Narrow Escape and Narrow Capture Problems in Three Dimensions: Modeling, Analysis, Optimization of Trap Configurations

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Outline

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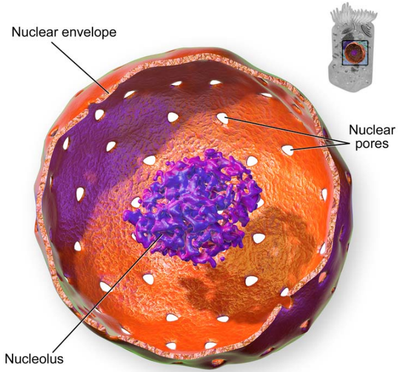
- A Brownian particle escapes from a bounded domain through small windows.

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

Continuum formulation

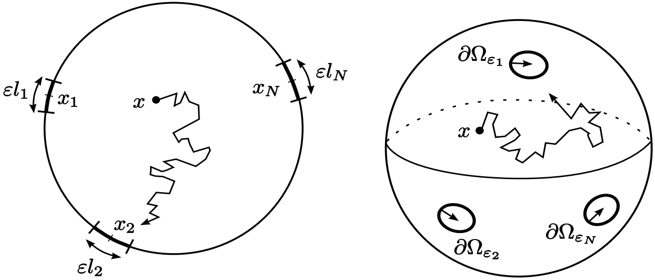


Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

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 $\sim \varepsilon$).

Continuum formulation

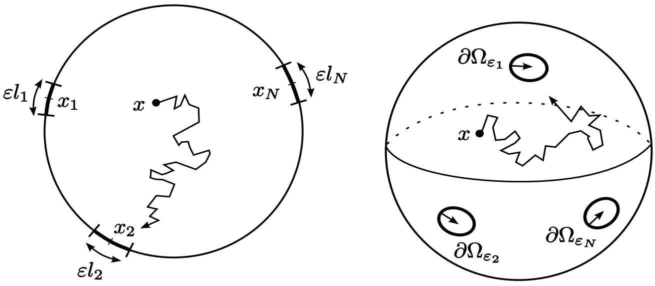


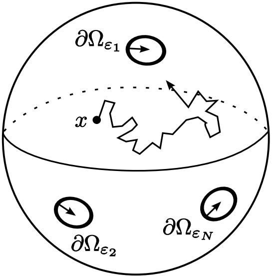
Figure 1: A Schematic of the Narrow Escape Problem in a 2-D and a 3-D domain.

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

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

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

The continuum model

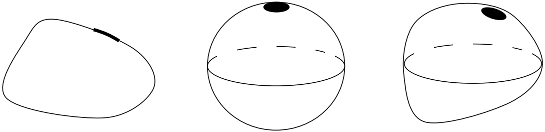


Continuum problem for the MFPT:

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

Boundary value problem-based model:

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



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.

Higher-order asymptotic MFPT for the sphere

Matched asymptotic expansions for:

- Sphere with N traps.
- 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; $\kappa_j = \mathrm{const}$;
- $p_c(x_1, \ldots, x_N)$: energy-like trap interaction term.

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).

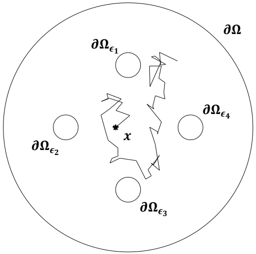
Outline

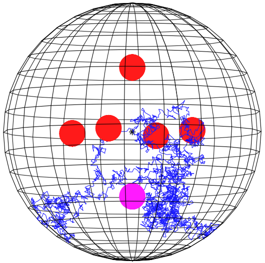
Trapping reactions: whenever a diffusing particle hits a trap, it is immediately and permanently trapped.

- exciton trapping
- fluorescence quenching
- spin relaxation processes
- mean first-passage time: $v(x)$
- narrow capture: small trap size

$$\begin{cases} \Delta v(x) = -\dfrac{1}{D} \,, \quad x \in \Omega \backslash \Omega_a, \\ \partial_n v = 0 \,, \quad x \in \partial\Omega, \\ v = 0 \,, \quad x \in \partial\Omega_a = \cup_{j=1}^{N} \partial\Omega_{\varepsilon_j} \end{cases}$$

$$\bar{v} = \frac{1}{|\Omega|} \int_\Omega v(x)\, d^n x$$





Unit sphere - exact and asymptotic solutions

- Exact solution when a single trap (radius$=\varepsilon$) is at the origin:

$$v_e(r) = \frac{1}{6D}\left[\frac{\varepsilon^3+2}{\varepsilon} - \frac{r^3+2}{r}\right], \quad \bar{v}_e = \frac{1}{6D}\left[\frac{\varepsilon^3+2}{\varepsilon} - \frac{18}{5}\right]$$

- Multiple traps: repel from each other and their own "reflections" in the boundary

- Asymptotic solutions: small, well-separated traps, far from the boundary; include an interaction term [*A.C., M. Ward, 2011*]

$$v_A(x) = \frac{|\Omega|}{4\pi N\bar{c}D\varepsilon}\left[1 - 4\pi\varepsilon\sum_{j=1}^{N} c_j G(x;x_j) + \frac{4\pi\varepsilon}{N\bar{c}} p_c(\xi_1,\ldots,\xi_N) + \mathcal{O}(\varepsilon^2)\right]$$

$$\bar{v}_A = \frac{|\Omega|}{4\pi N\bar{c}D\varepsilon}\left[1 + \frac{4\pi\varepsilon}{N\bar{c}} p_c(x_1,\ldots,x_N) + \mathcal{O}(\varepsilon^2)\right]$$

- Expressed in terms of the Green's functions $G(x,\xi)$ computed on trap pairs, and their regular parts $R(\xi)$, and trap capacitances c_j.

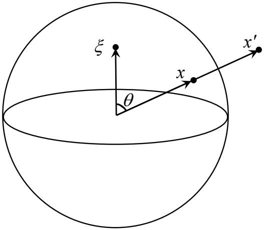
Exact and asymptotic solutions

- Capacitance depends on trap shape and size.

- Green's function:

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

- Every trap (ξ) interacts with other traps (x) and their images (x'): $xx' = r^2 = 1$.



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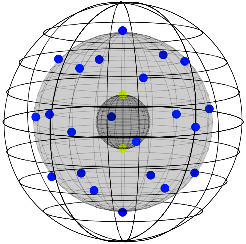
- Every trap (ξ) interacts with other traps (x) and their images (x'): $xx' = r^2 = 1$.
- Green's function regular part:

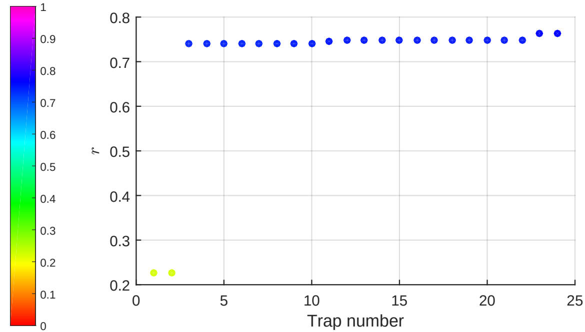
$$\Gamma(\xi;\xi) = R(\xi) = \frac{1}{4\pi(1-|\xi|^2)} + \frac{1}{4\pi}\log\left(\frac{1}{1-|\xi|^2}\right) + \frac{|\xi|^2}{4\pi} - \frac{7}{10\pi}$$

- Trap interaction term:

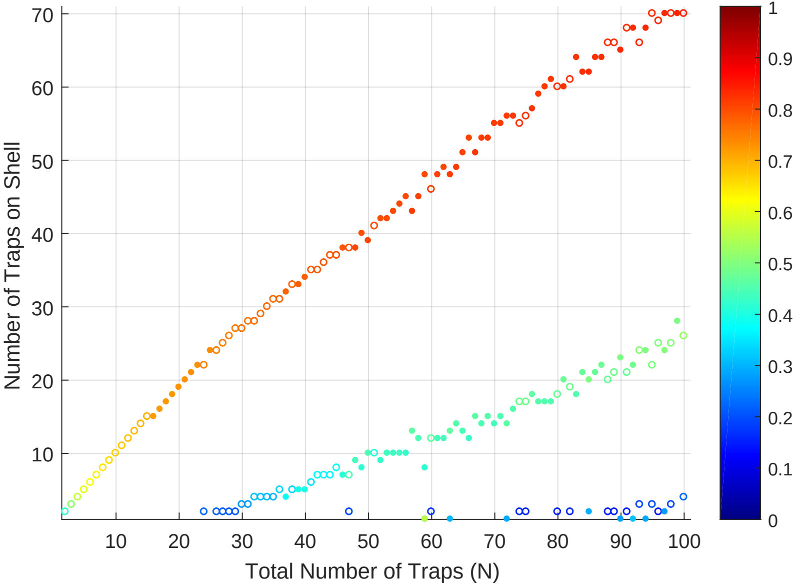
$$p_c(\xi_1,\ldots,\xi_N) = \sum_{i=1}^{N}\sum_{j=1}^{N} c_i c_j \Gamma(\xi_i,\xi_j)$$

- Asymptotic MFPT formulas tested vs. exact/numerical: work far beyond limits [*J. Gilbert and A.C., 2019*].
- Putative locally optimal configurations for $1 \leq N \leq 100$ computed.
- Traps often lie close to spherical shells.
- There may or may not be a trap at the center.
- Example: $N = 24$





Global optimization: traps (approximately) on shells



Outline

Projects and collaborators

- *with Michael Ward and R. Straube (2010):*
  Asymptotic mean first passage time (MFPT), NE, sphere with small surface traps
- *with Michael Ward (2010):*
  Asymptotic MFPT, NC, sphere with small interior traps
- *with Ashton Reimer and Michael Ward (2012):*
  NE asymptotic vs. numerical MFPT; applicability limits of asymptotic solutions
- *with Daniel Zawada (2013):*
  NE, unit sphere: homogenization limit and optimal arrangements of $N \gg 1$ traps, the N^2 conjecture
- *with Daniel Gomez (2015):*
  NE, nonspherical 3D domains, effects of boundary curvature
- *with Wesley Ridgway (2018, 2019):*
  Locally and globally optimal arrangements of particles repelling on the unit sphere surface. Results for NE and NC problems
- *with Jason Gilbert (2019, ongoing):*
  Globally optimal trap arrangements for NC in unit sphere. Optimal NC trap configurations in an ellipse
- *with Vaibhava Srivastava (finishing up):*
  Full Brownian simulations for NE in a sphere; comparison with PDE MFPT/asymptotic results; study of boundary effects & anisotropic diffusion

Thanks everyone for listening!.. and...

Happy birthday Michael!