Some mathematical models for drug delivery

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Introduction

In this poster we consider two problems that model drug release systems. The first model consists of a system of reaction diffusion equations that model the evolution of free drug, bound drug and binding sites in a biological tissue (an artery wall, for example). In particular, we investigate the issue of drug clearance time from a tissue as a function of the binding parameter. The second problem models drug release from a thermoresponsive polymer. One well known thermoresponsive polymer is Poly(N-isopropylacrylamide) (PNIPAAm). This polymer is hydrophilic below the lower critical solution temperature (LCST) 32^0C, but hydrophobic above 32^0C, a property that can be exploited to act as an on/off switch to control drug delivery by varying temperature. Preliminary results indicate that there is good agreement between theoretical and experimental profiles.

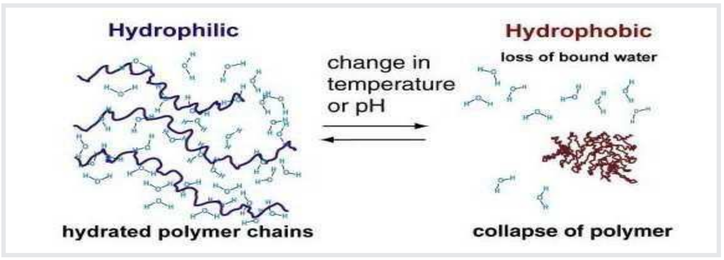

Figure 1: Above 32^0C, the polymer expels water and collapses.

Binding sites model

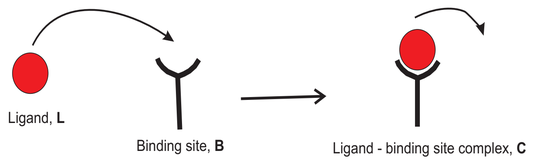

Figure 2: A ligand molecule can join a binding site and can subsequently leave this site.

Modelling issues: A ligand molecule **L** binding reversibly with a binding site **B** to form a ligand-binding site complex **C** can be represented by the chemical reaction

$$\mathbf{L} + \mathbf{B} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \mathbf{C}.$$

Denoting by L the concentration of **L**, B the concentration of **B**, and C the concentration of **C**, the approriate governing system of reaction diffusion equations is given by

$$\begin{aligned} \frac{\partial L}{\partial t} &= D\frac{\partial^2 L}{\partial x^2} - k_f BL + k_r C, \\ \frac{\partial B}{\partial t} &= -k_f BL + k_r C, \\ \frac{\partial C}{\partial t} &= k_f BL - k_r C, \end{aligned}$$

where D is diffusion coefficent of ligand, k_f is association constant between ligand and binding sites and k_r is dissociation constant.

Analysis and results: We denote by T, B_0 and L_0 a representative diffusion time, total concentration of binding sites and initial ligand concentration, respectively, and introduce the following dimensionless quantities:

$$\bar{t} = \frac{t}{T},\ \bar{x} = \frac{x}{\sqrt{DT}},\ \bar{L} = \frac{L}{L_0},\ \bar{B} = \frac{B}{B_0},\ \bar{C} = \frac{C}{B_0},$$

to obtain the following dimensionless equations (upon dropping the overbars for convenience):

$$\begin{aligned} \frac{\partial}{\partial t}(L + \eta C) &= \frac{\partial^2 L}{\partial x^2}, \\ \eta C &= K_b BL, \\ B + C &= 1, \end{aligned}$$

where $\eta = \frac{B_0}{L_0}$, $K_D = \frac{k_r}{k_f}$ is the equilibrium dissociation constant and $K_b = \frac{B_0}{K_D}$ is binding constant.

Assuming the binding reaction equilibriates quickly, we have shown that the reaction diffusion system above can be replaced by the following scalar diffusion model for a concentration dependent diffusivity

$$\frac{\partial C_T}{\partial t} = \frac{\partial}{\partial x}\left(D(C_T)\frac{\partial C_T}{\partial x}\right),$$

where $C_T = L + \eta C$ is the total impurity concentration and the concentration dependent diffusivity, $D(C_T)$, is given by

$$D(C_T) = \frac{1}{2}\left(1 + \frac{K_b C_T - K_b\eta + \eta}{\sqrt{(K_b C_T - K_b\eta - \eta)^2 + 4K_b\eta C_T}}\right).$$

It is easily seen that $D(C_T) \leq 1$ as would be expected since C_T contains the immobile species C.

Numerical solutions are calculated using MATLAB for the problem: drug delivery from the reservoir into the tissue. At $t = 0$, the concentration of drug is $L = L_0$ in reservoir and $L = 0$ in the tissue. The concentration of free drug $L(x,t)$ and the total impurity $C_T(x,t)$ are calculated by varying binding parameter K_b. The drug clearance time from a tissue is found as a function of the binding parameter.

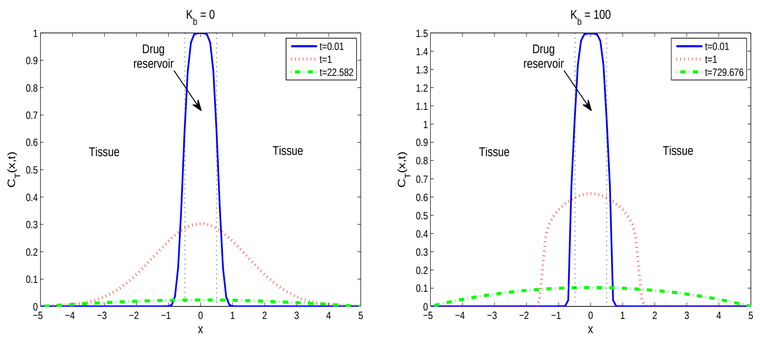

Figure 3: Numerical solutions of the total impurity $C_T(x,t)$ at various time with $\eta = 0.5$. For $K_b = 0$, 95% of drug has cleared the tissue at time $t = 22.582$ (left); and for $K_b = 100$, it is very slow to clear 95% of drug, $t = 729.676$ (right).

Modelling polymer swelling and collapsing

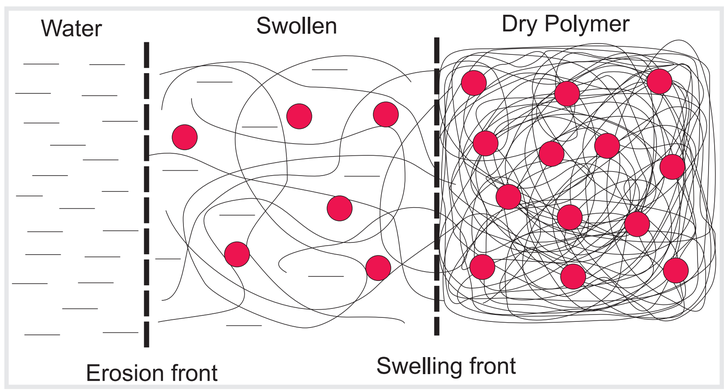

Figure 4: The polymer absorbs fluid and swells; moisture content in the polymer can affect the drug mobility significantly. Note that at least two moving boundaries need to be located: an erosion front and a swelling front.

Modelling issues: Denote by ϕ the volume fraction of water ($\phi = 0$: dry polymer; $\phi = 1$: pure water) and by c the concentration of drug in the polymer. The location of the erosion front and swelling front at time t are denoted by $s_w(t)$ and $s_c(t)$, respectively. Both the water diffusivity, $D_1(\phi)$, and the drug diffusivity, $D_2(\phi)$, depend on water content ϕ via a Fujita-type exponential dependence [5]:

$$D_1(\phi) = D_1\exp(\alpha\phi), D_2(\phi) = D_2\exp(\beta\phi),$$

with D_1, D_2, α, β are constants.

The volume fraction of water ϕ is determined by solving the following moving boundary problem

$$\begin{aligned} &\frac{\partial\phi}{\partial t} = \frac{\partial}{\partial x}\left(D_1(\phi)\frac{\partial\phi}{\partial x}\right) \quad \text{in } s_w(t) < x < s_c(t),\ t > 0, \\ &\phi = \phi_w,\ \ D_1\frac{\partial\phi}{\partial x} = (1-\phi_w)\frac{ds_w}{dt} \quad \text{on} \quad x = s_w(t),\ t > 0, \\ &\phi = \phi_c,\ \ D_1\frac{\partial\phi}{\partial x} = (-\phi_c)\frac{ds_c}{dt} \quad \text{on} \quad x = s_c(t),\ t > 0, \\ &s_w(0) = s_c(0) = 0, \end{aligned}$$

where ϕ_w is maximum water fraction that the polymer can absorb, and ϕ_c is critical water fraction above which the polymer undergoes polymer chain relaxation.

The conditions in $\frac{\partial\phi}{\partial x}$ on two boundaries were determined using conservation of polymer mass and conservation of fluid mass. We use these conditions to compute values of s_w and s_c at time $t > 0$.

As $\phi(x,t)$, $s_w(t)$ and $s_c(t)$ were calculated, the problem for the drug concentration $c(x,t)$ is given by

$$\begin{aligned} &\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D_2(\phi)\frac{\partial c}{\partial x}\right) \quad \text{in } s_w(t) < x < s_c(t),\ t > 0, \\ &c = 0, \quad \text{on} \quad x = s_w(t),\ t > 0, \\ &c = c_0, \quad \text{on} \quad x = s_c(t),\ t > 0, \end{aligned}$$

where c_0 is the initial drug loaded in the dry polymer.

Preliminary analysis and results: We have successfully numerically integrated the equations using a front-tracking method that uses explicit time-stepping and uses Lagrangian interpolation for points near the moving fronts. The numerical results are calculated using MATLAB.

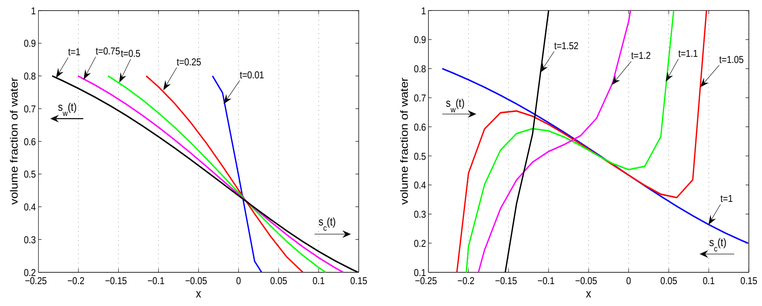

Figure 5: Volume fraction of water with $D_1 = 10^{-2}\exp(\phi)$, $\phi_w = 0.8$ and $\phi_c = 0.2$ at various time. At time $t = 1$, ϕ_w and ϕ_c switch values across the LCST in such a way that the erosion and swelling fronts change direction, accounting for the switch from swelling to collapsing behaviour.

Experimental data

Colleagues at the National Centre for Biomedical Engineering Science (NCBES) have provided us with experimental data for drug release profiles, and the behaviour observed has been successfully described using our modelling. The polymer used was PNIPAAm and drug released was Vinblastine; this drug is used in the treatment of restenosis. We see in the curves below that the agreement between experimental and theoretical profiles is excellent. In Figure 6, the curve on the left corresponds to high temperature $T > T_{LCST}$ and diffusion is extremely slow; using the method of least squares for the analytical solution

$$\frac{M(t)}{M(\infty)} = 1 - \sum_{n=1}^{\infty}\frac{8}{(2n-1)^2\pi^2}\exp\left(-\frac{(2n-1)^2\pi^2 Dt}{4H^2}\right),$$

we found that $D = O(10^{-15}cm^2/s)$ where D is the diffusivity. The curve on the right corresponds to low temperature $T < T_{LCST}$ and using least squares method we found that $D = O(10^{-9}cm^2/s)$, which is six order of magnitudes faster than diffusion for $T > T_{LCST}$.

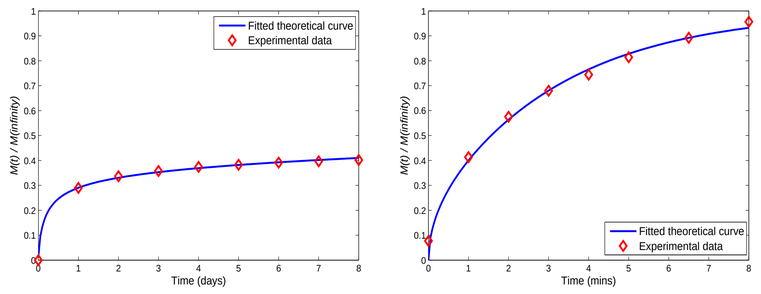

Figure 6: The percentage of total drug release at 37^0C with $D = 5.58\text{x}10^{-15}cm^2/s$ (left), and at 4^0C with $D = 4.71\text{x}10^{-9}cm^2/s$ (right).

Future work

I have recently developed a model to describe diffusion in a thermoresponsive polymer. This is a binary model where the material parameters ϕ_w and ϕ_c switch values across the LCST in such a way that the erosion and swelling fronts change direction, accounting for the switch from swelling to collapsing behaviour.

The next stage in this analysis is to calculate numerical solutions for parameter values corresponding to real systems. I also intend to calculate numerical solutions for higher dimensional problems; this may require the use of more sophisticated numerical techniques such as the level set method.

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