Stents with controlled drug release rates

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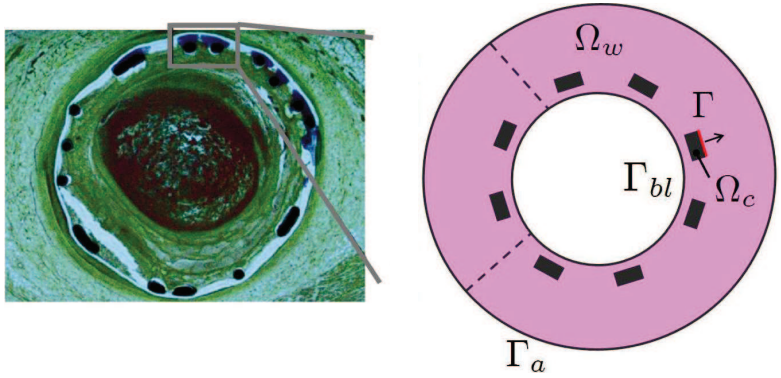
Controlled drug release

- *Diffusion controlled release*: drug dissolved in a matrix or a gel
- *Chemically controlled release*: degradation-dissolution of the polymer which bears the drug
- *Swelling controlled release*: diffusion induced by an inward flux

Aim: to achieve a prescribed (possibly time-dependent) release rate

Drug eluting stents

Courtesy of LaBS (Politecnico di Milano)



Cross section of an artery with an implanted stent

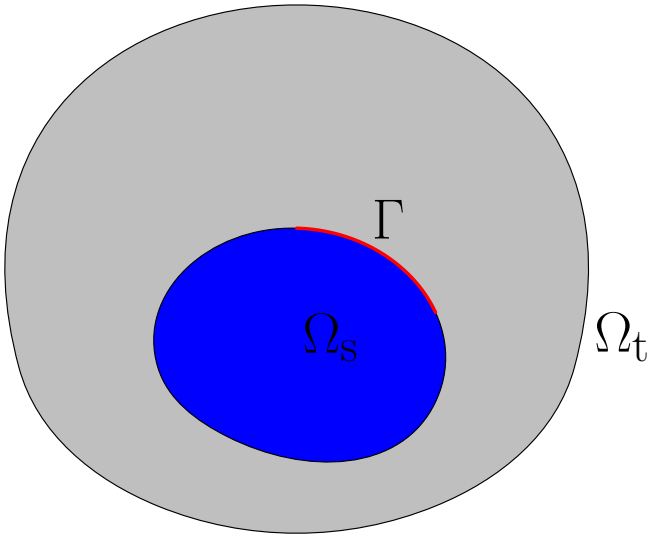
[L. Formaggia, S. Minisini, P. Zunino, 2010]

Model: geometry

Ω_t : (fixed) tissue domain

$\Omega_s \subset \Omega_t$: (possibly time-dependent) stent domain

$\Gamma \subseteq \partial\Omega_s$: (portion of the) interface where drug is released



Model: drug concentrations

We assume that the drug is initially loaded within Ω_{s} in its solid phase: let $S(X,T)$ be the solid drug density in $X \in \Omega_{\mathrm{s}}$ at the time T

The solid phase melts and yields a stent fluid phase concentration $C(X,T)$ within the stent

The fluid phase diffuses and eventually is released, giving rise to a tissue fluid phase concentration $C(Y,T)$, defined in $Y \in \Omega_{\mathrm{t}} \setminus \Omega_{\mathrm{s}}$

Erosion may destroy the stent by giving rise to a time-dependent $\Omega_{\mathrm{s}}(T) \subseteq \Omega_{\mathrm{s}}(0)$

Model: melting

[Noyes & Whitney, 1897; Frenning, 2003]

We assume that the solid drug melts at a rate

$$\frac{\partial S}{\partial T} = -K(S^+)^{\frac{2}{3}}(C_\mathrm{s} - C) \qquad \text{in } \Omega_\mathrm{s}$$

K: reaction coefficient

C_s: saturation concentration

The exponent $2/3$ follows from the assumptions that the solid drug is implanted in grains and that the melting occurs at the grains' area

$$R_\mathrm{g}(X,T) \sim S(X,T)^{\frac{1}{3}}, \qquad \frac{\partial S}{\partial T} \sim R_\mathrm{g}^2 \sim S^{\frac{2}{3}}$$

Model: transport/diffusion

[Higuchi, 1961; Sakarov et al, 2002]

The fluid drug diffuses with a possibly variable diffusion coefficients $D_{\rm s}(X,S,C,T)$, $D_{\rm t}$

$$\frac{\partial C}{\partial T} - \mathrm{Div}\,(D_{\rm s}\,\boldsymbol{\nabla} C) = K(S^+)^{\frac{2}{3}}(C_{\rm s}-C) \qquad \text{and}$$

$$\frac{\partial S}{\partial T} = -K(S^+)^{\frac{2}{3}}(C_{\rm s}-C) \qquad \text{in } \Omega_{\rm s}$$

$$\frac{\partial C}{\partial T} + \boldsymbol{u}\cdot\boldsymbol{\nabla} C - D_{\rm t}\,\Delta C = 0 \qquad \text{in } \Omega_{\rm t}$$

K: reaction coefficient

$C_{\rm s}$: saturation concentration

$\boldsymbol{u}$: flow velocity in the tissue

The solid drug is assumed not to diffuse

Model: erosion

[Uhrich et al, 1999]

The stent may dissolve during the release process

Erosion is defined either by specifying $\Omega_{\rm s}(T)$, or through a regression velocity $\mathbf{w} = -w\,\boldsymbol{\nu}$, with $\boldsymbol{\nu}$ the unit normal pointing towards $\Omega_{\rm t} \setminus \Omega_{\rm s}$, and $w \geq 0$

Several processes have been proposed for erosion

- $\Omega_{\rm s}(T) = \{S > 0\}$
- w, a prescribed function of time

Model: boundary/initial conditions

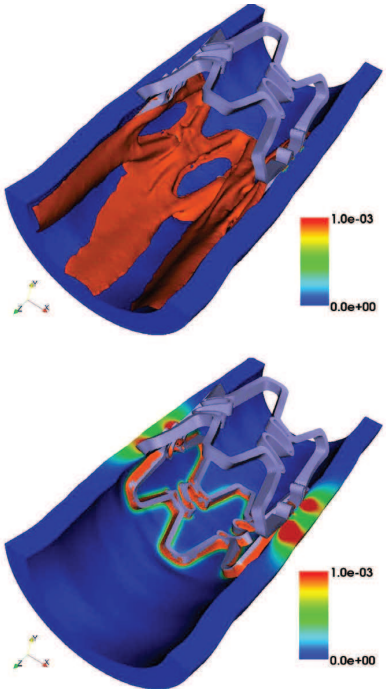
Initial conditions:

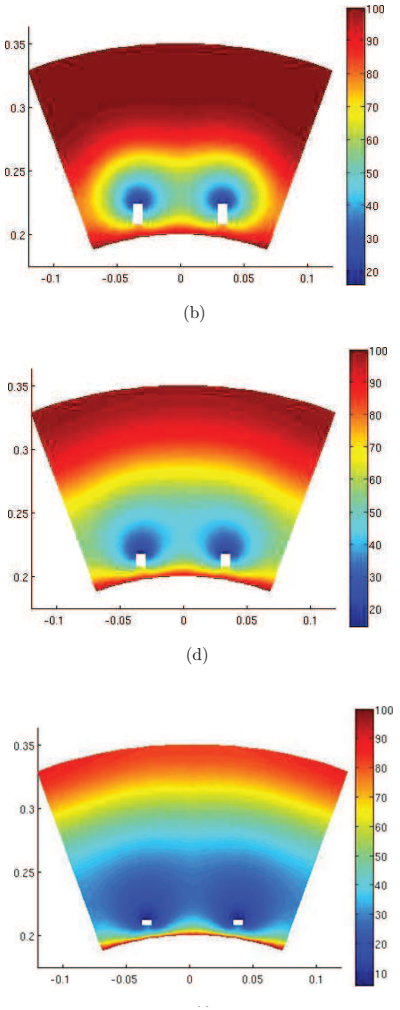
$$S(X,0) = S_0(X) \qquad \text{in } \partial\Omega_{\mathrm{s}}$$
$$C(X,0) = 0 \qquad \text{in } \partial\Omega_{\mathrm{t}}$$

Boundary conditions:

$$\boldsymbol{\nabla} C \cdot \boldsymbol{\nu} = 0 \qquad \text{on } \partial\Omega_{\mathrm{s}} \setminus \Gamma$$
$$D_{\mathrm{s}}\, \boldsymbol{\nabla} C \cdot \boldsymbol{\nu} + S\, w = D_{\mathrm{t}}\, \boldsymbol{\nabla} C \cdot \boldsymbol{\nu} \qquad \text{on } \Gamma$$
$$C \text{ continuous} \qquad \text{across } \Gamma$$
$$C = 0 \qquad \text{on } \partial\Omega_{\mathrm{t}} \setminus \partial\Omega_{\mathrm{s}}$$

Numerical results





(b)

(d)

[P. Zunino et al, 2009, L. Formaggia et al, 2010]

Target: release rate

Quantity of drug in the stent at time T

$$Q(T) = \int_{\Omega_s} \Big(C(X,T) + S(X,T) \Big) dV$$

Release rate $\quad R(T) = -\dot{Q}(T)$

$$R(T) = -\int_{\Omega_s} \frac{\partial}{\partial T} (C+S)\, dV + \int_{\partial\Omega_s} w(C+S)\, dA$$

$$= \int_{\Gamma} D_s\, \boldsymbol{\nabla} C \cdot \boldsymbol{\nu}\, dA + \int_{\partial\Omega_s} w(C+S)\, dA$$

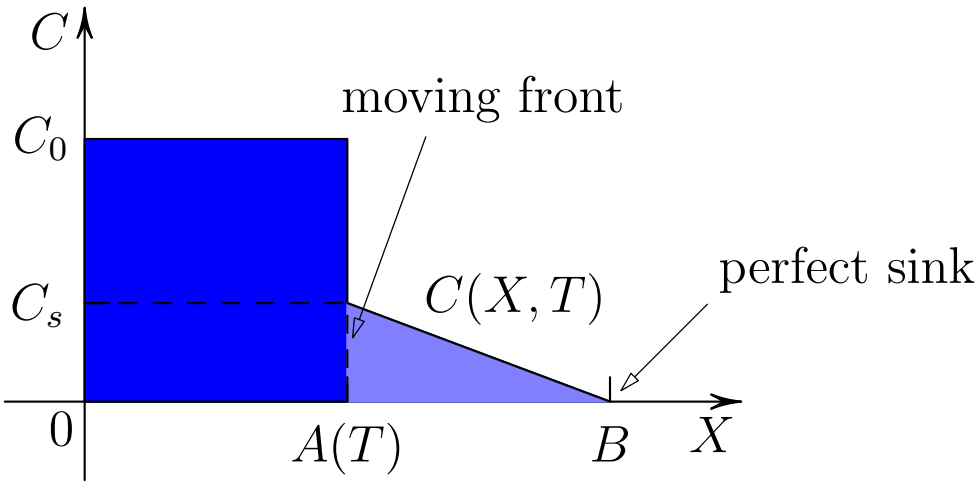
Aim: To achieve a prescribed release rate $R(T)$ by suitably tuning the design parameters $\quad \boldsymbol{\Omega_s}, \quad \boldsymbol{D_s}, \quad \boldsymbol{S_0}$

Simplifications: 1D Geometry,

$D_t \gg D_s \quad \Rightarrow \quad C \equiv 0$ outside Ω_s

Classical model: Higuchi

[Higuchi, J. Pharm. Sci. 1961]



Residual drug: $Q_{\text{res}}(T) = \int_0^{A(T)} C_0 \, dX + \int_{A(T)}^{B} C(X,T) \, dX.$

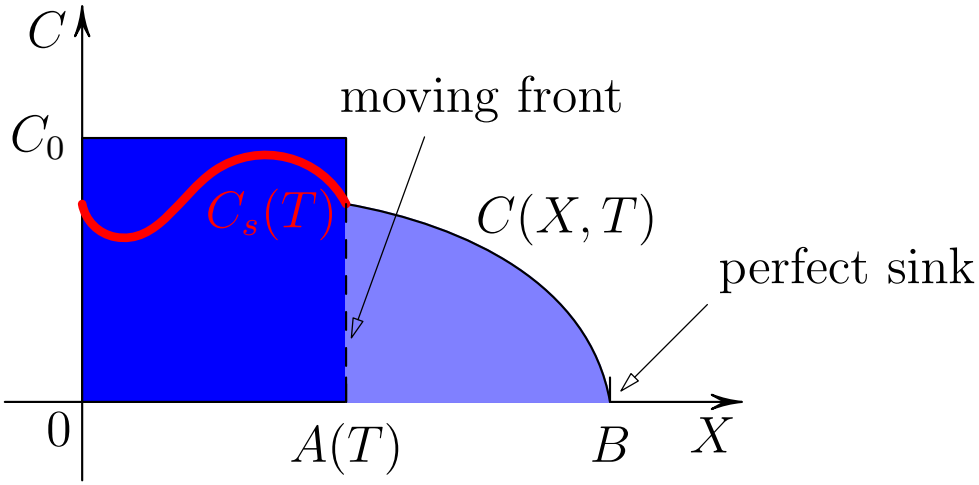
Quantity of drug released at time T:

$Q_{\text{rel}}(T) = Q_0 - Q_{\text{res}}(T) = Q_\infty \sqrt{T/\tau} \quad \Rightarrow \quad R(T) \sim T^{-\frac{1}{2}}$

(by assuming Fick's diffusion and $C_s \ll C_0$)

Variable solubility

[Cohen, Erneux, SIAM J. Appl. Math. 1998]



$$C_T = D\, C_{XX} \qquad \text{in } (A, B)$$

$$C(B, T) = 0$$

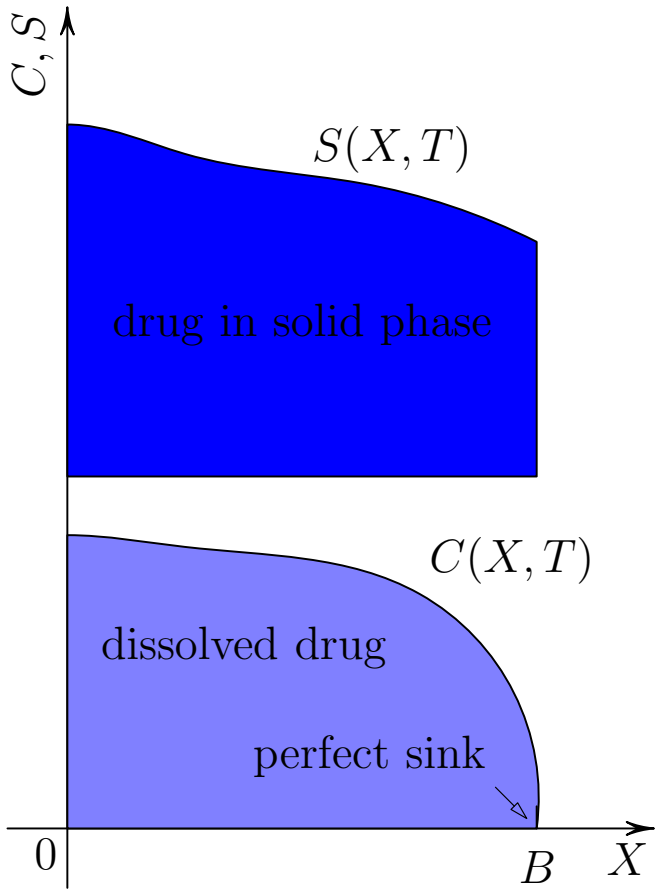
$$C\big(A(T), T\big) = C_s(T) \qquad \text{with prescribed } C_s(T)$$

$+$ mass conservation at $X = A(T)$

Release controlled by $C_s(T)$, but not easy to implement in practice

Biphasic drug release

[Frenning, J. Control. Release 2003]



$$C_T - D\,C_{XX} = K(S^+)^{\frac{2}{3}}(C_s - C)$$

and

$$S_T = -K(S^+)^{\frac{2}{3}}(C_s - C)$$

in (O, B)

$$C(X,0) = 0, \qquad S(X,0) = S_0(X)$$

$$C_X(0,T) = 0, \qquad C(B,0) = 0$$

Physical parameters: B, D, K, C_s; control function $S_0(X)$; no erosion

Adimensionalization

Let $\quad x = \dfrac{X}{B}, \quad t = \dfrac{KC_s^{2/3}T}{3}, \quad c = \dfrac{C}{C_s}, \quad s = \dfrac{S}{C_s}.$

Then the differential evolution problem can be stated as follows

$$\text{(RD)} \quad \begin{cases} c_t - \alpha c_{xx} = 3(s^+)^{2/3}(1-c) & 0 < x < 1,\ t > 0 \\ s_t = -3(s^+)^{2/3}(1-c) & 0 \le x \le 1,\ t > 0 \\ c(x,0) = 0, \quad s(x,0) = \sigma(x) & \\ c_x(0,t) = 0, \quad c(1,t) = 0. & \end{cases}$$

where now the only relevant (dimensionless) physical parameter is $\alpha = \dfrac{3D}{B^2 K C_s^{2/3}}$, and the control function is $\sigma = \dfrac{S_0}{C_s}$.

General properties of solutions 1/2

[P.B., S. Minisini, D. Pierotti, G. Verzini, P. Zunino, SIAM J. Appl. Math. 2011]

- The reaction-diffusion system (RD) admits a unique classical solution whenever $\sigma^{1/3}$ is piecewise of class C^2.

- Let $\sigma_1 = \max_{x\in[0,1]} \sigma(x)$ and $\lambda = \sqrt{3\sigma_1^{2/3}/\alpha}$. Then

$$0 \le c(x,t) \le 1 - (\cosh \lambda)^{-1} \quad \text{and} \quad 0 \le s(x,t) \le \sigma(x).$$

  As a consequence, s is a strictly monotonically decreasing function of time whenever it is not null. Finally, if $\sigma \neq 0$ in any finite interval, then $c = 0$ holds only at the initial time and at the point $x = 1$.

General properties of solutions 2/2

- The solid phase melts in a finite time since

$$s(x,t) \le \max\left\{\left(\sigma^{1/3}(x) - (\cosh\lambda)^{-1}t\right)^3, 0\right\}$$

Therefore we define the stopping time as

$$T(x) = \sup\{\bar{t} : s(x,t) > 0 \text{ in } [0,\bar{t})\} = \inf\{\bar{t} : s(x,t) \equiv 0 \text{ in } [\bar{t},+\infty)\}.$$

- The release rate is given by

$$R(t) := -\frac{d}{dt}\int_0^1 (c+s)\,dx = -\int_0^1 \alpha c_{xx}(x,t)\,dx = -\alpha\, c_x(1,t).$$

Large diffusion limit 1/2

Let $\alpha = 3D/\left(B^2 K C_s^{2/3}\right) \gg 1$.

- The solutions of (RD) admit a regular perturbative expansion such that

  $$c(x,t) = \alpha^{-1} c_1(x,t) + o(\alpha^{-1}), \quad s(x,t) = s_0(x,t) + \alpha^{-1} s_1(x,t) + o(\alpha^{-1})$$

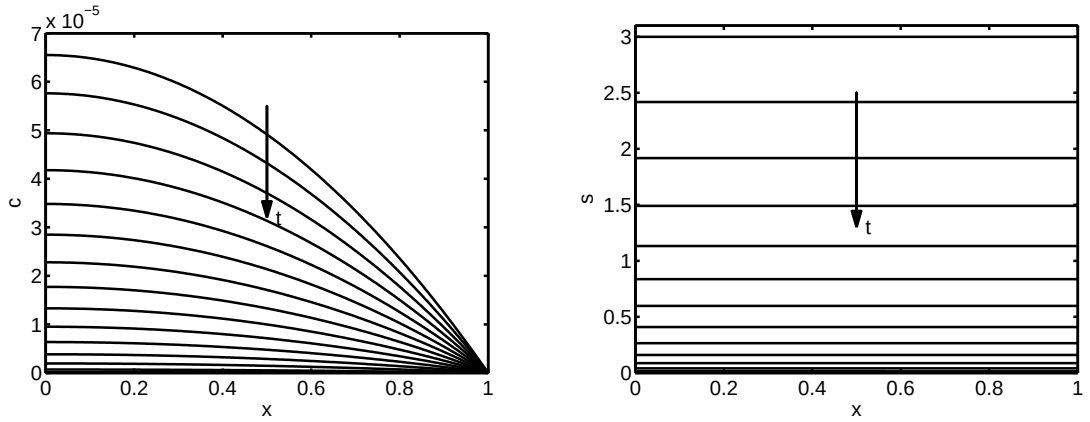
  and all contributions may be determined analytically because (RD) decouples in a sequence of independent ODE's.

- In particular, $s_0(x,t) = \left((\sigma^{1/3}(x) - t)^+\right)^3$, so that the stopping time is given by $T(x) = \sigma^{1/3}(x) + O(\alpha^{-1})$.

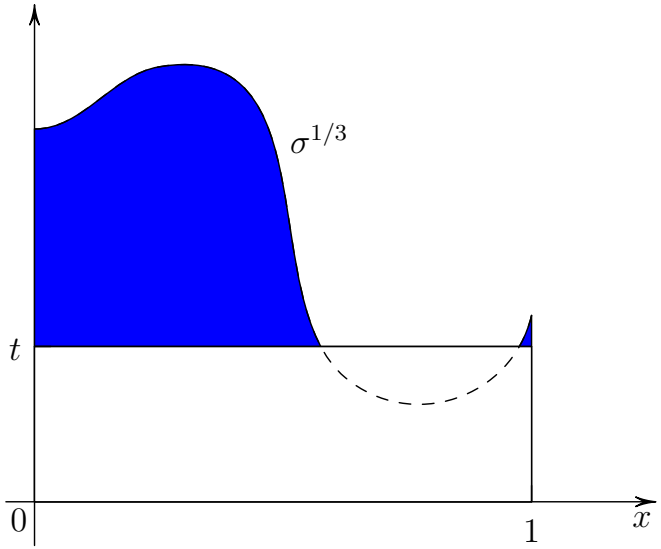
- The release rate is given by

  $$R(t) = 3 \int_0^1 \left[\left(\sigma^{1/3}(u) - t\right)^+\right]^2 du + O(\alpha^{-1}).$$

Large diffusion limit 2/2



Numerical approximation of the concentration profiles of $c(x,t)$ (left) and $s(x,t)$ (right) for $\alpha = 4.7 \times 10^4$, and $\sigma(x) \equiv \sigma_0 = 3$.



The release rate is a monotonically decreasing function of time

Small diffusion limit: initial times

The $\alpha = 3D/\left(B^2 K C_s^{2/3}\right) \ll 1$ gives rise to a singular perturbation problem.

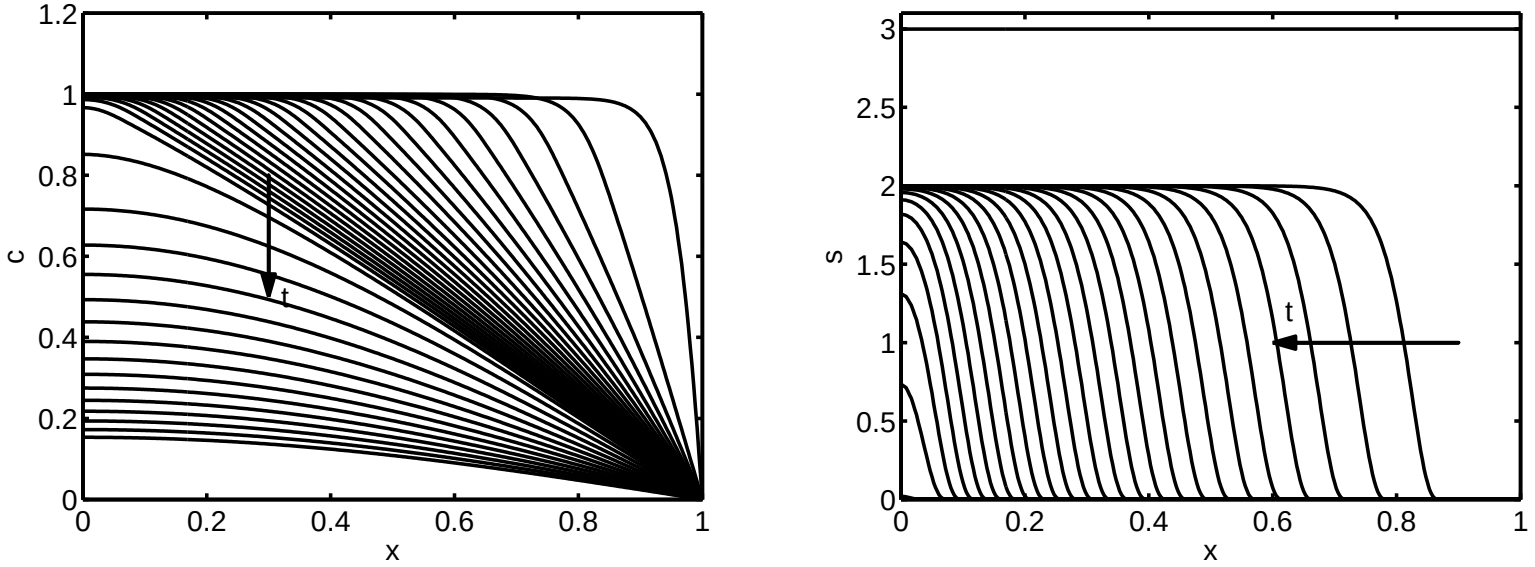
- In times of $O(1)$ with respect to α^{-1}, diffusion can be neglected, except in a boundary layer of width $\alpha^{1/2}$ close to the perfect sink at $x = 1$.
- In all other points, c approaches its saturation value $c_{\text{sat}} = 1$, while s simply decreases to $s_{\text{sat}} = \sigma - 1$.
  (We initially assume that $\sigma > 1$.)
- The release rate depends on the shape of the boundary layer, and in this initial regime is given by $\quad (\sigma_1 \equiv \sigma(1))$

$$R(t) = \frac{3\sqrt{\alpha}}{2\sqrt{5}} \sqrt{3(\sigma_1 - 1)^{8/3} + (8 - 3\sigma_1)\sigma_1^{5/3}}.$$

Small diffusion limit: travelling front 1/3

The presence of the perfect sink prevents c from saturating, and eventually (in a time $T(1) = \sigma(1)^{1/3}$) melts all the drug at $x = 1$.

At this stage a moving front leaves from $x = 1$ towards the inner boundary, and many features may be determined analytically.



Numerical approximation of the concentrations $c(x,t)$ and $s(x,t)$ at equidistant times when $\alpha = 4.7 \times 10^{-3}$ and $\sigma = 3$.

Small diffusion limit: travelling front 2/3

Let $x_0(t)$ be such that $s(x,t) > 0$ for $x < x_0(t)$ while $s(x,t) = 0$ for $x \geq x_0(t)$. Then

$$s(x,t) = \begin{cases} 0 & \text{if } x > x_0(t) \\ \varsigma\left(\dfrac{x - x_0(t)}{\sqrt{\alpha}}\right) & \text{if } x_0(t) - \Delta\sqrt{\alpha} < x < x_0(t) \\ \sigma - 1 & \text{if } x < x_0(t) - \Delta\sqrt{\alpha}, \end{cases}$$

$$c(x,t) = \begin{cases} \gamma\left(\dfrac{1-x}{1-x_0(t)}\right) & \text{if } x > x_0(t) \\ 1 & \text{if } x < x_0(t), \end{cases}$$

where ς and γ are suitable combinations of exponential and error functions.

Small diffusion limit: travelling front 3/3

The speed of the moving front follows from a mass-balance argument. It satisfies

$$\left(\sigma(x_0) - \int_0^1 \gamma(z)\, dz\right) \dot{x}_0 = -\frac{\alpha\gamma'(0)}{1 - x_0(t)}$$

The release rate is given by

$$R(t) = \frac{\alpha\gamma'(0)}{1 - x_0} \quad :$$

again monotonically decreasing!

Constant release rate 4/4

In order to obtain non-monotonic release rates we make resort to erosion.

Suppose erosion modifies the interval [0,1] into a $[0, x_{\max}(t)]$

If $x_{\max}(t) > x_0(t)$, the travelling solution still exists, but

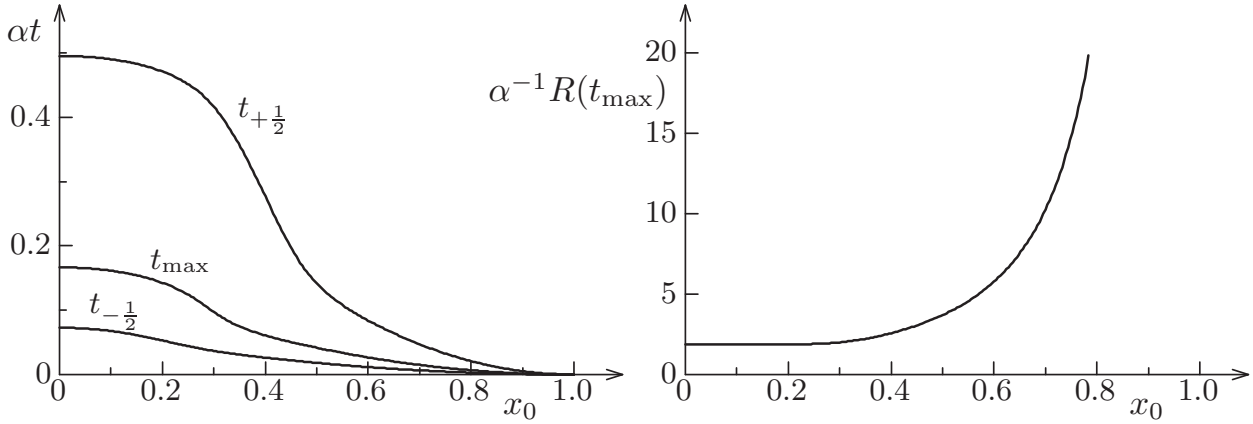
$$\left(\sigma(x_0) - \int_0^1 \gamma(z)\, dz\right) \dot{x}_0 = -\frac{\alpha\gamma'(0)}{x_{\max} - x_0(t)}$$

$$R(t) = \frac{\alpha\gamma'(0)}{x_{\max} - x_0}$$

Constant release rate if $\boldsymbol{w = |\dot{x}_{\max}| = |\dot{x}_0|}$

Small diffusion limit: unsaturated loading

In order to obtain a non-monotonically decreasing release rate we have to make resort to non-uniform and unsaturated loadings σ. A choice which allows for analytical results is $\sigma(x) = \delta(x - x_0)$.



Qualitative properties of the release rate in case of unsaturated loading.

The release rate attains its maximum at the time $t_{\max}$

$t_{\pm\frac{1}{2}}$ are the times at which $R(t) = \frac{1}{2} R(t_{\max})$.

Conclusions

Achieved results:

- Estimates for stopping time and release rate
- Interesting travelling-front regimes in small diffusion limit
- Non-monotonic release rates in case of erosion, or unsaturated and non-uniform loadings, in the small-diffusion limit

Possible extensions:

- Extension to realistic geometries
- Consider variable diffusion: D depends both on the device properties ($D(x)$) and/or on the solid/liquid concentrations ($D(s, c)$).

Credits

In collaboration with

- Luca Formaggia, Sara Minisini, Paolo Zunino
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- Dario Pierotti, Gianmaria Verzini
  (Department of Mathematics, Politecnico di Milano)

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