The Narrow Escape Problem for the Unit Sphere and Other 3D Domains: Asymptotic Solution, Homogenization Limit, and Optimal Trap Arrangements

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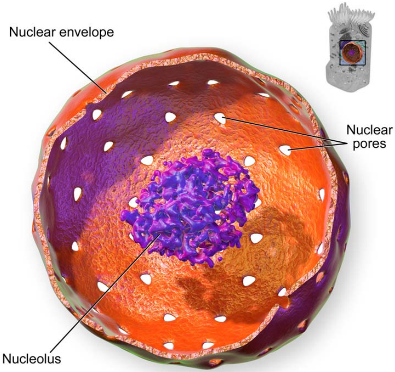
Outline

Outline

1. Narrow Escape Problems, Mean First Passage Time (MFPT)
2. Asymptotic Results for Small Traps; Higher-Order MFPT for the Sphere
3. Validity of the Asymptotic MFPT for the Sphere
4. Globally and Locally Optimal Trap Arrangements for the Unit Sphere
   - The N^2 Conjecture
   - Two Families of Traps
5. Homogenization Theory Approximation for $N \gg 1$ Small Equal Traps
6. Asymptotic Analysis of the MFPT Problem for Non-Spherical Domains
7. Highlights and talk summary

Narrow escape problems

- A Brownian particle escapes from a bounded domain through small windows.
- Examples: Pores of cell nuclei; synaptic receptors on dendrites, ...



Narrow escape problems

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

- Typical nucleus size: $\sim 6 \times 10^{-6}$ m
- Pore size $\sim 10^{-8}$ m
- $\sim$ 2000 nuclear pore complexes in a typical nucleus
- mRNA, proteins, smaller molecules
- $\sim$ 1000 translocations per complex per second
- Trap separation $\sim 5 \times 10^{-7}$ m

Mathematical formulation

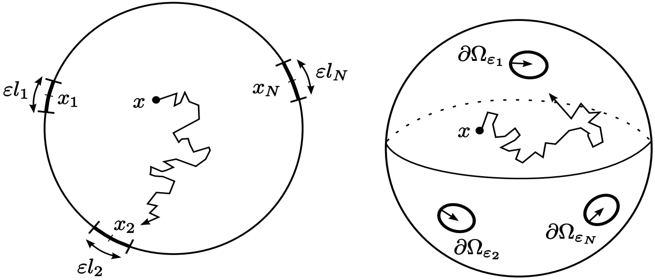


Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

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 $\sim \varepsilon$).

Mathematical formulation

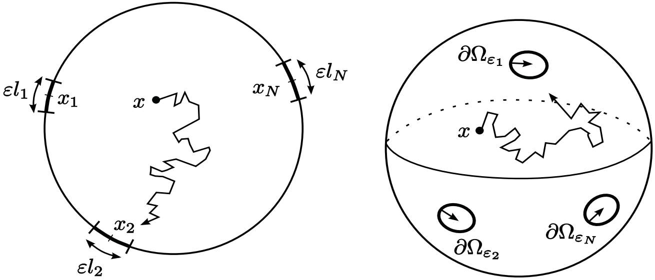
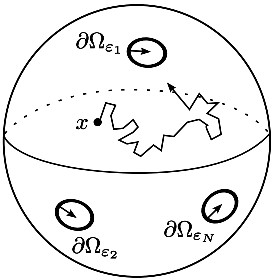


Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

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:

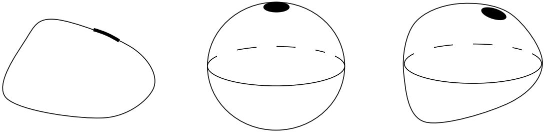
$$\begin{cases} \triangle v = -\dfrac{1}{D}, & x \in \Omega, \\ v = 0, & x \in \partial\Omega_a = \cup_{j=1}^{N} \partial\Omega_{\varepsilon_j}, \\ \partial_n v = 0, & x \in \partial\Omega_r. \end{cases}$$

Boundary Value Problem:

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

Outline

Some previously known results



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

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

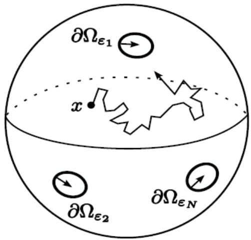
Unit sphere; one trap [*Singer et al (2006)*]

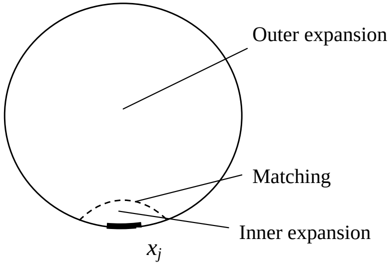
$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon D}\left[1 - \frac{\varepsilon}{\pi}\log\varepsilon + \mathcal{O}(\varepsilon)\right]$$

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.





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

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

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

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

- 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.
- Trap radii: $r_j = a_j\varepsilon$, $j = 1, \dots, N$; capacitances: $c_j = 2a_j/\pi$.

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

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

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

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

The Green's function

- The Green's function $G(x;\xi)$ is the unique solution of the BVP

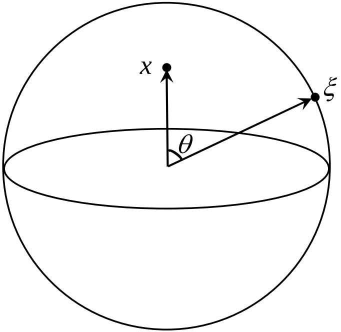
$$\triangle G = \frac{1}{|\Omega|}, \quad x \in \Omega;$$
$$\partial_n G = 0, \quad x \in \partial\Omega \setminus \{\xi\}; \qquad \int_\Omega G\, dx = 0,$$

- Singularity behaviour:

$$G(x;\xi) = \frac{1}{2\pi|x-\xi|} - \frac{\mathcal{H}_m}{4\pi} \log|x-\xi| + R(\xi;\xi),$$

where $\mathcal{H}_m = \mathcal{H}_m(\xi)$ is the mean curvature of the boundary at $\xi \in \partial\Omega$, with $\mathcal{H}_m = 1$ for the unit sphere.

The Green's function – unit sphere



- The Green's function for the unit sphere:

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

$$x\in\Omega,\quad \xi\in\partial\Omega,\quad |x|\cos\gamma = x\cdot\xi,\quad |\xi|=1.$$

MFPT for the sphere with N equal traps

N equal traps of radius ε:

- Average MFPT:

$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon DN}\left[1+\frac{\varepsilon}{\pi}\log\left(\frac{2}{\varepsilon}\right)+\frac{\varepsilon}{\pi}\left(-\frac{9N}{5}+2(N-2)\log 2+\frac{3}{2}+\frac{4}{N}\mathcal{H}(x_1,\ldots,x_N)\right)\right].$$

- Interaction energy:

$$\mathcal{H}(x_1,\ldots,x_N)=\sum_{i=1}^{N}\sum_{j=i+1}^{N}\left[\underbrace{\frac{1}{|x_i-x_j|}}_{\text{Coulomb}}\underbrace{-\frac{1}{2}\log|x_i-x_j|}_{\text{Logarithmic}}-\frac{1}{2}\log\left(2+|x_i-x_j|\right)\right].$$

Optimal arrangements

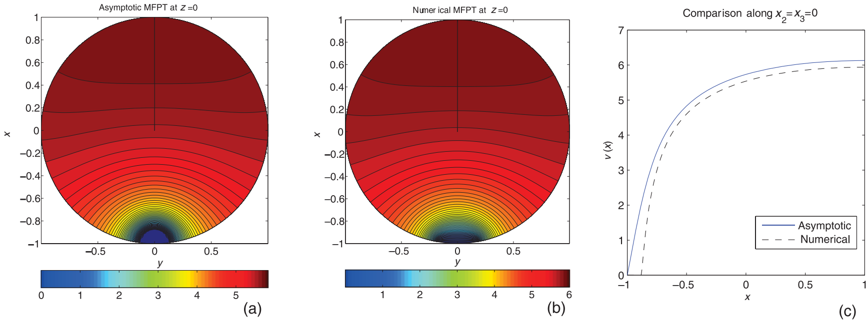
- $\min\ \bar{v} \ \Leftrightarrow\ \min\ \mathcal{H}(x_1,\ldots,x_N)$, a global optimization problem.
- "Thomson problem": optimal arrangements for the Coulomb potential.
- Optimal arrangements minimizing $\bar{v}$ for $N \lesssim 100$: general software (e.g., LGO).

Outline

Validity of the asymptotic MFPT for the sphere

- Asymptotic vs. numerical solutions for the unit sphere [*A.C., A.Reimer, M.Ward (2011)*]:

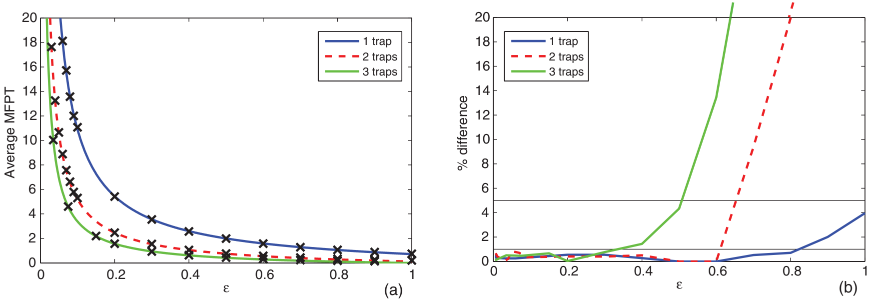
- Comparison of asymptotic (a) and numerical (b) results for the MFPT $v(x)$ for one trap of radius $\varepsilon = 0.2$ on the boundary of the unit sphere:



Validity of the asymptotic MFPT for the sphere

- Asymptotic vs. numerical solutions for the unit sphere [*A.C., A.Reimer, M.Ward (2011)*]:

- Dependence of the average MFPT on the common trap radius ε for one, two, and three traps that are equally spaced on the equator of the unit sphere:



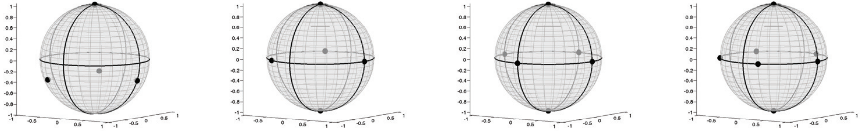
Outline

Globally and locally optimal trap arrangements

- Optimize the trap interaction term $p_c(x_1, \dots, x_N)$.
- $2N - 3$ degrees of freedom, quickly increasing numbers of local minima.
- How to distinguish configurations, modulo geometrical symmetries?

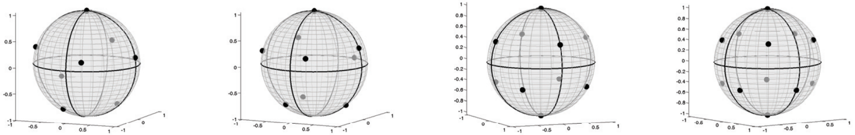
Identical traps on the unit sphere

- $N \lesssim 100$ traps: direct optimization, use software [*A.C., R. Straube, M.Ward (2010)*]



(a) $N = 4$ (b) $N = 5$ (c) $N = 6$ (d) $N = 7$

FIG. 4.3. *Minimal energy trap configurations for* $N = 4, 5, 6, 7$ *traps, common for the three discrete energy functions.*

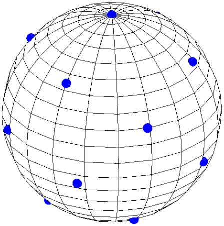


(a) $N = 8$ (b) $N = 9$ (c) $N = 10$ (d) $N = 12$

FIG. 4.4. *Minimal energy trap configurations for* $N = 8, 9, 10, 12$ *traps, common for the three discrete energy functions.*

$N \gg 1$: an iterative optimization procedure

- Example: optimal configuration for $N = 17$



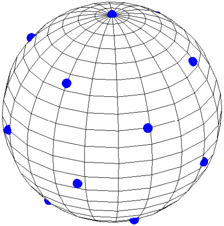
Topological derivative:

- Rate of change of $\bar{v}$ with respect to the size of the $(N+1)$st trap of radius $\alpha\varepsilon$ at the point x^* on the unit sphere, computed at $\alpha = 0$.

$$\mathcal{T}(x^*) = \lim_{\alpha \to 0} \frac{\bar{v}(x_1, \ldots, x_N, x^*) - \bar{v}(x_1, \ldots, x_N)}{\alpha} \sim \mathcal{M}(x^*),$$

$$\mathcal{M}(x^*) = \sum_{i=1}^{N} \left[\frac{1}{|x_i - x^*|} - \frac{1}{2} \log |x_i - x^*| - \frac{1}{2} \log \left(2 + |x_i - x^*|\right) \right].$$

- Example: optimal configuration for $N = 17$.



Introduction of a trap of an arbitrary radius $\alpha\varepsilon$ at the point x^*.

- Change of the asymptotic average MFPT:

$$\Delta \bar{v} \equiv \bar{v}_{N+1}(x_1, \ldots, x_N,\, x^*) - \bar{v}_N(x_1, \ldots, x_N) \sim f(\alpha, N)\mathcal{M}(x^*),$$

$$\mathcal{M}(x^*) = \sum_{i=1}^{N} \left[\frac{1}{|x_i - x^*|} - \frac{1}{2} \log |x_i - x^*| - \frac{1}{2} \log \left(2 + |x_i - x^*|\right) \right].$$

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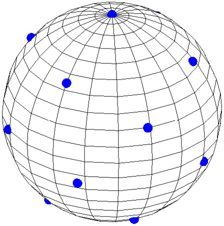

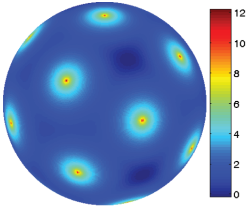

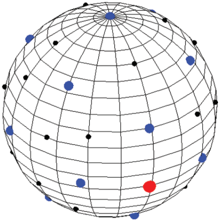

Introduction of a trap of an arbitrary radius $\alpha\varepsilon$ at the point x^*.

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$$\Delta\bar{v} \equiv \bar{v}_{N+1}(x_1,\ldots,x_N,\, x^*) - \bar{v}_N(x_1,\ldots,x_N) \sim f(\alpha,N)\mathcal{M}(x^*),$$

$$\mathcal{M}(x^*) = \sum_{i=1}^{N}\left[\frac{1}{|x_i - x^*|} - \frac{1}{2}\log|x_i - x^*| - \frac{1}{2}\log\left(2 + |x_i - x^*|\right)\right].$$

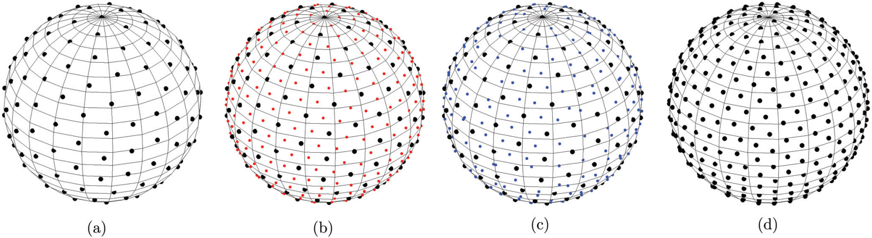
A heuristic algorithm

(a) Start from a given N-trap arrangement.

(b) Compute triangle vertices.

(c) Compute the adjacent local minima of $\mathcal{M}(x^*)$ by solving $\operatorname{grad} \mathcal{M}(x^*) = 0$.

(d) Introduce additional k traps at k lowest local minima of $\mathcal{M}$. Run a local optimization routine.



$160 \to 436$ traps.

The N^2 conjecture

For an optimal arrangement of $N \geq 2$ traps corresponding that minimizes the interaction energy $\mathcal{H}$ and the asymptotic average MFPT $\bar{v}$, the sum of squares of pairwise distances between traps is equal to N^2:

$$\mathcal{Q}(x_1, \ldots, x_N) \equiv \sum_{i=1}^{N} \sum_{j=i+1}^{N} |x_i - x_j|^2 = N^2.$$

Evidence

- Can be shown to hold for small N exactly.
- For known global minima $5 \leq N \leq 200$, holds numerically up to 10 significant digits.
- Supported by an asymptotic scaling law estimate of $\mathcal{Q}(x_1, \ldots, x_N)$ as $N \to \infty$ [See *A.C. & D. Zawada (2013)*].
- *Not tested* for all local minima for each N...

The N^2 conjecture

N	$\mathcal{H}$	$\mathcal{Q}$	N	$\mathcal{H}$	$\mathcal{Q}$	N	$\mathcal{H}$	$\mathcal{Q}$
2	−0.53972077	4.000000000	33	54.295972	1089.000000	64	324.08963	4096.000000
3	−1.0673453	9.000000000	34	59.379488	1156.000000	65	336.76971	4225.000000
4	−1.6671799	16.00000000	35	64.736711	1225.000000	70	403.83089	4900.000000
5	−2.0879876	25.00000000	36	70.276097	1296.000000	75	477.36359	5625.000000
6	−2.5810055	36.00000000	37	76.066237	1369.000000	80	557.23154	6400.000000
7	−2.7636584	49.00000000	38	82.080300	1444.000000	85	643.77234	7225.000000
8	−2.9495765	64.00000000	39	88.329560	1521.000000	90	736.65320	8100.000000
9	−2.9764336	81.00000000	40	94.817831	1600.000000	95	836.12537	9025.000000
10	−2.8357352	100.0000000	41	101.56854	1681.000000	100	942.12865	10000.00000
11	−2.4567341	120.9999505	42	108.54028	1764.000000	105	1054.8688	11025.00000
12	−2.1612842	144.0000000	43	115.77028	1849.000000	110	1174.1103	12100.00000
13	−1.3678269	168.9999763	44	123.16343	1936.000000	115	1300.1081	13225.00000
14	−0.55259278	196.0000000	45	130.90532	2025.000000	120	1432.6666	14400.00000
15	0.47743760	225.0000000	46	138.92047	2116.000000	125	1572.0271	15625.00000
16	1.6784049	256.0000000	47	147.15035	2209.000000	130	1718.0039	16900.00000
17	3.0751594	289.0000000	48	155.41742	2304.000000	135	1870.6706	18225.00000
18	4.6651247	324.0000000	49	164.21746	2401.000000	140	2030.3338	19600.00000
19	6.5461714	361.0000000	50	173.07868	2500.000000	145	2196.5017	21025.00000
20	8.4817896	400.0000000	51	182.26664	2601.000000	150	2369.6548	22500.00000
21	10.701320	441.0000000	52	191.72428	2704.000000	155	2549.6182	24025.00000
22	13.101742	484.0000000	53	201.38475	2809.000000	160	2736.2180	25600.00000
23	15.821282	529.0000000	54	211.28349	2916.000000	165	2929.8023	27225.00000
24	18.581981	576.0000000	55	221.46381	3025.000000	170	3130.1596	28900.00000
25	21.724913	625.0000000	56	231.85398	3136.000000	175	3337.4168	30625.00000
26	25.010031	676.0000000	57	242.51803	3249.000000	180	3551.5021	32400.00000
27	28.429699	729.0000000	58	253.43460	3364.000000	185	3772.5761	34225.00000
28	32.192933	784.0000000	59	264.57186	3481.000000	190	4000.3892	36100.00000
29	36.219783	841.0000000	60	275.90942	3600.000000	195	4235.2645	38025.00000
30	40.354439	900.0000000	61	287.62114	3721.000000	200	4477.0669	40000.00000
31	44.757617	961.0000000	62	299.48031	3844.000000			
32	49.240949	1024.000000	63	311.65585	3969.000000			

The N^2 conjecture

N	$\mathcal{H}$	$\mathcal{Q}$	N	$\mathcal{H}$	$\mathcal{Q}$	N	$\mathcal{H}$	$\mathcal{Q}$
206	4776.8410	42436.00000	406	20535.947	164836.0000	650	55251.870	422500.0000
219	5459.4441	47961.00000	413	21292.863	170569.0000	697	63918.659	485809.0000
248	7151.7851	61504.00000	424	22511.130	179776.0000	704	65263.714	495616.0000
253	7466.6853	64009.00000	436	23879.932	190096.0000	764	77386.805	583696.0000
260	7920.1793	67600.00000	437	23996.280	190969.0000	778	80361.722	605284.0000
268	8455.6701	71824.00000	442	24579.608	195364.0000	781	81008.459	609961.0000
272	8729.6105	73984.00000	449	25409.395	201601.0000	802	85602.707	643204.0000
291	10094.183	84681.00000	462	26987.790	213444.0000	850	96587.973	722500.0000
308	11401.557	94864.00000	480	29251.492	230400.0000	868	100878.53	753424.0000
310	11560.554	96100.00000	529	35888.599	279841.0000	891	106503.70	793881.0000
333	13471.931	110889.0000	536	36896.959	287296.0000	922	114327.22	850084.0000
337	13819.916	113569.0000	546	38354.222	298116.0000	928	115873.47	861184.0000
368	16669.611	135424.0000	548	38648.578	300304.0000	992	133031.24	984064.0000
369	16766.235	136161.0000	577	43063.555	332929.0000	1004	136383.69	1008016.000
380	17846.466	144400.0000	618	49718.287	381924.0000			
382	18045.887	145924.0000	636	52794.233	404496.0000			

Two families of traps

- 2N traps: N having radius ε; N having radius $\alpha\varepsilon$, $\alpha > 1$.

Two families of traps

- $2N$ traps: N having radius ε; N having radius $\alpha\varepsilon$, $\alpha > 1$.

Asymptotic MFPT [*A.C., A.Reimer, M.Ward (2012)*]:

$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon D N(1+\alpha)} \left[1 + \frac{\varepsilon}{\pi} \log\left(\frac{2}{\varepsilon}\right) \left(\frac{1+\alpha^2}{1+\alpha}\right) + \frac{\varepsilon}{\pi} \left(S + \frac{4}{N(1+\alpha)} \widetilde{\mathcal{H}}(x_1, \ldots, x_N) \right) \right],$$

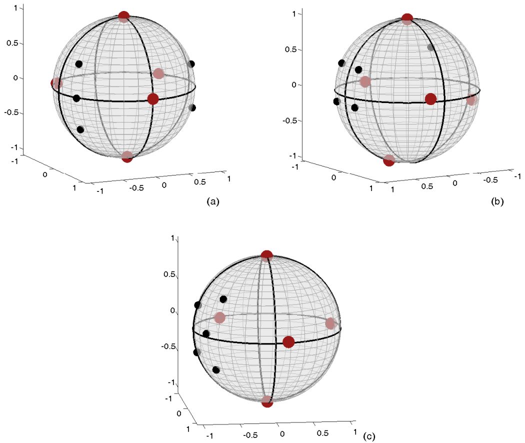
$$S = S(N, \alpha),$$

$$\widetilde{\mathcal{H}}(x_1, \ldots, x_N) = \sum_{i=1}^{N} \sum_{j=i+1}^{N} h(x_i; x_j) + \alpha \sum_{i=1}^{N} \sum_{j=N+1}^{2N} h(x_i; x_j) + \alpha^2 \sum_{i=N+1}^{2N} \sum_{j=i+1}^{2N} h(x_i; x_j),$$

with the same pairwise energy function

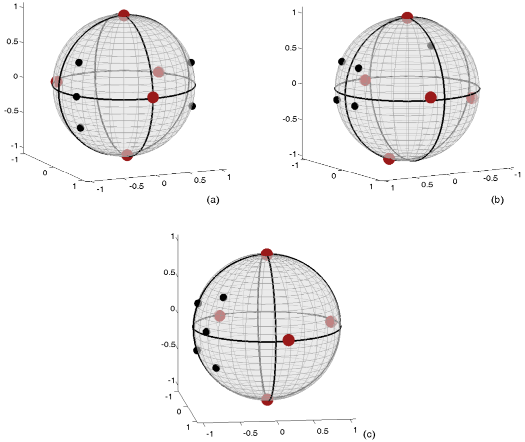
$$h(x_i; x_j) = \frac{1}{|x_i - x_j|} - \frac{1}{2} \log|x_i - x_j| - \frac{1}{2} \log(2 + |x_i - x_j|).$$

- Example: three locally optimal configurations of $2N{=}10$ traps; $\alpha = 10$.
- Global minimum:
- Nearby local minima:



Two families of traps

- Example: three locally optimal configurations of $2N{=}10$ traps; $\alpha = 10$.
- Global minimum (a): $\widetilde{\mathcal{H}} = -198.80759$.
- Nearby local minima (b,c): $\widetilde{\mathcal{H}} = (-198.36939, -197.76083)$.



Outline

Dilute trap fraction limit of homogenization theory

- $N \gg 1$ small boundary traps, distributed "homogeneously" over the sphere.
- Dilute trap limit [*Muratov & Shvartsman, 2008*, unit disk]:
  - Approximate the mixed Dirichlet-Neumann problem for the MFPT $v(x)$ by a Robin problem for $v_h(x) \simeq v(x)$.

Assumptions:

- $N \gg 1, \quad \varepsilon \ll 1,$
- Total trap area fraction $\sigma = \pi\varepsilon^2 N/(4\pi) = N\varepsilon^2/4 \ll 1$.
- $v(x) \sim v_h(\rho)$, where the latter satisfies the Robin problem

$$\triangle v_h = -\frac{1}{D}, \quad \rho = |x| < 1;$$

$$f(\varepsilon)\partial_r v_h + \kappa(\sigma) v_h = 0, \quad \rho = 1.$$

- Functions $f(\varepsilon)$, $\kappa(\sigma)$ can be estimated using the asymptotic formula for $v(x)$ derived earlier.

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- The solution is given by a simple formula

$$v_h(\rho) = \frac{f(\varepsilon)}{3D\kappa(\sigma)} + \frac{1-\rho^2}{6D}, \qquad \bar{v}_h = \frac{f(\varepsilon)}{3D\kappa(\sigma)} + \frac{1}{15D}.$$

Principal result [*A.C. & D. Zawada, 2013*]:

In an asymptotic limit $\varepsilon \to 0$, $N \ll \mathcal{O}(\log \varepsilon)$, *the asymptotic expression for* $v(x)$ *and the average MFPT* $\bar{v}$ *can be approximated, within the four leading terms, by a solution* $v_h(\rho)$ *of the Robin problem with parameters*

$$f(\varepsilon) = \varepsilon - \frac{\varepsilon^2}{\pi} \log \varepsilon + \frac{\varepsilon^2}{\pi} \log 2, \quad \kappa(\sigma) = \frac{4\sigma}{\pi - 4\sqrt{\sigma}}.$$

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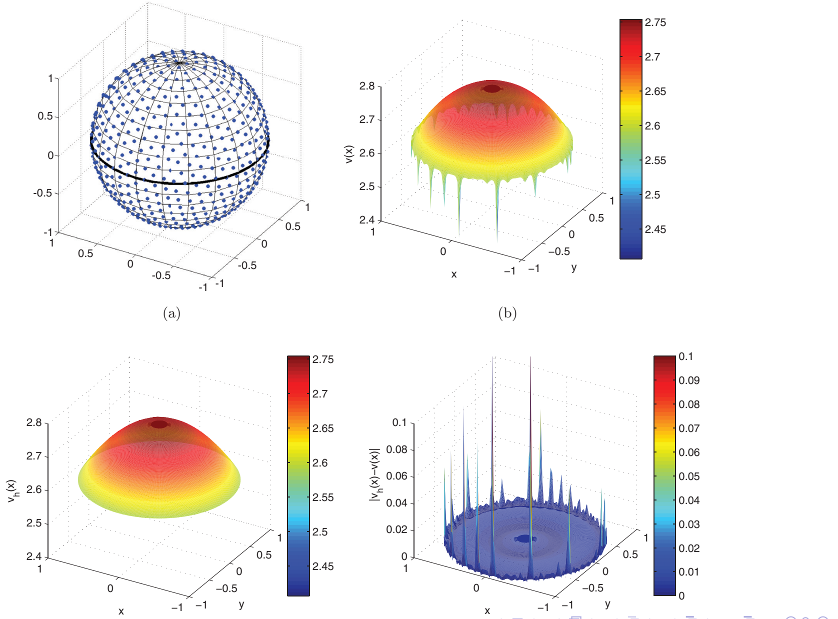
- Example: $N = 802$ traps of radius $\varepsilon = 0.0005$. Comparison of asymptotic and homogenization solution.

Dilute trap fraction limit of homogenization theory



Compare average asymptotic and homogenization MFPT

Homogenization MFPT:

$$\bar{v}_h = \frac{f(\varepsilon)}{3D\kappa(\sigma)} + \frac{1}{15D}, \qquad f(\varepsilon) = \varepsilon - \frac{\varepsilon^2}{\pi}\log\varepsilon + \frac{\varepsilon^2}{\pi}\log 2, \qquad \kappa(\sigma) = \frac{4\sigma}{\pi - 4\sqrt{\sigma}}.$$

Asymptotic MFPT Scaling Law:

$$\bar{v} \sim \frac{|\Omega|}{4\varepsilon DN}\left[1 + \frac{\varepsilon}{\pi}\log\left(\frac{2}{\varepsilon}\right) + \frac{\varepsilon}{\pi}\left(-\frac{9N}{5} + 2(N-2)\log 2 + \frac{3}{2} + \frac{4}{N}\mathcal{H}(x_1, \ldots, x_N)\right)\right],$$

$$\mathcal{H} \sim \frac{N^2}{2}(1 - \log 2) + b_1 N^{3/2} + b_2 N \log N + b_3 N + b_4\sqrt{N} + b_5 \log N + b_6 + o(1).$$

Outline

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.

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

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

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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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.

The average MFPT asymptotic expression

Average MFPT for a general domain [*D. Gomez, A.C. (2015)*]:

- 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 $|x - x_j| \gg \mathcal{O}(\varepsilon)$:

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

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Compare to the spherical MFPT formula:

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

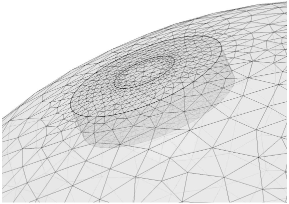
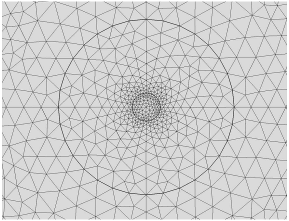
- $\mathcal{O}(1)$ term for the sphere depends on *trap positions*.
- A similar expression of the same order for a general domain can be derived, with some details still missing...

Nonspherical MFPT: comparison of asymptotic and numerical results

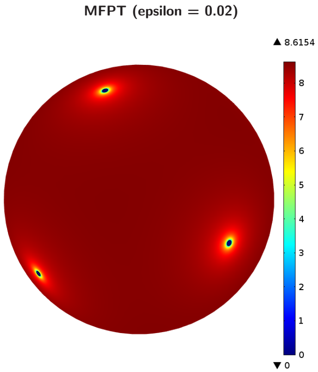
- Numerical solver: COMSOL Multiphysics 4.3b
- Compare numerical and asymptotic average MFPT for three distinct geometries
- $N = 3$ and $N = 5$ traps
- Relative error:

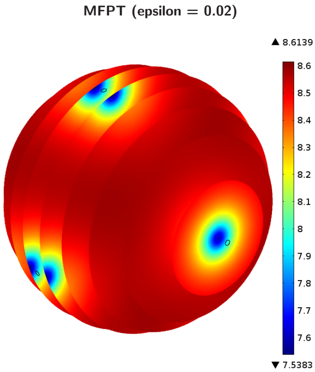
$$\text{R.E.} = 100\% \times \left|\bar{v}_{\text{numerical}} - \bar{v}_{\text{asymptotic}}\right| / \bar{v}_{\text{numerical}}$$

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

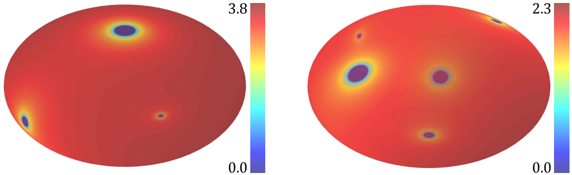



Sample COMSOL MFPT computations for the unit sphere



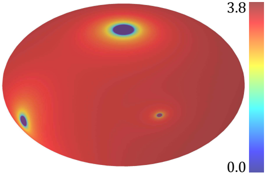


Oblate spheroid

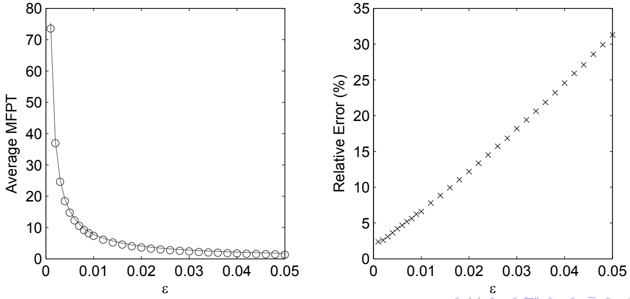


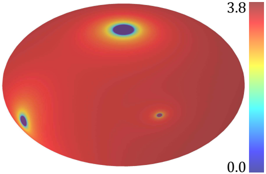
- $x = \rho \cosh \xi \cos \nu \cos \phi, \qquad y = \rho \cosh \xi \cos \nu \sin \phi, \qquad z = \rho \sinh \xi \sin \nu$
- $\xi \in [0, \infty)$, $\nu \in [-\pi/2, \pi/2]$, $\phi \in [0, 2\pi)$
- $\partial\Omega$: $\quad \xi = \xi_0 = \tanh^{-1}(0.5)$, $\rho = (\cosh \xi_0)^{-1}$

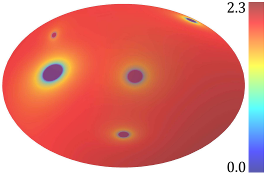
Oblate spheroid



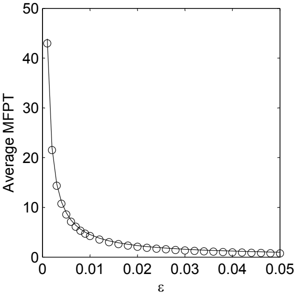
- Numerical vs. asymptotic average MFPT for the oblate spheroid, $N = 3$:

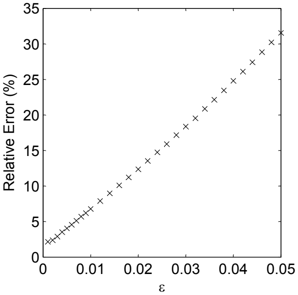




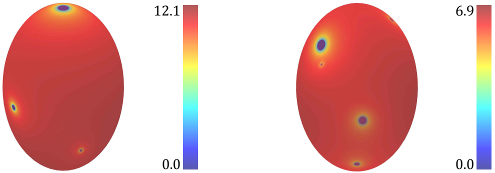


- Numerical vs. asymptotic average MFPT for the oblate spheroid, $N = 5$:

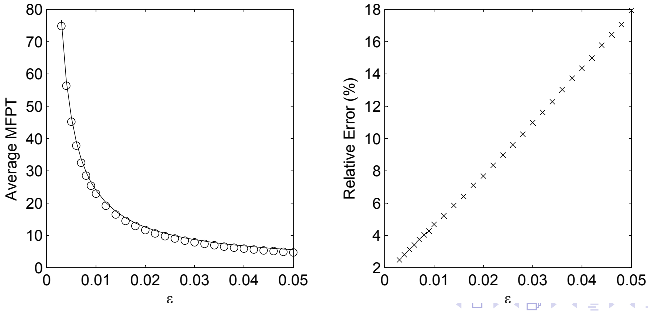




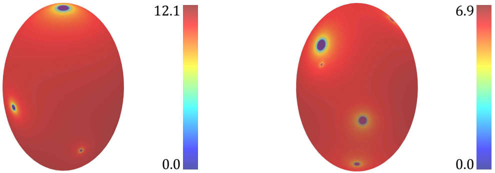
Prolate spheroid



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



Prolate spheroid



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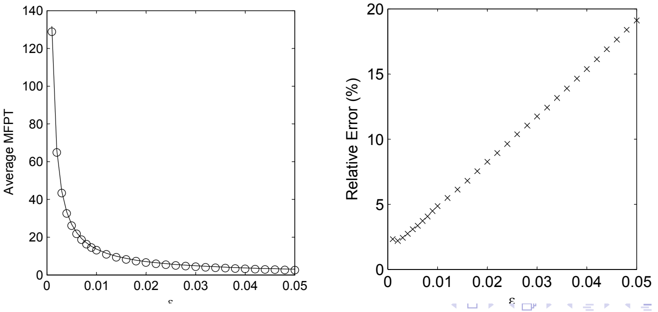
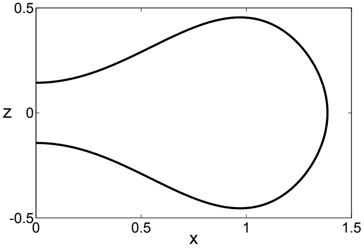


Biconcave disk (blood cell shape)



- 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)*]:

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

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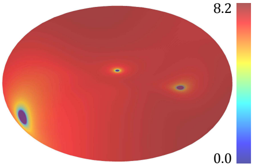
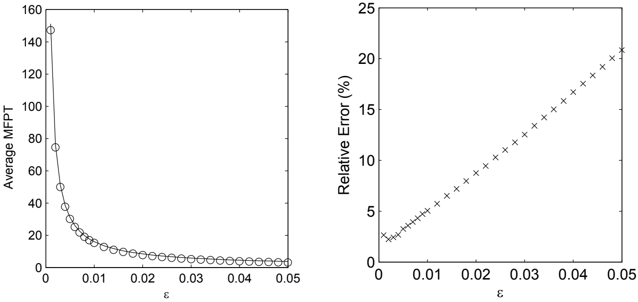


- Numerical vs. asymptotic average MFPT for the biconcave disk, $N = 3$:



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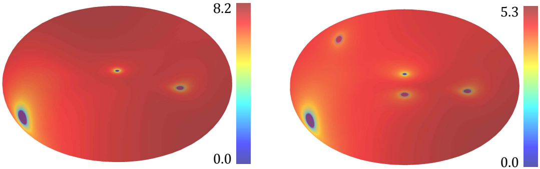

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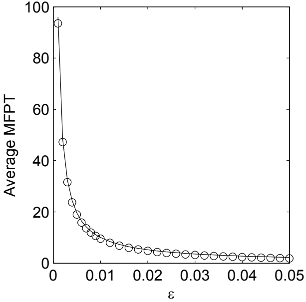
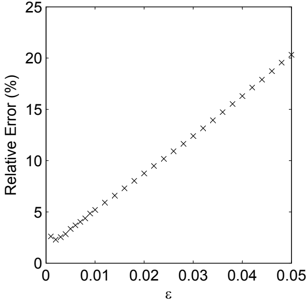
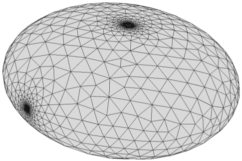


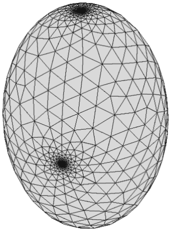


Sample COMSOL meshes

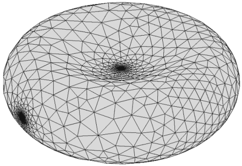
Oblate Spheroid with Three Traps



Prolate Spheroid with Three Traps



Biconcave Disk with Three Traps



Highlights and talk summary

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- The narrow escape problem, asymptotic solutions as $\varepsilon \to 0$.
- Numerical comparisons, validity.
- Global and locally MFPT-minimizing arrangements; topological derivative.
- Dilute trap limit, homogenization, Robin problem.
- Non-spherical domains.

- Green's unction for nonspherical domains?
- Better understanding of locally and globally optimal configurations?
- The N^2 result explanation?
- Non-homogeneous media?
- Many open questions!

Some references

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Thank you for attention!