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A Thermally Activated Drug Delivery System Based on a Thermoresponsive Polymer and a Cooling Device: a Theoretical Assessment

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A mathematical model is developed to evaluate the feasibility of an in vivo implanted drug delivery system. The delivery device consists of a cooling material coated by a drug-loaded thermoresponsive polymer film. Drug release is initiated by remotely dropping the temperature of the cooling material sufficiently for the temperature throughout the polymer

coating to drop below its lower critical solution temperature (LCST), causing the polymer to swell and release the drug. Drug release switches off again when heat conduction from an external fluid medium raises the polymer temperature to above the LCST causing the polymer to collapse. Candidate cooling mechanisms based on endothermic chemical reactions, the Peltier effect, and the magnetocaloric effect are considered. In the thin polymer film limit, the model provides an upper bound for the temperature the cooling material must be lowered for drug release to be initiated. Significantly, the model predicts that the duration a thin polymer will continue to release drug in a single cycle is proportional to the square of the thickness of the cooling material. It is found that the system may be realised for realistic parameter values and materials. A simple illustrative calculation incorporating the presence of a heat source is presented, and the results suggest that conduction due to the initial temperature difference between the water and the cooling material can make the dominant contribution to heat transfer in the polymer as it reheats to its LCST.

1 Introduction

Thermoresponsive polymers undergo a volume phase transition in aqueous solution when the temperature of their fluid environment is varied across a critical value. If the polymer goes from being in a swollen, hydrophilic state to a shrunken, hydrophobic state as the temperature is increased through the critical value, the critical temperature is referred to as the lower critical solution temperature (LCST). The LCST of a thermoresponsive polymer can be readily varied by, for example, changing the pH or composition of its fluid environment, by varying the molecular weight of the polymer, or by the incorporation of hydrophilic or hydrophobic groups [1, 2]. LCST values as low as -7.5°C [1] and as high as 80°C [2] have been observed experimentally. Poly(*N*-isopropylacrylamide) (pNIPAm) is a thermoresponsive polymer that has been extensively studied [3, 4]. The LCST of pNIPAm occurs over a narrow temperature range, and is manifested as a sharp transition close to 32°C [5]. Furthermore, the LCST of pNIPAm can be easily increased to near human physiological temperature (37°C) [6, 7].

Thermoresponsive polymers have numerous potential applications in areas such as drug delivery [8–10], gene delivery [11], tissue engineering [12], chemical valve technology [13], and catalysis [14]. However, a biomedical device based on a thermoresponsive polymer that enables the pulsatile release of drug *in vivo* has yet to be developed, principally because of the difficulty of locally decreasing the temperature of human tissue *in vivo*. Nevertheless, candidate mechanisms for cooling polymers *in vivo* have been proposed, and some of these are now briefly discussed.

A potential chemically-based cooling mechanism is to add a substance to the polymer's fluid environment that gives rise to an endothermic chemical process. In an endothermic process, heat is absorbed from the environment as the reactions involved proceed causing a drop in its temperature. The dissolution of ammonium nitrate in water is an example of an

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endothermic process; when ammonium nitrate is dissolved in water at room temperature at a concentration of 1 M, a drop in fluid temperature of 6 K is observed. However, the choice of substances that could be safely used *in vivo* is limited since most endothermic reactions involve toxic chemicals [15].

Another candidate cooling mechanism is based on the Peltier effect, which is a thermoelectric phenomenon [16]. The Peltier effect arises at the junction of two dissimilar conductors through which a current is flowing, and refers to the transfer of heat from one of the conductors to the other across the junction. The Peltier effect allows for the transfer of heat at the junction against the temperature gradient, and cooling devices have been manufactured based on the effect [17, 18]. Bi_2Te_3 and Bi_2Se_3 [19] are amongst the best performing thermoelectric materials at room temperature, and exhibit a temperature-independent thermoelectric effect [20, 21]. A thermoelectric cooling device based on the Peltier effect has recently been developed by Morizane *et al.* [22] for the treatment of spinal cord injury in rats, although the cooling component of their device was deployed outside of the body as it was too large to be implanted *in vivo*. However, extremely thin thermoelectric cooling devices can now be fabricated that are less than 200 μm thick [23], making feasible the development of devices that may be implanted *in vivo*.

The magnetocaloric effect (MCE) provides another possible mechanism for externally lowering the temperature of the cooling material. The MCE refers to the heating or cooling of magnetic materials due to the application of time-varying magnetic fields. The effect, which has been substantially understood for a long time [24], is caused by the change in magnetic entropy of a material due to the application or removal of an external magnetic field. Specifically, the cooling of a magnetic material is caused by an increase in its magnetic entropy when an external magnetic field is removed. The MCE has been a subject of considerable interest since 1997 when Pecharsky and Gschneidner [25] discovered a giant MCE in some $\text{Gd}_5(\text{Si}_x\text{Ge}_{1-x})_4$ alloys. Many alloys have subsequently been found to possess a colossal MCE [24, 26], although only some of these were found to undergo their maximum temperature change close to room temperature and ambient pressure. Of these, only a very few were found to possess their MCE peak near physiological temperature (37°C). De Campos *et al.* [27] reported that the MCE peak of $\text{Mg}_{1-x}\text{Fe}_x\text{As}$ is at 37°C when x is 0.003.

The three cooling technologies just described can in principle be used to locally decrease the temperature of tissue in the body. It should be emphasised, however, that a system will only be of practical value if it can be manufactured at a sufficiently small scale for it to be implanted *in vivo*.

In this paper, a mathematical model is formulated to investigate the feasibility of developing a pulsatile drug release system that is based on dropping the temperature of a thermoresponsive drug-loaded polymer coating below its LCST. The candidate cooling mechanisms discussed above are not incorporated in the modelling presented here. Rather, the model is used to determine the properties a cooling system should have for a drug release device to produce practically

useful pulsatile release profiles.

2 The mathematical model

Introduction

The proposed release system is composed of a thermoresponsive drug-loaded polymer bonded to a cooling device which consists of a slab of cooling material. The device and polymer are immersed in water that is initially held at a temperature above the polymer's LCST, so that the polymer is collapsed and drug release is negligible; see Fig. 1 (a). Drug delivery is initiated by quickly lowering the temperature of the cooling material sufficiently for the temperature throughout the adjacent polymer to drop to below its LCST, thereby causing the polymer to swell. Drug then releases from the swollen polymer. Drug release spontaneously switches off again when heat conduction from the fluid environment raises the polymer temperature to above its LCST causing it to collapse. In the current theoretical study, mathematical modelling is used to assess the feasibility of a system of this kind.

Modelling assumptions

The principal assumptions made in formulating the mathematical model are now listed.

- (i) Heat conduction in the cooling material, polymer and water is governed by Fourier's law of conduction.
- (ii) The thermal conductivity and diffusivity of the cooling material, polymer and water are taken to be constant. The thickness of the cooling material and polymer are also assumed constant and the water is taken to occupy an infinite domain. Although these are reasonable assumptions for the cooling material and the water, they are not valid for a thermoresponsive polymer since its properties and thickness change during the swelling and collapsing processes. However, for the important case of a thin polymer film, these assumptions are frequently acceptable since it will be shown in this study that the polymer temperature can then be dominated by the properties of the cooling material and the water. For polymers whose thickness is comparable to that of the cooling material, the assumptions of constant polymer conductivity, thermal diffusivity and thickness may be viewed as providing a starting point for the analysis of the system.
- (iii) The temperature and heat flux are taken to be continuous at the cooling material-polymer and polymer-water interfaces.
- (iv) It is assumed that the presence of drug does not affect the thermal properties of the polymer or the water. The model thus does not incorporate drug concentrations, and is used instead to predict the evolution of the temperature profiles in the cooling material, polymer and water. This is sufficient to establish the feasibility of the system.
- (v) The temperature of the cooling material may be instantaneously dropped to the same value throughout its vol-

ume. There is no further cooling of the system subsequent to this. These assumptions will not affect the conclusions of the modelling presented here since allowing for a finite cooling period will only serve to delay the reheating of the system by the fluid environment, thereby prolonging the time the polymer remains swollen.

- (vi) The phase transition for the polymer is assumed to be perfectly sharp, so that for temperatures immediately above its LCST, the polymer collapses fully.

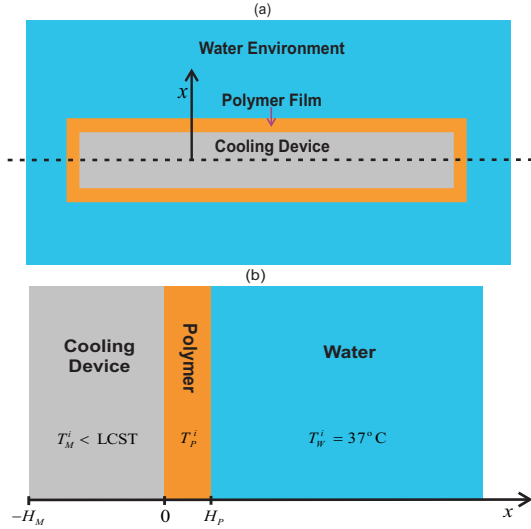


Fig. 1. A schematic representation of (a) the polymer coated cooling device, and (b) a slice of the cooling material, polymer, and water at time $t = 0$ in the semi-infinite domain $-H_M < x < \infty$. The complete system lies along the infinite domain $-\infty < x < \infty$, but is symmetric about the centreline of the cooling material at $x = -H_M$.

Geometry and model equations

For simplicity, the cooling device is taken to be composed of an infinite slab of homogeneous material of thickness $2H_M$ that occupies $-2H_M < x < 0, -\infty < y, z < \infty$. At $x = -2H_M$ and $x = 0$, the cooling material is taken to be in thermal contact with polymer films of thickness H_P . At $x = -H_M - H_P$ and $x = H_P$, the polymer films are in turn taken to be in thermal contact with water that occupies $-\infty < x < -2H_M - H_P$ and $H_P < x < \infty$. Water is chosen as the fluid medium here since it is the dominant component of biological fluids. The system is clearly symmetric about the centreline of the cooling material at $x = -H_M$, and so a symmetry condition is imposed at $x = -H_M$, and the semi-infinite domain $-H_M < x < \infty$ only is considered; see Fig. 1 (b).

The temperatures in the cooling material, polymer and water at location x and time t are denoted by $T_M(x, t)$, $T_P(x, t)$ and $T_W(x, t)$, respectively. The initial temperature of the entire system is taken to be at the constant temperature of the water, T_W^i , say. Since the behaviour of the device in the human body is being modelled, T_W^i is taken to be 37°C in the numerical calculations of this paper. The LCST of the thermoresponsive polymer is denoted by T_L , and it is supposed

that $T_L < T_W^i$ so that the polymer is initially in its collapsed state. At time $t = 0$, it is assumed that the temperature throughout the cooling material is instantaneously lowered to $T_M^i < T_L$. The purpose of the analysis of this paper is to investigate the subsequent temperature evolution for $t > 0$ in the adjoining polymer, and in particular, the possibility of the polymer temperature dropping to below its LCST throughout its thickness so that it can swell and release drug. The subsequent reheating of the polymer above its LCST due to heat conduction from the adjacent fluid medium will also be tracked.

In view of the discussion immediately above and the modelling assumptions of the previous section, the temperature in the cooling material $T_M(x, t)$ satisfies:

$$\begin{aligned} \frac{\partial T_M}{\partial t} &= k_M \frac{\partial^2 T_M}{\partial x^2} \quad \text{for } -H_M < x < 0, t > 0, \\ \frac{\partial T_M}{\partial x} &= 0 \quad \text{on } x = -H_M, t \geq 0, \\ T_M &= T_M^i \quad \text{for } -H_M < x < 0, t = 0, \end{aligned} \quad (1)$$

where k_M is the constant thermal diffusivity of the material. The boundary condition (1)₂ is the symmetry condition that allows the spatial domain to be halved. The temperature in the polymer $T_P(x, t)$ satisfies:

$$\begin{aligned} \frac{\partial T_P}{\partial t} &= k_P \frac{\partial^2 T_P}{\partial x^2} \quad \text{for } 0 < x < H_P, t > 0, \\ T_P &= T_W^i \quad \text{for } 0 < x < H_P, t = 0, \end{aligned} \quad (2)$$

where k_P is the constant thermal diffusivity of the polymer, and the temperature in the water medium $T_W(x, t)$ satisfies:

$$\begin{aligned} \frac{\partial T_W}{\partial t} &= k_W \frac{\partial^2 T_W}{\partial x^2} \quad \text{for } H_P < x < \infty, t > 0, \\ T_W &= T_W^i \quad \text{for } H_P < x < \infty, t = 0, \\ T_W &\rightarrow T_W^i \quad \text{as } x \rightarrow \infty, t \geq 0, \end{aligned} \quad (3)$$

where k_W is the constant thermal diffusivity of the water. Imposing continuity in temperature and heat flux at the cooling material-polymer and the polymer-water interfaces gives:

$$\begin{aligned} T_M &= T_P, \quad -K_M \frac{\partial T_M}{\partial x} = -K_P \frac{\partial T_P}{\partial x} \quad \text{on } x = 0, t \geq 0, \\ T_P &= T_W, \quad -K_P \frac{\partial T_P}{\partial x} = -K_W \frac{\partial T_W}{\partial x} \quad \text{on } x = H_P, t \geq 0, \end{aligned} \quad (4)$$

where K_M, K_P, K_W give the constant thermal conductivities of the cooling material, polymer, and water, respectively. The thermal diffusivities are related to the thermal conductivities via:

$$k_M = \frac{K_M}{\rho_M c_M}, \quad k_P = \frac{K_P}{\rho_P c_P}, \quad k_W = \frac{K_W}{\rho_W c_W}, \quad (5)$$

where, using an obvious notation, the ρ 's give the densities and the c 's the specific heat capacities of the three media. The ratio of the conductivity to the thermal diffusivity, $K/k = \rho c$, is referred to as the volumetric heat capacity of a material.

The mathematical model is now complete and consists of equations (1)-(4).

3 Results and discussion

3.1 The thin polymer film limit

In the appendices, a non-dimensionalisation of the governing equations (1)-(4) is presented, and the asymptotic limit $\varepsilon = H_p/H_M \rightarrow 0$ is considered, with the other independent dimensionless parameters arising being taken to be $O(1)$. This limit is of practical relevance since it corresponds to the case of a thin polymer film coating. It is found that $T_p \sim T_{p0}(t)$ as $\varepsilon \rightarrow 0$, where:

$$T_{p0}(t) = T_M^i - \frac{1}{2}(T_M^i - T_W^i)(1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{H_M n}{\sqrt{k_M t}} \right) + \operatorname{erfc} \left(\frac{H_M(n+1)}{\sqrt{k_M t}} \right) \right), \quad (6)$$

with:

$$\alpha = \frac{\sqrt{K_M \rho_M c_M} - \sqrt{K_W \rho_W c_W}}{\sqrt{K_M \rho_M c_M} + \sqrt{K_W \rho_W c_W}} = \frac{I_M - I_W}{I_M + I_W}, \quad (7)$$

where:

$$I_M = \sqrt{K_M \rho_M c_M}, \quad I_W = \sqrt{K_W \rho_W c_W},$$

give the thermal inertias of the cooling device and water, respectively. It is clear from (7) that $|\alpha| < 1$. It is noteworthy that at leading order, the temperature in the polymer does not depend on position, and is also independent of the conductivity, thermal diffusivity and thickness of the polymer. Hence, for a thin polymer film, the temperature in the polymer will frequently be dominated by the properties of the cooling material and the water medium, as would be expected.

An elementary calculation shows that T_{p0} is an increasing function of time for $|\alpha| < 1$ and $T_M^i < T_W^i$ so that the polymer has its minimum temperature at leading order immediately after the temperature in the cooling material has been lowered. From equation (6), this minimum temperature is given by:

$$T_{p0}(t) \rightarrow \frac{1}{2} \left((1 + \alpha) T_M^i + (1 - \alpha) T_W^i \right) = \frac{I_M T_M^i + I_W T_W^i}{I_M + I_W} \quad \text{as } t \rightarrow 0^+,$$

which is a weighted average of the initial temperatures of the cooling material and the water, with the weights being given by the thermal inertias of the two media. As time progresses, the leading order temperature of the polymer increases toward the initial water temperature, T_W^i . Hence, in the thin film limit, a necessary condition for the polymer to fully swell is that:

$$\frac{I_M T_M^i + I_W T_W^i}{I_M + I_W} < T_L, \quad \text{or,} \quad T_M^i < T_L - \frac{I_W}{I_M} (T_W^i - T_L). \quad (8)$$

The second inequality in (8) is of considerable practical value since it provides an upper bound for the temperature the cooling material must be dropped to for drug release to be initiated.

If inequality (8) is satisfied, it is of interest to estimate the time $t = t_L$ by which the polymer has heated back up to its LCST, as t_L then provides an estimate for the duration the polymer releases drug. If $t_L \sim t_{L0}$ as $\varepsilon \rightarrow 0$, then $T_{p0}(t_{L0}) = T_L$, and using equation (6):

$$\sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{H_M n}{\sqrt{k_M t_{L0}}} \right) + \operatorname{erfc} \left(\frac{H_M(n+1)}{\sqrt{k_M t_{L0}}} \right) \right) = \frac{2}{1 - \alpha} \frac{T_L - T_M^i}{T_W^i - T_M^i}. \quad (9)$$

Elementary calculations show that equation (9) has a unique solution $0 < t_{L0} < \infty$ provided $|\alpha| < 1$, $T_M^i < T_L < T_W^i$, and inequality (8) is satisfied. It also follows from equation (9) that t_{L0} has the general structure:

$$t_{L0} = \frac{H_M^2}{k_M} F \left(\frac{T_L - T_M^i}{T_W^i - T_M^i}, \frac{I_M - I_W}{I_M + I_W} \right), \quad (10)$$

for some function F , or:

$$t_{L0} = t_M F(\theta, \alpha), \quad (11)$$

where:

$$t_M = \frac{H_M^2}{k_M}, \quad \theta = \frac{T_L - T_M^i}{T_W^i - T_M^i}. \quad (12)$$

Note that $0 < \theta < 1$ for $T_M^i < T_L < T_W^i$ and that inequality (8) corresponds to $\theta > (1 - \alpha)/2$. In Table 1, values are displayed for $F(\theta, \alpha)$ in the range $(1 - \alpha)/2 < \theta < 1$, $|\alpha| < 1$, which were found by numerically solving equation (9) using the mathematical package MAPLE.

The formula (10) is instructive because it implies that in the thin film limit, the duration the polymer is held below its LCST is proportional to the square of the thickness of the cooling material. Since $F(\theta, \alpha) > 0$ for $(1 - \alpha)/2 < \theta < 1$, $|\alpha| < 1$, it is in principle possible to adjust the thickness of the cooling material so as to maintain the polymer in the swollen state for a desired time interval for *any* parameter pair θ, α with $(1 - \alpha)/2 < \theta < 1$, $|\alpha| < 1$. Furthermore, since the dependence on the thickness of the cooling material is quadratic, it is an effective parameter to adjust to tune the system. It is also noteworthy in equation (10) that the three temperature parameters T_M^i, T_L, T_W^i appear only in a single divided difference ratio. However, it remains to show that the system is realisable for realistic parameter values, and this issue is now addressed.

3.2 Cooling materials

The feasibility of a particular system may be evaluated using the formula (11) since t_{L0} estimates the time the polymer will remain in the swollen state. In (11), it is seen that t_{L0} depends on the three parameters t_M, θ and α . The parameter t_M depends on the properties of the cooling material only, θ depends on the three temperature scales that arise in the system (one each for the cooling material, polymer and water), and α depends on the ratio of the thermal inertias of the cooling material and water. It is noteworthy that in the thin film limit, the properties of the polymer only enter at leading order via its LCST in the parameter θ . However, it is clear that the properties of the cooling material are critical to the behaviour of the system.

In Table 2, parameter values for four potential cooling materials are displayed. However, only two of these materials, water and copper, are evaluated in detail here. Water is chosen because it may be used as the medium for a cooling system based on endothermic chemical reactions. Copper has a large thermal and electrical conductivity, and has been chosen to represent metallic materials; thermoelectric and

Table 1. Table of values for $F(\theta, \alpha)$ in the range $(1 - \alpha)/2 < \theta < 1$ and $0 \leq \alpha < 1$.

	$\alpha = 0$	$\alpha = 0.2$	$\alpha = 0.4$	$\alpha = 0.6$	$\alpha = 0.64$	$\alpha = 0.8$	$\alpha = 0.83$	$\alpha = 0.87$	$\alpha = 0.9$	$\alpha = 0.92$
$\theta = 0.05$										0.86
$\theta = 0.10$						0.01	0.72	1.61	3.05	5.05
$\theta = 0.15$						1.57	2.37	4.46	7.98	12.89
$\theta = 0.20$					0.60	3.38	4.94	9.01	15.90	25.50
$\theta = 0.25$				0.98	1.37	6.06	8.76	15.80	27.70	44.32
$\theta = 0.30$				1.79	2.39	9.89	14.23	25.53	44.66	71.35
$\theta = 0.35$			0.82	2.90	3.81	15.27	21.91	39.22	68.52	109.40
$\theta = 0.40$			1.40	4.41	5.76	22.77	32.62	58.31	101.81	162.49
$\theta = 0.45$		0.76	2.15	6.51	8.47	33.22	47.55	84.95	148.24	236.56
$\theta = 0.50$		1.25	3.18	9.44	12.26	47.89	68.53	122.37	213.51	340.68
$\theta = 0.55$	0.74	1.90	4.64	13.61	17.65	68.82	98.44	175.76	306.62	489.24
$\theta = 0.60$	1.22	2.80	6.73	19.67	25.50	99.35	142.10	253.68	442.54	706.06
$\theta = 0.65$	1.86	4.13	9.87	28.80	37.33	145.39	207.95	371.24	647.60	1033.23
$\theta = 0.70$	2.82	6.20	14.80	43.21	56.01	218.17	312.04	557.08	971.80	1550.48
$\theta = 0.75$	4.40	9.66	23.11	67.53	87.54	341.11	487.91	871.07	1519.58	2424.49
$\theta = 0.80$	7.27	16.07	38.55	112.83	146.28	570.27	815.72	1456.40	2540.75	4053.94
$\theta = 0.85$	13.47	29.96	72.11	211.39	274.11	1069.06	1529.29	2730.53	4763.69	7602.26

magnetocaloric cooling technologies typically involve metals.

Table 2. Parameters values for some potential cooling materials [28–31].

Material	Volumetric Heat Capacity	Conductivity	α
	$c\rho$ ($\text{J m}^{-3}\text{K}^{-1}$)	K ($\text{J m}^{-1}\text{K}^{-1}\text{s}^{-1}$)	
Water	4.2×10^6	0.6	0.00
Copper	3.4×10^6	386.0	0.92
Aluminum	2.4×10^6	204.0	0.87
Stainless Steel 316	3.9×10^6	13.4	0.64

In Fig. 2 (a), the leading order polymer temperature, $T_{p0}(t)$, has been plotted as a function of time, with copper being the cooling material. In the plot, $T_M^i = 32^\circ\text{C}$, $T_w^i = 37^\circ\text{C}$ (physiological temperature), and various thicknesses for the cooling material are used, ranging from 2 mm to 8 mm. The strong dependency of the behaviour on cooling material thickness is evident in these plots. If, for example, the LCST of the polymer is 35.5°C , then it is clear from the figure that a drug release time of some minutes may be achieved for a device thickness of some millimetres if a temperature drop of the order of 5°C can be induced in the cooling material. A drug release duration of a couple minutes for a single dose can be appropriate for many systems of practical interest; see, for example [32].

In Fig. 2 (b), plots for the leading order time it takes the polymer to reheat to its LCST, t_{L0} , are given as a function of T_M^i , the temperature to which the cooling material is initially dropped. In these plots, parameter values for both copper and

water being the cooling material are used, and $T_L = 35.5^\circ\text{C}$, $T_w^i = 37^\circ\text{C}$. It is evident from this figure that the system is realisable for reasonable parameter values for both materials.

3.3 Thicker polymers

The case where the polymer thickness is not small compared to that of the cooling material is now very briefly considered. For this case, the full set of equations (1)-(4) are integrated numerically. However, it should be emphasised again here that some of the modelling assumptions may not now be valid; see Section 2.

In Fig. 3, numerical solutions for the temperature of the polymer at its interface with the water medium are plotted as functions of time, that is, $T_p(H_p, t)$ versus t . The model predicts that the polymer will remain swollen while $T_p(H_p, t) < T_L$ since $T_p(x, t)$ has its maximum value at $x = H_p$. In the figure, parameter values for poly(methyl methacrylate) [33] have been used for the polymer; poly(methyl methacrylate) is known to have similar properties to pNIPAm in its collapsed state. The cooling material is water in Fig. 3 (a), and copper in Fig. 3 (b). The model predicts, as would be expected, that thicker polymers are more difficult to cool thoroughly, although the results also indicate that the system can be feasible for ratios H_p/H_M as large as $O(1/10)$.

3.4 Incorporating a heat source in the modelling

A limitation of the modelling presented here is that no attempt has been made to incorporate the possible presence of heat sources or sinks. In the human body, tissues generate heat via metabolic processes, and blood flowing in or nearby to tissue can exchange thermal energy with it. The subject

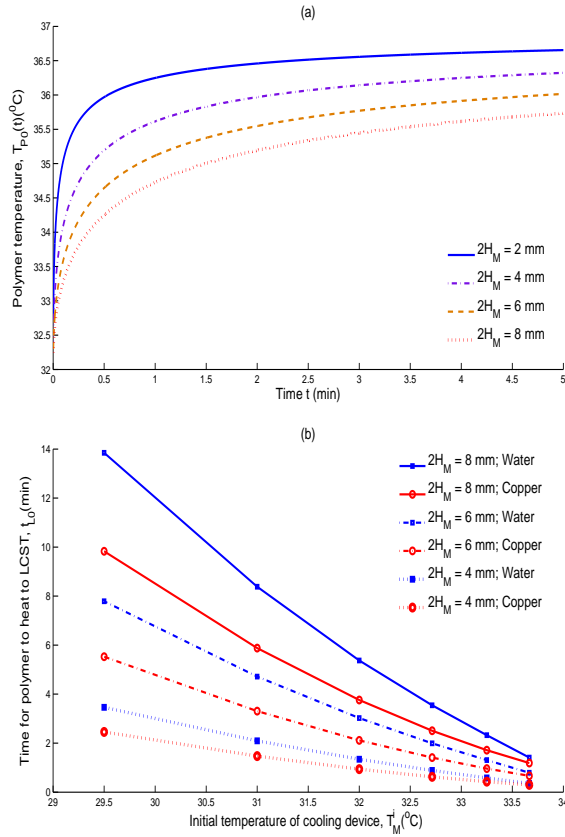


Fig. 2. (a) The leading order temperature of the polymer as a function of time, $T_{p0}(t)$, with copper being the cooling material. Here the initial temperature of cooling device and water are $T_M^i = 32^\circ\text{C}$ and $T_W^i = 37^\circ\text{C}$, respectively, and various cooling material thicknesses, $2H_M$, have been used. (b) The leading order time it takes the polymer to heat back up to its LCST as a function of T_M^i for various cooling material thicknesses. Here, the LCST is $T_L = 35.5^\circ\text{C}$, the initial temperature of the water is $T_W^i = 37^\circ\text{C}$, and plots for both copper and water being the cooling material are displayed.

of bioheat transfer has been extensively studied in the past, and numerous mathematical models have been proposed to describe it [34–38].

The model presented here can be justified for systems where heat conduction due to the initial temperature difference between the cooling material and the water makes the dominant contribution to heat transfer in the polymer as it reheats to its LCST. Fourier’s law implies that heat transfer via conduction at a given location is proportional to the temperature gradient at that location. In our system, the temperature gradients in and near a thin polymer are large for times $t \ll H_M^2/k_M$ and $t = O(H_M^2/k_M)$ compared to these gradients for times $t \gg H_M^2/k_M$ (with the dimensionless parameters other than H_p/H_M being $O(1)$), so that heat conduction in the polymer is strong in this sense for $t = O(H_M^2/k_M)$ or smaller. However, it should be emphasised that the model presented here cannot be used to estimate the time taken for a polymer to reheat to 37°C in the human body. This is because the model predicts that $T_p \rightarrow 37^\circ\text{C}$ as $t \rightarrow \infty$, and since heat conduction becomes weaker as time progresses, other

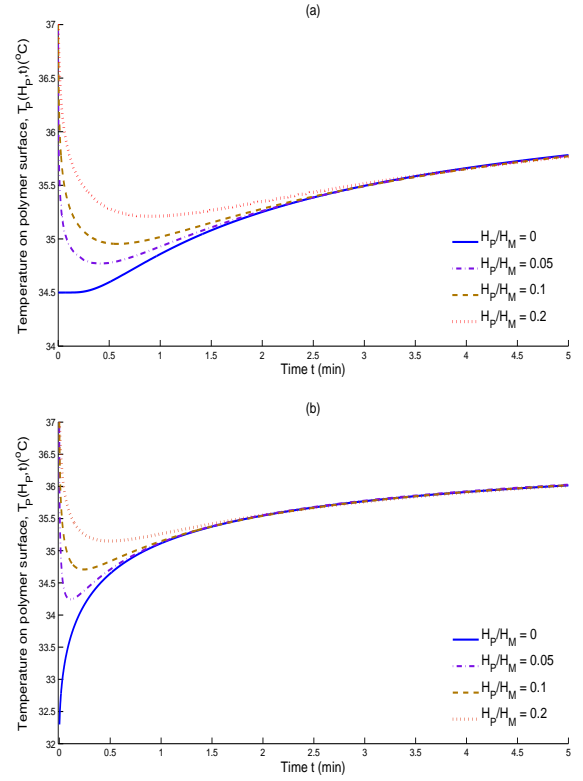


Fig. 3. Plots of the temperature at the polymer-water interface as a function of time for various ratios of the polymer thickness H_p to half the cooling device thickness H_M , with $H_M = 3$ mm. The cooling material is water in (a), and copper in (b). The thermal diffusivity and conductivity chosen for the polymer are $k_p = 1 \times 10^{-7} \text{m}^2 \text{s}^{-1}$ and $K_p = 0.15 \text{J m}^{-1} \text{K}^{-1} \text{s}^{-1}$, respectively. The initial temperature of the cooling device and the water are $T_M^i = 32^\circ\text{C}$ and $T_W^i = 37^\circ\text{C}$, respectively.

factors that can contribute to heat transfer, such as the presence of blood vessels or metabolism, can become significant, or even dominant, as time goes on.

A simple illustrative calculation is now presented that models the presence of a constant heat source at 37°C that is at a distance H_w from the polymer. This is achieved by replacing the boundary condition $T_w \rightarrow 37^\circ\text{C}$ as $x \rightarrow +\infty$ by:

$$T_w = 37^\circ\text{C} \quad \text{on } x = H_p + H_w. \quad (13)$$

This condition could serve as a crude model for the presence of a major artery at $x = H_p + H_w$, for example; more realistic models for heat transfer in the body can be found in the literature cited above. Numerical solutions corresponding to the boundary condition (13) are presented in Fig. 4, and the results are broadly as expected. It is seen that for $H_w \leq 6$ mm, the profiles for the first few minutes are close to the $H_w \rightarrow \infty$ curve, but that the curves with $H_w = 1, 6, 12$ mm recover to close to 37°C much more quickly than the $H_w \rightarrow \infty$ curve. This suggests that for some geometries and materials, heat conduction due to the initial temperature mismatch between the cooling material and the water can make the major contribution to heat transfer in the polymer in the first few minutes. In Table 3, numerical estimates for the time taken

for the polymer to reheat to its LCST and to 36.9°C are displayed for various separations between the polymer and the constant heat source, H_w .

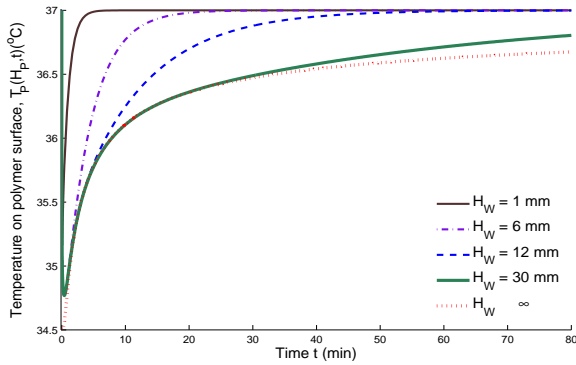


Fig. 4. Numerical solutions for the temperature at the polymer-water interface as a function of time, and for various separations H_w between the polymer and a constant heat source held at 37°C . The polymer is of thickness $H_p = 150 \mu\text{m}$, and the cooling material is water of thickness $H_M = 3 \text{ mm}$. The thermal diffusivity and conductivity chosen for the polymer are $k_p = 1 \times 10^{-7} \text{ m}^2 \text{ s}^{-1}$ and $K_p = 0.15 \text{ J m}^{-1} \text{ K}^{-1} \text{ s}^{-1}$, respectively. The initial temperature of cooling device and water are $T_M^i = 32^\circ\text{C}$ and $T_w^i = 37^\circ\text{C}$, respectively.

Table 3. Estimated times taken for the polymer to heat back to its LCST, $T_L = 35.5^\circ\text{C}$ (t_L), and to 36.9°C ($t_{36.9^\circ\text{C}}$), with water being the cooling material. The times are estimated for various separations H_w between the polymer and the heat source. The thickness of the cooling material and the polymer here are $2H_M = 6 \text{ mm}$ and $H_p = 150 \mu\text{m}$, respectively. The initial temperature of the cooling material is $T_M^i = 32^\circ\text{C}$, and of the water is $T_w^i = 37^\circ\text{C}$.

H_w (mm)	t_L (min)	$t_{36.9^\circ\text{C}}$ (min)
1	0.2	2.85
3	1.3	6.5
6	2.4	13.3
12	3.0	32.0
18	3.0	56.0
30	3.0	115.0
∞	3.0	840.0

4 Conclusions

A mathematical model has been developed to evaluate the feasibility of a proposed local drug delivery that may be implanted *in vivo*. The delivery system is composed of an

appropriate cooling material coated by a drug-loaded thermoresponsive polymer film. Some candidate cooling mechanisms for the device have been proposed based on endothermic chemical reactions, thermoelectric effects, and the magnetocaloric effect. In the thin polymer film limit, the model provides an upper bound for the temperature the cooling material must be dropped to for drug delivery to be initiated. The independent non-dimensional parameters governing the behaviour of the system have also been identified. For thin polymers, a useful formula has been derived to estimate the duration the polymer will remain swollen in a single cycle; in particular, it is found that this duration is proportional to the square of the cooling material thickness. A calculation that incorporates a constant heat source in the modelling has been presented. The results indicate that while the presence of heat sources in the body cause the polymer to recover to 37°C on a realistic time scale, heat conduction due to the initial temperature difference between the water and the cooling material can make the dominant contribution to heat transfer in the polymer for sufficiently small times. Finally, it has been established that the system may be realised for realistic materials and parameter values.

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Appendix A: Non-dimensionalisation and non-dimensional parameters

The independent non-dimensional parameters that may be varied to tune the system are identified by non-dimensionalising the governing equations (1)-(4). Introducing the dimensionless variables:

$$\bar{x} = \frac{x}{H_M}, \quad \bar{t} = \frac{t}{(H_M^2/k_M)}, \quad \bar{T}_M = \frac{T_M}{T_W^i}, \quad \bar{T}_P = \frac{T_P}{T_W^i}, \quad \bar{T}_W = \frac{T_W}{T_W^i},$$

the following dimensionless equations are obtained:

Cooling Material

$$\begin{aligned} \frac{\partial T_M}{\partial t} &= \frac{\partial^2 T_M}{\partial x^2} \quad \text{for } -1 < x < 0, t > 0, \\ \frac{\partial T_M}{\partial x} &= 0 \quad \text{on } x = -1, t \geq 0, \\ T_M &= T_{M/W}^i \quad \text{for } -1 < x < 0, t = 0, \end{aligned} \quad (14)$$

Cooling material/polymer interface

$$T_M = T_P, \quad -\frac{\partial T_M}{\partial x} = -K_{P/M} \frac{\partial T_P}{\partial x} \quad \text{on } x = 0, t \geq 0; \quad (15)$$

Polymer

$$\begin{aligned} \frac{\partial T_P}{\partial t} &= k_{P/M} \frac{\partial^2 T_P}{\partial x^2} \quad \text{for } 0 < x < \varepsilon, t > 0, \\ T_P &= 1 \quad \text{for } 0 < x < \varepsilon, t = 0, \end{aligned} \quad (16)$$

Polymer/water interface

$$T_P = T_W, \quad -\frac{\partial T_P}{\partial x} = -K_{W/P} \frac{\partial T_W}{\partial x} \quad \text{on } x = \varepsilon, t \geq 0, \quad (17)$$

Water

$$\begin{aligned} \frac{\partial T_W}{\partial t} &= k_{W/M} \frac{\partial^2 T_W}{\partial x^2} \quad \text{for } \varepsilon < x < \infty, t > 0, \\ T_W &= 1 \quad \text{for } \varepsilon < x < \infty, t = 0, \\ T_W &\rightarrow 1 \quad \text{as } x \rightarrow \infty, t \geq 0, \end{aligned} \quad (18)$$

where the over bars have been dropped for convenience, and where:

$$\begin{aligned} T_{M/W}^i &= \frac{T_M^i}{T_W^i}, \quad \varepsilon = \frac{H_P}{H_M}, \quad K_{P/M} = \frac{K_P}{K_M}, \quad K_{W/P} = \frac{K_W}{K_P}, \\ k_{P/M} &= \frac{k_P}{k_M} = \frac{K_{P/M} \rho_M c_M}{\rho_P c_P}, \quad k_{W/M} = \frac{k_W}{k_M} = \frac{K_W \rho_M c_M}{K_M \rho_W c_W}, \end{aligned} \quad (19)$$

are the non-dimensional parameters arising.

It is noteworthy from (19) that for a given polymer and cooling material, there are two parameters that may be independently varied to tune the system, namely the temperature ratio, $T_{M/W}^i$, and the geometrical parameter, ε . The remaining four quantities appearing in equation (19) are material parameters, and are fixed for a given choice of polymer and cooling material. If both the cooling material and the polymer are allowed to change, then in principle all six parameters in equation (19) may be independently varied.

The problem defined by equation (14)-(18) is linear and analytical progress is possible using, for example, the method of Laplace transforms [28]. However, the algebra arising is quite heavy and it is more convenient to solve the full problem numerically. Fortunately, a convenient analytical solution may be written down at leading order in the thin polymer film limit (which is probably the most important case from the point of view of applications), and this is considered now.

Appendix B: The thin polymer film limit

The asymptotic limit $\varepsilon = H_P/H_M \rightarrow 0$ is considered, which corresponds to the thickness of the polymer being small compared to the thickness of the cooling material. The remaining parameters are taken to be $O(1)$, and as $\varepsilon \rightarrow 0$ the following expansions are posed for $t = O(1)$:

$$T_M \sim T_{M0}(x, t) \quad \text{in } -1 < x < 0, \quad T_W \sim T_{W0}(x, t) \quad \text{in } x > 0.$$

It is easily shown that T_{M0} satisfies (14), T_{W0} satisfies (18) with $\varepsilon = 0$, and:

$$T_{M0} = T_{W0}, \quad -\frac{\partial T_{M0}}{\partial x} = -K_{W/M} \frac{\partial T_{W0}}{\partial x} \quad \text{on } x = 0, t \geq 0,$$

where $K_{W/M} = K_{P/M} K_{W/P} = K_W/K_M$. This leading order problem can be readily solved using Laplace transforms (similar problems are considered in the book [28], for example) to obtain:

$$\begin{aligned} T_{M0} &= T_{M/W}^i - \frac{1}{2}(T_{M/W}^i - 1)(1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{2n-x}{2\sqrt{t}} \right) + \operatorname{erfc} \left(\frac{2(n+1)+x}{2\sqrt{t}} \right) \right), \\ T_{W0} &= 1 + \frac{1}{2}(T_{M/W}^i - 1)(1 + \alpha) \sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{2n+x\sqrt{k_{M/W}}}{2\sqrt{t}} \right) \right. \\ &\quad \left. - \operatorname{erfc} \left(\frac{2(n+1)+x\sqrt{k_{M/W}}}{2\sqrt{t}} \right) \right), \end{aligned} \quad (20)$$

where:

$$\alpha = \frac{\sqrt{k_{W/M}} - K_{W/M}}{\sqrt{k_{W/M}} + K_{W/M}} = \frac{\sqrt{K_M \rho_M c_M} - \sqrt{K_W \rho_W c_W}}{\sqrt{K_M \rho_M c_M} + \sqrt{K_W \rho_W c_W}},$$

so that $|\alpha| < 1$. The leading order temperature in the polymer film, T_{P0} (say), is then given by:

$$T_{P0}(t) = T_{M0}(0, t) = T_{M/W}^i - \frac{1}{2}(T_{M/W}^i - 1)(1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{n}{\sqrt{t}} \right) + \operatorname{erfc} \left(\frac{n+1}{\sqrt{t}} \right) \right),$$

or, in dimensional terms:

$$T_{P0}(t) = T_M^i - \frac{1}{2}(T_M^i - T_W^i)(1 - \alpha) \sum_{n=0}^{\infty} \alpha^n \left(\operatorname{erfc} \left(\frac{H_M n}{\sqrt{k_M t}} \right) + \operatorname{erfc} \left(\frac{H_M(n+1)}{\sqrt{k_M t}} \right) \right).$$