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Drug delivery from multi-layer micro-capsules: how can we estimate the release time?

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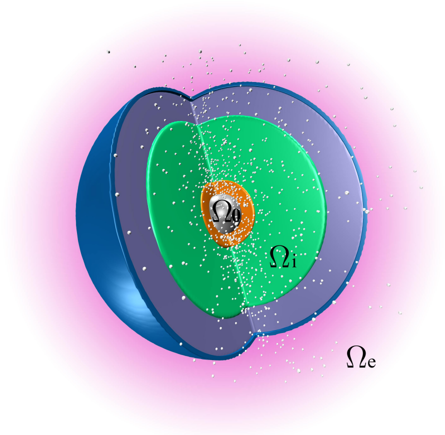
Ω_0: drug-filled core

Ω_i: outer shells
$i = 1, \ldots, n$

Ω_e: external medium



Focus: Time required for the capsule to be depleted of drug.

Multi-layer capsule

Rotational symmetry produces a one-dimensional problem

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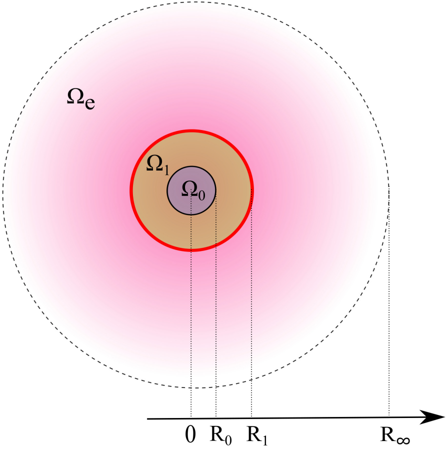


- Multi-layer diffusion model [Kaoui et al.(2018), Carr and Pontrelli (2018)]:

Inner Core: $$\frac{\partial c_0}{\partial t} = \frac{D_0}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_0}{\partial r}\right), \qquad r \in (0, R_0),$$

Outer Shells: $$\frac{\partial c_i}{\partial t} = \frac{D_i}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_i}{\partial r}\right), \qquad r \in (R_{i-1}, R_i) \text{ for } i = 1,\ldots,n,$$

External Medium: $$\frac{\partial c_e}{\partial t} = \frac{D_e}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_e}{\partial r}\right), \qquad r \in (R_n, R_\infty),$$

- Initial conditions: $c_0(r,0) = C_0$ and $c_i(r,0) = 0$ for $i = 1,\ldots,n,e$.
- Boundary conditions:

$$\frac{\partial c_0}{\partial r} = 0, \quad \text{at } r = 0; \qquad c_e = 0, \quad \text{at } r = R_\infty.$$

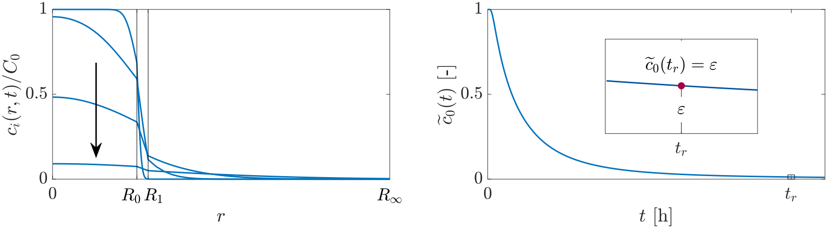
- Interface conditions:

$$c_i = c_{i+1}, \qquad D_i\frac{\partial c_i}{\partial r} = D_{i+1}\frac{\partial c_{i+1}}{\partial r}, \qquad \text{at } r = R_{i-1} \text{ for } i = 1,\ldots,n-1,$$

$$D_e\frac{\partial c_e}{\partial r} = P(c_e - c_n), \qquad D_n\frac{\partial c_n}{\partial r} = D_e\frac{\partial c_e}{\partial r} \qquad \text{at } r = R_n.$$

Multi-layer capsule

Definition of release time



- Dimensionless concentration at the centre of the capsule:

$$\widetilde{c}_0(t) := \frac{c_0(0,t)}{C_0}.$$

- Release time: time $t_r > 0$ satisfying:

$$\widetilde{c}_0(t_r) = \varepsilon$$

  where ε is a small specified tolerance (e.g. $\varepsilon = 10^{-p}$).

- **Objective**: Estimate t_r using temporal moments of $\widetilde{c}_0(t)$.

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- Definition of ***k*th moment** at $r = 0$:

$$\mathcal{M}_k = \int_0^\infty t^k \widetilde{c}_0(t)\,\mathrm{d}t,$$

- Introduce the kth moment at any spatial location:

$$u_{i,k}(r) = \int_0^\infty t^k \widetilde{c}_i(r,t)\,\mathrm{d}t, \qquad \widetilde{c}_i(r,t) = c_i(r,t)/C_0. \tag{1}$$

- Apply the linear operator $\mathcal{L}\varphi := \frac{D_i}{r^2}\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}\varphi}{\mathrm{d}r}\right)$ to both sides of (1):

$$\mathcal{L}u_{i,k}(r) = \int_0^\infty t^k \mathcal{L}\widetilde{c}_i(r,t)\,\mathrm{d}t$$

$$\mathcal{L}u_{i,k}(r) = \int_0^\infty t^k \frac{\partial \widetilde{c}_i}{\partial t}\,\mathrm{d}t$$

$$\mathcal{L}u_{i,k}(r) = \begin{cases} \widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0 \\ [t^k\widetilde{c}_i(r,t)]_0^\infty - k\int_0^\infty t^{k-1}\widetilde{c}_i(r,t)\,\mathrm{d}t & \text{if } k = 1,2,\ldots \end{cases}$$

$$\frac{D_i}{r^2}\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}u_{i,k}}{\mathrm{d}r}\right) = \begin{cases} \widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0 \\ -ku_{i,k-1} & \text{if } k = 1,2,\ldots \end{cases}$$

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- Boundary value problem for $u_k(r)$:

Inner Core: $$\frac{D_0}{r^2}\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}u_{0,k}}{\mathrm{d}r}\right) = \begin{cases}\widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0\\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+\end{cases}, \quad r \in (0, R_0)$$

Outer Shells: $$\frac{D_i}{r^2}\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}u_{i,k}}{\mathrm{d}r}\right) = \begin{cases}\widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0\\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+\end{cases}, \quad \begin{array}{l} r \in (R_{i-1}, R_i)\\ i = 1,\ldots,n,\end{array}$$

External Medium: $$\frac{D_e}{r^2}\frac{\mathrm{d}}{\mathrm{d}r}\left(r^2\frac{\mathrm{d}u_{e,k}}{\mathrm{d}r}\right) = \begin{cases}\widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0\\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+\end{cases}, \quad r \in (R_n, R_\infty),$$

subject to boundary and interface conditions formulated by combining the definition of $u_{i,k}(r)$ and the boundary and interface conditions of the multi-layer diffusion model.

- Recursively solve boundary value problems:
  - $k = 0$: solve for $u_{i,0}$ and calculate zeroth moment: $\mathcal{M}_0 = u_{0,0}(0)$.
  - $k = 1$: using $u_{i,0}$ solve for $u_{i,1}$ and calculate first moment: $\mathcal{M}_1 = u_{0,1}(0)$.
  - Repeat for $k = 2, 3, \ldots$

- **We can compute $\mathcal{M}_0$, $\mathcal{M}_1$ etc without the need to compute $\widetilde{c}_0(t)$!**

Estimating the release time
Asymptotic estimate based on the moments

- At each location x, transient solution takes the form [Kaoui et al.(2018)]:

$$\widetilde{c}_0(t) = \sum_{j=0}^{\infty} \gamma_j e^{-t\beta_j}, \quad 0 < \beta_0 < \beta_1 < \beta_2 < \ldots,$$

- Follows that:

$$\widetilde{c}_0(t) = \sum_{j=0}^{\infty} \gamma_j e^{-t\beta_j} \simeq \gamma_0 e^{-t\beta_0}, \quad \text{for large } t.$$

- Asymptotic estimate of response time:

$$\widetilde{c}_0(t_r) = \varepsilon \quad \Rightarrow \quad \gamma_0 e^{-t_r\beta_0} \simeq \varepsilon \quad \Rightarrow \quad t_r \simeq \frac{1}{\beta_0}\ln\left(\frac{\gamma_0}{\varepsilon}\right),$$

  where ε is a small prescribed tolerance (e.g. $\varepsilon = 10^{-p}$).

- **Can we estimate β_0 and γ_0 using the moments?**

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- Yes, because of the asymptotic relation:

$$\mathcal{M}_k \simeq \frac{k!\,\gamma_0}{\beta_0^{k+1}} \quad \text{as } k \to \infty.$$

- Matching consecutive moments:

$$\begin{aligned} (k-1)!\,\frac{\gamma_0}{\beta_0^k} &\simeq \mathcal{M}_{k-1} \\ k!\,\frac{\gamma_0}{\beta_0^{k+1}} &\simeq \mathcal{M}_k \end{aligned} \quad \Rightarrow \quad \begin{aligned} \gamma_0 &\simeq \frac{M_k}{k!}\left(\frac{kM_{k-1}}{M_k}\right)^k \\ \beta_0 &\simeq \frac{kM_{k-1}}{M_k}. \end{aligned}$$

- Asymptotic estimate of release time:

$$t_r \simeq \frac{\mathcal{M}_k}{k\mathcal{M}_{k-1}} \ln\left[\frac{\mathcal{M}_k}{k!\,\varepsilon}\left(\frac{k\mathcal{M}_{k-1}}{\mathcal{M}_k}\right)^k\right] \quad \text{as } k \to \infty.$$

- **No need for $\widetilde{c}_0(t)$ or complete solution of diffusion model!**

Results

Asymptotic estimate of the release time

	$\varepsilon = 10^{-4}$		$\varepsilon = 10^{-5}$		$\varepsilon = 10^{-6}$	
k	t_r	$\widetilde{c_0}(t_r)$	t_r	$\widetilde{c_0}(t_r)$	t_r	$\widetilde{c_0}(t_r)$
1	02:06:22:59	$7.2152 \cdot 10^{-4}$	02:22:53:05	$4.8197 \cdot 10^{-4}$	03:15:23:12	$3.5016 \cdot 10^{-4}$
2	07:23:03:31	$8.6792 \cdot 10^{-5}$	13:02:30:33	$2.0023 \cdot 10^{-5}$	18:05:57:35	$4.6400 \cdot 10^{-6}$
3	07:21:39:42	$8.8261 \cdot 10^{-5}$	15:11:32:11	$1.0190 \cdot 10^{-5}$	23:01:24:40	$1.1822 \cdot 10^{-6}$
4	07:14:19:34	$9.6411 \cdot 10^{-5}$	15:14:06:10	$9.8849 \cdot 10^{-6}$	23:13:52:46	$1.0199 \cdot 10^{-6}$
5	07:11:49:55	$9.9360 \cdot 10^{-5}$	15:13:37:58	$9.9401 \cdot 10^{-6}$	23:15:26:02	$1.0013 \cdot 10^{-6}$
6	07:11:02:47	$1.0031 \cdot 10^{-4}$	15:13:18:53	$9.9777 \cdot 10^{-6}$	23:15:34:58	$9.9953 \cdot 10^{-7}$
7	07:10:48:25	$1.0060 \cdot 10^{-4}$	15:13:11:17	$9.9926 \cdot 10^{-6}$	23:15:34:10	$9.9969 \cdot 10^{-7}$
8	07:10:44:09	$1.0069 \cdot 10^{-4}$	15:13:08:41	$9.9977 \cdot 10^{-6}$	23:15:33:14	$9.9988 \cdot 10^{-7}$
9	07:10:42:54	$1.0071 \cdot 10^{-4}$	15:13:07:52	$9.9994 \cdot 10^{-6}$	23:15:32:50	$9.9996 \cdot 10^{-7}$
10	07:10:42:33	$1.0072 \cdot 10^{-4}$	15:13:07:37	$9.9999 \cdot 10^{-6}$	23:15:32:41	$9.9999 \cdot 10^{-6}$
11	07:10:42:27	$1.0072 \cdot 10^{-4}$	15:13:07:32	$1.0000 \cdot 10^{-5}$	23:15:32:38	$1.0000 \cdot 10^{-6}$
12	07:10:42:25	$1.0072 \cdot 10^{-4}$	15:13:07:31	$1.0000 \cdot 10^{-5}$	23:15:32:37	$1.0000 \cdot 10^{-6}$
13	07:10:42:25	$1.0072 \cdot 10^{-4}$	15:13:07:31	$1.0000 \cdot 10^{-5}$	23:15:32:37	$1.0000 \cdot 10^{-6}$
14	07:10:42:25	$1.0072 \cdot 10^{-4}$	15:13:07:31	$1.0000 \cdot 10^{-5}$	23:15:32:37	$1.0000 \cdot 10^{-6}$

Asymptotic estimate: $$t_r \simeq \frac{\mathcal{M}_k}{k\mathcal{M}_{k-1}} \ln\left[\frac{\mathcal{M}_k}{k!\,\varepsilon}\left(\frac{k\mathcal{M}_{k-1}}{\mathcal{M}_k}\right)^k\right] \quad \text{as } k \to \infty.$$

Estimating the release time

Crude approximation based on zeroth and first moments only

- The zeroth and first moments ($\mathcal{M}_0$ and $\mathcal{M}_1$) have somewhat simple algebric expressions involving the physical parameters (diffusivities D_i, radii R_i, etc.)

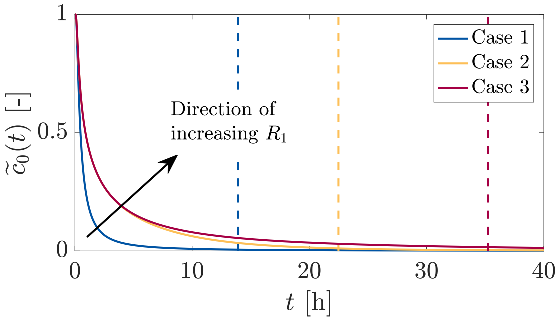
$$
\mathcal{M}_0 = \frac{R_0^2}{6D_0} + \frac{R_0^2\,(R_1 - R_0)}{3D_1R_1} + \frac{R_0^3\,(R_\infty - R_1)}{3D_eR_1R_\infty} + \frac{R_0^3}{3R_1^2P}
$$

$$
\begin{aligned}
\mathcal{M}_1 = {} & \frac{7R_0^4}{180D_0^2} + \frac{7R_0^4(R_1 - R_0)}{45D_0D_1R_1} + \frac{7R_0^5(R_\infty - R_1)}{45D_0D_eR_1R_\infty} + \frac{7R_0^5}{45D_0PR_1^2} \\
& + \frac{2R_0^3(R_1 - R_0)^2(R_0 + R_1 - R_0)}{9D_1^2R_1^2} + \frac{4R_0^3(R_\infty - R_1)(R_0^3 - R_0^3 + R_1^3)}{9D_ePR_1^3R_\infty} \\
& + \frac{2R_0^3(R_1 - R_0)(2R_0^2 - 2R_0^2 + R_0R_1 + R_1^2)}{9D_1R_1^2}\left[\frac{(R_\infty - R_1)}{D_eR_\infty} + \frac{1}{PR_1}\right] \\
& + \frac{2R_0^3(R_\infty - R_1)^2(R_0^3 - R_0^3 + R_1^3 - R_1^3 + R_1^2R_\infty)}{9D_e^2R_1^2R_\infty^2}
\end{aligned}
$$

- **Crude approximation: $t_r \approx \mathcal{M}_0 + \eta\sqrt{\mathcal{M}_1}$, where η is a heuristic factor** [Simpson et al. (2013)].

Results

Crude approximation of the release time



Crude approximation: $t_r \approx \mathcal{M}_0 + 3\sqrt{\mathcal{M}_1}$

- Proposed two novel approaches to estimate the release time for a composite spherical microcapsule with rotational symmetry.
- Both approaches make use of temporal moments of the drug concentration at the centre of the capsule ($r = 0$):

$$\mathcal{M}_k = \int_0^\infty t^k \widetilde{c}_0(t)\,\mathrm{d}t, \quad k = 0, 1, 2, \ldots$$

- Moments can be computed exactly without explicit calculation of the full transient solution of the multi-layer diffusion model ($c_i(r,t)$, $i = 1, \ldots, n, e$).
- First approach yields a highly accurate asymptotic estimate of the release time involving consecutive higher order moments.
- Second approach involving the first two moments yields a crude approximation of the release time taking the form of a simple algebraic expression involving the various parameters in the model (diffusivities and radii).
- Future work will focus on spatially-varying ($D(r)$) and nonlinear ($D(c,r)$) coefficients.

Further reading
Carr and Pontrelli (2019)

Preprint available on the arXiv repository: https://arxiv.org/abs/1901.08231.

Drug delivery from microcapsules: how can we estimate the release time?

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References

[Kaoui et al.(2018)] B. Kaoui, M. Lauricella, and G. Pontrelli. Mechanistic modelling of drug release from multilayer capsules. *Comput. Biol. Med.*, 93:149–157, 2018.

[Carr and Pontrelli (2018)] E. J. Carr and G. Pontrelli. Modelling mass diffusion for a multi-layer sphere immersed in a semi-infinite medium: application to drug delivery. *Math. Biosci.*, 303:1–9,2018.

[Simpson et al. (2013)] M. J. Simpson, F. Jazaei, and T. P. Clement. How long does it take for aquifer recharge or aquifer discharge processes to reach steady state? *J. Hydrology*, 501:241–248, 2013.