Controlled Release Drug Delivery

Mixed Boundary Problem

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ANZIAM Symposium, Sydney
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Wollongong, NSW 2500, Aus

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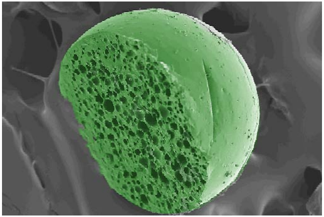
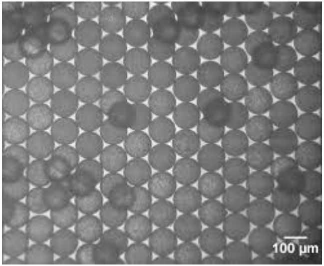
"*The reviewers said it couldn't be done. My grad students proved them wrong time and again and have gone on to have stellar careers. The reviewers? Notsomuch.*"

- Prof. Bob Langer (MIT)

Contents

Polymeric micro/nanospheres





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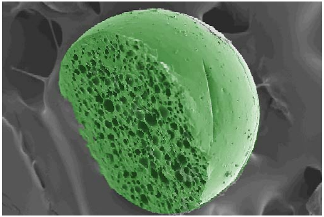
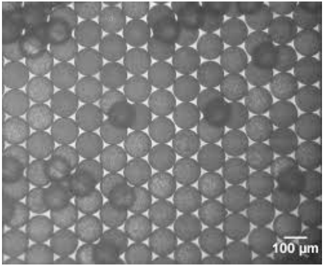
Polymeric micro/nanospheres





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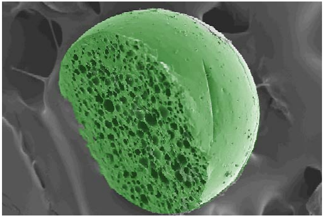

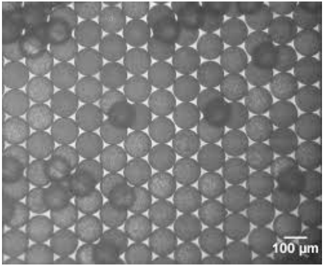

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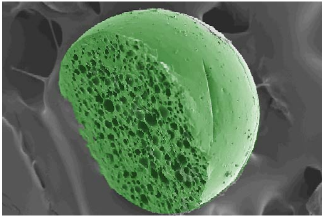

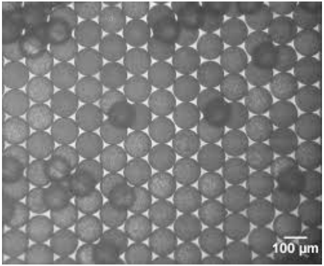

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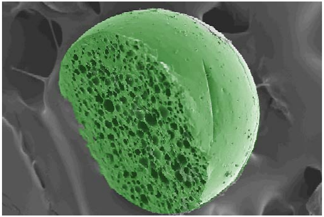
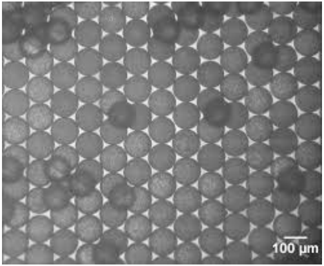
- $10^{-9} - 10^{-3}$m
- surgical implants or subdermal injection

Polymeric micro/nanospheres





- Diffusion: matrix & reservoir

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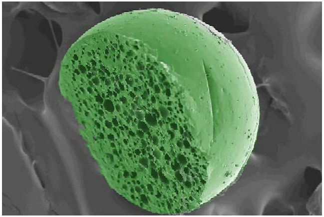
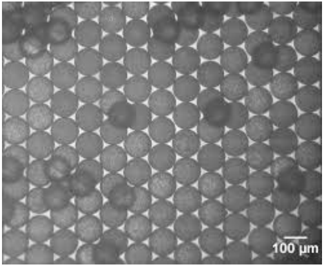
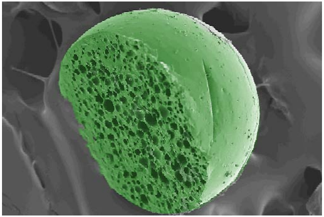
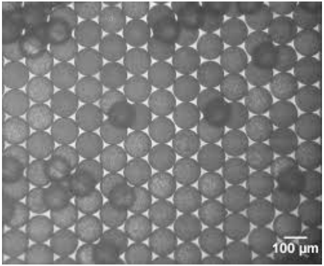




- Diffusion: matrix & reservoir
- Solvent: Swelling & osmotic

Polymeric micro/nanospheres





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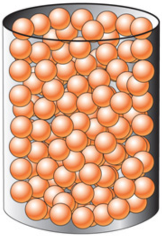

Matrix Configuration

Reservoir Configuration

Simple Spherical Model: Analytics

Diffusion equation

$$\frac{\partial u}{\partial t} = \kappa \left[\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial u}{\partial r} \right) \right] \quad \text{for } 0 \leq r \leq a$$

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with the BCs and IC

$$\lim_{r \to 0} |u(r,t)| < \infty, \quad u(a,t) = 0 \text{ for } t > 0, \quad u(r,0) = U_0.$$

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Laplace Transform, for $t < 1$ (Tables [1]):

$$u(r,t) = aU_0 \left(1 - \frac{1}{r} \sum_{n=0}^{\infty} \operatorname{erfc} \frac{(2n+1) - r/a}{2\sqrt{\kappa t}} + \frac{1}{r} \sum_{n=0}^{\infty} \operatorname{erfc} \frac{(2n+1) + r/a}{2\sqrt{\kappa t}} \right) \quad \text{Crank(6.20)}$$

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Separation of Variables, for $t > 1$:

$$u(r,t) = \frac{2a\,U_0}{\pi r} \sum_{n=1}^{\infty} \frac{(-1)^{n+1}}{n} \sin \tfrac{n\pi}{a} r \, \exp\left[-\left(\tfrac{n\pi}{a}\right)^2 \kappa\, t\right]. \quad \text{Crank(6.18)}.$$

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Computational Pharmacology quantities

Outward boundary flux:

$$-\left.\frac{\partial u}{\partial r}\right|_{r=a} = \begin{cases} \frac{2\,U_0}{a}\sum_{n=1}^{\infty} \exp\left(-\left(\frac{n\pi}{a}\right)^2 \kappa\, t\right), & t > 1 \\ -aU_0 \sum_{n=0}^{\infty} \operatorname{erfc}\left(\frac{n}{\sqrt{\kappa t}}\right) - \frac{1}{\sqrt{\kappa \pi t}} \exp\left(-n^2/\kappa t\right) \ldots \\ \qquad - \operatorname{erfc}\left(\frac{n+1}{\sqrt{\kappa t}}\right) + \frac{1}{\sqrt{\kappa\pi t}} \exp\left(-(n+1)^2/\kappa t\right), & t < 1. \end{cases}$$

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Normalised mass transfer: Crank form $\bar{U} = (u(r,t) - U_0)/(U_a - U_0)$

$$m_t = \iiint_V \bar{U}(\rho, t)\, dV = \tfrac{4}{3}\pi a^3 - \frac{8a^3}{\pi}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\kappa\left(\frac{n\pi}{a}\right)^2\ t\right)$$

$$\therefore\ m_\infty = \tfrac{4}{3}\pi a^3$$

$$\text{and}\ \frac{m_t}{m_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\kappa\left(\frac{n\pi}{a}\right)^2\ t\right) \qquad \text{Crank 6.23}$$

Also has short-time (erfc) form.

Finite Difference Method

Explicit Matrix scheme

- Review paper: Ford-Versypt & Braatz (2014) [2]

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- 'ghost' node: $u_r(0, t_j) = 0 \quad \Longrightarrow \quad \frac{u_{1,j} - u_{-1,j}}{2\Delta r} = 0 \quad \Longrightarrow \quad u_{-1,j} = u_{1,j}$

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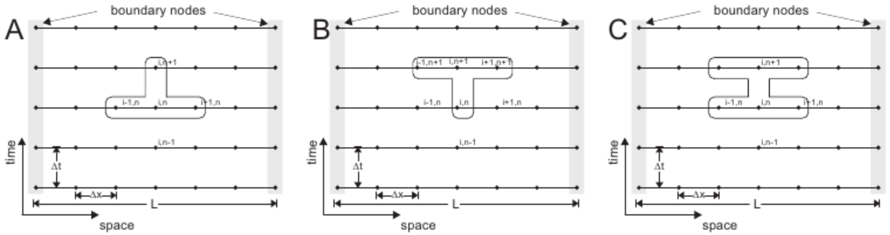
- $\mathbf{u}^{(j+1)} = A\mathbf{u}^{(j)}$, where A is tri-diagonal but not symmetric.

$$A = \begin{pmatrix} 1-6\mu & 6\mu & 0 & 0 & \dots & 0 \\ \mu(1-1) & 1-2\mu & \mu(1+1) & 0 & \dots & 0 \\ 0 & \frac{1}{2}\mu & 1-2\mu & \frac{3}{2}\mu & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \dots & \frac{i-1}{i}\mu & 1-2\mu & \frac{i+1}{i}\mu & \vdots \\ \vdots & \dots & \dots & 0 & \frac{n-2}{n-1}\mu & 1-2\mu \end{pmatrix}$$

[3]

Crank-Nicholson scheme

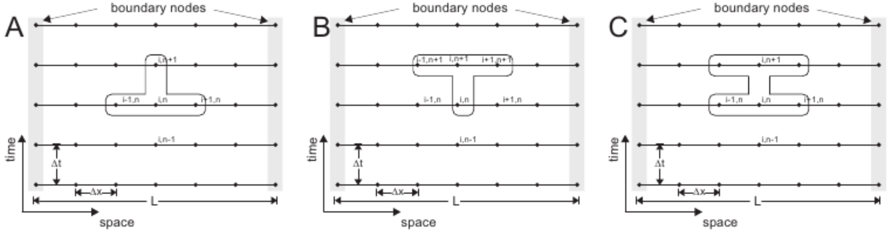


- C-N is an average of the Forward and Backward Euler methods.

$$u_{i+1,j} - u_{i,j} = \frac{1}{2}\mu \left[(u_{i+1,j+1} - 2u_{i+1,j} + u_{i+1,j-1}) + (u_{i,j+1} - 2u_{i,j} + u_{i,j-1}) \right]$$

for $i = 0, \ldots, m$ and $j = 1, \ldots, (n-1)$ with $\mu = \frac{\Delta t}{(\Delta r)^2}$.

Crank-Nicholson scheme



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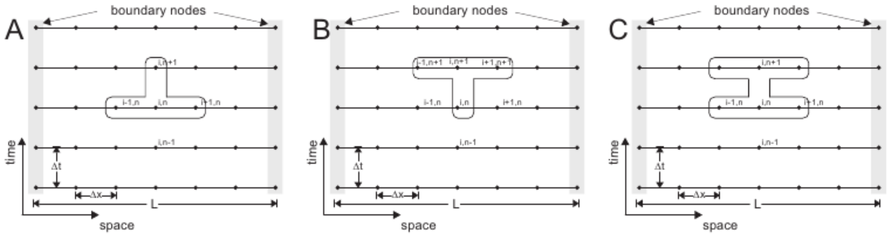

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- $B\,\mathbf{u}^{(i+1)} = C\,\mathbf{u}^{(i)} + \frac{1}{2}(\mathbf{b}^{(i)} + \mathbf{b}^{(i+1)})$
- Use LU decomp or Gaussian reduction (Thomas algorithm).

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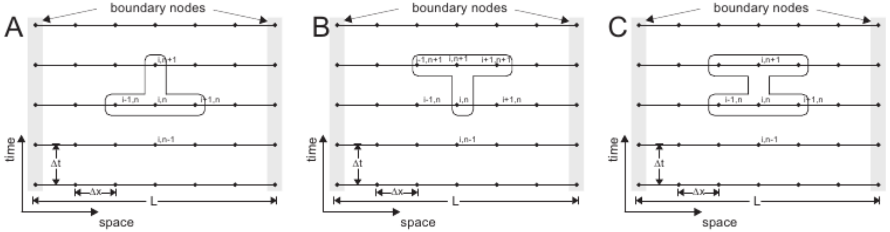

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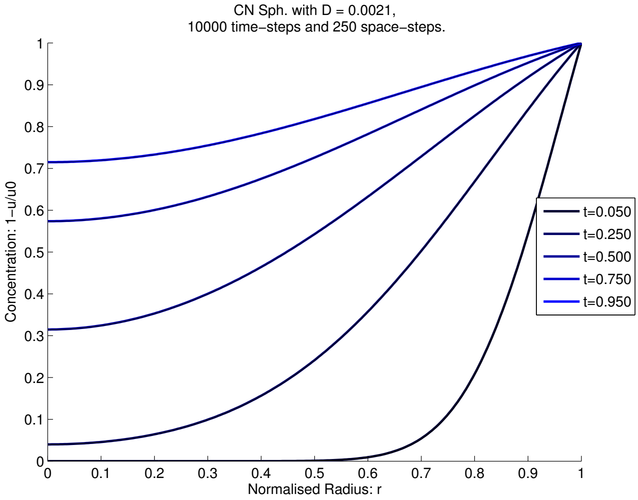
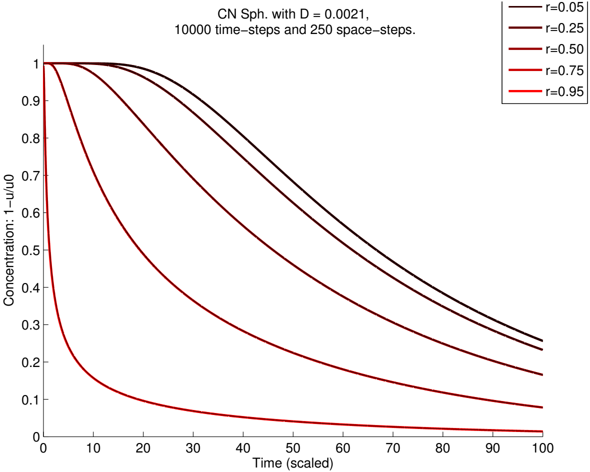
- $B\,\mathbf{u}^{(i+1)} = C\,\mathbf{u}^{(i)} + \frac{1}{2}(\mathbf{b}^{(i)} + \mathbf{b}^{(i+1)})$
- Use LU decomp or Gaussian reduction (Thomas algorithm).
- unconditionally stable but 'noise' sensitive.

Radius

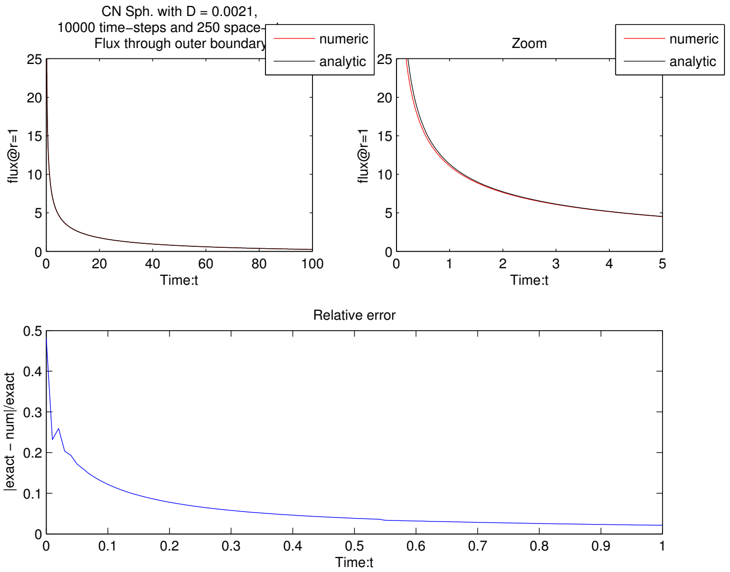


CN Sph. with D = 0.0021,
10000 time−steps and 250 space−steps.
Concentration: 1−u/u0
Normalised Radius: r
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
t=0.050
t=0.250
t=0.500
t=0.750
t=0.950

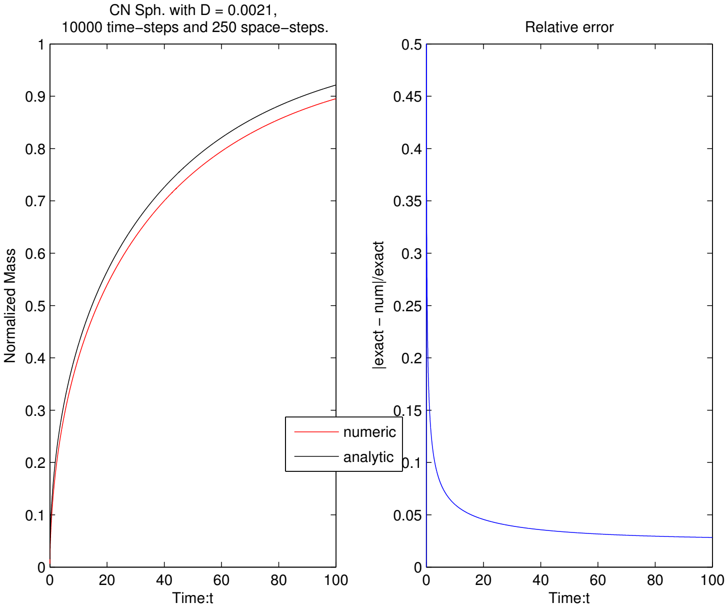
Time


CN Sph. with D = 0.0021,
10000 time−steps and 250 space−steps.
r=0.05
r=0.25
r=0.50
r=0.75
r=0.95
Concentration: 1−u/u0
Time (scaled)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0
10
20
30
40
50
60
70
80
90
100

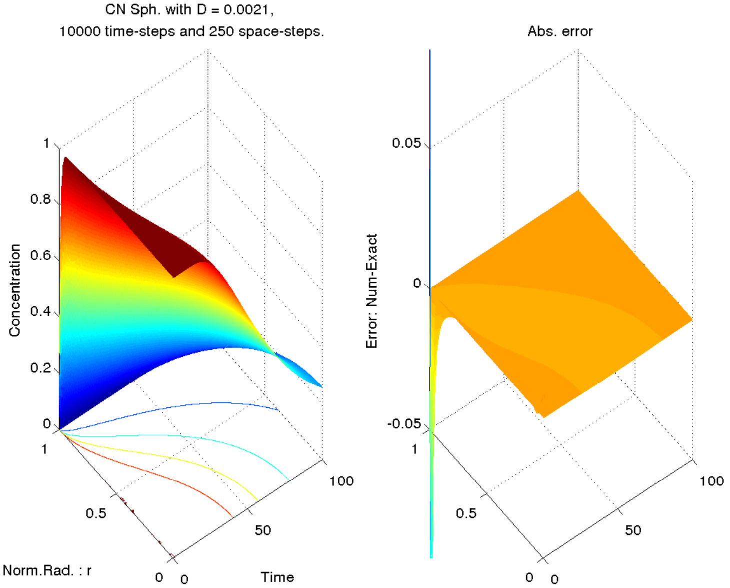
Outward Flux: $-\frac{\partial}{\partial r} u$



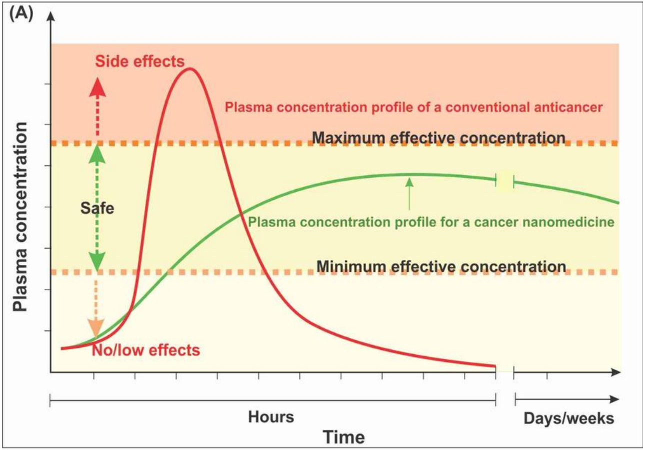
Mass transfer through outer boundary



Mesh


CN Sph. with D = 0.0021,
10000 time-steps and 250 space-steps.
Concentration
Norm.Rad. : r
Time
1
0.8
0.6
0.4
0.2
0
1
0.5
0
0
50
100
Abs. error
Error: Num-Exact
0.05
0
-0.05
1
0.5
0
0
50
100

What is Controlled Release?



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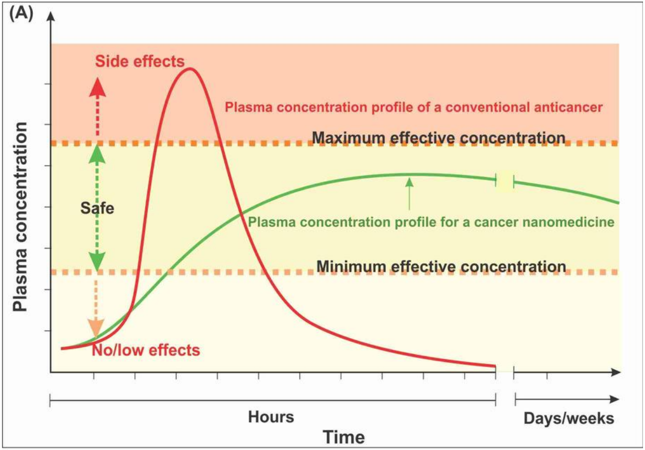

- Higuchi - (1961): 'Higuchi equation: Derivation, applications, use and misuse.'Siepman &, Peppas (2011) [4]

Some papers . . .

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- Singh et al (2008) [**Singh.S:2008**]
  No imaginary eigenvalues to 2D polar diffusion.
- Peppas (1985), 2 pages with $>$ 1100 citations!

A bit of Fun

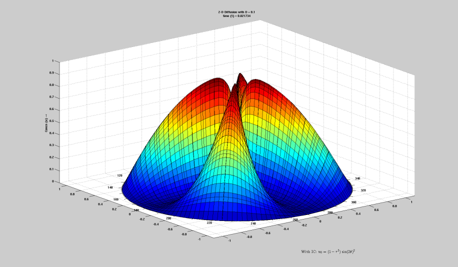
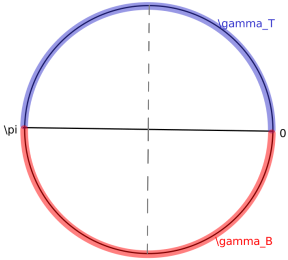


Figure : Circular diffusion with IC and Robin BC

Mixed BVP: Formulation



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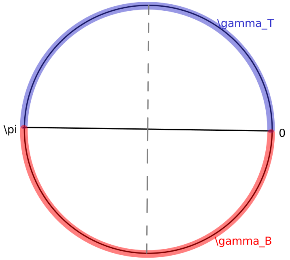
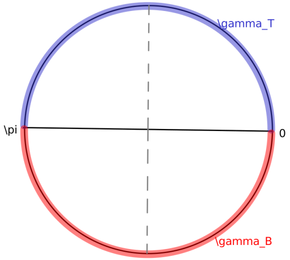


Non-axisymmetric circular diffusion equation:

$$\frac{\partial u}{\partial t} = D\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial u}{\partial r}\right) + \frac{1}{r}\frac{\partial}{\partial \theta}\left(r\frac{\partial u}{\partial \theta}\right)\right]$$

Mixed BVP: Formulation



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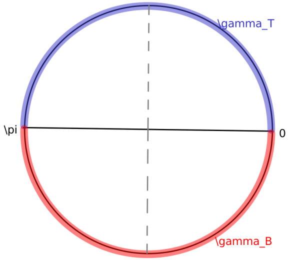

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With conditions:

$$\begin{aligned} u(r,\theta,t) &= u(r,\theta+2\pi,t) \text{ (Periodicity)}, \\ u(r,\theta,0) &= u_0 \in \mathbb{R}, \\ |u(r,\theta,t)| &< \infty. \end{aligned}$$

Outline solution method

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- Invert LT using residues

[10, 11, 12, 13]

Laplace-space Solution

It can be shown that

$$A_0 = \frac{\bar{\gamma}}{s \cdot [\xi \;\; I_0'(\xi a) + \bar{\gamma} I_0(\xi a)]}, \quad \text{where } \bar{\gamma} = \frac{\gamma_T + \gamma_B}{2},$$

$$A_n = 0,$$

$$B_{2n-1} = \frac{4}{s \;\, \pi(2n-1)} \; \frac{(\gamma_B - \gamma_T)/2}{\xi I_{2n-1}'(\xi a) + \bar{\gamma} I_{2n-1}(\xi a)}.$$

$$V(r,\theta) \; = \; \left(\frac{\bar{\gamma}}{s \cdot \Psi_0}\right) \; I_0(\xi r) \; + \sum_{n \in \mathbb{N}} \left(\frac{2}{\pi(2n-1)} \; \frac{\gamma_B - \gamma_T}{s \cdot \Psi_{2n-1}}\right) I_{2n-1}(\xi r) \; \sin((2n-1)\theta),$$

$$\text{where } \Psi_k = \xi \;\; I_k'(\xi a) + \bar{\gamma} I_k(\xi a).$$

Solution

Solution

The Full Monty:

$$u(r,\theta,t) = 1 - \sum_{m\in\mathbb{N}} \frac{2\bar{\gamma}\; J_0(\zeta_{0,m} r)\, \exp(-D\zeta_{0,m}^2 t)}{a\left[\bar{\gamma}\zeta_{0,m} J_1(\zeta_{0,m} a) + \zeta_{0,m}^2 J_0(\zeta_{0,m} a)\right]}$$

$$-\sum_{n\in\mathbb{N}} \sum_{m\in\mathbb{N}} \frac{4a\hat{\gamma}\; \sin(\nu\theta) \quad J_\nu(\zeta_{\nu,m} r)\, \exp(-D\zeta_{\nu,m}^2 t)}{\pi\nu\left[\bar{\gamma}\zeta_{\nu,m} a^2 J_{\nu+1}(\zeta_{\nu,m} a) + \left(\zeta_{\nu,m}^2 a^2 - \nu^2\left(1 + \frac{a}{\nu}\bar{\gamma}\right)\right) J_\nu(\zeta_{\nu,m} a)\right]}$$

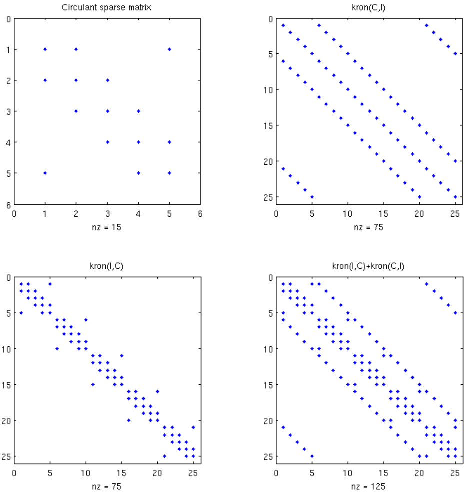
Where the $\zeta_{\nu,m}$ satisfy the transcendental equation:

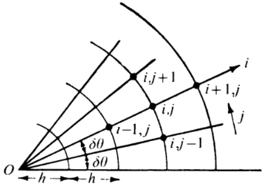
$$(a\bar{\gamma} + \nu)\, J_\nu(\zeta a) - \zeta a\, J_{\nu+1}(\zeta a) = 0$$

with

$$\nu = 2n - 1, \quad \bar{\gamma} = \tfrac{1}{2}(\gamma_B + \gamma_T) \quad \text{and} \quad \hat{\gamma} = \gamma_B - \gamma_T. \;.$$

Numerics: Polar (2 space + time)





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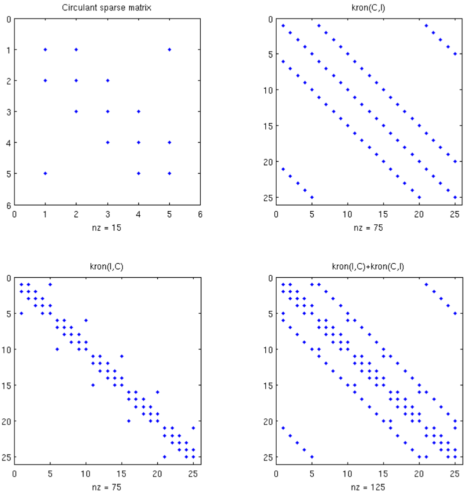

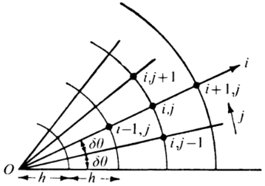

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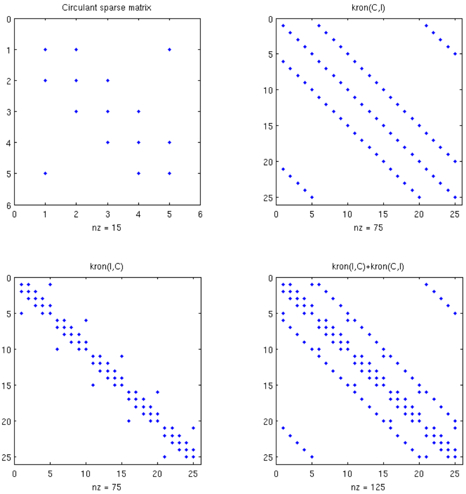

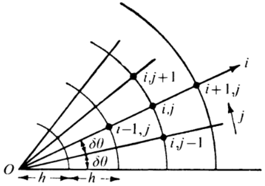

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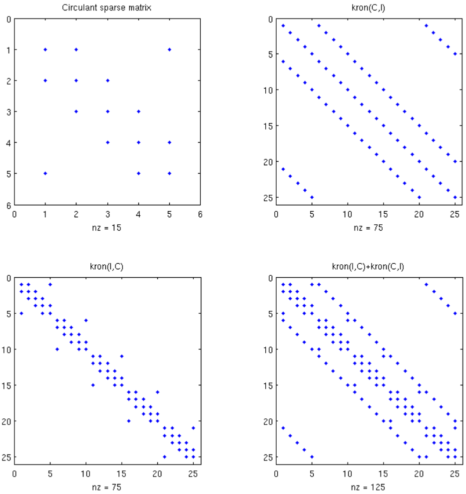

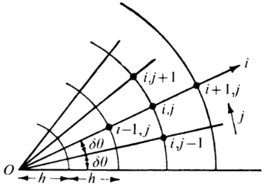

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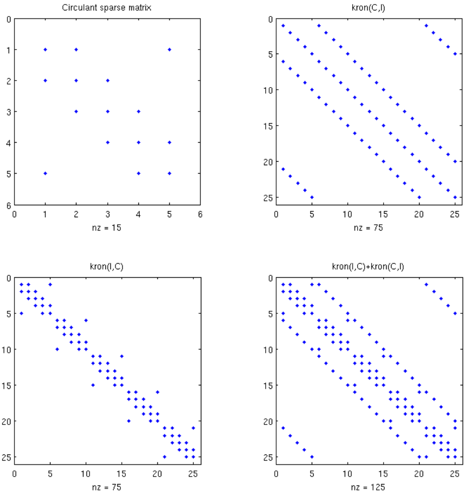

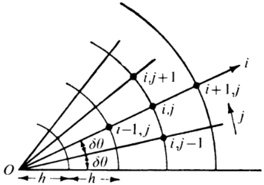

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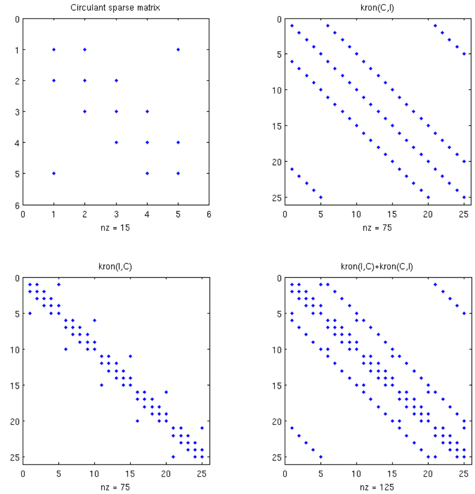

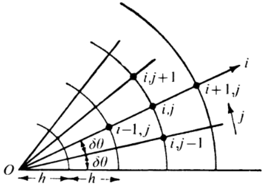

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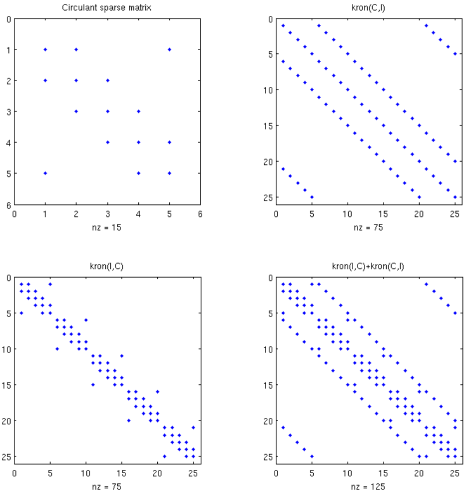

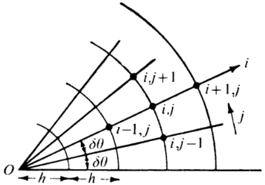

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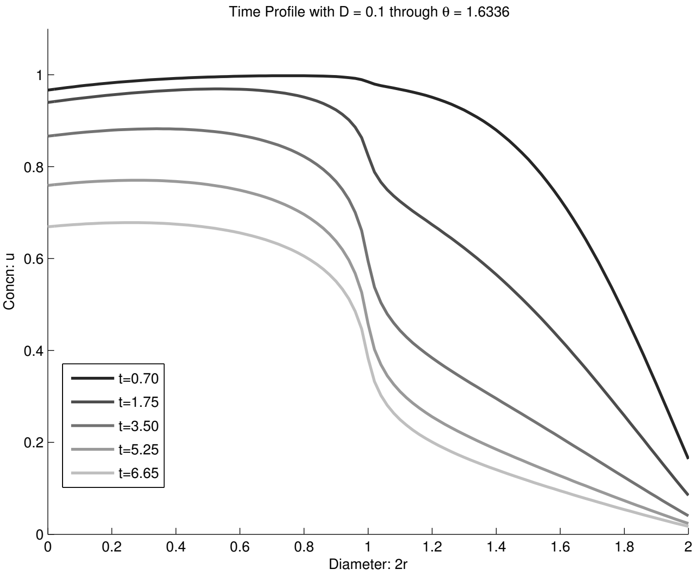
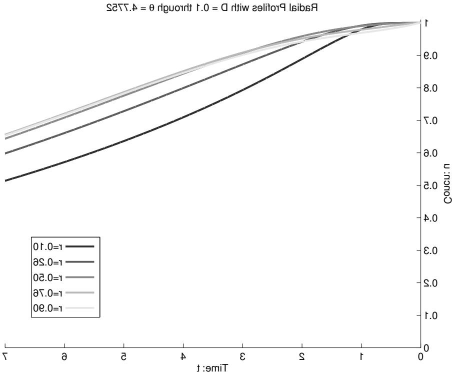
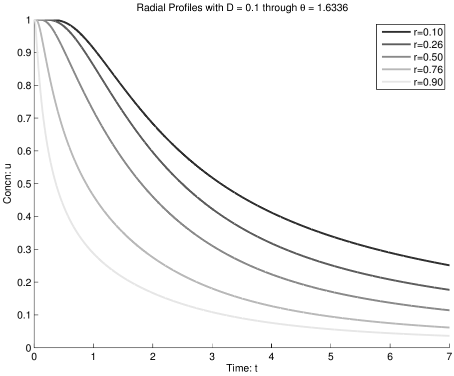
Time Curves



$\gamma_T = 0.1,$
$\gamma_B = 10.$





Use SQUEEZE to get a 1D string of data from a 3D matrix

A bit more fun?

Figure : Circular diffusion with IC $U_0 = 1$ and Mixed Robin BC, Flux through outer boundary.

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- Singh (2011)[15] nuclear fuel, multiple layers, no residues -'gob-stopper' model.

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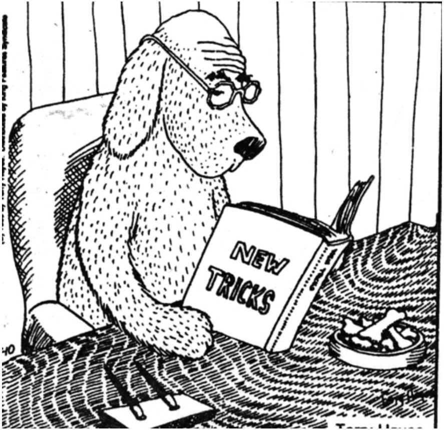
Acknowledgement



My thanks to

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Questions