Mathematical modeling of delivery of chemotherapeutic drugs to human tissues: an analytical approach

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Introduction

Man's war against dangerous afflictions has led to the development of potent formulations and requires complicated dosage patterns. They require controlled and targeted delivery to maximize therapeutic efficacy and minimize side-effects. Chemotherapy has been recognized as a successful means of arresting cancer, which is the third biggest killer among humans. Cancerous tumors are characterized by their rapid spread across the diseased tissue and successively deteriorating conditions. However, it necessitates repeated dosage at specific times, and conventional delivery methods result in unnecessary delay in reaching the targeted location and expose other organs to the effect of the drugs. The drug delivery is thus desired to be precisely targeted and controlled.

This has resulted in previous attempts at designing novel, bio-implantable, polymer-coated delivery devices that can release the drug at a specified rate. We design and model a novel device that allows electrically regulated release of an ionic drug through an electroactive polymer membrane into a tumor-affected tissue. Doped electro active polymers like polypyrrole show considerable ability to conduct ions and even behave as a switch by alternating its oxidized and reduced states on reversal of electric potential.

Our drug delivery device consists of a cylindrical capsule comprising of a drug reservoir containing the ionic drug solution and a set of batteries for creating the desired electric field. The entire capsule is surrounded by a layer of selectively doped electroactive polymer. The device has been implanted at the center of the tumor such that the tumor has progressed symmetrically from all sides. The anionic drug diffuses out under the action of the electric field, permeates through the electroactive membrane as it reacts with the charged polymer groups and is released into the tissue, where it reacts with the biological cells.

1. Modeling

The transport of the anionic drug into the affected tissue occurs due to three factors: the concentration gradient, the electric field created by the batteries and the reaction of the anionic drug with the polymer groups inside the doped-polymer membrane.

1.1 The potential distribution: The potential field distribution is not an independent entity but is a function of the distribution of the ions in the medium as also the strength of the fixed charges within the membrane. This distribution is obtained by application of the Poisson-Boltzmann equation, which is given by:

$$\nabla^2\psi = -\frac{1}{\varepsilon}\left[\rho^* - 2qn_o \sinh\left(q\psi \Big/ kT\right)\right], \tag{1.1}$$

where, ψ is the potential distribution, ρ^* is the fixed charge density, ρ of the surrounding membrane normalized over the entire space of the reservoir, i.e. $\rho^* = \rho\left(\nu_m / \nu_s\right)$, ν_m and ν_s being the volumes of the membrane and solution respectively, n_o is the no. density of ions in the drug solution and q is the basic unit of electric charge. Eq.(1.1) is solved to get the potential distribution.

1.2 Transport in the reservoir: The transport in the drug reservoir in the presence of the electric field is given by the Nernst-Planck equation which may be expressed as:

$$\frac{\partial c_D}{\partial t} + \nabla\left[-D_s\left\{\left(\nabla c_D\right) + \frac{zF}{RT} c_D\left(\nabla\psi\right)\right\}\right] = 0\,, \tag{1.2}$$

Some assumptions are made for the solution of this equation analytically. They are (i) the drug reservoir has infinite amount of drug, i.e., there is no depletion of drug within the reservoir, (ii) there are no convection effects in the system and (iii) the membrane is thin compared to the diameter of the reservoir. Based on these assumptions, the solution of eqn. (1.2) is given by

$$c = c_o^s\left(t - \frac{R-r}{D_s k_1}\right)\exp\left[\frac{k_2}{k_1}\left(R-r\right)\right], \tag{1.3}$$

1.2.2 Electric double layer: The **Nernst-Planck-Poisson (NPP)** system of model equations was used to model the system during the positive scan. For the negative scan, the sign of the potential will be reversed and there will also be the formation of the electric double layer. We use the modified-Stern model to quantify the effect of the electric double layer on the applied electric potential and the **Nernst-Planck-Poisson-Modified Stern (NPPMS)** equation is

$$\frac{1}{D_s}.\frac{\partial\hat{c}}{\partial t} = -k_1'\frac{\partial\hat{c}}{\partial r'} + k_2'\left(\hat{c} + c_b\right), \tag{1.4}$$

solving which we get:

$$c = c_o^s\left(t + \frac{R-r}{D_s k_1'}\right)\exp\left[\frac{k_2'}{k_1'}\left(R-r\right)\right], \tag{1.5}$$

1.3 Transport in the polymeric membrane: For modeling the transport in the membrane, we do not need to find out a separate potential distribution. Since the membrane (~ 10^{-3}m) is very thin compared to the reservoir, we can assume the potential to follow a linear profile, with the same slope as that near the membrane.

1.3.1 Positive scan: The drug transport within the membrane is modeled with the same Nernst-Planck (NP) equation, with an extra reaction term being included due to the interaction between the drug and polymer group

$$\frac{\partial c_D}{\partial t} = \hat{D}_m \left(\frac{\partial^2 c_D}{\partial r^2} + \frac{1}{r}\frac{\partial c_D}{\partial r} \right) + D_m \frac{zFs}{RT}.\frac{\partial c_D}{\partial r} - k_f c_p c_D \quad , \tag{1.6}$$

where, $\hat{D}_m = D_m - RTk$

Taking $r' = \frac{r - R}{h}$ we have the solution of Eq.(1.8) as:

$$c_D = c_o \left(t - \frac{r'}{\mu} \right) \exp\left(-\frac{k_f P_o}{\mu} r' \right), \tag{1.7}$$

1.3.2 Negative scan: The same form of the NP equation is used here for the drug D but with the sign of the potential reversed.

$$\frac{\partial c_D}{\partial t} = \hat{D}_m \left(\frac{\partial^2 c_D}{\partial r^2} + \frac{1}{r}\frac{\partial c_D}{\partial r} \right) - D_m \frac{zFs}{RT}.\frac{\partial c_D}{\partial r} + k_r c_c \quad , \tag{1.8}$$

where, $\hat{D}_m = D_m - RTk$

For the complex C, we can write:

$$\frac{\partial c_c}{\partial t} = D_c \left(\frac{\partial^2 c_D}{\partial r^2} + \frac{1}{r}\frac{\partial c_D}{\partial r} \right) - k_r c_c \, , \tag{1.9}$$

Putting, $r' = \frac{r - R}{h}$ and $\mu' = \frac{D_m F s'}{RTh}$ we have the solution of Eq.(1.10) as:

$$c_D = c_o \left(t + r'/\mu' \right) + \frac{1}{k_3} \left[k_r \left(t_p - r'/\mu' \right) - \frac{k_r}{k_3} \right] \exp\left(-k_r t - \frac{k_f P_o}{\mu'} r' \right) \quad , \tag{1.10}$$

where $k_3 = k_r - k_f P_o$

1.4 Transport and drug reaction in normal tissue: The tissue is considered separated into two compartments – the normal tissue and the tumor-affected tissue. The dimensions of the tissue being too large compared to that of the drug reservoir, the system can be approximately described by Cartesian coordinates.

$$\frac{\partial c_D}{\partial t} = D.\frac{\partial^2 c_D}{\partial x^2} + R \, , \tag{1.11}$$

The reaction of the drug is modeled by Michaelis-Menten kinetics as $R = \frac{v_{\max}.c_D}{c_D + K_m}$ which for low values of concentration can be approximated by a 1st order equation, given by:

$$\frac{\partial c_D}{\partial t} = D.\frac{\partial^2 c_D}{\partial x^2} - kc_D \,. \tag{1.12}$$

1.4.1 The negative scan: The governing equation along with the boundary conditions is:

$$\frac{\partial c_D}{\partial t} = D.\frac{\partial^2 c_D}{\partial x^2} - kc_D \qquad \begin{aligned} c(x,0) &= 0 \\ c(0,t) &= a - b\left(e^{-\alpha t} - 1\right) \\ c(1,t) &= a_1 + b_1 e^{-\beta_1 t} \end{aligned} \tag{1.13}$$

The solution using suitable boundary conditions is given by

$$c_D(x,t) = \left(a + b - be^{-\alpha t}\right)(1-x) + \left(a_1 + b_1 e^{-\beta t}\right)x + \sum_{n=1}^{\infty}\left[\frac{2Dn\pi \sin(n\pi x)}{P_n}\left\{(-1)^n\left(a_1 + b_1\right) - a\right\}e^{-P_n t}\right], \tag{1.14}$$

where, $P_n = Dn^2\pi^2 + k$, $a_1 = a + b$, $\alpha = \beta = k$.

1.4.2 The positive scan: The modeling for the positive scan will be carried out in much the same way as in the negative scan, but we use a Neumann boundary condition at the membrane-tissue interface and a Dirichlet condition at the other boundary. The spatial concentration profile at the end of the negative scan is used as the initial condition for the positive scan. The equation is

$$\frac{\partial c}{\partial t} = D.\frac{\partial^2 c}{\partial x^2} - kc\,, \tag{1.15}$$

$$\begin{aligned} c(x,0) &= f(x) = g + hx \\ \frac{\partial c}{\partial x}(0,t) &= 0 \\ c(1,t) &= a_1 + b_1 e^{-\beta t} \end{aligned} \tag{1.16}$$

The solution is

$$c_D(x,t) = b_1 e^{-kt} + 2\sum_{n=1}^{\infty}\left[b_1(-1)^n \frac{\cos\left(n-1/2\right)\pi x}{\left(n-1/2\right)\pi} e^{-M_n t}\right] - 2\sum_{n=1}^{\infty}\left[\frac{h\cos\left(n-1/2\right)\pi x}{\left(n-1/2\right)^2\pi^2} e^{-M_n t}\right] - 2\sum_{n=1}^{\infty}\left[(-1)^n \frac{(g+h)\cos\left(n-1/2\right)\pi x}{\left(n-1/2\right)\pi} e^{-M_n t}\right], \tag{1.17}$$

where, $M_n = D\left(n-1/2\right)^2\pi^2 + k$.

1.5 Transport and drug reaction in tumor-affected tissue: The drug diffusivity, *D* should have a lower value in the tumor region.

1.5.1 The negative scan

The corresponding solution for the tumor-affected region for the negative scan is:

$$c(x,t) = \left(a_1 + b_1 e^{-kt}\right)(1-x) + \left(a_1 + b_2 e^{-kt}\right)x + \sum_{n=1}^{\infty}\left[\frac{2Dn\pi \sin(n\pi x)}{P_n}\left\{a_1 + b_1 - (-1)^n (a_1 + b_2)\right\} e^{-P_n t}\right], \quad (1.18)$$

1.5.2 The positive scan

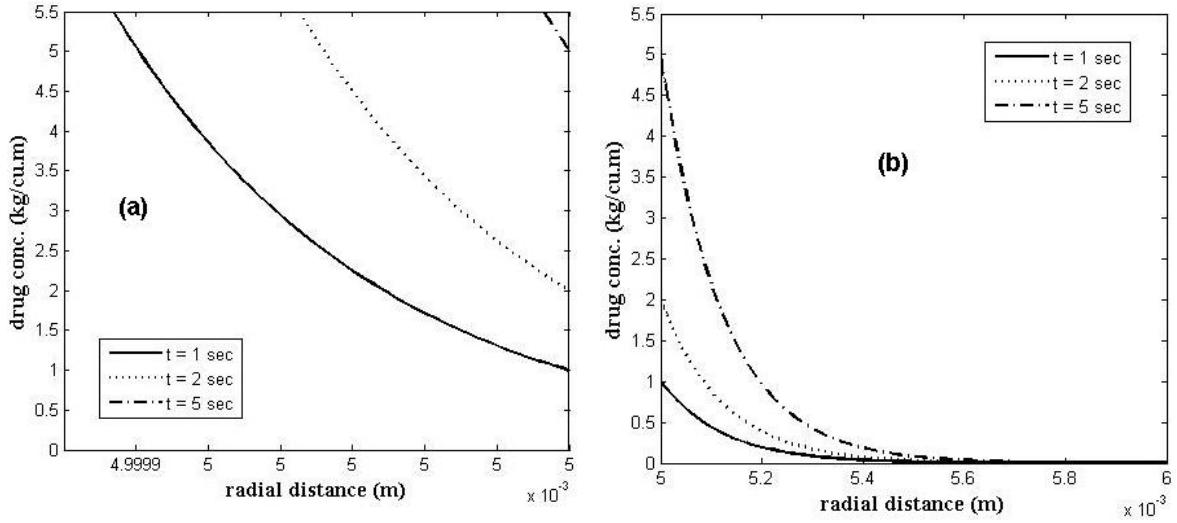
The corresponding solution for the tumor-affected region for the positive scan is:

$$c_D(x,t) = b_1 e^{-kt}(1-x) + b_2 e^{-kt} x + 2\sum_{n=1}^{\infty}\left[\frac{\sin(n\pi x)}{n\pi}\left\{p - (-1)^n (p+q)\right\} e^{-P_n t}\right] + 2\sum_{n=1}^{\infty}\left[\frac{\sin(n\pi x)}{n\pi}\left\{b_2 (-1)^n - b_1\right\} e^{-P_n t}\right]. \quad (1.19)$$

2. Results and discussions

The results are shown for the complete 4 compartment model having the drug reservoir, the membrane, the normal tissue and the tumor-affected tissue. Diffusivity of the drug in the four zones – the reservoir, the membrane, the normal tissue and the tumor-affected tissue are taken as 1.6×10^{-6} m^2/sec, 1×10^{-9} m^2/sec, 1.2×10^{-6} m^2/sec and 1.2×10^{-8} m^2/sec respectively. The voltage scan times for both positive and negative scans is taken as 5 seconds. Drug concentration in the reservoir solution is 0.1M and the dopant concentration in the membrane is 10M. The membrane chosen is polypyrrole. The drug and biological data conform to the diffusion of the anti-tumor drug doxorubicin in rat-liver.

2.1 Drug concentration: Figures 2.1 and 2.2 show the spatial plots of drug concentration at various times for the 4 compartments. The fast disappearance of drug in the membrane in the positive scan is due to the fast ionic reaction which converts the drug into the neutral complex. The reverse reaction is also fast and hence a constant profile is obtained in the same region during the negative scan, as the fast evolving anions are unable to diffuse out.



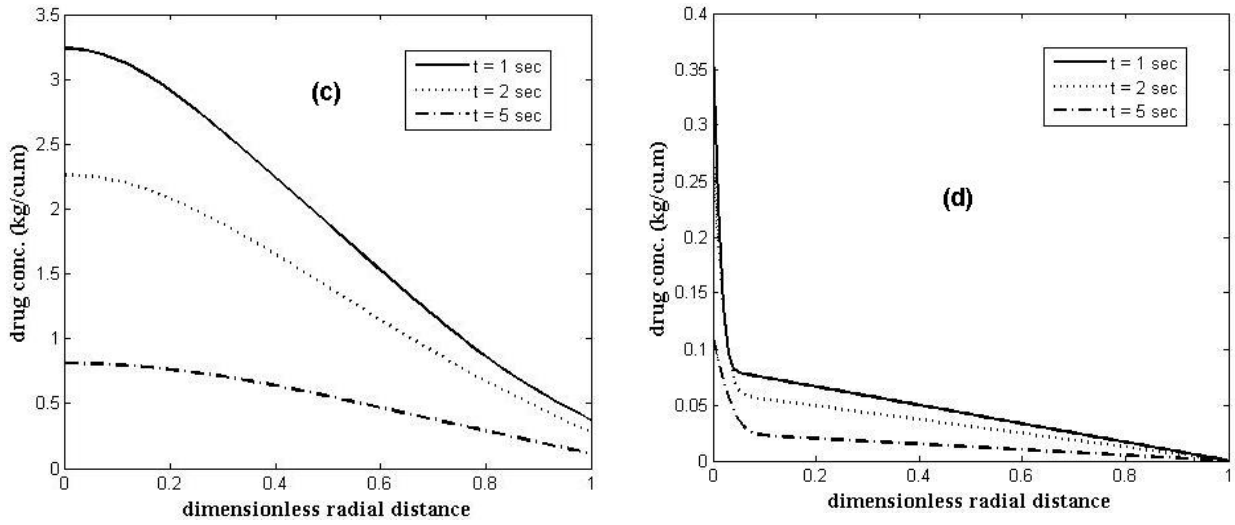


Figure-2.1: Spatial drug concentration plots during the positive scan for (a) reservoir, (b) membrane, (c) normal tissue and (d) tumor-affected tissue

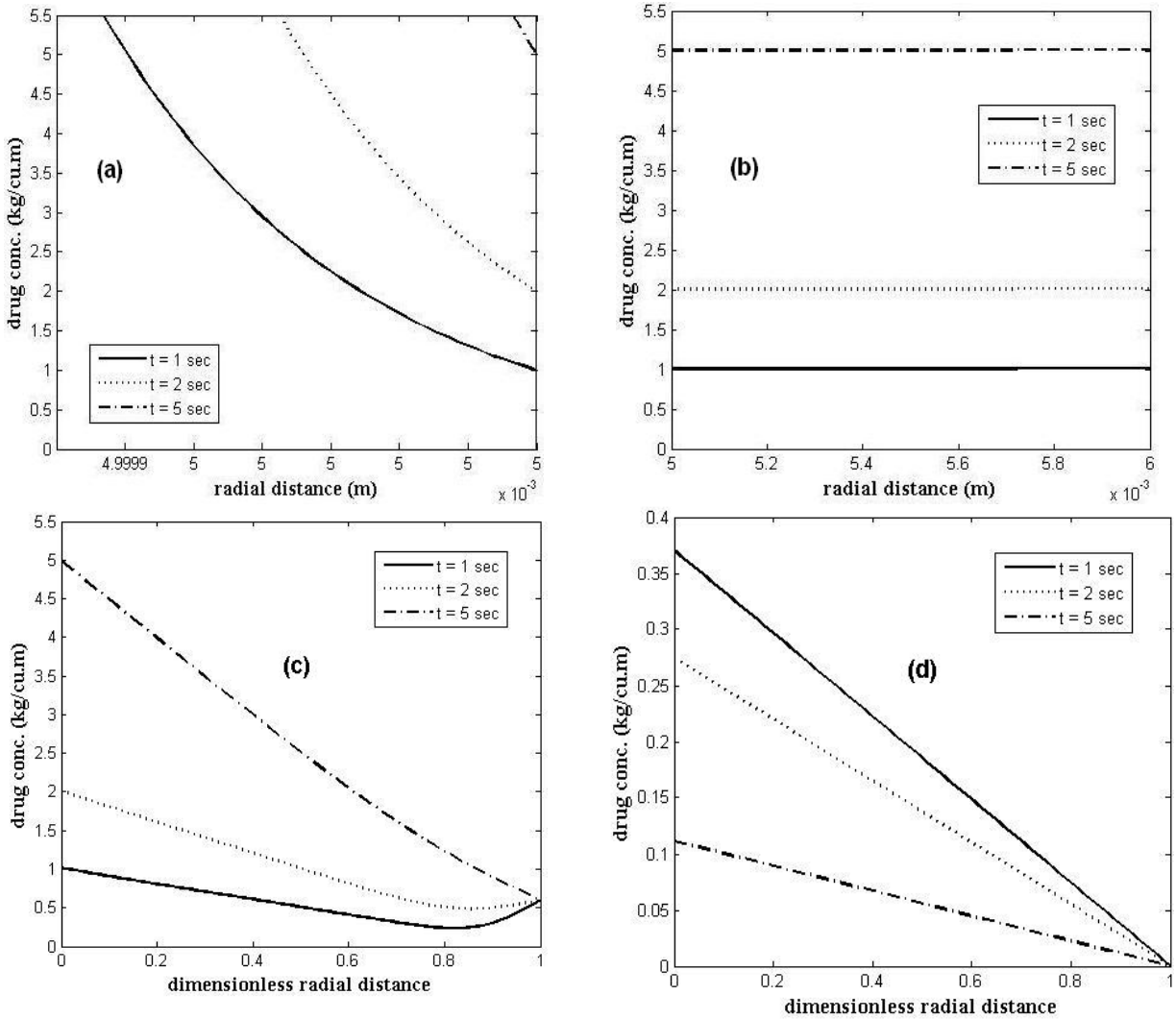


Fig 2.2: Spatial drug concentration plots during the negative scan for (a) reservoir, (b) membrane, (c) normal tissue and (d) tumor-affected tissue

3. Conclusion

Our modeling and simulation quantifies the drug concentration levels under normal conditions (characterized by the normal values of the parameters) and also for different parametric values. This can serve as an effective tool for predicting the drug level for a particular patient and help an oncologist make his decision regarding the optimal parametric values for a particular patient and his condition.

Voltage: Increase in voltage causes an increase in drug delivery rate and is the only option for drugs having a very high depletion rate. It is also an option for rapid drug supply in emergency situations.

Scan times: The study shows that the drug is stored in the membrane during positive scan which is released during the negative scan. Increase in positive scan times, with short negative scan times can supply the drug at high rate in short bursts, which may be required considering the physiological condition of the patient.

Membrane thickness: Reduction of membrane thickness increases the rate of drug delivery but also reduces the amount of drug that can be stored in the membrane during the positive scan. The thickness should be judiciously chosen keeping in mind whether the patient needs higher rate of drug supply or more amount of drug slowly over a longer period.

Therapeutic concentration: It is found that the solutions of the drug transport models predict a relation between various parameters of the boundary conditions. The therapeutic concentration – which in this model is a boundary condition – is also a design parameter that needs to be decided upon by the oncologist. So we have a relation between the therapeutic concentration required for the particular physiological condition and the voltage to be applied for the cure.

References:

[1] Blacher S., Jost M., Melen-Lamalle L., Lund L.R., Romer J., Foidart J.M., Noel A., Quanification of in-vivo tumor invasion and vascularization by computerized image analysis, *Microvascular Research* 75 (2008) 169-178.

[2] Bolto B.A and Weiss D.E, Electronic Conduction in Polymers. II. The Electrochemical Reduction of Polypyrrole at Controlled Potential, Australian *Journal of Chemistry* 16 (1963) 1076-1089.

[3] Gustafson D. A., Pritsos C. A., Kinetics and mechanism of Mitomycin C bioactivation by Xanthene Dehydrogenase under aerobic and hypoxic conditions, *Cancer Research* 53 (1993) 5470-5474.

[4] Helfferich F., Ion Exchange; McGraw Hill, NY, 1962.

[5] Lim J., Whitcomb J., Boyd J., Varghese J., Transient finite element analysis of electric double layer using Nernst-Planck-Poisson equations with a modified Stern layer, *Journal of Colloid and Interface Science* 305 (2007) 159-174.

[6] Ricka J., Tanaka T., Swelling of ionic gels: Quantitative performance of the Donnan Theory, *Macromolecules* 17 (1984) 2916-2921.

[7] Skotheim T.A., Elsenbaumer R. L., Reynolds J. R., Handbook of Conducting Polymers, CRC Press, 1998.

[8] Zhang J., Ye Z., Lou Y., Metabolism of chlorambucil by rat-liver microsomal glutathione S-tranferase, *Chemico-Biological Interactions* 149 (2004) 61-67.