Asymptotic Analysis of Narrow Escape Problems in Non-Spherical 3D Domains

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Collaborators

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- **Daniel Gomez,** UofS/UBC, Canada

   

Outline

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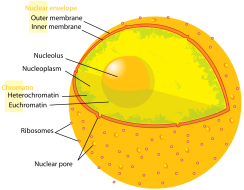
- A Brownian particle escapes from a bounded domain through small windows.

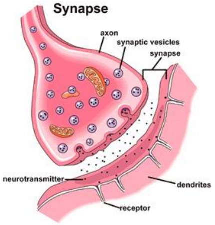
Examples of applications:

- Pores of cell nuclei.
- Synaptic receptors on dendrites.
- Ion channels in cell membranes.
- Typical cell sizes: $\sim 10^{-5}$ m; pore sizes $\sim 10^{-9} \ldots 10^{-8}$ m.

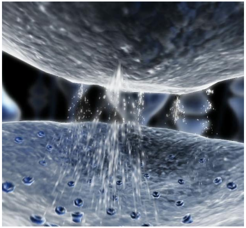
Pores in cell nuclei:



Synaptic receptors on dendrites:



Ion channels in cell membranes:



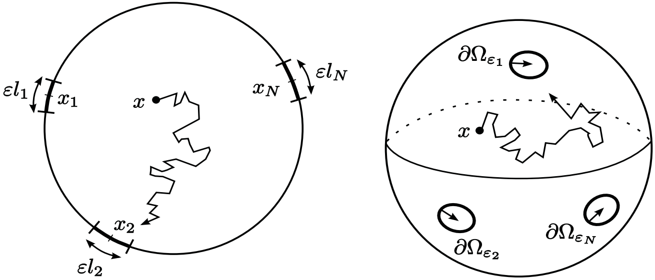


Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

Given:

- A Brownian particle confined in a domain $\Omega \in \mathbb{R}^3$.
- Initial position: $x \in \Omega$.
- Mean First Passage Time (MFPT): $v(x)$.
- Domain boundary: $\partial\Omega = \partial\Omega_r$ (reflecting) $\cup$ $\partial\Omega_a$ (absorbing).
- $\partial\Omega_a = \bigcup_{i=1}^{N} \partial\Omega_{\varepsilon_i}$: small absorbing traps (size $\sim \varepsilon$).

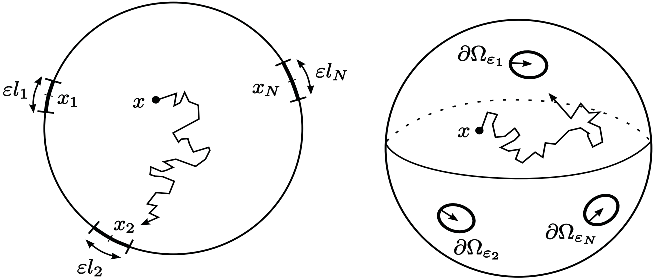
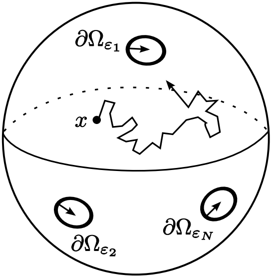


Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

Problem for the MFPT $v = v(x)$ [*Holcman, Schuss (2004)*]:

$$\begin{cases} \triangle v = -\dfrac{1}{D}, & x \in \Omega, \\ v = 0, \quad x \in \partial\Omega_a; & \partial_n v = 0, \quad x \in \partial\Omega_r. \end{cases}$$

Average MFPT: $\bar{v} = \dfrac{1}{|\Omega|} \displaystyle\int_\Omega v(x)\, dx = \text{const.}$



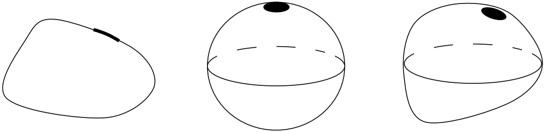
Problem for the MFPT:

$$\begin{cases} \triangle v = -\frac{1}{D}, & x \in \Omega, \\ v = 0, & x \in \partial\Omega_a = \cup_{j=1}^{N} \partial\Omega_{\varepsilon_j}, \\ \partial_n v = 0, & x \in \partial\Omega_r. \end{cases}$$

Boundary Value Problem:

- Linear;
- Strongly heterogeneous Dirichlet/Neumann BCs;
- Singularly perturbed:
  - $\varepsilon \to 0^+ \quad \Rightarrow \quad v \to +\infty$ a.e.

Some General Results



Arbitrary 2D domain with smooth boundary; one trap [*Holcman et al (2004, 2006)*]

$$\bar{v} \sim \frac{|\Omega|}{\pi D}\left[-\log\varepsilon + \mathcal{O}(1)\right]$$

Unit sphere; one trap [*Singer et al (2006)*]

$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon D}\left[1 - \frac{\varepsilon}{\pi}\log\varepsilon + \mathcal{O}(\varepsilon)\right]$$

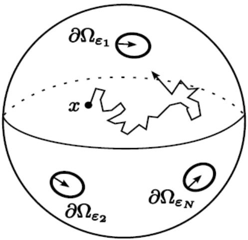
Arbitrary 3D domain with smooth boundary; one trap [*Singer et al (2009)*]

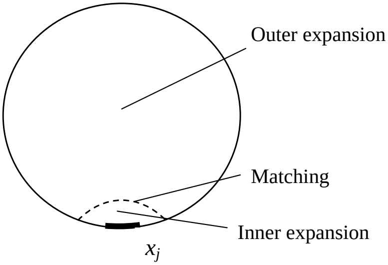
$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon D}\left[1 - \frac{\varepsilon}{\pi}H\log\varepsilon + \mathcal{O}(\varepsilon)\right]$$

H: mean curvature at the center of the trap.

Outline

1. Narrow Escape Problems, Mean First Passage Time (MFPT)
2. Asymptotic Results for Small Traps; Higher-Order MFPT for the Sphere
3. Asymptotic Analysis of the MFPT Problem for Non-Spherical Domains
4. Asymptotic vs. and Numerical Average MFPT for Non-Spherical Domains
   - Oblate Spheroid
   - Prolate Spheroid
   - Biconcave Disk–Blood Cell Shape
5. Towards Higher-order MFPT Asymptotics
6. Highlights and Open Problems





- Outer expansion, defined at $\mathcal{O}(1)$ distances from traps:

$$v_{out} \sim \varepsilon^{-1} v_0(x) + v_1(x) + \varepsilon \log\left(\frac{\varepsilon}{2}\right) v_2(x) + \varepsilon v_3(x) + \cdots .$$

- Inner expansion of solution near trap centered at x_j uses scaled coordinates y:

$$v_{in} \sim \varepsilon^{-1} w_0(y) + \log\left(\frac{\varepsilon}{2}\right) w_1(y) + w_2(y) + \cdots .$$

- Matching condition: when $x \to x_j$ and $y = \varepsilon^{-1}(x - x_j) \to \infty$,

$$v_{in} \sim v_{out}.$$

Higher-Order Asymptotic MFPT for the Sphere

Given:

- Sphere with N traps located at $\{x_j\}$.
- Trap radii: $r_j = a_j \varepsilon, \;\; j = 1, \ldots, N$; capacitances: $c_j = 2a_j/\pi$.

MFPT and average MFPT [*A.C., M.Ward, R.Straube (2010)*]:

$$v(x) = \bar{v} - \frac{|\Omega|}{DN\bar{c}} \sum_{j=1}^{N} c_j G_s(x; x_j) + \mathcal{O}(\varepsilon \log \varepsilon)$$

$$\bar{v} = \frac{|\Omega|}{2\pi\varepsilon DN\bar{c}} \left[1 + \varepsilon \log\left(\frac{2}{\varepsilon}\right) \frac{\sum_{j=1}^{N} c_j^2}{2N\bar{c}} + \frac{2\pi\varepsilon}{N\bar{c}} p_c(x_1, \ldots, x_N) - \frac{\varepsilon}{N\bar{c}} \sum_{j=1}^{N} c_j \kappa_j + \mathcal{O}(\varepsilon^2 \log \varepsilon) \right]$$

- $G_s(x; x_j)$: spherical Neumann Green's function (known).
- $\bar{c}$: average capacitance; $\kappa_j = \mathrm{const.}$
- $p_c(x_1, \ldots, x_N)$: trap interaction term involving $G_s(x_i; x_j)$.

Applications of the MFPT Formula for the Sphere

MFPT and average MFPT:

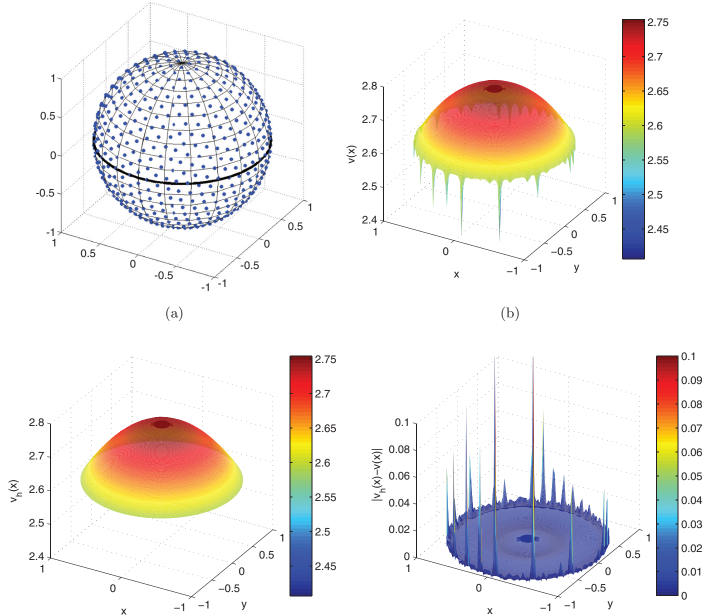
$$v(x) = \bar{v} - \frac{|\Omega|}{DN\bar{c}} \sum_{j=1}^{N} c_j G_s(x; x_j) + \mathcal{O}(\varepsilon \log \varepsilon)$$

$$\bar{v} = \frac{|\Omega|}{2\pi\varepsilon DN\bar{c}} \left[1 + \varepsilon \log\left(\frac{2}{\varepsilon}\right) \frac{\sum_{j=1}^{N} c_j^2}{2N\bar{c}} + \frac{2\pi\varepsilon}{N\bar{c}} p_c(x_1, \ldots, x_N) - \frac{\varepsilon}{N\bar{c}} \sum_{j=1}^{N} c_j \kappa_j + \mathcal{O}(\varepsilon^2 \log \varepsilon) \right]$$

Applications:

- Fast MFPT computations.
- Optimal N-trap arrangements – local and global optimization.
- Dilute trap limit – homogenization limit for of $N \gg 1$ small traps [*A.C., M. Ward, & R. Straube (2010); A.C. & D. Zawada (2013)*]

Dilute Trap Fraction Limit; $N = 802$, $\varepsilon = 0.0005$



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A General Class of 3D Domains

- (μ, ν, ω) : an orthogonal coordinate system in $\mathbb{R}^3$.
- Consider Ω defined by

$$\Omega \equiv \{(\mu, \nu, \omega) \,|\, 0 \le \mu \le \mu_0,\ 0 \le \nu \le \nu_0,\ 0 \le \omega \le \omega_0\},$$
$$\partial\Omega \equiv \{(\mu, \nu, \omega) \,|\, \mu = \mu_0,\ 0 \le \nu \le \nu_0,\ 0 \le \omega \le \omega_0\}.$$

- At the boundary: $\partial_n|_{\partial\Omega} = \partial_\mu|_{\mu=\mu_0}$.
- Scale factors:

$$h_{\mu_j} = h_\mu(x_j), \qquad h_{\nu_j} = h_\nu(x_j), \qquad h_{\omega_j} = h_\omega(x_j).$$

- Local stretched coordinates (centered at the j^{th} trap):

$$\eta = -h_{\mu_j}\frac{\mu - \mu_j}{\varepsilon}, \qquad s_1 = h_{\nu_j}\frac{\nu - \nu_j}{\varepsilon}, \qquad s_2 = h_{\omega_j}\frac{\omega - \omega_j}{\varepsilon}.$$

- Example: axially symmetric domains.

The Laplacian in Local Stretched Coordinates

Laplacian in orthonormal coordinates (μ, ν, ω):

$$\Delta\Psi = \frac{1}{h_\mu h_\nu h_\omega}\left[\frac{\partial}{\partial\mu}\left(\frac{h_\nu h_\omega}{h_\mu}\frac{\partial\Psi}{\partial\mu}\right) + \frac{\partial}{\partial\nu}\left(\frac{h_\mu h_\omega}{h_\nu}\frac{\partial\Psi}{\partial\nu}\right) + \frac{\partial}{\partial\omega}\left(\frac{h_\mu h_\nu}{h_\omega}\frac{\partial\Psi}{\partial\omega}\right)\right].$$

Leading terms:

$$\Delta = \frac{1}{\varepsilon^2}\Delta_{(\eta,s_1,s_2)} + \frac{1}{\varepsilon}\mathcal{L}_\Delta + \mathcal{O}(1),$$

where

$$\Delta_{(\eta,s_1,s_2)} \equiv \frac{\partial^2}{\partial\eta^2} + \frac{\partial^2}{\partial s_1^2} + \frac{\partial^2}{\partial s_2^2},$$

and

$$\mathcal{L}_\Delta \equiv \Lambda_\eta\frac{\partial^2}{\partial\eta^2} + \Lambda_{s_1}\frac{\partial^2}{\partial s_1^2} + \Lambda_{s_2}\frac{\partial^2}{\partial s_2^2} + \lambda_\eta\frac{\partial}{\partial\eta} + \lambda_{s_1}\frac{\partial}{\partial s_1} + \lambda_{s_2}\frac{\partial}{\partial s_2}.$$

- Λ_α, λ_α: rather complicated expressions in terms of scale factors h_β.

The Surface Neumann Green's Function

Green's Function problem:

$$\Delta G_s(x;x_j) = \frac{1}{|\Omega|}, \quad x \in \Omega, \qquad \partial_n G_s(x;x_j) = \delta_s(x - x_j), \quad x \in \partial\Omega,$$

$$\int_\Omega G \, dx = 0.$$

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$$\int_\Omega G\, dx = 0.$$

Expression for a general domain [*A. Singer, Z. Schuss & D. Holcman (2008)*]:

$$G_s(x;x_j) = \frac{1}{2\pi|x - x_j|} - \frac{H(x_j)}{4\pi} \log|x - x_j| + v_s(x;x_j).$$

- $H(x_j)$: the mean curvature of $\partial\Omega$ at x_j.
- $v_s(x;x_j)$: a bounded function of x and x_j in Ω.

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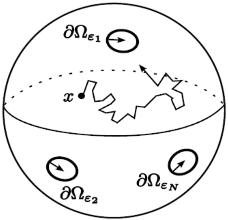
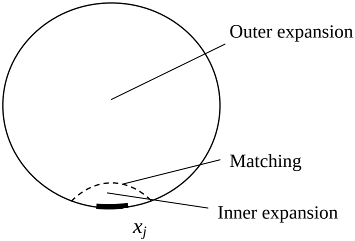
Asymptotic expansion:

$$G_s(\eta, s_1, s_2) = \frac{1}{2\pi\rho}\frac{1}{\varepsilon} - \frac{H(x_j)}{4\pi}\log\frac{\varepsilon}{2} + g_0(\eta, s_1, s_2) + g_1(\eta, s_1, s_2)\,\varepsilon\log\frac{\varepsilon}{2} + \mathcal{O}(\varepsilon),$$

$$\rho = \sqrt{\eta^2 + s_1^2 + s_2^2}.$$





- Inner expansion of solution near trap centered at x_j uses stretched coordinates:

$$v_{in} = w(\eta, s_1, s_2) \sim \frac{1}{\varepsilon} w_0 + \log\left(\frac{\varepsilon}{2}\right) \, w_1 + w_2 + \cdots .$$

- Outer expansion far from each of the boundary traps x_j, $|x - x_j| = \mathcal{O}(1)$:

$$v_{out} \sim \frac{1}{\varepsilon} v_0 + v_1 + \varepsilon \log\left(\frac{\varepsilon}{2}\right) \, v_2 + \varepsilon v_3 + \cdots .$$

- Matching condition: as $x \to x_j$ and as $\rho = \sqrt{\eta^2 + s_1^2 + s_2^2} \to \infty$,

$$\frac{1}{\varepsilon} v_0 + v_1 + \varepsilon \log\left(\frac{\varepsilon}{2}\right) \, v_2 + \varepsilon v_3 + \cdots \sim \frac{1}{\varepsilon} w_0 + \log\left(\frac{\varepsilon}{2}\right) \, w_1 + w_2 + \cdots .$$

The Average MFPT Asymptotic Expression

Average MFPT for a general domain:

- Under the assumption $g_1 = 0$ in the Green's function, as it is for the sphere, matched solutions for first terms of the asymptotic expansions can be computed.

- Average MFPT expression in the outer region $|x - x_j| \gg \mathcal{O}(\varepsilon)$:

$$\boxed{\bar{v} = \frac{|\Omega|}{2\pi D N \bar{c} \varepsilon} \left[1 - \left(\frac{1}{2N\bar{c}} \sum_{i=1}^{N} c_i^2 H(x_i) \right) \varepsilon \log \left(\frac{\varepsilon}{2} \right) + \mathcal{O}(\varepsilon) \right]}$$

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Compare to the spherical MFPT formula:

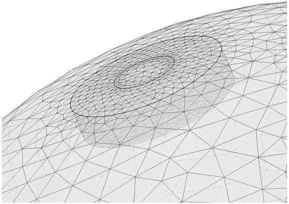
$$\bar{v} = \frac{|\Omega|}{2\pi D N \bar{c} \varepsilon} \left[1 - \left(\frac{1}{2N\bar{c}} \sum_{j=1}^{N} c_j^2 \right) \varepsilon \log\left(\frac{\varepsilon}{2}\right) + \frac{2\pi\varepsilon}{N\bar{c}} p_c(x_1, \ldots, x_N) - \frac{\varepsilon}{N\bar{c}} \sum_{j=1}^{N} c_j \kappa_j + \ldots \right]$$

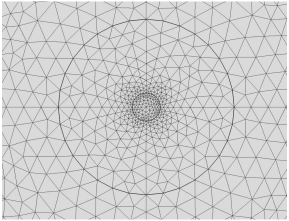
- $\mathcal{O}(1)$ term for the sphere depends on *trap positions*.
- A similar expression of the same order for a general domain can be derived, with some details still missing...

- Numerical solver: COMSOL Multiphysics 4.3b
- Compare numerical and asymptotic average MFPT for three distinct geometries
- $N = 3$ and $N = 5$ traps
- Relative error:

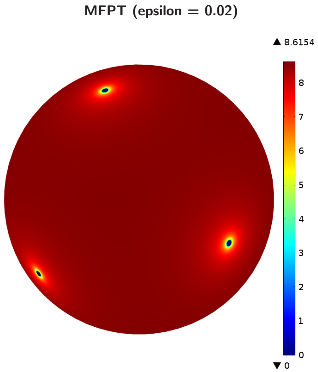
$$\text{R.E.} = 100\% \times \left|\bar{v}_{\text{numerical}} - \bar{v}_{\text{asymptotic}}\right| / \bar{v}_{\text{numerical}}$$

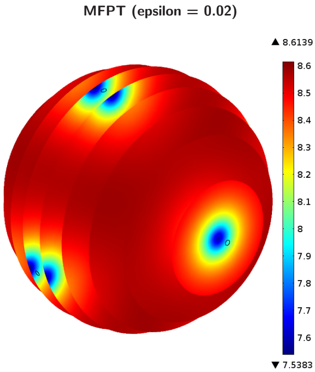
- "Extremely fine" and "fine" mesh regions:



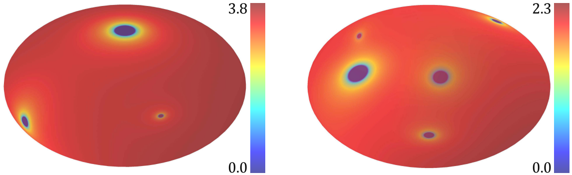


Sample COMSOL MFPT Computations for the Unit Sphere

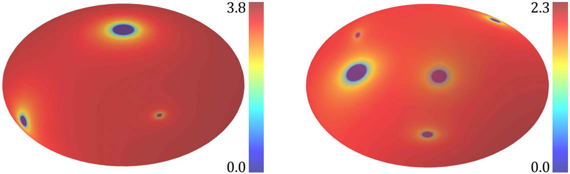




Oblate Spheroid



- $x = \rho \cosh \xi \cos \nu \cos \phi, \qquad y = \rho \cosh \xi \cos \nu \sin \phi, \qquad z = \rho \sinh \xi \sin \nu$
- $\xi \in [0, \infty)$, $\nu \in [-\pi/2, \pi/2]$, $\phi \in [0, 2\pi)$
- $\partial\Omega$: $\quad \xi = \xi_0 = \tanh^{-1}(0.5)$, $\rho = (\cosh \xi_0)^{-1}$

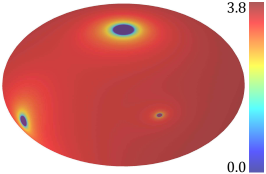


- Trap radii: $r_j = a_j \, \varepsilon$

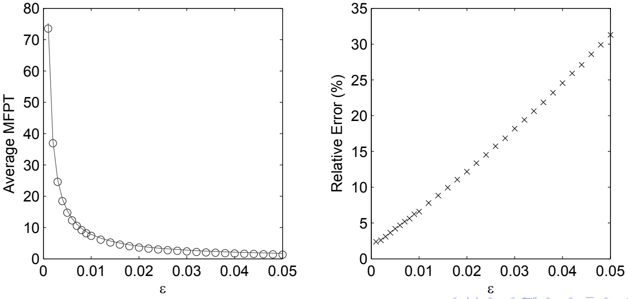
Number of Traps	a	ν	ϕ
$N = 3$	1	$-3\pi/8$	0
	2	0	π
	4	$\pi/2$	0
$N = 5$	1	0	$\pi/2$
	2	$\pi/4$	0
	2	$-\pi/2$	0
	3	$-\pi/4$	$\pi/4$
	4	$\pi/4$	π

Trap locations and relative radii for oblate and prolate spheroids

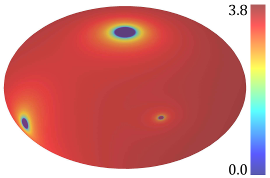
Oblate Spheroid



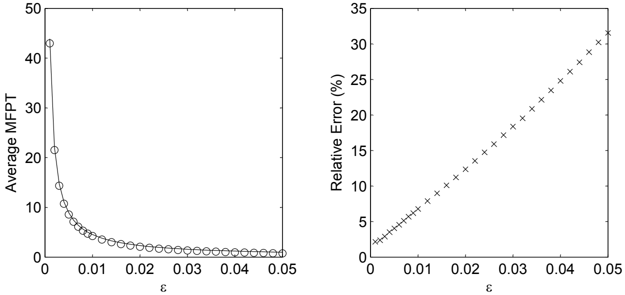
- Numerical vs. asymptotic average MFPT for the oblate spheroid, $N = 3$:



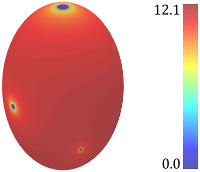
Oblate Spheroid

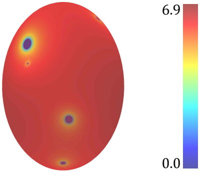


- Numerical vs. asymptotic average MFPT for the oblate spheroid, $N = 5$:

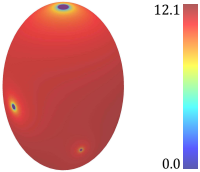


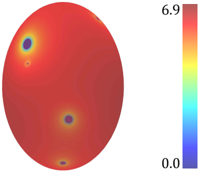
Prolate Spheroid



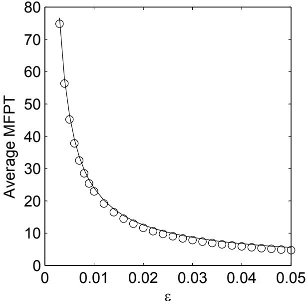


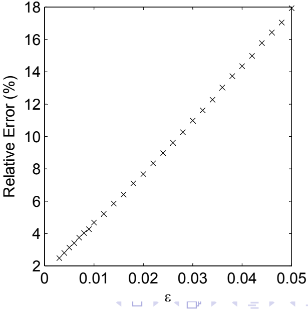
- $x = \rho \sinh \xi \cos \nu \cos \phi$, $\qquad y = \rho \sinh \xi \cos \nu \sin \phi$, $\qquad z = \rho \cosh \xi \sin \nu$
- $\xi \in [0, \infty)$, $\nu \in [-\pi/2, \pi/2]$, and $\phi \in [0, 2\pi)$
- $\partial\Omega$: $\quad \xi_0 = \tanh^{-1}(1/1.5)$ and $\rho = (\sinh \xi_0)^{-1}$

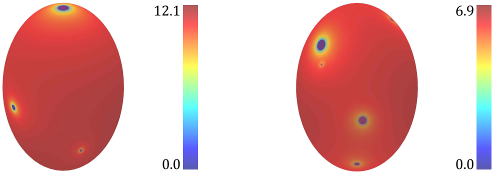




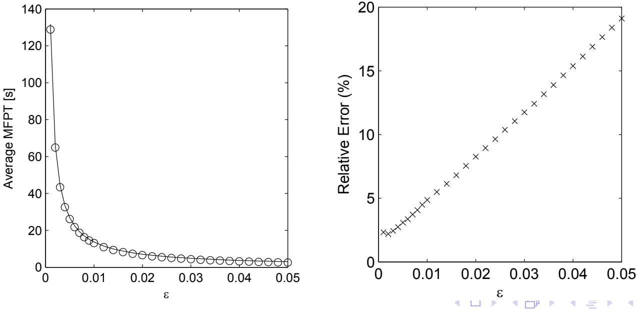
- Numerical vs. asymptotic average MFPT for the prolate spheroid, $N = 3$:



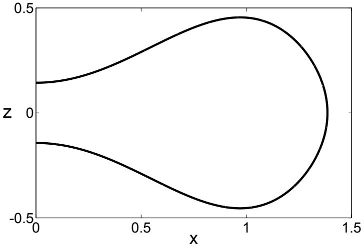




- Numerical vs. asymptotic average MFPT for the prolate spheroid, $N = 5$:



Biconcave Disk (Blood Cell Shape)

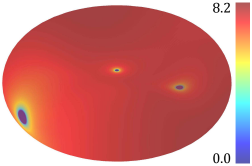


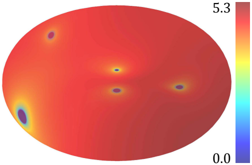
- Shape obtained by rotating the following curve about the z-axis:

$$x = a\alpha \sin\chi, \qquad z = a\frac{\alpha}{2}(b + c\sin^2\chi - d\sin^4\chi)\cos\chi, \qquad \chi \in [0, \pi].$$

- Common parameters [*Pozrikidis (2003)*]:

$$a = 1, \qquad \alpha = 1.38581994, \qquad b = 0.207, \qquad c = 2.003, \qquad d = 1.123.$$



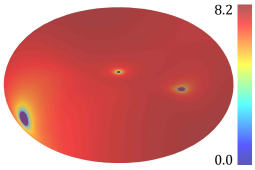


- Trap radii: $r_j = a_j \, \varepsilon$

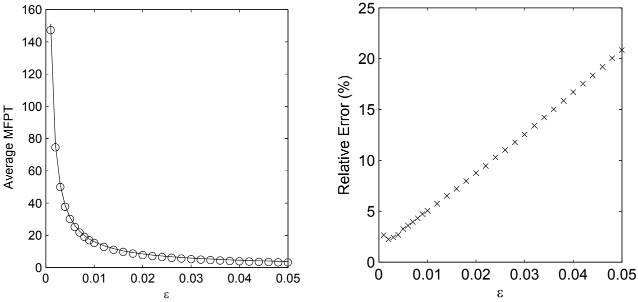
Number of Traps	a	χ	ϕ
$N = 3$	1	0	0
	2	$3\pi/4$	0
	4	$\pi/2$	π
$N = 5$	1	0	0
	2	$3\pi/4$	0
	2	π	0
	2	$\pi/2$	$\pi/2$
	4	$\pi/2$	π

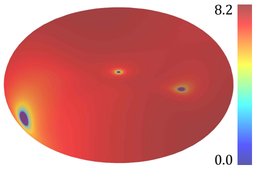
Trap locations and relative radii for biconcave disk (blood cell)

Biconcave Disk (Blood Cell Shape)

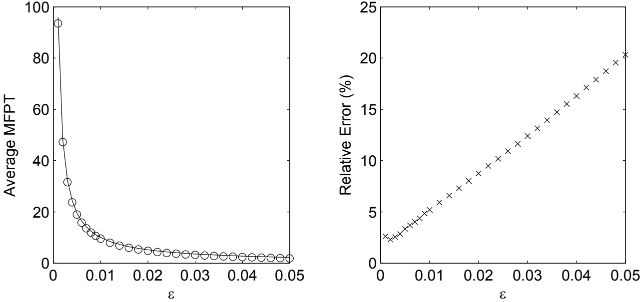


- Numerical vs. asymptotic average MFPT for the biconcave disk, $N = 3$:



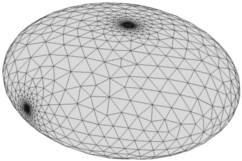


- Numerical vs. asymptotic average MFPT for the biconcave disk, $N = 5$:

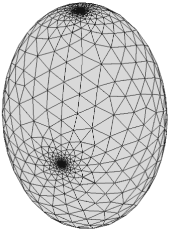


Sample COMSOL Meshes

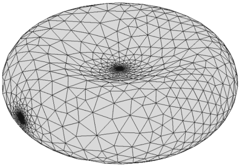
Oblate Spheroid with Three Traps



Prolate Spheroid with Three Traps



Biconcave Disk with Three Traps



Towards Higher-order MFPT Asymptotics

- Based on certain assumptions, higher terms in MFPT formulas can be written, generalizing those for the unit sphere:

$$\bar{v} = \frac{|\Omega|}{2\pi\varepsilon D N\bar{c}}\left[1 - \frac{1}{2N\bar{c}} \sum_{j=1}^{N} c_j^2 H(x_j)\, \varepsilon \log \frac{\varepsilon}{2} + \frac{\varepsilon}{N\bar{c}}\left(\sum_{j=1}^{N} b_j + p_c(x_1, \ldots, x_N)\right) + \mathcal{O}(\varepsilon^2 \log \varepsilon)\right].$$

$$v(x) = \bar{v} - \frac{|\Omega|}{DN\bar{c}} \sum_{j=1}^{N} c_j G_s(x; x_j),$$

- The "interaction energy":

$$p_c(x_1, \ldots, x_N) \equiv 2\pi \sum_{j=1}^{N} \sum_{i \neq j} c_j c_i G_s(x_j; x_i).$$

- Ingredients still required: $G_s(x; x_j)$, b_j.

Outline

Highlights and Open Problems

Results

- For the average MFPT $\bar{v}$, a two-term asymptotic expansion is derived for a wide class of non-spherical domains.
- Directly generalizes the results for the sphere.
- Full finite-element MFPT numerical calculations have been performed to compare average MFPT with asymptotic expansions – close agreement observed for small ε.
- Steps towards the derivation of a higher-order formula for $v(x)$, $\bar{v}$ involving trap positions are taken.

Open problems

- Assumptions on surface Neumann Green's function expansion have been made – justification or modification is required.
- The trap interaction term for non-spherical domains requires further work...
- ... when clarified, global optimization of the average MFPT with respect to trap locations may be performed.

Some References

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Thank you for attention!