COMPUTATIONAL MODELING: AN EMERGING APPLICATION FOR DRUG-COATED BALLOON THERAPY

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Abstract:

Computational modeling of biological and physical activities has become a popular method of assessing medical devices, offers some insight that can be used to explain present performance, inspire future designs, and even allow for individualized use. However, due to a lack of resources, one must make do with reduced-order computational models and ideal assumptions, which produce either qualitative or quantitative ways to solve challenges of concern. We presented two models for drug delivery to the artery wall considered: (i) 2-D drug-coated balloons (DCBs), and (ii) 3-D drug-eluting stents (DESs).

Keywords: Drug coated balloon, cardiovascular therapy, mathematical modeling.

1. Introduction

The emergence of computational modeling (CM) or simulations in the field of medical science for achieving accuracy in drug release is considered a revolutionary step by some experts [1,2]. An increased fascination with CM by the national regulatory division, medical device manufacturing companies, and local clinics stems from its ability to provide information on yield accuracy, the optimization of device design, and understanding the performance before implementation in a patient's specific environment but also in virtual feasibility studies before the execution of the procedures [3]. The most common application of the simulations is in cardiovascular procedures which already have a huge number of publications. Two of the main devices which are widely documented are balloon catheters or drug-coated balloons (DCB) and drug eluted stunts (DES) [4, 5]. These devices are used to manage the most lethal disease, the coronary heart disease (CHD). In CHD, the blockage occurs in blood vessels that supply blood to the heart. The blockage must be cleared to prevent cardiovascular problems that may even cause death. Disease progression and working (success or failure) of these devices depend on physicochemical within a physiologically complex environment [6]. By using these devices, the accurate delivery of chemotherapeutics is crucial [7]. Therefore, optimized performance and the design of the device needed to be handled carefully while the drug is being transported due to the flow of chemotherapeutic fluid, and reactivity of target tissues within the patient-specific environment.

2. DCB Therapy Model

DCBs seem to be a feasible therapeutic option for the treatment of CHD. DCBs enabled the delivery of chemotherapeutic drugs to the target location without any danger. From an

enlarged DCB the transient arterial tissue distribution is modeled as a 2-D time-dependent transport problem. Kolachalama et al. (2013) proposed a computational domain comprised of width (W = 0.5 mm) and an arterial cross-section with a radius of 3 mm [8]. A similar model was also presented by Kolandaivelu et al. with a similar thickness and radius [9]. According to the studies, the available drug was able to diffuse and bind with the target site with a constant diffusibility (Dw) in conformity with the reaction-diffusion equation:

$$\frac{\partial C}{\partial t} = D_w \nabla^2 C - k_a C(B_M - B) + k_d B \tag{1.1}$$

Here B and C denote the free chemotherapeutics in the arterial wall and the localized concentrations of bound, respectively, while the values of apparent net diffusivity (D_w) and the net tissue binding capacity (B_M) are 1.712×10^{-11} m^2 s^{-1} and 0.356 mmol l^{-1}, respectively. k_a and k_d are the association and dissociation rate constants and they can be calculated as $k_a = D_w D_a / B_M W_2$ and $k_d = k_a k_d$, where the Damköhler number and the equilibrium dissociation constant are denoted as Da and k_d [8].

Equation (1.1) can be solved subordinated to zero initial free plus bound chemotherapeutic concentrations within the target tissue, an ideal sink condition at the adventitial surface, and a flux boundary condition at the mural surface defined as:

$$J_b(t) = \{\frac{k_1 A_1 e^{-k1t}}{Z_{MW}} t \leq t_0 \, , t > t_0 \tag{1.2}$$
$$\quad 0$$

In this equation, the approximal releasing flux ($J_b^{(t)}$) of chemotherapeutics from DCB during inflation, DCB inflation time (t_0) 30 s. Experimental constants (A_1 = 23.95 kg m^{-3} and k_1 = 0.009208 s^{-1}) take the values from bench-top release kinetics experiments [8, 9]. The molecular weight of chemotherapeutics used is denoted as Z_{MW}, while zero concentration condition (A) was used for the free drug.

The constrained drug and the perivascular portions of the arterial wall can be assigned a zero-flux boundary condition. Byusing the Delaunay triangulation scheme, time-dependent simulations can be performed on the computational domain

3. The DES Therapy Model

DESs unlike DCBs stay permanently inside the heart. However, they are able to deliver sustained chemotherapeutics. Due to their extraordinary clinical approva, they are the primary choice for CAD [4]. In 2009, Kolachalama et al. and later O'Brien et al. (2013) adopted a 3-D computational model of DES [10, 11]. They used an atrial vessel with the diameter (D) of 3.6mm, a wall thickness (T) of 0.35mm and the length (L) of 11.36mm. While the dimension of the stent was D=3.5mm and shaped as a square sized $10^{-4} \times 10^{-4}$ m^2. They used steady-state flow to calculate the effect of pulsatile flow within the artery.
Inside the arterial lumen, they used the continuity equation

$$\nabla \cdot v_f = 0 \tag{1.3}$$

And momentum equation

$$\rho_f (v_f \cdot \nabla v_f) = -\nabla P + \mu_f \nabla^2 v_f \tag{1.4}$$

Where ρ_f and v_f are 1060 kg m^{-3}, μ_f and Pis 3.5×10^{-3}Pa · s and they represent density, velocity, viscosity of blood flow, and pressure. If the arterial wall is seen as porous surface the continuity equation can be solved with the following formula:

$$\nabla \cdot v_t = 0 \tag{1.5}$$

Where, interstitial fluid velocity is v_t.

The momentum equation was solved with the assumption that it follows Darcy's Law.

$$\frac{\rho_t}{\epsilon}\left((v_t \cdot \nabla)\frac{v_t}{\epsilon}\right) = -\nabla P + \frac{\mu_t}{\in}\nabla^2 v_t - (\frac{\mu_t}{\epsilon K})v_t \quad (1.6)$$

Here, Darcy's wall permeability (K) is 1.43×10^{-18} m^2, and wall porosity (ε) is 0.43. While fluid density (ρ_t) and fluid viscosity (μ_t) are 1000 kg m^{-3} and 8.9×10^{-4} Pa · s, respectively [12]. The advection-diffusion process that is usually used for the modeling of chemotherapeutics transportation in the lumen is defined as:

$$v_f \cdot \nabla C_f = D_f \nabla^2 C_f \quad (1.7)$$

Here, the drug concertation in the lumen is denoted by C_f and model drug infusibility in the lumen is denoted by D_f. The transportation of the drug in the walls of the arteries follows the model named advection–diffusion–reaction and is written as:

$$v_t \cdot \nabla C_t = D_t \nabla^2 C_t - k_a C_t (B_M - B) k_d B \quad (1.8)$$

In this equation, the infusibility of chemotherapeutics in the walls of the artery is represented as D_t., while local concentrations of free and bound chemotherapeutics in the walls of the artery are represented as C_t and B, respectively. The net tissue binding capacity (B_M) is 1.3mM. Association and dissociation rate constants are denoted by k_a and k_d, respectively. Association and dissociation rate constants can be calculated as:

$$k_a = \frac{D_t D_a}{B_M T^2} \quad (1.9)$$

$$k_d = k_a k_d \quad (1.10)$$

Here, the Damköhler number and equilibrium dissociation constant are represented as Da and k_d, respectively [11].

4. Gaussian Process Modelling (GPM)

GPM is a bayesian supervised machine learning framework that has been widely used in the classification and regression applications. When training DCB and DES models, a predefined set of *l* input vector is necessary:

$$X = [x^1, x^2, \ldots\ldots, x^l] \epsilon \mathbb{R}^{q \times 1} \quad (1.11)$$

Here, q = 2J + 1 with assumed available output correspondent values of:

$$y = [y^1, y^2, \ldots\ldots, y^l] \epsilon \mathbb{R}^l \quad (1.12)$$

By utilizing this training model, the prediction of output y(x) can be created for a new point x [13]. Therefore, we can write the equation for GPM as:

$$Y(x) = \beta + Z(x) \quad (1.13)$$

In this equation, *Z(x)* represents the Gaussian stochastic process with zero covariance and mean. While β denotes an unknown hyperparameter.

$$Cov(Z(x), Z(x')) = \sigma^2 R(x, x') \quad (1.14)$$

In this equation, σ^2 and $R(x, x')$ corresponds to process variance and correlation function. A frequently used correlation function that follows the rule of product correlation [13].

$$R(x, x') = \prod_{j=1}^{p} \exp\left(-\vartheta_j |x_j - x_j'|^{p_j}\right) \quad (1.15)$$

Here, $\vartheta_j = 0$ and $0 < p_j \leq 2$.

5. Conclusions

The Growing applications in health and medical device design require the scientific community to find efficient solutions to deliver high-fidelity knowledge. To solve this difficulty, a combination of machine learning and traditional physics-based computational models is ideal. In this paper, information about the possibility of fidelity augmentation in the domain of endovascular device-based pharmacological therapy was presented. The use of such a framework could aid computational tools in overcoming barriers, allowing them to be used in real-world medical applications with fundamental modeling complications and time-sensitive nature.

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