Narrow Escape Problems in 3D Domains

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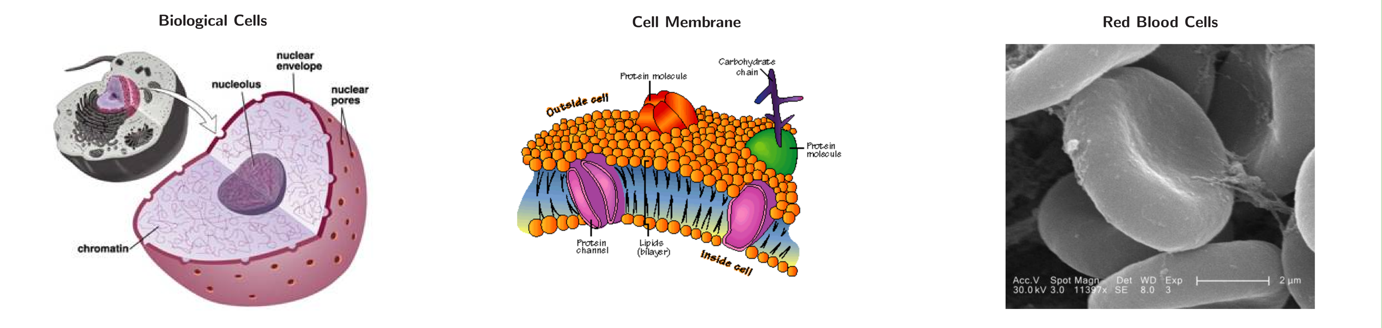
Motivation/Application

Numerous biological processes involve the transport of particles from a cell through its membrane:

- RNA transport through nuclear pores.
- Passive diffusion of molecules (e.g. CO_2 and O_2) through cell membrane.
- Diffusion of ions through protein channels (e.g. Na-K-Cl co-transporter in blood cells).

Typical size of transport regions is $\sim 0.1\%$ relative to overall cell size.



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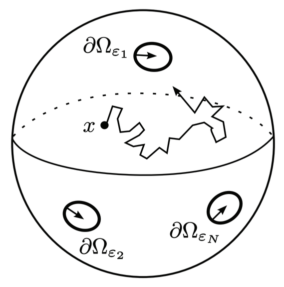
The Narrow Escape Problem

The Narrow Escape Problem (NEP) consists in finding the mean first passage time (MFPT) for a particle undergoing Brownian motion to escape an enclosing three-dimensional domain.

- Ω: three-Dimensional domain.
- $\partial\Omega_{\epsilon_j}$: absorbing boundary trap ($j = 1, ..., N$).
- $v(\mathbf{x})$: MFPT for particle starting at $\mathbf{x} \in \Omega$.
- D: diffusion coefficient.
- Average MFPT: $\bar{v} \equiv \dfrac{1}{|\Omega|}\displaystyle\int_\Omega v(\mathbf{x})\, d^3\mathbf{x}$.



- Dirichlet-Neumann Boundary Value Problem [3]:

$$\Delta v(\mathbf{x}) = -\frac{1}{D}, \quad \mathbf{x} \in \Omega;$$
$$\partial_n v(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Omega \setminus \bigcup_j \partial\Omega_{\epsilon_j}; \qquad v(\mathbf{x}) = 0, \quad \mathbf{x} \in \bigcup_j \partial\Omega_{\epsilon_j}.$$

Asymptotic Solutions

The boundary value problem (1) does not admit a known analytic solution. Difficulties arise because of the strongly heterogeneous boundary conditions.

Instead focus on finding high-order asymptotic approximations. Benefits of asymptotic solutions over numerical methods include:

- Faster computation times.
- Properties of exact solutions can be extracted.

Asymptotic approximations are of the form

$$v(\mathbf{x}) \sim \epsilon^{-1} v_0(\mathbf{x}) + v_1(\mathbf{x}) + \epsilon \log\left(\frac{\epsilon}{2}\right) v_2(\mathbf{x}) + \epsilon v_3(\mathbf{x}) + \dots .$$

where ϵ is the order of magnitude of trap sizes.

Surface Neumann-Green's Function

Of critical importance to the NEP is the surface Neumann-Green's Function, $G_s(\mathbf{x}, \mathbf{x}_j)$, satisfying

$$\Delta G_s(\mathbf{x}; \mathbf{x}_j) = \frac{1}{|\Omega|}, \qquad \mathbf{x} \in \Omega;$$
$$\partial_n G_s(\mathbf{x}; \mathbf{x}_j) = \delta_s(\mathbf{x} - \mathbf{x}_j), \quad \mathbf{x} \in \partial\Omega; \qquad \int_\Omega G_s(\mathbf{x}; \mathbf{x}_j) d^3\mathbf{x} = 0.$$

Using the method of matched asymptotic expansions, the surface Neumann-Green's function appears in the expression for the MFPT as

$$v(\mathbf{x}) = \bar{v} + \sum_{j=1}^N k_j G_s(\mathbf{x}; \mathbf{x}_j), \qquad k_j = \text{const.}$$

The Unit Sphere

The special case when Ω is a unit sphere with N holes of radii ϵa_j centred at $\mathbf{x}_j$ respectively yields numerous results [1].

- Surface Neumann-Green's Function:

$$G_s(\mathbf{x}, \mathbf{x}_j) = \frac{1}{2\pi|\mathbf{x} - \mathbf{x}_j|} + \frac{1}{8\pi}\left(|\mathbf{x}|^2 + 1\right) + \frac{1}{4\pi}\log\left(\frac{2}{1 - |\mathbf{x}|\cos\gamma + |\mathbf{x} - \mathbf{x}_j|}\right) - \frac{7}{10\pi}$$

- Mean First Passage Time:

$$v(\mathbf{x}) = \frac{|\Omega|}{2\pi\epsilon D N\bar{c}}\Bigg[1 + \epsilon\log\left(\frac{2}{\epsilon}\right)\frac{\sum_{j=1}^N c_j^2}{2N\bar{c}} - 2\pi\epsilon\sum_{j=1}^N c_j G_s(\mathbf{x}, \mathbf{x}_j) + \frac{2\pi\epsilon}{N\bar{c}} p_c(\mathbf{x}_1, ..., \mathbf{x}_N) - \frac{\epsilon}{N\bar{c}}\sum_{j=1}^N c_j\kappa_j + \mathcal{O}(\epsilon^2\log\epsilon).$$

- Average MFPT:

$$\bar{v} = \frac{|\Omega|}{2\pi\epsilon D N\bar{c}}\left[1 + \epsilon\log\left(\frac{2}{\epsilon}\right)\frac{\sum_{j=1}^N c_j^2}{2N\bar{c}} + \frac{2\pi\epsilon}{N\bar{c}} p_c(\mathbf{x}_1, ..., \mathbf{x}_N) - \frac{\epsilon}{N\bar{c}}\sum_{j=1}^N c_j\kappa_j + O(\epsilon^2\log\epsilon)\right].$$

- Two important quantities depending only on $\partial\Omega_{\epsilon_j}$:

$$c_j = \frac{2a_j}{\pi} \text{ (trap capacitance)}, \qquad \kappa_j = \frac{c_j}{2}\left[2\log 2 - \frac{3}{2} + \log a_j\right].$$

Self-Interaction Term $p_c(\mathbf{x}_1, ..., \mathbf{x}_N)$

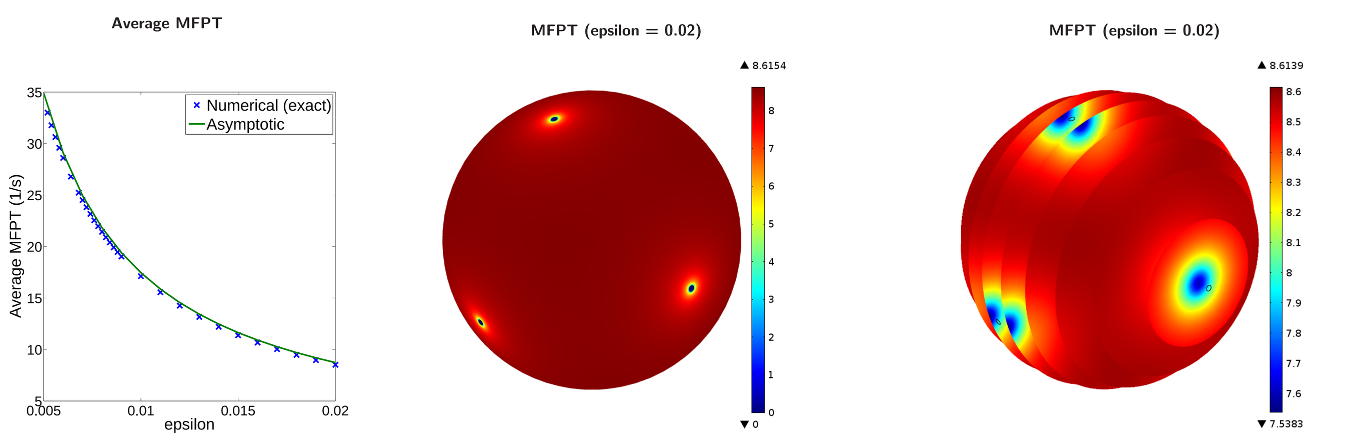
Term $p_c(\mathbf{x}_1, ..., \mathbf{x}_N)$ appearing in expressions for $v(\mathbf{x})$ and $\bar{v}(\mathbf{x})$ is a self-interaction term.

- Describes interaction between individual traps $\Rightarrow$ important for optimization.
- Depends only on $G_s(\mathbf{x}_i, \mathbf{x}_j)$ and each c_j according to

$$p_c(\mathbf{x}_1, ..., \mathbf{x}_N) = \mathcal{C}^T \mathcal{G}_s \mathcal{C}$$

$$\mathcal{G}_s \equiv \begin{pmatrix} -\frac{9}{20\pi} & G_s(\mathbf{x}_1, \mathbf{x}_2) & \cdots & G_s(\mathbf{x}_1, \mathbf{x}_N) \\ G_s(\mathbf{x}_2, \mathbf{x}_1) & -\frac{9}{20\pi} & \cdots & G_s(\mathbf{x}_2, \mathbf{x}_N) \\ \vdots & \vdots & \ddots & \\ G_s(\mathbf{x}_N, \mathbf{x}_1) & \cdots & G_s(\mathbf{x}_N, \mathbf{x}_{N-1}) & -\frac{9}{20\pi} \end{pmatrix}, \quad \mathcal{C} \equiv \begin{pmatrix} c_1 \\ \vdots \\ c_N \end{pmatrix}.$$

Asymptotic and Numerical MFPT for Unit Sphere with Six Identical Traps



Singer, Schuss, and Holcman Approximation

When Ω is a general three-dimensional domain, previous results are limited to the case of one trap $\partial\Omega_\epsilon$ of radius ϵ (i.e. $a = 1$) located at $\mathbf{x}_0$ [4].

- Surface-Neumann Green's Function:

$$G_s(\mathbf{x}, \mathbf{x}_0) = \frac{1}{2\pi|\mathbf{x} - \mathbf{x}_j|} - \frac{H(\mathbf{x}_0)}{4\pi}\log|\mathbf{x} - \mathbf{x}_0| + v_s(\mathbf{x}, \mathbf{x}_0),$$

where $v_s(\mathbf{x}, \mathbf{x}_j)$ is an unknown bounded function of $\mathbf{x}, \mathbf{x}_j \in \Omega$.

- Average MFPT:

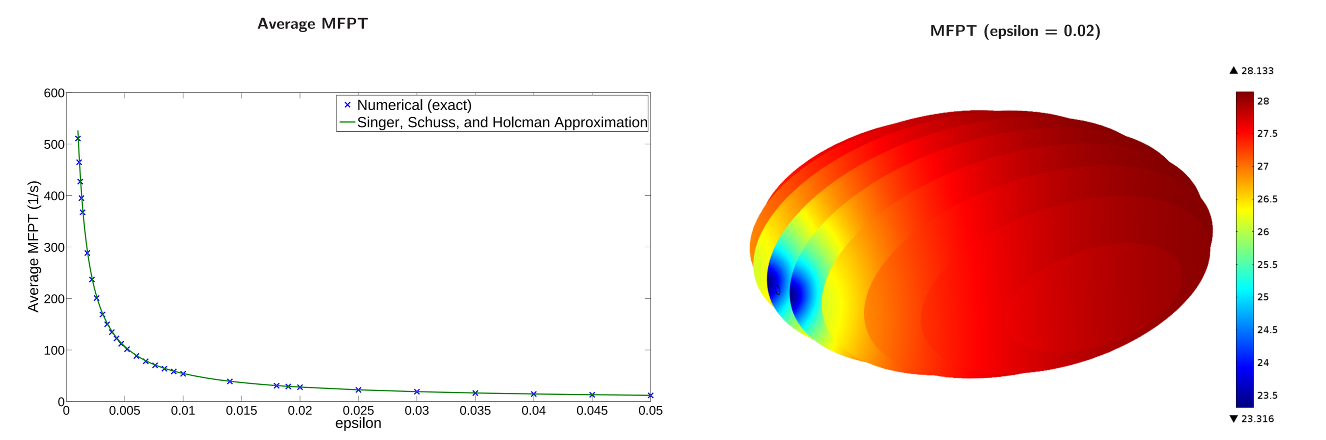
$$\bar{v} \equiv \frac{|\Omega|}{4\epsilon D}\left[1 + \frac{H(\mathbf{x}_0)}{\pi}\epsilon\log\epsilon + O(\epsilon)\right]^{-1}.$$

Limitations of this approach are:

- Approximation is only valid for one absorbing window.
- No asymptotic expression for the (non-averaged) MFPT is given.
- Error bound of $\mathcal{O}(\epsilon)$ is worse than that for sphere.

Singer,Schuss, and Holcman Approximation for Oblate Spheroid with One Trap

Oblate Spheroid with One Trap

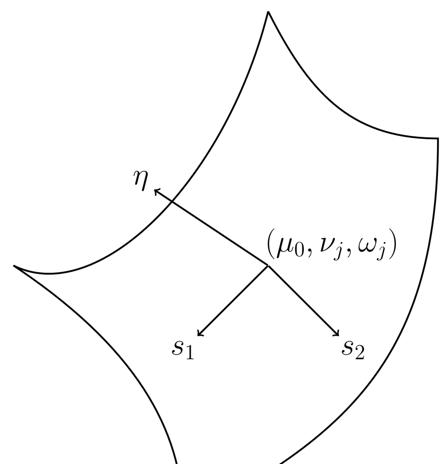


Towards a Wider Class of Three-Dimensional Domains

Consider a class of 3D domains where boundary is a coordinate surface for some orthonormal coordinate system (μ, ν, ω). Then assume the coordinate surface is $\mu = \mu_0$.

- Examples: spheres, spheroids, ellipsoids, surfaces of rotation.
- N traps located at (μ_0, ν_j, ω_j) for $j = 1, ..., N$.
- h_μ, h_ν, h_ω: scale factors of particular coordinate system.
- Local stretched coordinates:

$$\eta = -h_{\mu_0}\frac{\mu - \mu_0}{\epsilon}, \quad s_1 = h_{\nu_j}\frac{\nu - \nu_j}{\epsilon}, \quad s_2 = h_{\omega_j}\frac{\omega - \omega_j}{\epsilon}.$$



Local Form of Surface Neumann-Green's Function

Using the expression for the surface Neumann-Green's function (1) and introducing the local stretched coordinates gives:

$$G_s(\eta, s_1, s_2; \mathbf{x}_j) = \frac{1}{2\pi\rho\epsilon} - \frac{H(\mathbf{x}_j)}{4\pi}\log\frac{\epsilon}{2} + g_0(\eta, s_1, s_2; \mathbf{x}_j) + \epsilon\log\frac{\epsilon}{2}g_1(\eta, s_1, s_2; \mathbf{x}_j) + \mathcal{O}(\epsilon),$$

where $\rho = \sqrt{\eta^2 + s_1^2 + s_2^2}$ and g_0 and g_1 are bounded functions depending on the geometry at $\mathbf{x}_j$.

Method of Matched Asymptotic Expansions

The solution is formulated in terms of inner and outer solutions, each satisfying a corresponding problem.

Inner Problem (near $\mathbf{x}_j$)

- Local stretched coordinates (η, s_1, s_2).
- $w(\eta, s_1, s_2) \sim \frac{1}{\epsilon}w_0 + \log\frac{\epsilon}{2}w_1 + w_2 + \mathcal{O}(\epsilon).$
- Domain: $\eta \geq 0,\ s_1, s_2 \in \mathbb{R}$.
- Linear PDE: $\Delta_{(\eta, s_1, s_2)} w_k = \delta_{k2}\mathcal{L}w_0$.

  ($\mathcal{L}$ is a second-order linear differential operator.)
- Boundary Conditions:

$$\partial_\eta w_k = 0, \qquad \eta = 0,\ s_1^2 + s_2^2 \geq a_j^2,$$
$$w_k = 0, \qquad \eta = 0,\ s_1^2 + s_2^2 \leq a_j^2.$$

Outer Problem (far from $\mathbf{x}_j$)

- Global coordinates (μ, ν, ω).
- $v(\mu, \nu, \omega) \sim \frac{1}{\epsilon}v_0 + v_1 + \epsilon\log\frac{\epsilon}{2}v_2 + \epsilon v_3 + \mathcal{O}(\epsilon).$
- Domain: $(\mu, \nu, \omega) \in \Omega$.
- PDE: $\Delta v_k = -\frac{1}{D}\delta_{k1}$.
- Boundary Conditions:

$$\partial_n v_k = 0, \qquad \mathbf{x} \in \partial\Omega \setminus \{\mathbf{x}_1, ..., \mathbf{x}_N\}.$$

Matched Asymptotic Expansions Condition

$$\frac{1}{\epsilon}w_0 + \log\frac{\epsilon}{2}w_1 + w_2 + \cdots \sim \frac{1}{\epsilon}v_0 + v_1 + \epsilon\log\frac{\epsilon}{2}v_2 + \epsilon v_3 + \cdots .$$

- Collect like coefficients of ϵ and sequentially solve for w_k and v_k using the inner problem, the outer problem, and the matching condition.

Proposed Asymptotic Solutions for MFPT and Average MFPT

- Assumptions: $g_1 = 0$ and $w_2 \sim \dfrac{v_0 b_j}{\rho}$.
- MFPT:

$$v(\mathbf{x}) = \frac{|\Omega|}{2\pi\epsilon D N\bar{c}}\Bigg[1 - \epsilon\log\left(\frac{\epsilon}{2}\right)\frac{\sum_{j=1}^N c_j^2 H(\mathbf{x}_j)}{2N\bar{c}} - 2\pi\epsilon\sum_{j=1}^N c_j G_s(\mathbf{x}, \mathbf{x}_j) + \frac{2\pi\epsilon}{N\bar{c}}\tilde{p}_c(\mathbf{x}_1, ..., \mathbf{x}_N) - \frac{\epsilon}{N\bar{c}}\sum_{j=1}^N b_j + \mathcal{O}(\epsilon^2\log\epsilon)\Bigg].$$

- Average MFPT:

$$\bar{v} = \frac{|\Omega|}{2\pi\epsilon D N\bar{c}}\left[1 - \epsilon\log\left(\frac{\epsilon}{2}\right)\frac{\sum_{j=1}^N c_j^2 H(\mathbf{x}_j)}{2N\bar{c}} + \frac{2\pi\epsilon}{N\bar{c}}\tilde{p}_c(\mathbf{x}_1, ..., \mathbf{x}_N) - \frac{\epsilon}{N\bar{c}}\sum_{j=1}^N b_j + \mathcal{O}(\epsilon^2\log\epsilon)\right].$$

- $\tilde{p}_c(\mathbf{x}_1, ..., \mathbf{x}_N)$ is a modified version of $p_c(\mathbf{x}_1, ..., \mathbf{x}_N)$ for the sphere, depending only on $G_s(\mathbf{x}_i, \mathbf{x}_j)$.
- b_j is modified version of κ_j for the sphere, determined by the far field behaviour of w_2.

Testing Procedure and COMSOL

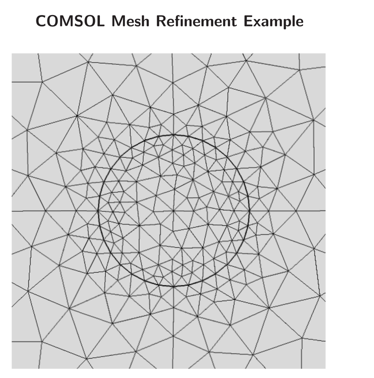
Used oblate spheroid, prolate spheroid, and biconcave disk geometries.

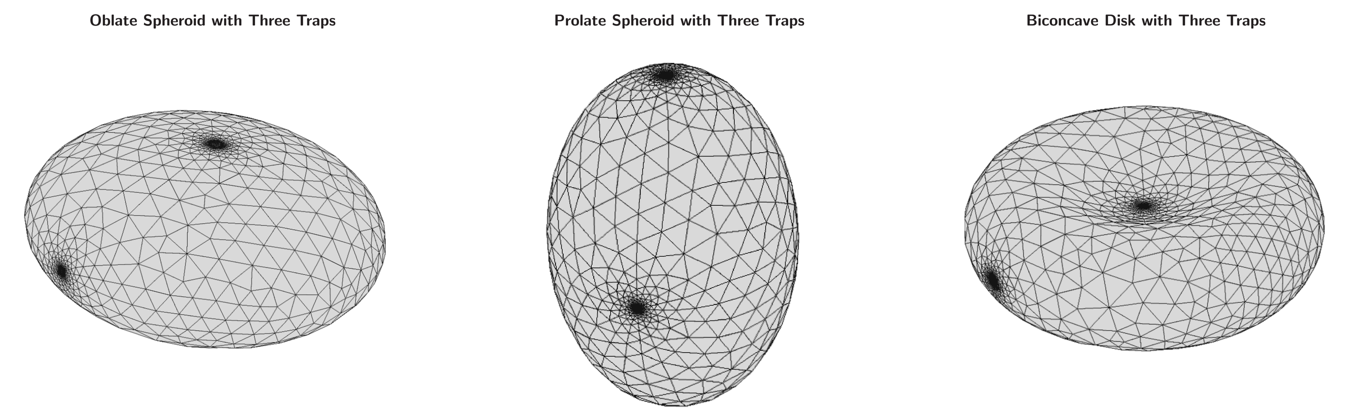
- Provide range of local curvatures.
- Represent different biological cells.

COMSOL Multiphysics 4.3b software used for numerical results.

- Finite element PDE solver.
- Tetrahedral mesh.

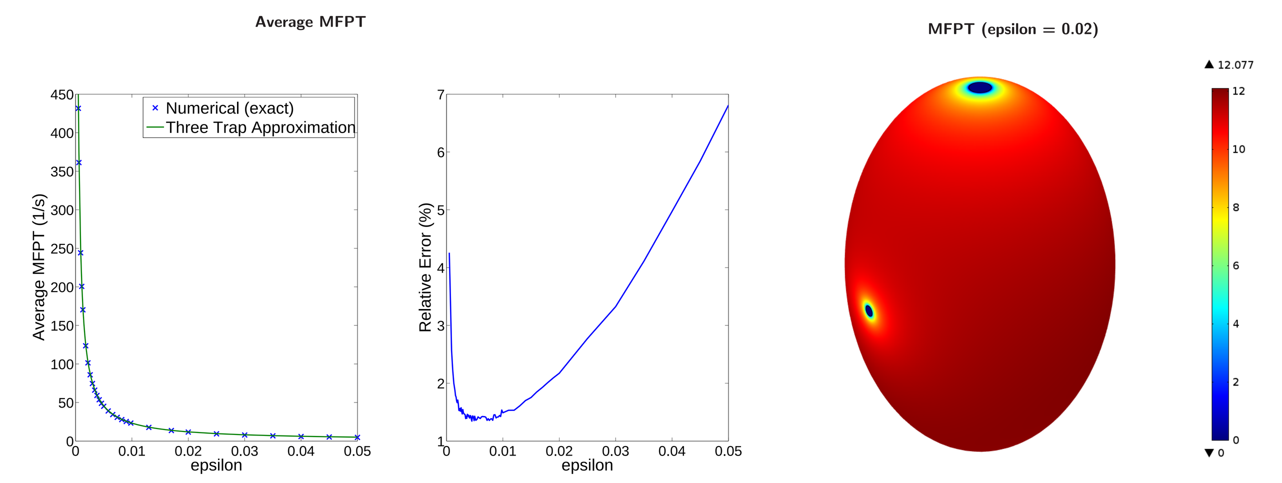
Numerical results for two and three traps of equal and different sizes compared to proposed multi-trap approximation in MATLAB.



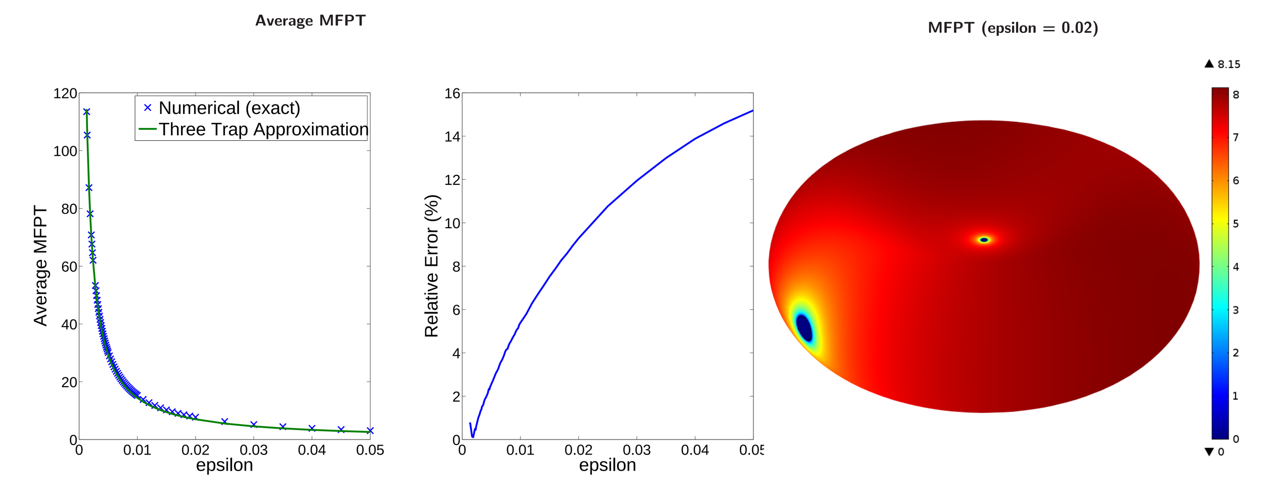


Results for Three Traps of Different Sizes

Prolate Spheroid



Biconcave Disk



Conclusions

- Expressions for the MFPT and average MFTP were developed for a more general class of three dimensional domains.
- The average MFPT values following from the proposed asymptotic formulae were found to be in close agreement with numerical simulation results.

Future Research

- Comparison to numerical simulation for a more extensive variety of geometries.
- Rigorous justification of assumptions used for proposed MFPT and average MFPT formulas.
- Study of dilute trap limit of homogenization theory for non-spherical domains [2].

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