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

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Drug delivery
Composite spherical capsule

\( \Omega_0 \): drug-filled core

\( \Omega_i \): outer shells
\( i = 1, \ldots, n \)

\( \Omega_e \): external medium

**Focus:** Time required for the capsule to be depleted of drug.
Multi-layer capsule
Rotational symmetry produces a one-dimensional problem
Multi-layer capsule
Mathematical model for the drug concentration


  **Inner Core:** 
  \[
  \frac{\partial c_0}{\partial t} = \frac{D_0}{r^2} \frac{\partial}{\partial r} \left( r^2 \frac{\partial c_0}{\partial r} \right), \quad r \in (0, R_0),
  \]

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

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

- Initial conditions: 
  \[c_0(r, 0) = C_0 \text{ and } c_i(r, 0) = 0 \text{ for } i = 1, \ldots, n, e.\]

- Boundary conditions: 
  \[
  \left. \frac{\partial c_0}{\partial r} \right|_{r=0} = 0, \quad \text{at } r = 0; \quad c_e = 0, \quad \text{at } r = R_\infty.
  \]

- Interface conditions: 
  \[
  c_i = c_{i+1}, \quad D_i \frac{\partial c_i}{\partial r} = D_{i+1} \frac{\partial c_{i+1}}{\partial r}, \quad \text{at } r = R_{i-1} \text{ for } i = 1, \ldots, n-1,
  \]
  \[
  D_e \frac{\partial c_e}{\partial r} = P(c_e - c_n), \quad D_n \frac{\partial c_n}{\partial r} = D_e \frac{\partial c_e}{\partial r} \quad \text{at } r = R_n.
  \]
Multi-layer capsule
Definition of release time

- Dimensionless concentration at the centre of the capsule:
  \[ \tilde{c}_0(t) := \frac{c_0(0, t)}{C_0}. \]

- Release time: time \( t_r > 0 \) satisfying:
  \[ \tilde{c}_0(t_r) = \varepsilon \]
  where \( \varepsilon \) is a small specified tolerance (e.g. \( \varepsilon = 10^{-p} \)).

- **Objective**: Estimate \( t_r \) using temporal moments of \( \tilde{c}_0(t) \).
Definition of \textit{kth moment} at \( r = 0 \):

\[
\mathcal{M}_k = \int_0^\infty t^k \tilde{c}_0(t) \, dt,
\]

Introduce the \( k \)th moment at any spatial location:

\[
u_{i,k}(r) = \int_0^\infty t^k \tilde{c}_i(r, t) \, dt, \quad \tilde{c}_i(r, t) = c_i(r, t)/C_0. \tag{1}\]

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

\[
\mathcal{L}u_{i,k}(r) = \int_0^\infty t^k \mathcal{L}\tilde{c}_i(r, t) \, dt
\]

\[
\mathcal{L}u_{i,k}(r) = \int_0^\infty t^k \frac{\partial \tilde{c}_i}{\partial t} \, dt
\]

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

\[
\frac{D_i}{r^2} \frac{d}{dr} \left( r^2 \frac{du_{i,k}}{dr} \right) = \begin{cases} 
\widetilde{c}_{i,\infty}(r) - \widetilde{c}_{i,0}(r) & \text{if } k = 0 \\
-ku_{i,k-1} & \text{if } k = 1, 2, \ldots
\end{cases}
\]
Temporal moments
Temporal moments satisfy boundary value problems

Boundary value problem for $u_k(r)$:

- **Inner Core:**
  \[ D_0 \frac{d}{r^2} \left( r^2 \frac{du_{0,k}}{dr} \right) = \begin{cases} c_{i,\infty}(r) - c_{i,0}(r) & \text{if } k = 0 \\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+ \end{cases}, \quad r \in (0, R_0) \]

- **Outer Shells:**
  \[ D_i \frac{d}{r^2} \left( r^2 \frac{du_{i,k}}{dr} \right) = \begin{cases} c_{i,\infty}(r) - c_{i,0}(r) & \text{if } k = 0 \\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+ \end{cases}, \quad r \in (R_{i-1}, R_i), \quad i = 1, \ldots, n, \]

- **External Medium:**
  \[ D_e \frac{d}{r^2} \left( r^2 \frac{du_{e,k}}{dr} \right) = \begin{cases} c_{i,\infty}(r) - c_{i,0}(r) & \text{if } k = 0 \\ -ku_{i,k-1} & \text{if } k \in \mathbb{N}^+ \end{cases}, \quad r \in (R_n, R_\infty), \]

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: $M_0 = u_{0,0}(0)$.
- $k = 1$: using $u_{i,0}$ solve for $u_{i,1}$ and calculate first moment: $M_1 = u_{0,1}(0)$.
- Repeat for $k = 2, 3, \ldots$.

We can compute $M_0, M_1$ etc without the need to compute $\tilde{c}_0(t)$!
At each location $x$, transient solution takes the form [Kaoui et al. (2018)]:

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

Follows that:

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

Asymptotic estimate of response time:

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

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

Can we estimate $\beta_0$ and $\gamma_0$ using the moments?
Estimating the release time
Asymptotic estimate based on the moments

- 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:
  \[
  (k - 1)! \frac{\gamma_0}{\beta_0^k} \simeq \mathcal{M}_{k-1} \\
  k! \frac{\gamma_0}{\beta_0^{k+1}} \simeq \mathcal{M}_k
  \]
  \[\Rightarrow \quad \gamma_0 \simeq \frac{M_k}{k!} \left( \frac{kM_{k-1}}{M_k} \right)^k \]
  \[\beta_0 \simeq \frac{kM_{k-1}}{M_k}.\]

- Asymptotic estimate of release time:
  \[ t_r \simeq \frac{\mathcal{M}_k}{kM_{k-1}} \ln \left[ \frac{\mathcal{M}_k}{k! \varepsilon \left( \frac{kM_{k-1}}{M_k} \right)^k} \right] \quad \text{as } k \to \infty. \]

- No need for \( \tilde{c}_0(t) \) or complete solution of diffusion model!
Results

Asymptotic estimate of the release time

<table>
<thead>
<tr>
<th>$k$</th>
<th>$t_r$</th>
<th>$\tilde{c}_0(t_r)$</th>
<th>$t_r$</th>
<th>$\tilde{c}_0(t_r)$</th>
<th>$t_r$</th>
<th>$\tilde{c}_0(t_r)$</th>
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<td>02:06:22:59</td>
<td>$7.2152 \cdot 10^{-4}$</td>
<td>02:22:53:05</td>
<td>$4.8197 \cdot 10^{-4}$</td>
<td>03:15:23:12</td>
<td>$3.5016 \cdot 10^{-4}$</td>
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<td>07:23:03:31</td>
<td>$8.6792 \cdot 10^{-5}$</td>
<td>13:02:30:33</td>
<td>$2.0023 \cdot 10^{-5}$</td>
<td>18:05:57:35</td>
<td>$4.6400 \cdot 10^{-6}$</td>
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<td>3</td>
<td>07:21:39:42</td>
<td>$8.8261 \cdot 10^{-5}$</td>
<td>15:11:32:11</td>
<td>$1.0190 \cdot 10^{-5}$</td>
<td>23:01:24:40</td>
<td>$1.1822 \cdot 10^{-6}$</td>
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<tr>
<td>11</td>
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<td>$1.0072 \cdot 10^{-4}$</td>
<td>15:13:07:32</td>
<td>$1.0000 \cdot 10^{-5}$</td>
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<td>$1.0072 \cdot 10^{-4}$</td>
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<td>$1.0000 \cdot 10^{-5}$</td>
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<td>$1.0000 \cdot 10^{-5}$</td>
<td>23:15:32:37</td>
<td>$1.0000 \cdot 10^{-6}$</td>
</tr>
</tbody>
</table>

Asymptotic estimate: \( t_r \simeq \frac{M_k}{kM_{k-1}} \ln \left[ \frac{M_k}{k! \varepsilon} \left( \frac{kM_{k-1}}{M_k} \right)^k \right] \) as \( k \to \infty \).
The zeroth and first moments ($\mathcal{M}_0$ and $\mathcal{M}_1$) have somewhat simple algebraic expressions involving the physical parameters (diffusivities $D_i$, radii $R_i$, etc.)

\[
\mathcal{M}_0 = \frac{R_0^2}{6D_0} + \frac{R_0^2 (R_1 - R_0)}{3D_1 R_1} + \frac{R_0^3 (R_\infty - R_1)}{3D_e R_1 R_\infty} + \frac{R_0^3}{3R_1^2 P} \\
\mathcal{M}_1 = \frac{7R_0^4}{180D_0^2} + \frac{7R_0^4 (R_1 - R_0)}{45D_0 D_1 R_1} + \frac{7R_0^5 (R_\infty - R_1)}{45D_0 D_e R_1 R_\infty} + \frac{7R_0^5}{45D_0 PR_1^2} \\
\quad + \frac{2R_0^3(R_1 - R_0)^2(R_0 + R_1 - R_0)}{9D_1^2 R_1^2} + \frac{4R_0^3(R_\infty - R_1)(R_0^3 - R_0^3 + R_1^3)}{9D_e PR_1^3 R_\infty} \\
\quad + \frac{2R_0^3(R_1 - R_0)(2R_0^2 - 2R_0^2 + R_0 R_1 + R_1^2)}{9D_1 R_1^2} \left[ \frac{(R_\infty - R_1)}{D_e R_\infty} + \frac{1}{PR_1} \right] \\
\quad + \frac{2R_0^3(R_\infty - R_1)^2(R_0^3 - R_0^3 + R_1^3 - R_1^3 + R_1^2 R_\infty)}{9D_e^2 R_1^2 R_\infty^2}
\]

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

Crude approximation of the release time

Crude approximation: \[ t_r \approx M_0 + 3 \sqrt{M_1} \]
Summary and Future Work
Temporal moments provide insight into the release time

- 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 ($r = 0$):

$$M_k = \int_0^\infty t^k \tilde{c}_0(t) \, dt, \quad k = 0, 1, 2, \ldots$$

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

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