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The Drug Diffusion Problem: Comparison of Analytic Methods

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The University of Newcastle

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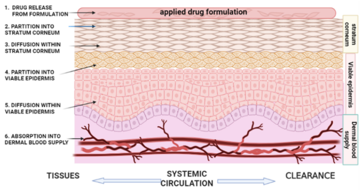
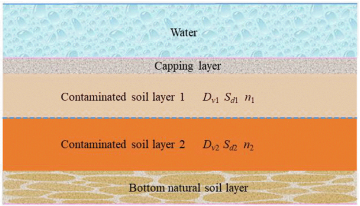
Outline

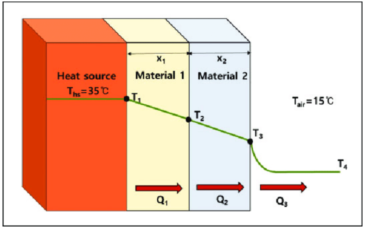
Motivation



Drug diffusion(1)

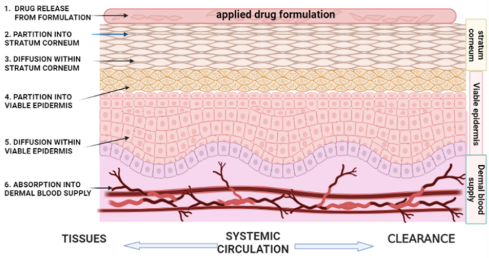


Soil contamination(2)



Composite heat flow(3)

(1) Tapfumaneyi et al., *Pharmaceutics* (2025)
(2) Li et al., Environmental Engineering Research (2022)
(3) Kim and Han, Multi-layer heat transfer simulation

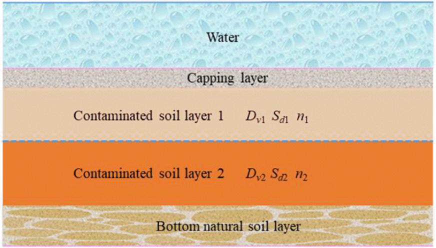


Drug diffusion

→

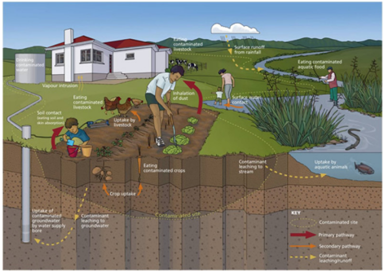
Transdermal patches[4]

(4) AdhexPharma, Transdermal patches in healthcare



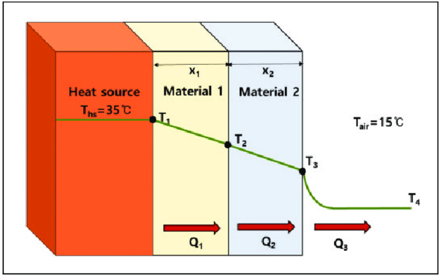
Soil contamination

$\longrightarrow$



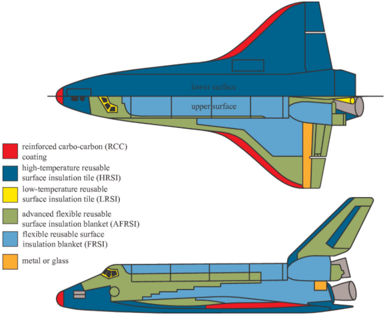
Agriculture[5]

(5) Ministry for the Environment (NZ), "Contaminated land" (2021)



Composite heat flow

$\longrightarrow$

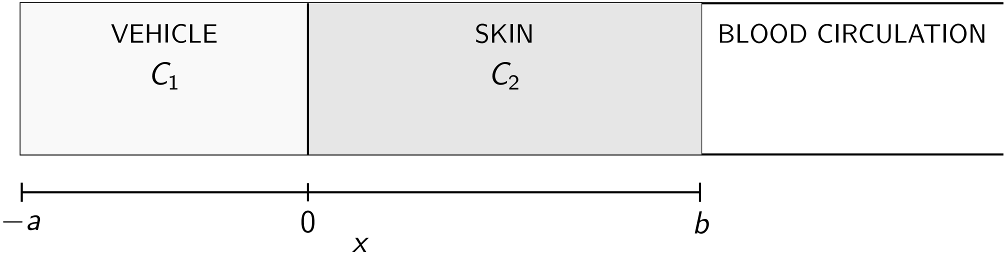


Thermal protection systems(6)

(6) Mooij (2024), Thermal Protection Systems

Assumptions

- Drug applied at skin surface with transport governed by Fickian diffusion
- Simplified problem with only two layers
- No chemical reactions, binding, or metabolism within the skin

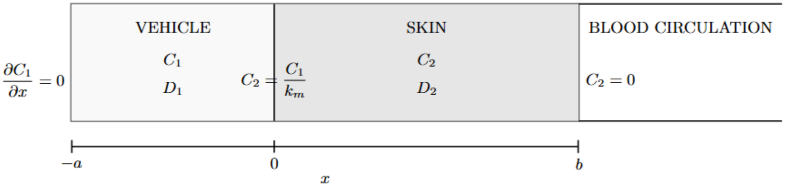


- Why Analytic Methods?
  - Exact solutions reveal structure not visible in purely numerical approaches
  - Access to asymptotics
  - Clear parameter dependence
- Why multiple?
  - Consistency check: same physical model, same solution
  - Highlight strengths and weaknesses of each route

Mathematical model

$$[\partial_t - D_1\partial_{xx}]\, C_1(x,t) = 0, \qquad (x,t) \in [-a,0] \times (0,T) \qquad \text{(1.PDE1)}$$

$$[\partial_t - D_2\partial_{xx}]\, C_2(x,t) = 0, \qquad (x,t) \in [0,b] \times (0,T) \qquad \text{(1.PDE2)}$$



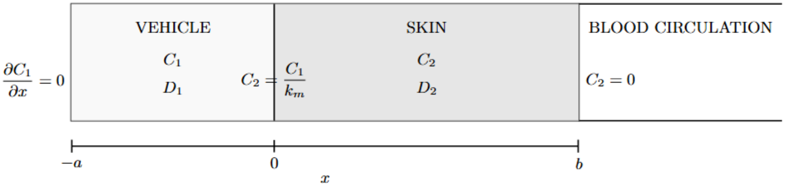
Mathematical model

$$[\partial_t - D_1\partial_{xx}]\, C_1(x,t) = 0, \qquad (x,t) \in [-a,0] \times (0,T) \qquad \text{(1.PDE1)}$$

$$[\partial_t - D_2\partial_{xx}]\, C_2(x,t) = 0, \qquad (x,t) \in [0,b] \times (0,T) \qquad \text{(1.PDE2)}$$

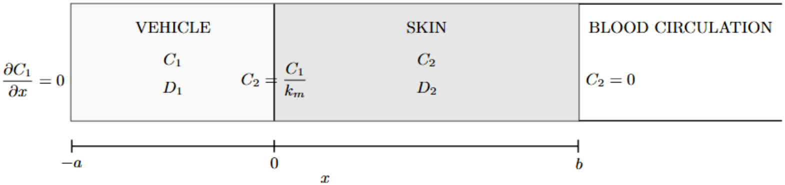
$$C_1(x,0) = C_{1,0}, \qquad x \in [-a,0] \qquad \text{(1.IC1)}$$

$$C_2(x,0) = 0, \qquad x \in [0,b] \qquad \text{(1.IC2)}$$



Mathematical model

$$
\begin{aligned}
&[\partial_t - D_1 \partial_{xx}]\, C_1(x,t) = 0, && (x,t) \in [-a, 0] \times (0, T) && \text{(1.PDE1)}\\
&[\partial_t - D_2 \partial_{xx}]\, C_2(x,t) = 0, && (x,t) \in [0, b] \times (0, T) && \text{(1.PDE2)}\\
&C_1(x,0) = C_{1,0}, && x \in [-a, 0] && \text{(1.IC1)}\\
&C_2(x,0) = 0, && x \in [0, b] && \text{(1.IC2)}\\
&\frac{\partial C_1}{\partial x}(-a,t) = 0, && t \in [0, T] && \text{(1.BC1)}\\
&C_2(b,t) = 0, && t \in [0, T] && \text{(1.BC2)}\\
&D_1 \frac{\partial C_1}{\partial x}(0^-,t) = D_2 \frac{\partial C_2}{\partial x}(0^+,t), && t \in [0, T] && \text{(1.BC3)}\\
&C_1(0,t) = k_m C_2(0,t) && t \in [0, T] && \text{(1.BC4)}
\end{aligned}
$$



Analytic approaches

1. Laplace Transform Approach
2. Unified Transform Method

Laplace Transform Approach

We begin by taking the temporal Laplace transform of (1.PDE1) and (1.PDE2) to obtain:

$$\frac{d^2\bar{C}_1}{dx^2}(x,s) - \frac{s}{D_1}\bar{C}_1(x,s) = -\frac{C_{1,0}}{D_1}$$

and

$$\frac{d^2\bar{C}_2}{dx^2}(x,s) - \frac{s}{D_2}\bar{C}_2(x,s) = 0$$

The respective solutions to these ODEs are:

$$\bar{C}_1(x,s) = K_1(s)\cosh\left(\sqrt{\frac{s}{D_1}}(x+a)\right) + \frac{C_{1,0}}{s}$$

and

$$\bar{C}_2(x,s) = K_2(s)\sinh\left(\sqrt{\frac{s}{D_2}}(b-x)\right)$$

After applying boundary conditions, we arrive at the following transformed expressions:

$$\bar{C}_1(x,s) = \frac{C_{1,0}}{s}\left[1 - \frac{\sqrt{\frac{D_2}{D_1}}\cosh\left(\sqrt{\frac{s}{D_2}}\,b\right)\cosh\left(\sqrt{\frac{s}{D_1}}(x+a)\right)}{\Delta(s)}\right]$$

$$\bar{C}_2(x,s) = \frac{C_{1,0}\sinh\left(\sqrt{\frac{s}{D_2}}(b-x)\right)\sinh\left(\sqrt{\frac{s}{D_1}}\,a\right)}{s\Delta(s)}$$

where $\Delta(s) := k_m \sinh\left(\sqrt{\frac{s}{D_2}}\,b\right)\sinh\left(\sqrt{\frac{s}{D_1}}\,a\right) + \sqrt{\frac{D_2}{D_1}}\cosh\left(\sqrt{\frac{s}{D_1}}\,a\right)\cosh\left(\sqrt{\frac{s}{D_2}}\,b\right)$

By inversion of the Laplace Transform, we can represent the concentration profiles.

$$C_1(x,t) = \mathcal{L}_s^{-1}\{\bar{C}_1(x,s)\}(t)$$

and

$$C_2(x,t) = \mathcal{L}_s^{-1}\{\bar{C}_2(x,s)\}(t).$$

Then we use Cauchy's Residue Theorem for inversion.

$$C_1(x,t) = C_{1,0} - C_{1,0} \sum_{s_k \Delta(s_k)=0} \operatorname{Res}\left(\frac{e^{st}\sqrt{\frac{D_2}{D_1}}\cosh\left(\sqrt{\frac{s}{D_2}}\,b\right)\cosh\left(\sqrt{\frac{s}{D_1}}(x+a)\right)}{s\Delta(s)}, s = s_k \right)$$

and

$$C_2(x,t) = C_{1,0} \sum_{s_k \Delta(s_k)=0} \operatorname{Res}\left(\frac{e^{st}\sinh\left(\sqrt{\frac{s}{D_2}}(b-x)\right)\sinh\left(\sqrt{\frac{s}{D_1}}\,a\right)}{s\Delta(s)}, s = s_k \right).$$

Final Form

After applying the quotient rule for Residues, our final concentration profiles are:

$$C_1(x,t) = C_{1,0} \sum_{k\geq 1} \left[\frac{\sqrt{\frac{D_2}{D_1}} \cos\left(\frac{b\lambda_k}{\sqrt{D_2}}\right)}{\lambda_k^2 \Delta'(-\lambda_k^2)} \right] \cos\left(\frac{\lambda_k(x+a)}{\sqrt{D_1}}\right) e^{-\lambda_k^2 t}$$

$$C_2(x,t) = C_{1,0} \sum_{k\geq 1} \left[\frac{\sin\left(\frac{a\lambda_k}{\sqrt{D_1}}\right)}{\lambda_k^2 \Delta'(-\lambda_k^2)} \right] \sin\left(\frac{\lambda_k(b-x)}{\sqrt{D_2}}\right) e^{-\lambda_k^2 t}$$

where $\{\lambda_k\}_{k\geq 1}$ are the positive solutions of $\tan\left(\frac{a}{\sqrt{D_1}}\lambda\right) \tan\left(\frac{b}{\sqrt{D_2}}\lambda\right) = \frac{1}{k_m}\sqrt{\frac{D_2}{D_1}}$.

Unified Transform Method

We define:

$$
\begin{aligned}
p(x,t) &:= C_1(-x,t) \qquad && 0 < x < a \\
q(x,t) &:= C_2(x,t) \qquad && 0 < x < b
\end{aligned}
$$

Unified Transform Method

We define:

$$p(x,t) := C_1(-x,t) \qquad 0 < x < a$$
$$q(x,t) := C_2(x,t) \qquad 0 < x < b$$

So the important changes are:

$$[\partial_t - D_1 \partial_{xx}]\, p(x,t) = 0, \qquad (x,t) \in [0,a] \times (0,T) \qquad \text{(2.PDE1)}$$
$$[\partial_t - D_2 \partial_{xx}]\, q(x,t) = 0, \qquad (x,t) \in [0,b] \times (0,T) \qquad \text{(2.PDE2)}$$
$$-D_1 \frac{\partial p}{\partial x}(0^+,t) = D_2 \frac{\partial q}{\partial x}(0^+,t), \qquad t \in [0,T] \qquad \text{(2.BC3)}$$

We now define the Fourier Transforms:

$$\hat{p}(\lambda; t) = \int_0^a e^{-i\lambda x} p(x,t)dx \qquad \hat{q}(\lambda; t) = \int_0^b e^{-i\lambda x} q(x,t)dx$$

And apply the respective transforms to (2.PDE1) and (2.PDE2):

$$\partial_t \hat{p}(\lambda; t) - D_1 \int_0^a e^{-i\lambda x} p_{xx}(x,t)dx = 0$$

$$\partial_t \hat{q}(\lambda; t) - D_2 \int_0^b e^{-i\lambda x} q_{xx}(x,t)\, dx = 0$$

After integration by parts and applying ICs and BCs, we obtain the following results:

$$\hat{p}(\lambda; t)e^{D_1\lambda^2 t} = \hat{P}(\lambda) + D_1 \int_0^t e^{D_1\lambda^2 s}\left[i\lambda e^{-i\lambda a}p(a, s) - p_x(0, s) - i\lambda p(0, s)\right] ds \tag{GR: p}$$

where $\hat{P}(\lambda) := \hat{p}(\lambda, 0)$

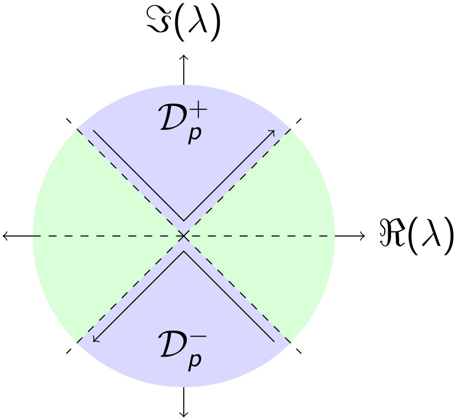
$$\hat{q}(\lambda; t)e^{D_2\lambda^2 t} = D_2 \int_0^t e^{D_2\lambda^2 s}\left[e^{-i\lambda b}q_x(b, s) - q_x(0, s) - i\lambda q(0, s)\right] ds \tag{GR: q}$$

Applying the Inverse Fourier Transform yields:

$$2\pi p(x,t) = \int_{-\infty}^{\infty} e^{i\lambda x - D_1\lambda^2 t}\,\hat{P}(\lambda)\,d\lambda$$
$$+ D_1 \int_{-\infty}^{\infty} e^{i\lambda x - D_1\lambda^2 t} \int_0^t e^{D_1\lambda^2 s} \left(i\lambda e^{-i\lambda a} p(a,s) - \left(p_x + i\lambda p\right)(0,s)\right)\,ds\,d\lambda$$

and

$$2\pi q(x,t) = D_2 \int_{-\infty}^{\infty} e^{i\lambda x - D_2\lambda^2 t} \int_0^t e^{D_2\lambda^2 s} \left(e^{-i\lambda b}\, q_x(b,s) - \left(q_x + i\lambda q\right)(0,s)\right)\,ds\,d\lambda.$$



We denote $\partial\mathcal{D}_p^{\pm}$ as the positively oriented boundaries of $\mathcal{D}_p^{\pm}$.

$$2\pi\, p(x,t) = \int_{-\infty}^{\infty} e^{i\lambda x - D_1\lambda^2 t}\, \hat{P}(\lambda)\, d\lambda - D_1 \int_{\partial\mathcal{D}_p^-} e^{i\lambda(x-a) - D_1\lambda^2 t} \left[i\lambda \int_0^t e^{D_1\lambda^2 s}\, p(a,s)\, ds \right] d\lambda$$

$$- D_1 \int_{\partial\mathcal{D}_p^+} e^{i\lambda x - D_1\lambda^2 t} \left[\int_0^t e^{D_1\lambda^2 s} \left(p_x(0,s) + i\lambda p(0,s) \right) ds \right] d\lambda. \qquad \text{(EF: p)}$$

$$2\pi\, q(x,t) = - D_2 \int_{\partial\mathcal{D}_p^-} e^{i\lambda(x-b) - D_2\lambda^2 t} \left[\int_0^t e^{D_2\lambda^2 s}\, q_x(b,s)\, ds \right] d\lambda$$

$$- D_2 \int_{\partial\mathcal{D}_p^+} e^{i\lambda x - D_2\lambda^2 t} \left[\int_0^t e^{D_2\lambda^2 s} \left(q_x(0,s) + i\lambda q(0,s) \right) ds \right] d\lambda. \qquad \text{(EF: } q\text{)}$$

We have 6 unknown spectral boundary data!

$p(0, s)$, $p_x(0, s)$, $p(a, s)$, $q(0, s)$, $q_x(0, s)$, and $q_x(b, s)$.

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To make it worse, we only have 2 unused boundary conditions!

We have 6 unknown spectral boundary data!

$p(0, s)$, $p_x(0, s)$, $p(a, s)$, $q(0, s)$, $q_x(0, s)$, and $q_x(b, s)$.

To make it worse, we only have 2 unused boundary conditions!

But all is ok.

With a changes of variables,

$$\lambda \mapsto \frac{\lambda}{\sqrt{D_j}}, \qquad \lambda \mapsto -\frac{\lambda}{\sqrt{D_j}},$$

And define the following spectral functions:

$$F_j^\flat(\lambda) = \int_0^T e^{\lambda^2 s}\, \partial_x^j p(0,s)\, ds \qquad F_j^\#(\lambda) = \int_0^T e^{\lambda^2 s}\, \partial_x^j q(0,s)\, ds$$

$$G_j^\flat(\lambda) = \int_0^T e^{\lambda^2 s}\, \partial_x^j p(a,s)\, ds \qquad G_j^\#(\lambda) = \int_0^T e^{\lambda^2 s}\, \partial_x^j q(b,s)\, ds$$

(2.BC3) gives us $F_1^\flat(\lambda) = -\frac{D_2}{D_1} F_1^\#(\lambda)$.

And (2.BC4) gives us $F_0^\flat(\lambda) = k_m\, F_0^\#(\lambda)$.

$$\begin{pmatrix} i\sqrt{D_1}\,\lambda e^{-i\lambda a/\sqrt{D_1}} & 0 & -i\sqrt{D_1}\,k_m\lambda & D_2 \\ -i\sqrt{D_1}\,\lambda e^{i\lambda a/\sqrt{D_1}} & 0 & i\sqrt{D_1}\,k_m\lambda & D_2 \\ 0 & D_2 e^{-i\lambda b/\sqrt{D_2}} & -i\lambda\sqrt{D_2} & -D_2 \\ 0 & D_2 e^{i\lambda b/\sqrt{D_2}} & i\lambda\sqrt{D_2} & -D_2 \end{pmatrix} \begin{pmatrix} G_0^\flat(\lambda) \\ G_1^\#(\lambda) \\ F_0^\#(\lambda) \\ F_1^\#(\lambda) \end{pmatrix} = e^{\lambda^2 T} \begin{pmatrix} \hat{p}\left(\frac{\lambda}{\sqrt{D_1}}; T\right) \\ \hat{p}\left(-\frac{\lambda}{\sqrt{D_1}}; T\right) \\ \hat{q}\left(\frac{\lambda}{\sqrt{D_2}}; T\right) \\ \hat{q}\left(-\frac{\lambda}{\sqrt{D_2}}; T\right) \end{pmatrix} - \begin{pmatrix} \hat{P}\left(\frac{\lambda}{\sqrt{D_1}}\right) \\ \hat{P}\left(-\frac{\lambda}{\sqrt{D_1}}\right) \\ 0 \\ 0 \end{pmatrix}$$

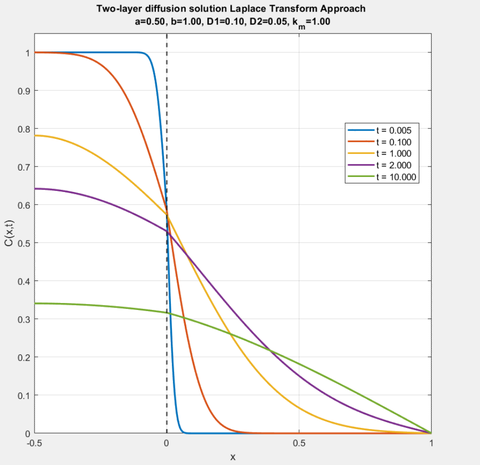
With a little bit of work, we have our solutions!

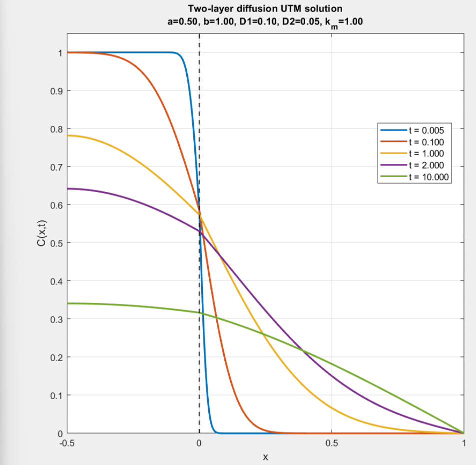
$$2\pi p(x,t) = \int_{-\infty}^{\infty} e^{i\lambda x - D_1\lambda^2 t}\,\hat{P}(\lambda)\,d\lambda - D_1\int_{\partial\mathcal{D}_p^-} e^{i\lambda(x-a)-D_1\lambda^2 t}\left[i\lambda G_0^\flat(\lambda\sqrt{D_1})\right]d\lambda$$
$$- D_1\int_{\partial\mathcal{D}_p^+} e^{i\lambda x - D_1\lambda^2 t}\left[-\frac{D_2}{D_1}F_1^\#(\lambda\sqrt{D_1}) + i\lambda k_m F_0^\#(\lambda\sqrt{D_1})\right]d\lambda$$

Similarly, we obtain:

$$2\pi q(x,t) = -D_2\int_{\partial\mathcal{D}_p^-} e^{i\lambda(x-b)-D_2\lambda^2 t}\,G_1^\#(\lambda\sqrt{D_2})\,d\lambda$$
$$- D_2\int_{\partial\mathcal{D}_p^+} e^{i\lambda x - D_2\lambda^2 t}\left[F_1^\#(\lambda\sqrt{D_2}) + i\lambda F_0^\#(\lambda\sqrt{D_2})\right]d\lambda$$

Results: Concentration Profile





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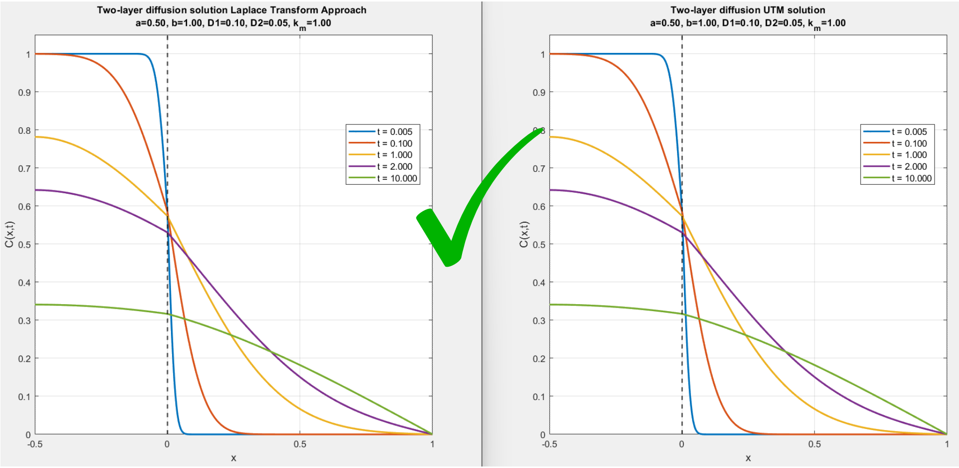
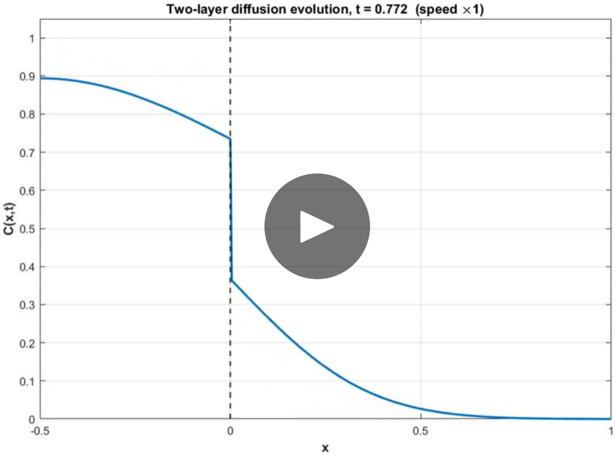


Animation $(k_m = 2)$



Qualitative Comparison of Methods

Laplace Transform Method

- + Familiar and classical approach
- + Clear physical interpretation in time domain
- + Series solution via residues
- − Inversion can be very difficult
- − Hard to generalise and extend model

Unified Transform Method (UTM)

- + Can easily change initial conditions
- + Systematic treatment of boundary and interface conditions
- + Handles composite and multilayer domains naturally
- − Technically more involved
- − Can be computationally heavier to evaluate numerically

Future Work

- Embedding method
- More complex boundary and initial conditions
- Reaction–diffusion extensions
- Time-dependent interface conditions
- More layers

Acknowledgements

- Australian Mathematical Sciences Institute (AMSI)
- Dr. Dave Smith, Dr. Ravi Pethiyagoda, and Prof. Natalie Thamwattana
- School of Computer and Information Sciences, University of Newcastle

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- B. Deconinck, B. Pelloni, and N. Sheils, *Non-steady state heat conduction in composite walls* (arXiv:1402.3007)

- M. Fernandes, L. Simon, and N. W. Loney, *Mathematical modeling of transdermal drug-delivery systems: Analysis and applications* (ResearchGate)

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$$G_1^{\#}(\lambda) = \frac{R_2\sqrt{D_1}\,\sin\left(\frac{a\lambda}{\sqrt{D_1}}\right) - R_1\,\cos\left(\frac{a\lambda}{\sqrt{D_1}}\right)}{\Delta_{\mathrm{core}}(\lambda)}$$

$$G_0^{\flat}(\lambda) = \frac{R_1 k_m\sqrt{D_2}\,\sin\left(\frac{b\lambda}{\sqrt{D_2}}\right) - R_2 D_2\,\cos\left(\frac{b\lambda}{\sqrt{D_2}}\right)}{\Delta(\lambda)}$$

$$F_0^{\#}(\lambda) = -\frac{\sqrt{D_2}}{\lambda}\,\sin\left(\frac{b\lambda}{\sqrt{D_2}}\right)\,G_1^{\#}(\lambda),$$

$$F_1^{\#}(\lambda) = \cos\left(\frac{b\lambda}{\sqrt{D_2}}\right)\,G_1^{\#}(\lambda).$$

where $$R_1 = -\frac{1}{2}\left[\hat{P}\left(\frac{\lambda}{\sqrt{D_1}}\right) + \hat{P}\left(-\frac{\lambda}{\sqrt{D_1}}\right)\right], \qquad R_2 = -\frac{1}{2i\sqrt{D_1}}\left[\hat{P}\left(\frac{\lambda}{\sqrt{D_1}}\right) - \hat{P}\left(-\frac{\lambda}{\sqrt{D_1}}\right)\right]$$

and $$\Delta_{core}(\lambda) = \frac{1}{\lambda}\Delta(\lambda) = k_m\sqrt{D_1 D_2}\sin\left(\frac{a\lambda}{\sqrt{D_1}}\right)\sin\left(\frac{b\lambda}{\sqrt{D_2}}\right) - D_2\cos\left(\frac{a\lambda}{\sqrt{D_1}}\right)\cos\left(\frac{b\lambda}{\sqrt{D_2}}\right).$$