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PHARMACOKINETIC AND OPTIMIZATION MODEL FOR PHOTODYNAMIC THERAPY

B. K. Singh
Deptt. of Mathematics
IFTM University,
Moradabad

Paras Bhatnagar
Deptt. of Mathematics
Ideal Institute of Technology,
Ghaziabad

Chitra Gupta
Deptt. of Mathematics
IFTM University,
Moradabad

ABSTRACT

Photodynamic therapy (PDT) is an emerging treatment that destroys undesirable tissues and is based on the idea that chemical compounds, called photo sensitizers, cause cellular damage when activated by light. Photo sensitizer exists in a variety of molecular compositions and structures, and different compositions react to different wavelength of light. When a photo sensitizer is activated by light, an electron is excited from a ground state to a more reactive state, converting it to a more energetic species.

The photosensitizer we consider is photofrin, which is the only FDA approved photosensitizer for cancer treatment. While other photosensitizers are being clinically tested, accurate pharmacokinetic data is not available for these photosensitizers. Photofrin is intravenously injected at 2mg/kg over a period of five minutes, and it attains a high saturation level from 48 to 72 hours after injection. The 24 hour period between the 49^{th} and 72^{nd} hour is called the treatment window, and at some time within this period a physician focuses a 630nm light on the targeted area. After treatment, a patient is asked to avoid light exposure for six weeks.

Keywords:- photofrin, photosensitizer, first order linear differential equation, optimization model for photofrin.

INTRODUCTION: - Our pharmacokinetic model estimates a region's concentration by first calculation the arterial concentration and second using this concentration to gauge the amount of Photofrin in the remaining tissue. The arterial concentration is modeled via a differential equation that describes how Photofrin accumulates and degrades in blood-plasma. We let C_I be the plasma concentration during injection, k be the rate of elimination, and k_o be the rate of infusion. The volume of distribution, V, for a particular drug is the volume of fluid that the drug would occupy if the total amount of drug in the body were at the same concentration as is present in the plasma. We model C_I with the following first order, linear differential equation,

$$\frac{dC_I}{dt} = \frac{k_0}{V} - kC_I$$

Whose solution is

$$C_I = \frac{k_0}{Vk}\left[1 - e^{-kt}\right].$$

The plasma concentration after infusion is C_A which exponentially decays. So assuming that the infusion ends at time τ, we have that

$$\frac{dC_A}{dt} = -kC_A, t \geq \tau,$$

from which we conclude that

$$C_A = C_I(\tau)e^{-kt} = \frac{k_0}{Vk}\left[1 - e^{-k\tau}\right]e^{-k(t-\tau)}, t \geq \tau.$$

The infusion rate k_o is based on the fact that the drug is injected at 2mg/kg over a period of 5 minutes. Using an average 70kg adult, we have that 140mg of Photofrin are delivered in 5 minutes, and thus k_o is 1680 mg/h. The mean volume of distribution for Photofrin is 0.491/kg, and in the case of 70 kg person, V is 34.3L. The rate of elimination, k is calculated by solving,

$$t_{1/2} = In(2)/k;$$

Where the half–life for Photofrin is $t_{1/2}$ = 516 hours. Hence $k = 0.00134h^{-1}$. Using these Pharmacokinetic parameters for Photofrin and an infusion time of τ = .083 h (5min), we have for $t \geq .083$ that. The plasma concentration is

$$C_A = 4.08e^{-.00134\,(t-.083)}$$

We convert C_A to Molarity by dividing the concentrations by the molar mass of Photofrin (596798.4 mg/mol), which means we redefine C_A to be

$$C_A = \frac{1}{596798.4}\left(4.08e^{-.00134(t-.083)}\right)$$

We use the arterial concentration C_A to model Photofrin's concentration within a region that contains both arterial and non arterial tissues. We adapt the blood and tissue flow equations in [7], where a two-stage blood flow model sufficiently estimates tissue concentration of radioactively labeled water. We let C_p (t) be the Photofrin concentration at time t in the non-arterial tissue and $C_{porph}(t)$ be the photofrin Concentration in the entire region. We let k_1 and k_2 be the tracer rate constants that describes the flow from tissue to blood and from blood to tissue; respectively. Allowing V_A to be the percentage of arterial tissue in a region, we use the following model to calculate a region's concentration at time T,

$$\left.\begin{aligned} C_p(T) &= k_1\int_0^T C_A(t)\,dt - k_2\int_0^T C_p(t)\,dt \\ C_{Porph}(T) &= V_A C_A(T) + C_p(T) \end{aligned}\right\} \quad \ldots\ldots \quad (1)$$

We assume that the rates k_1 and k_2 are the same ($k_1 = k_2 = 1$). The time interval is divided into equal time steps of length Δt, and we have from [7] that Model (1) leads to the following approximate Photofrin concentration,

$$C_{Porph}(T) \approx$$

$$\frac{V_A C_A(T) + (k_1 + V_A k_2)\int_0^T C_A(t)\,dt - k_2\left[\int_0^{T-\Delta t} C_{Porph}(t)\,dt + \Delta t\, C_{Porph}(T-\Delta t)/2\right]}{1 + k_2\Delta t/2}$$

This approximation is exact as $\Delta t \downarrow 0.$

OPTIMIZATION MODEL: –

In this part we design an optimization model that is based on the rates $\alpha_{(p,a,t)}$ to be the rate at which Photofrin is activated in region *p* by a light source focused along angle *a* at time *t*

$$\alpha_{(p,a,t)}x_{(a,t)}$$

We point out that our problem is similar to that of optimally designing radiotherapy treatments, for which a substantial literature already exists [1, 4, 9]. From an optimization perspective, the problems are nearly identical, and we modify the model in [9] to meet our needs. However, radiotherapy uses high-energy particle physics to model how ionizing radiation damages cells, whereas PDT uses biochemical models to understand how an activated photosensitizer destroys tissue.

If $X_{(a,\,t)}$ be the time (in seconds) that a light source is directed along angle *a* in time period *t.* Since $\alpha_{(p,a,t)}$ is the rate, at which the concentration of activated Photofrin accumulates in regions *p,* we have that the concentration of activated Photofrin accumulates in regions *p* is $\sum_{(a,t)}\alpha_{(p,a,t)}x_{(a,t)}$. Notice that we are assuming an additive accumulation of activated Photofrin, which means that we are ignoring cell regeneration during treatment. Cell growth and division have been investigated in the radiotherapy literature, where it is understood that cellular repair is negligible compared to the damage observed treatment.

We from a dose matrix, *A,* from the rate $\alpha_{(p,a,t)}$ by allowing the rows of *A* to be indexed by *p* and the columns by (a,t). Allowing *x* to be the vector of $x_{(a,t)}$ where the indices correspond to the columns of *A,* we have that $x \mapsto Ax$ is the linear operator that takes exposure times, *x,* and maps them to concentrations of activated Photofrin, *Ax.* We partition the rows of in the following way,

$$A = \begin{bmatrix} A_T \\ A_C \\ A_N \end{bmatrix} \begin{matrix} \leftarrow \text{Tumor dose points} \\ \leftarrow \text{Critical dose points} \\ \leftarrow \text{Normal dose points} \end{matrix}$$

With this notation we have that $A_T x, A_x$ and $A_N x$ are the concentrations of activated Photofrin in the tumorous, critical, and normal tissues, respectively.

One of our goals is to decide exposure times that best treat the patient. We assume that the patient image is divided into a 64 × 64 grid (so a patient image has 4096 regions).

CONCLUSION: –

Our model a photosonsitizer's blood and tissues concentration show that optimization can aid in the design and delivery of treatments, and investigate how increased localization in cancerous cells affects a treatment's success. As one would expect, magnifying a photo sensitizer's concentration in timorous tissue improves the optimal treatment.

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