
I = m*A/Vb #mmol/mL or #mmol/cm^3

# Drug Diffusion and Action
Pe = D*v/Dab # Peclet number, unitless
kc = (Dab/D)*((1.01*Pe)^(1/3)) #cm/hr, Convective mass transfer coeffi
cient
α = Sa*kc/V
β = α + ke
ϕ = kg*log(K/n̄) - kg - kd*c̄

# Process Dynamics
G1 = 1/(s + ke)
G2 = (α)/(s + β)
G3 = (-kd*n̄)/(s + ϕ)
G = G1*G2*G3
```

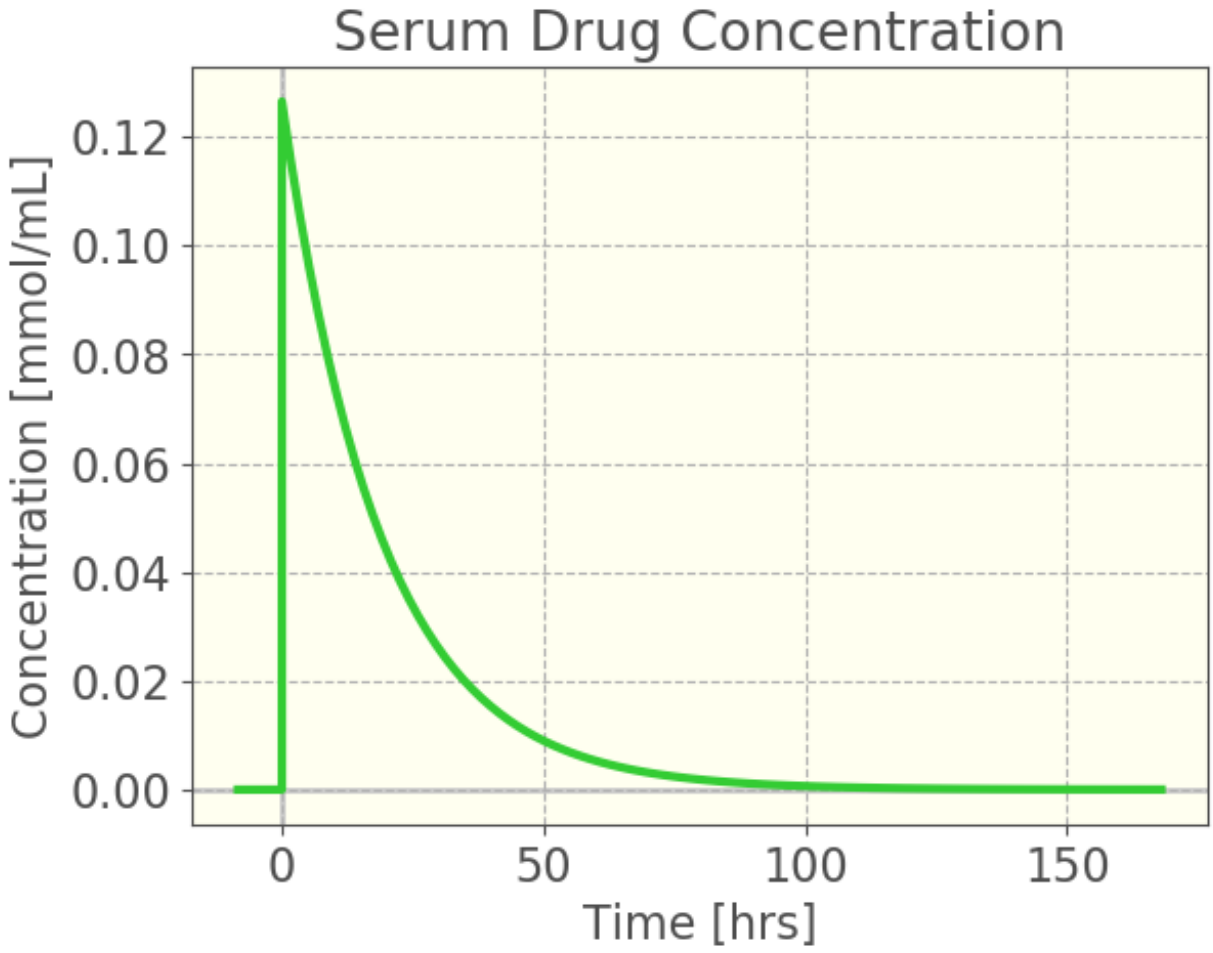
Out[9]:
$$\frac{-1.344755365804222e6}{1.0*s^3 + 0.4422197527771084*s^2 + 0.03163111526778498*s + 0.0005837284884648385}$$

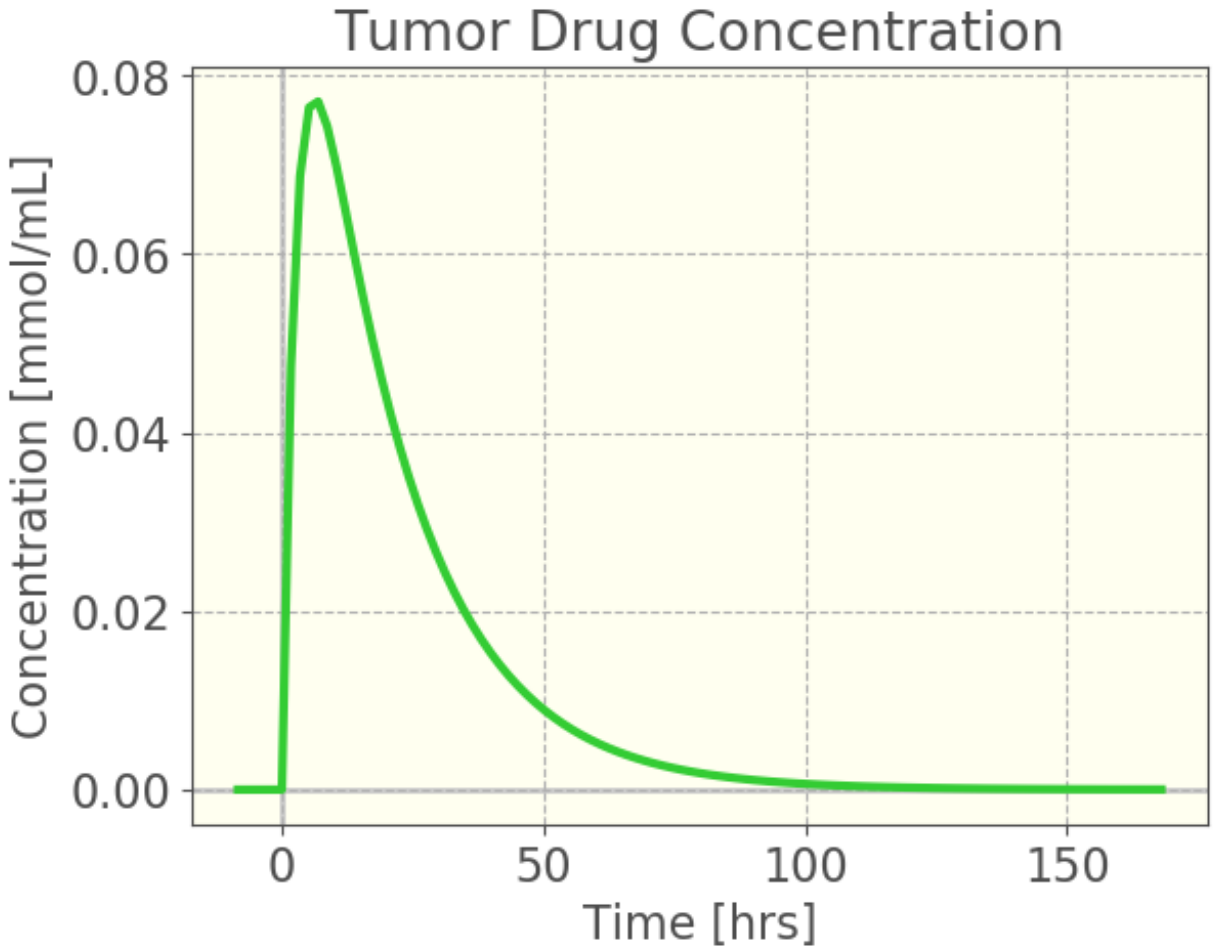
In [10]:
```
# Simulation
# Simulate function created by Dr. Cory Simon as a tool to analyze con
trols problems in CHE 361
N = I*G
t, n = simulate(N, T)
cell = n .+ ñ;
viz_response(t, cell, plot_ylabel="Number of Cells",plot_xlabel="Time
[hrs]",plot_title="Tumor Dynamics")
cell[100]
```



Out[10]: 9.999987015207928e7

In [12]:
```
# The commands below were used to produce figures 2 and 3 to graphically describe the relation between the amount of drug administered and the resulting serum/tumor concentrations

Cb = I*G1
t, p = simulate(Cb, 168.0);
P = p.*1000 # mmol/L, mM, more in line with current medicine units
viz_response(t, P, plot_ylabel="Concentration [mmol/mL]",plot_xlabel="Time [hrs]",plot_title="Serum Drug Concentration")

Gtum = G1*G2
Ct = I*Gtum
t, c = simulate(Ct, T);
Ctum = c.*1000; # mmol/L, mM, more in line with current medicine units
viz_response(t, Ctum, plot_ylabel="Concentration [mmol/mL]",plot_xlabel="Time [hrs]",plot_title="Tumor Drug Concentration")
Ctum[100]
```






```
Out[12]: 1.7430595623215026e-5
```