Modeling Diffusion and Capture.

A.E. Lindsay
Applied and Computational Math & Stats
University of Notre Dame.
a.lindsay@nd.edu www.nd.edu/~alindsa1

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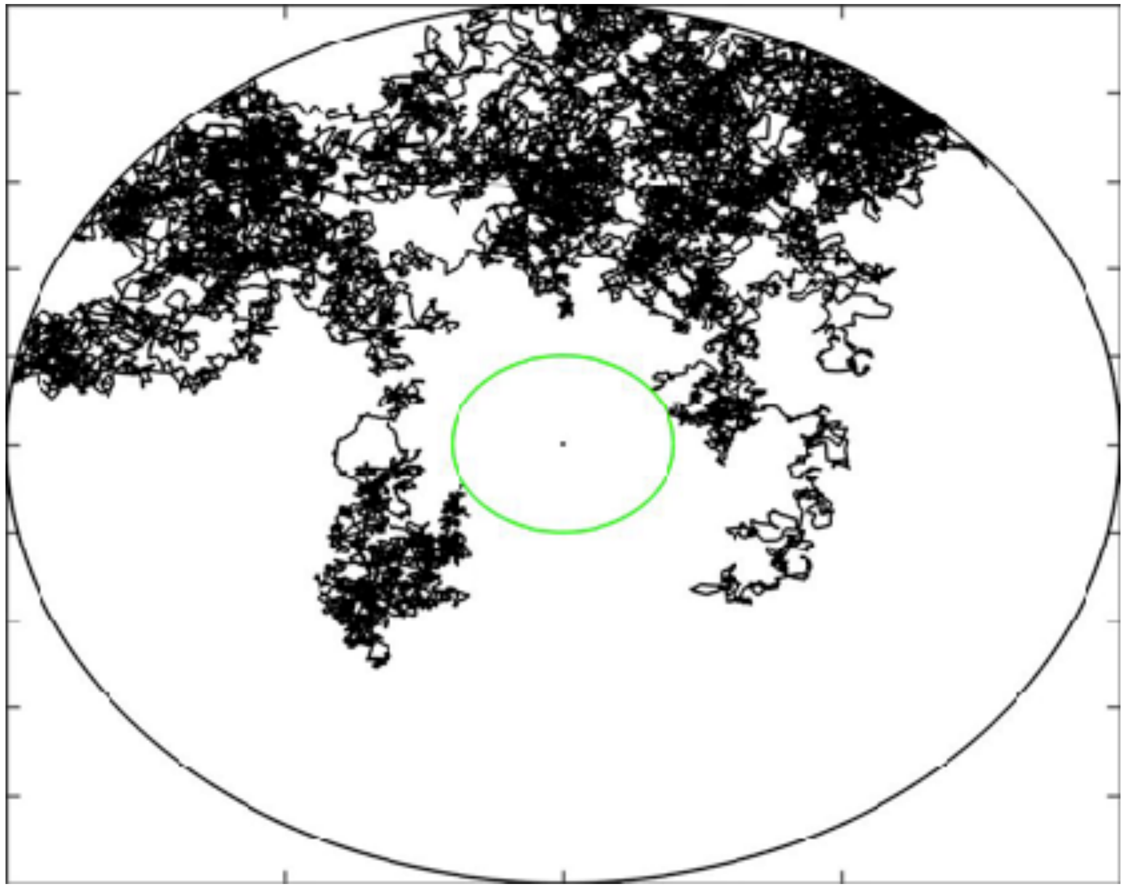
Pollen grains on the stamen of a flower.

Collaborators:
Andrew Bernoff (Harvey Mudd),
Theo Kolokolnikov (Dalhousie University),
Daniel Scmidt (Harvey Mudd)
Ryan Spoonmore (Notre Dame),
Justin Tzou, (U. British Columbia),
Michael Ward (U. British Columbia)

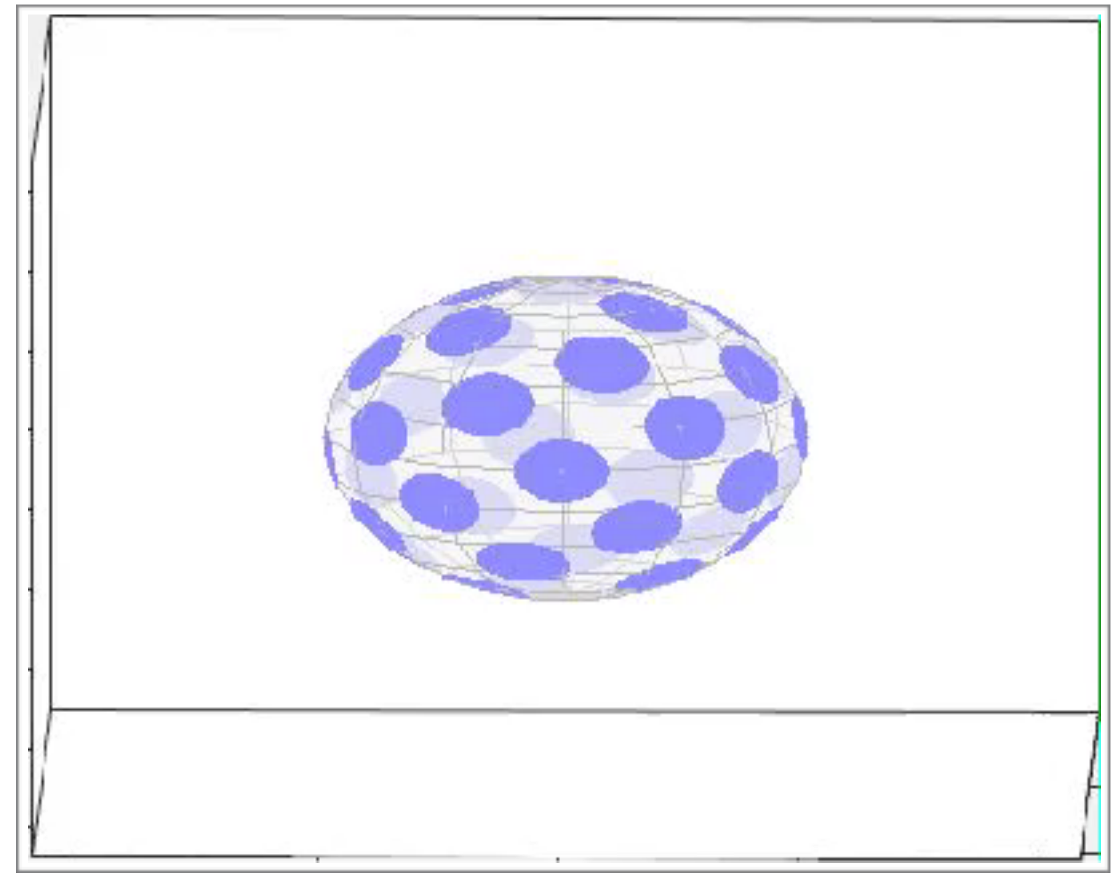
Support:

NSF DMS - 1516753

Diffusion in heterogeneous and dynamic environments.



2D diffusion in bounded region.



3D diffusion in unbounded region.

$$\mathrm{d}X_t = D\mathrm{d}W_t;$$

$$< X >^2 = D < dt >$$

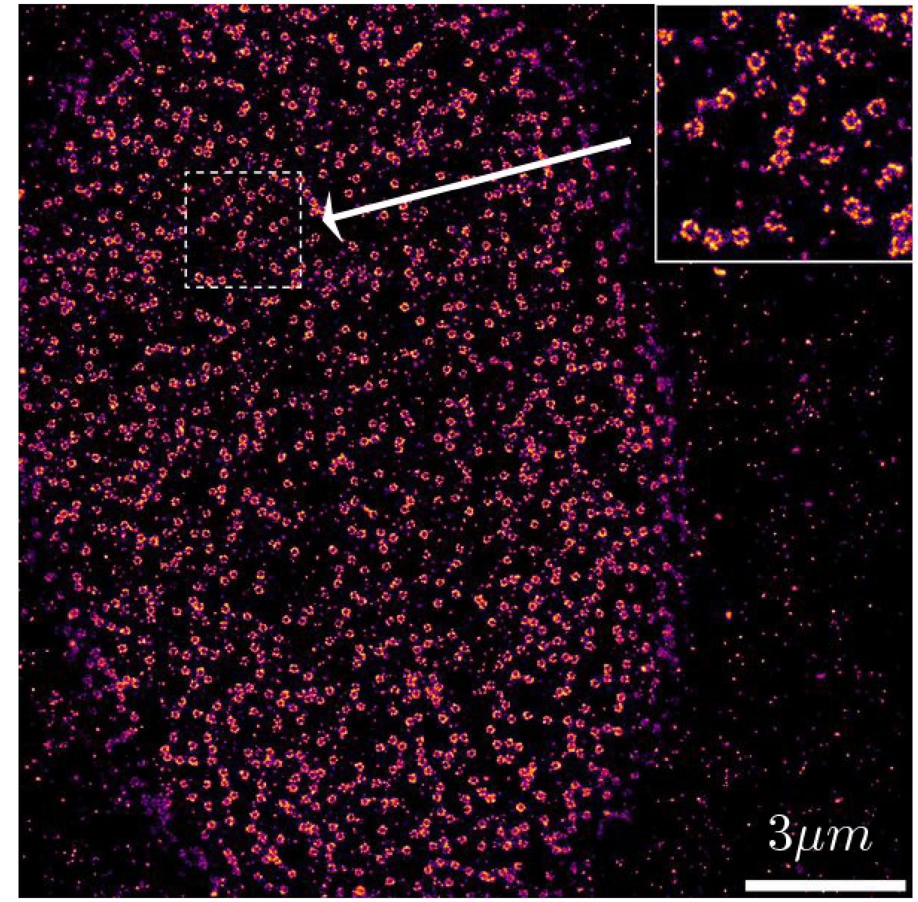
square mean displacement
=
D x time

Main Questions:

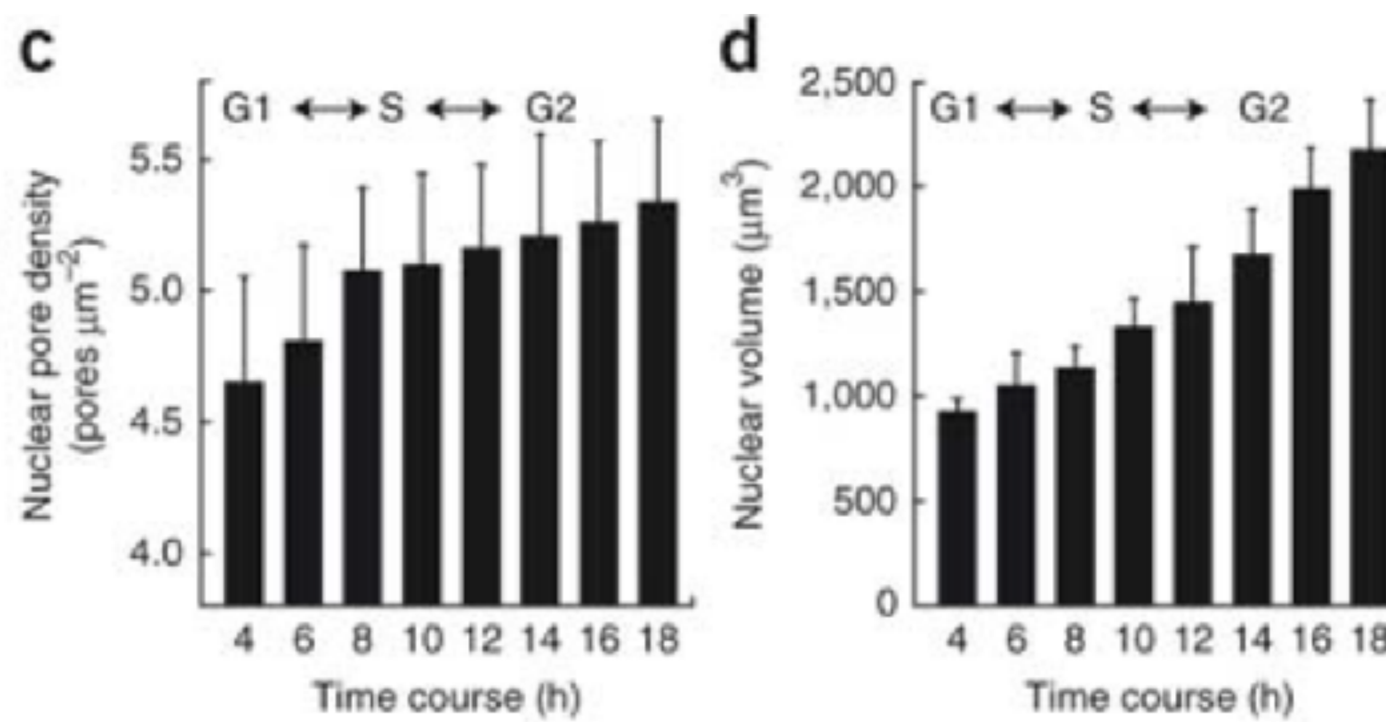
- How long till a diffusing particle finds a target?
- How does the distribution and target site mobility control possibility for, and time of capture?

Application I: Intracellular Transport.

- The cell nucleus - genetic material passes from the interior/exterior through small pores celled Nuclear Pore Complexes (NPCs).
- Nucleus ~10% of cell volume.
- Roughly N = 2000 surface pores which occupy 2% of the surface area.
- Ref: Eilenberg et.al. Science 341(6146), 2013.

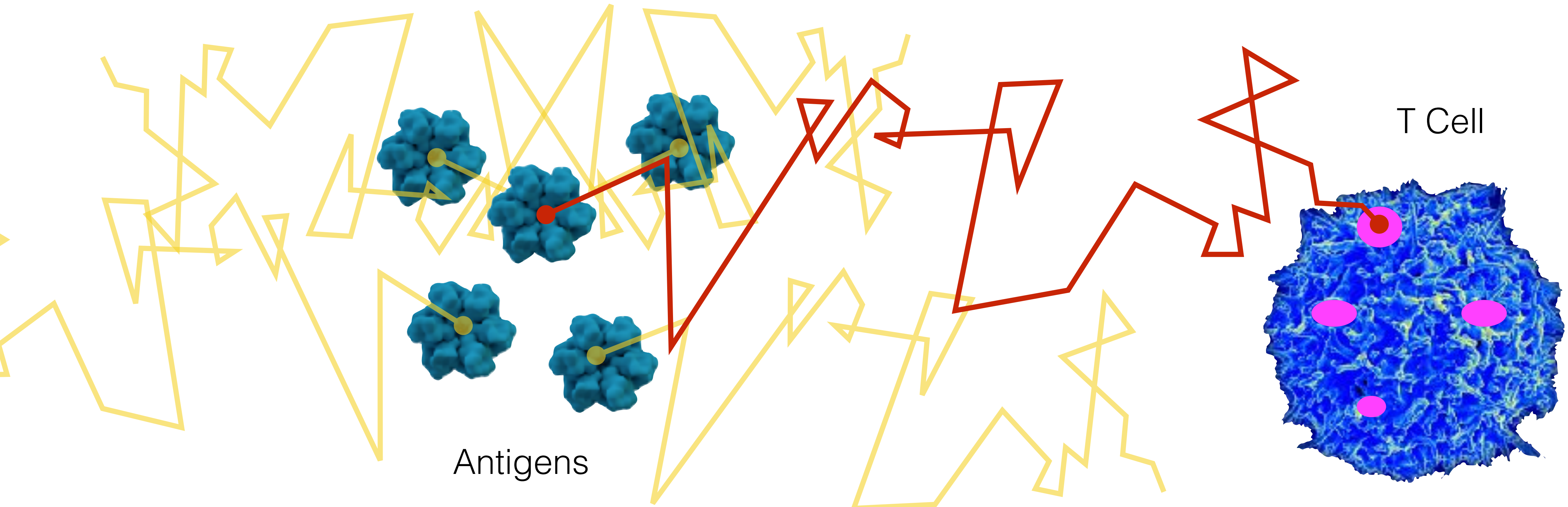


- Pore density dynamic.
- Nuclear volume dynamic.
- Experimentalists measure pore densities, not individual positions.



Maeshima et. al. Nature Struct. & Mol. Bio. 17 (2010)

Application II: Molecular Signaling



When an antigen (a toxin or a protein that promotes an immune response) binds to a receptor on a T-cell it can trigger the creation of antibodies.

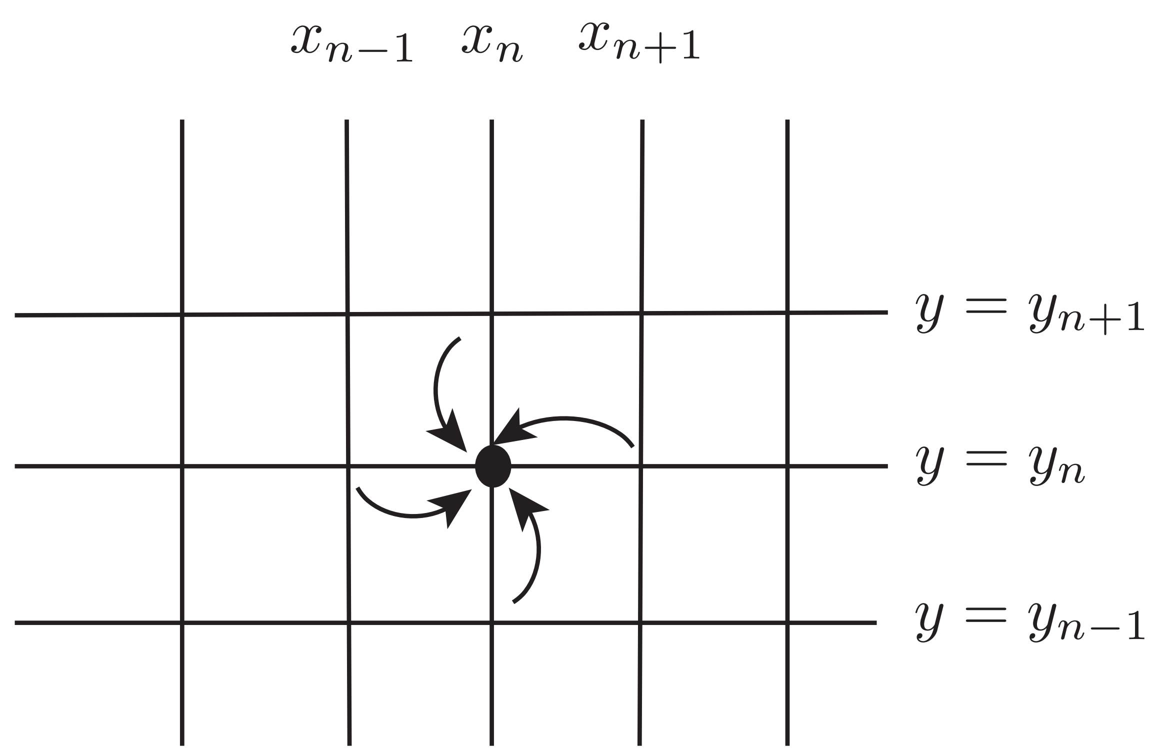
- What is the probability of this binding occurring?
- On average, how long does this take?
- How does the distribution of the receptors affect this?

TalkOutline

- General Aspects of the mathematical theory.
- Boundary Homogenization for spheres, disks and planes.
- A spectral boundary element method for capture problems.
- The roles of dynamics and cooperation factors in capture problems.
- Conclusions and Future Work.

The probability of absorption I

$p(\mathbf{x},t)$ – probability that particle starting at $\mathbf{x}=(x,y)$ is free at time t



$$x_n = n\Delta x$$

$$y_n = n\Delta y$$

$$p(x_n, y_n, t+\Delta t) = \frac{1}{4}\Big[p(x_{n-1}, y_n, t) + p(x_{n+1}, y_n, t) + p(x_n, y_{n+1}, t) + p(x_n, y_{n-1}, t)\Big]$$

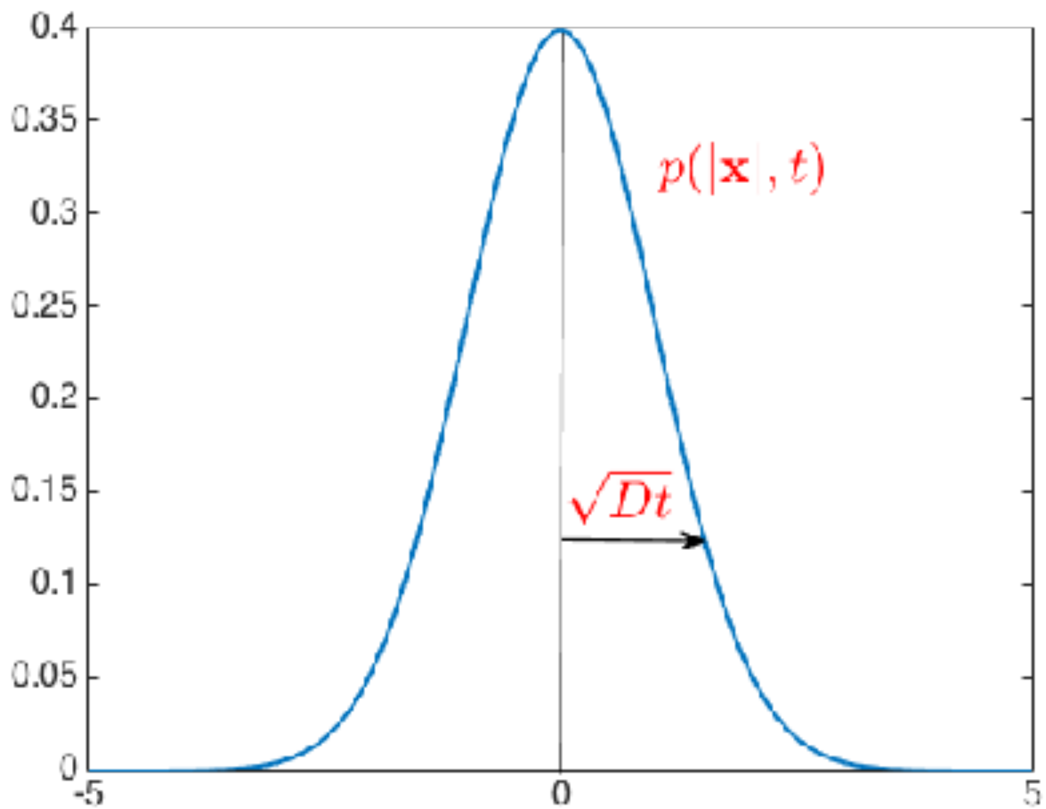
$$\begin{aligned} \Delta x = \Delta y &\to 0 \\ \Delta t &\to 0 \end{aligned} \qquad \frac{(\Delta x)^2}{4\Delta t} = D$$

$$\boxed{\begin{gathered} \frac{\partial p}{\partial t} = D\,\Delta p \equiv D\left[\frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2}\right] \\ p(\mathbf{x},0) = \delta(\mathbf{x}-\mathbf{x}_0) \end{gathered}}$$

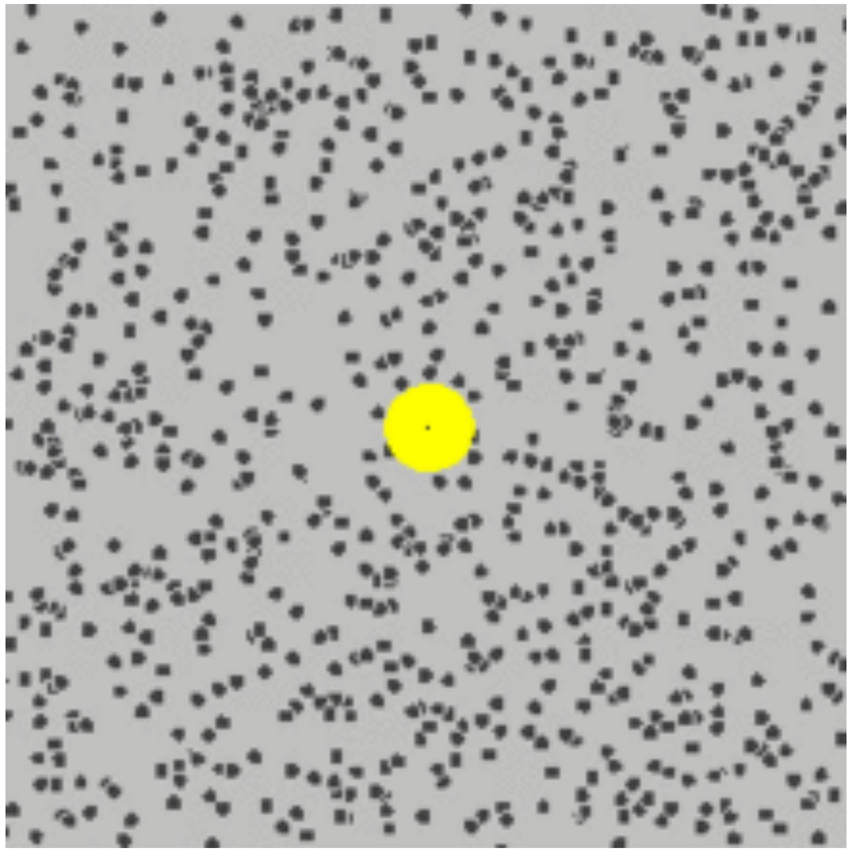
The probability of absorption II

In N dimensional free space:

$$p(\mathbf{x},t) = \left(\frac{1}{\sqrt{4\pi D t}}\right)^N e^{-|\mathbf{x}-\mathbf{x}_0|/(4Dt)}$$



Diffusion Kernel

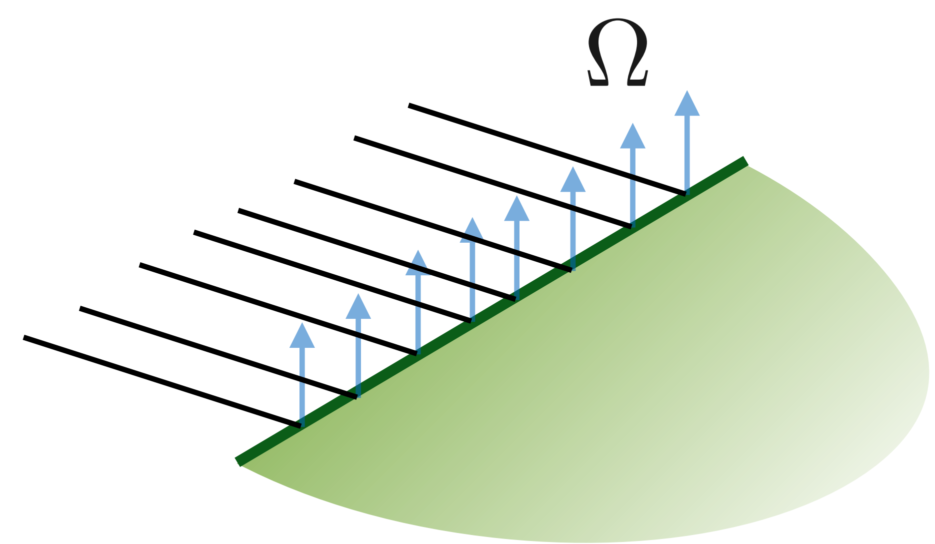


https://en.wikipedia.org/wiki/Brownian_motion

Boundary Conditions.

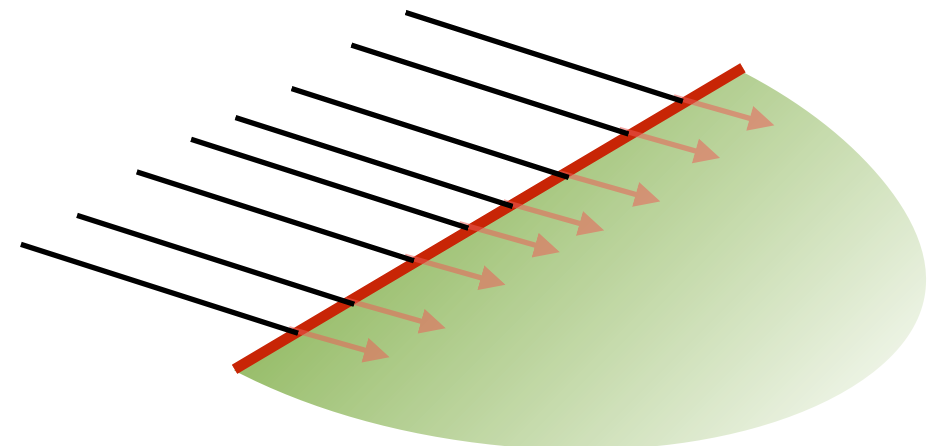
Reflecting (or Neumann).

$$\boxed{\nabla p \cdot \hat{n} = 0 \text{ on } \partial\Omega}$$



Absorbing (or Dirichlet).

$$\boxed{p = 0 \text{ on } \partial\Omega}$$

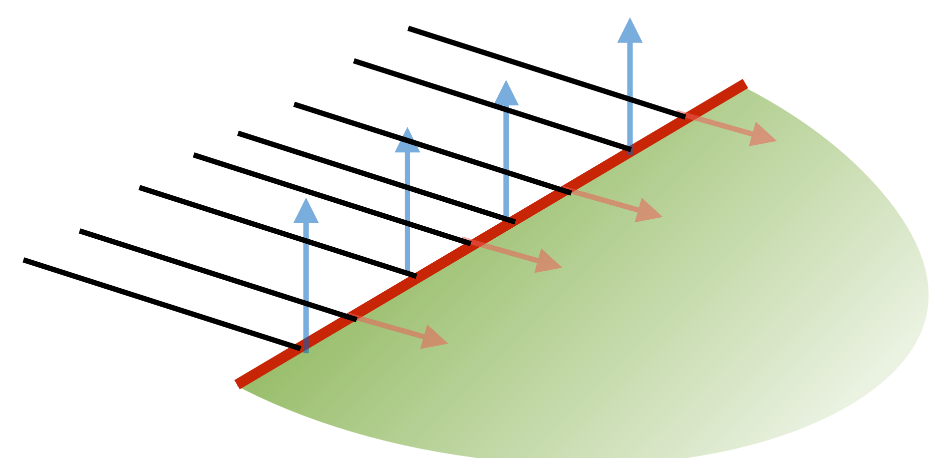


Partially Absorbing (or Robin)

$$\boxed{\nabla p \cdot \hat{n} + \kappa\, p = 0 \text{ on } \partial\Omega}$$

$\kappa \ll 1$ Mostly Reflecting

$\kappa \gg 1$ Mostly Absorbing



The probability of Escape

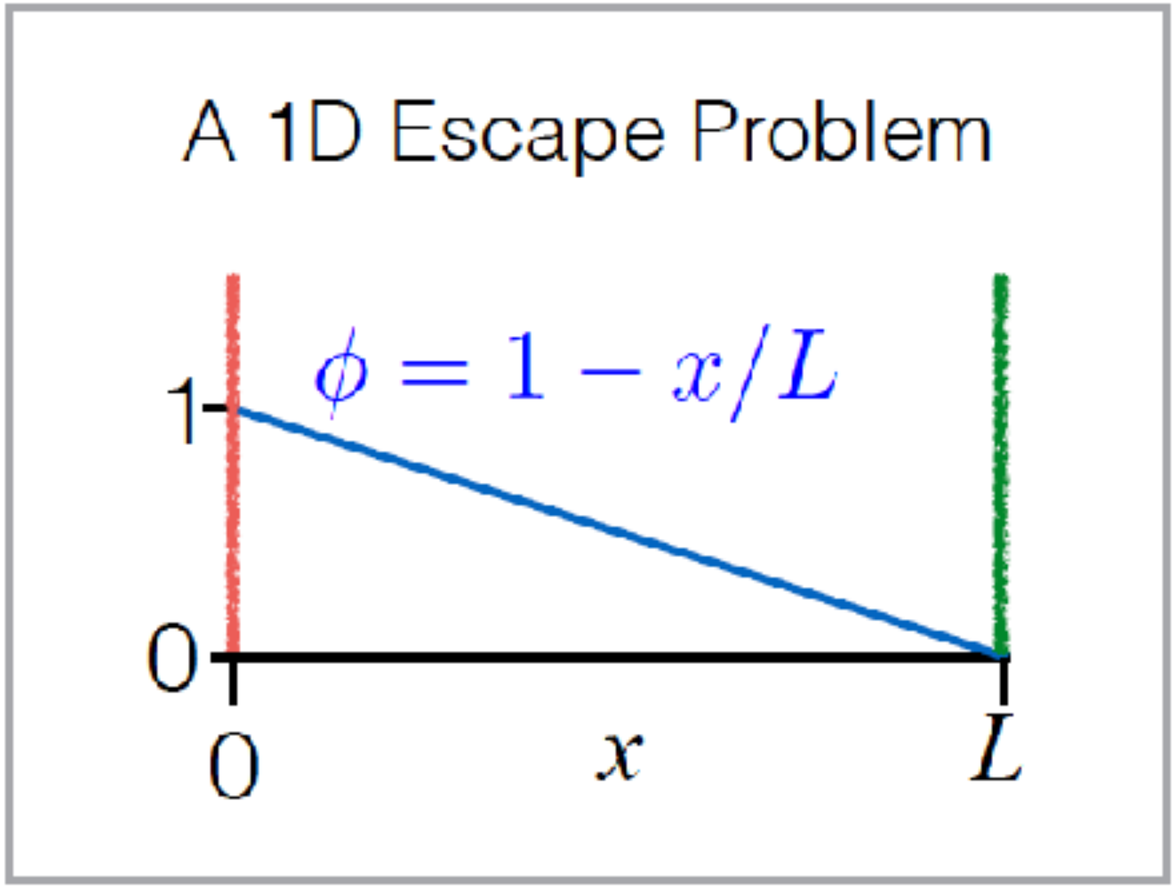
Consider a domain with a target boundary and an escape boundary.

The probability, $\phi(x)$, that a molecule is captured satisfies Laplace's equation:

$$\nabla^2 \phi = 0 \text{ in } \Omega$$

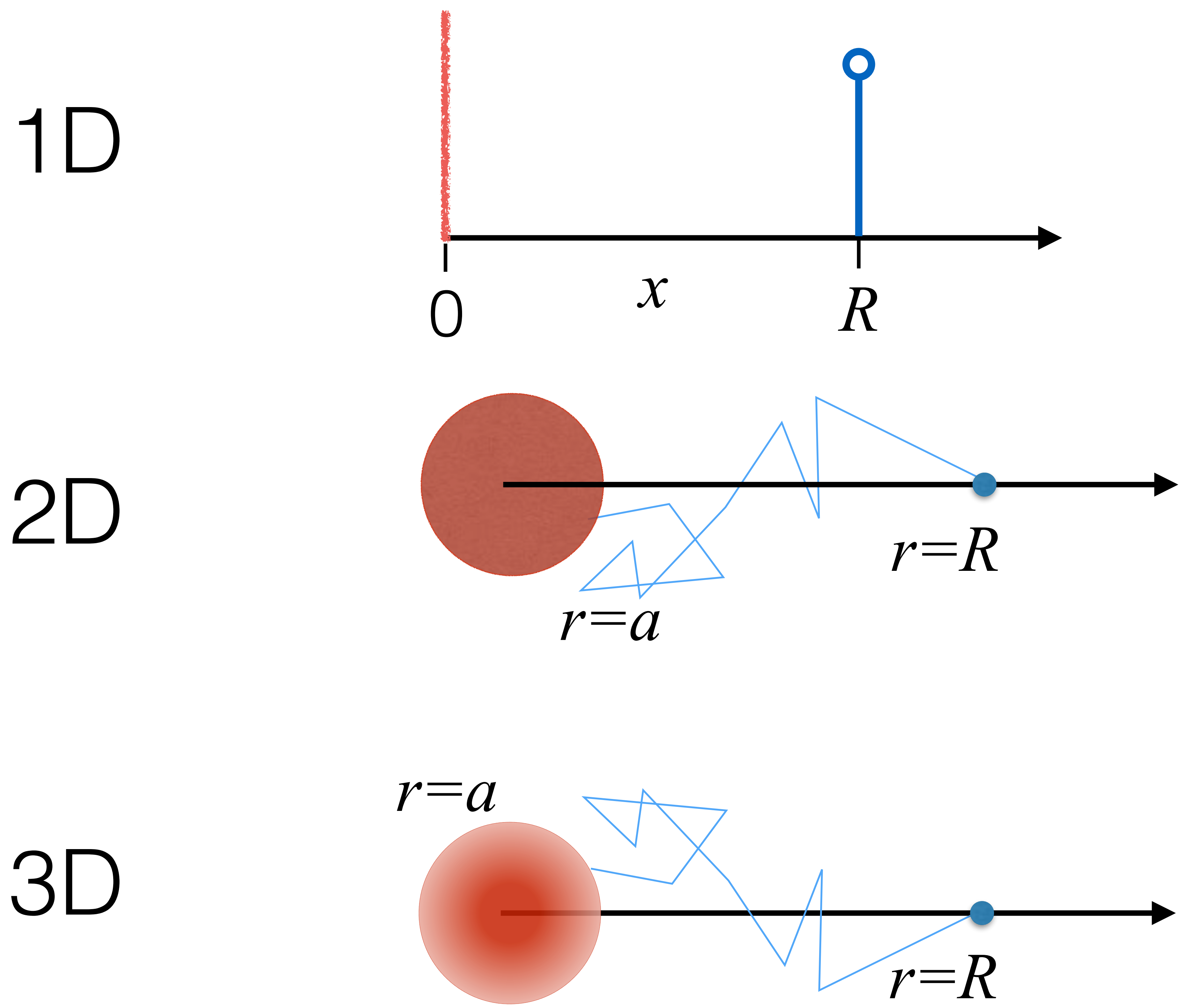
$$\phi = 1 \quad \text{on } \partial\Omega \text{ for capture}$$

$$\phi = 0 \quad \text{on } \partial\Omega \text{ for escape}$$



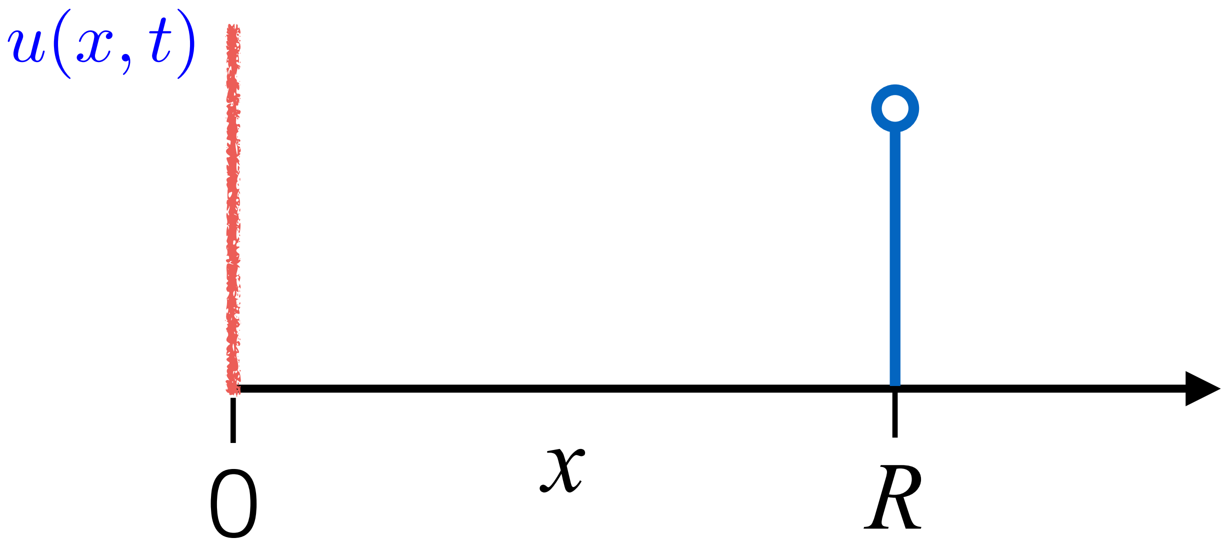
This is sometimes called *harmonic measure*.

The importance of dimension in diffusion and capture problems



Capture in 1D

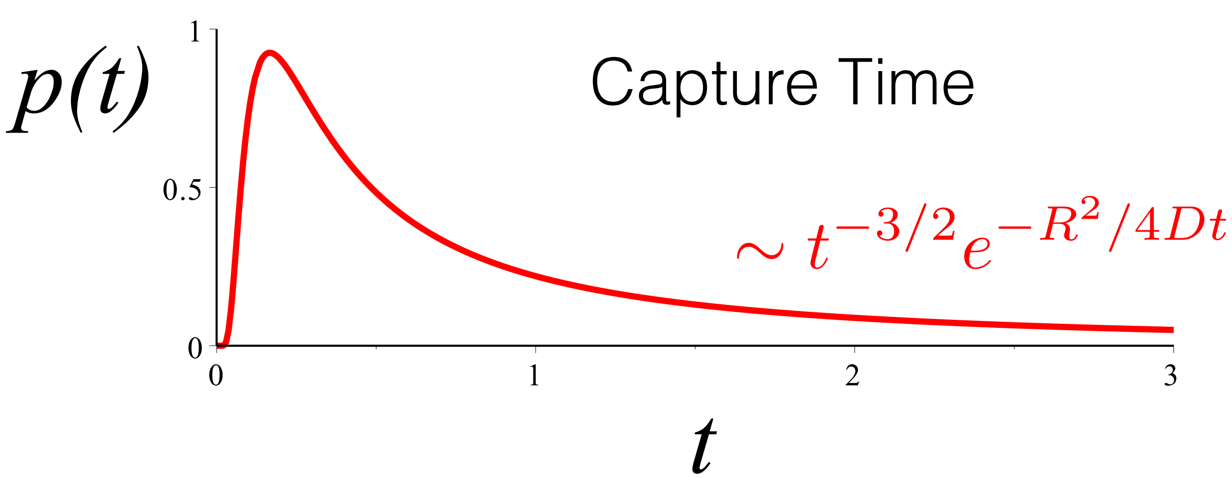
Consider a delta-function release at $x=R$.



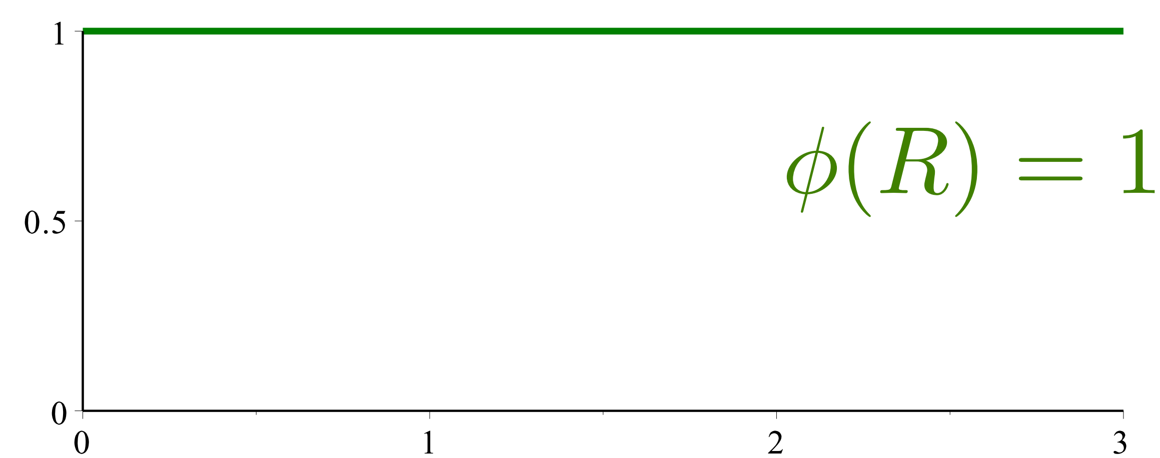
$$u_t = D u_{xx} \qquad x>0,\ t>0$$
$$u(x,0) = \delta(x-R) \qquad x>0$$
$$u(0,t) = 0 \qquad t>0$$

By method of images: $u(x,t) = \dfrac{1}{2\sqrt{\pi D t}}[e^{-(X-R)^2/4Dt} - e^{-(X+R)^2/4Dt}]$

FPT: $p(t) = -Du_x(0,t) = \dfrac{Re^{-R^2/4Dt}}{2\sqrt{\pi D}t^{3/2}}$

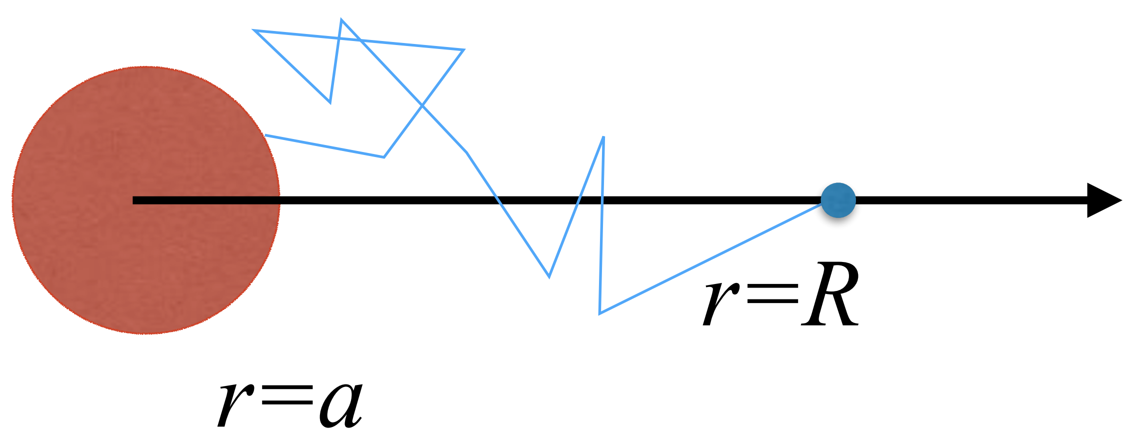


Probability of capture:



Capture in 2D

Consider a **d**-function release at r=R and a circular trap of radius a.



$$u_t = D\left[u_{rr} + \frac{1}{r}u_r\right] \qquad r > 0,\ t > 0$$

$$u(r,0) = \frac{1}{2\pi R}\delta(r-R) \quad r > a$$

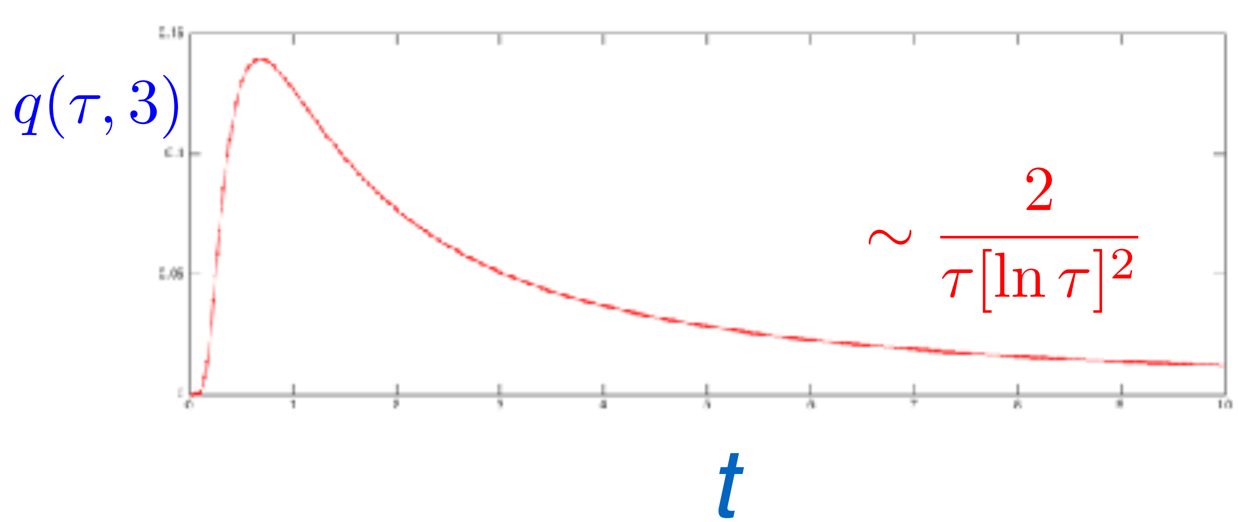
$$u(a,t) = 0 \quad t > 0$$

FPT: $p(t) = \dfrac{a^2}{D} q(\tau,\delta), \quad \delta = \dfrac{R}{a}, \quad \tau = \dfrac{a^2 t}{D}$

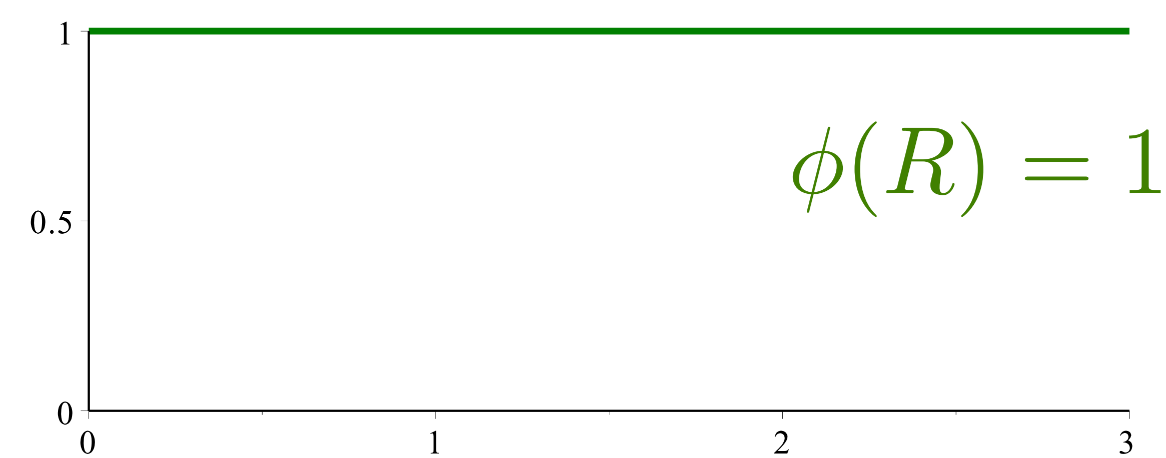
Obtained with a Laplace Transform

$$q(\tau,\delta) = \frac{2}{\pi}\int_{s=0}^{\infty} s e^{-s^2\tau} \frac{J_0(s)Y_0(\delta s) - J_0(\delta s)Y_0(s)}{[J_0(s)]^2 + [Y_0(s)]^2}\, ds$$

Capture Time

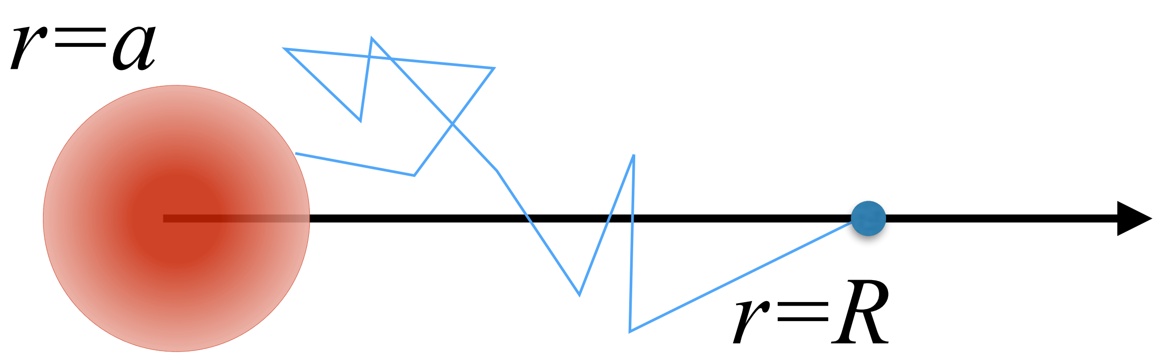


Probability of capture:



Capture in 3D

Consider a d-function release at $r=R$ and a spherical trap of radius a.



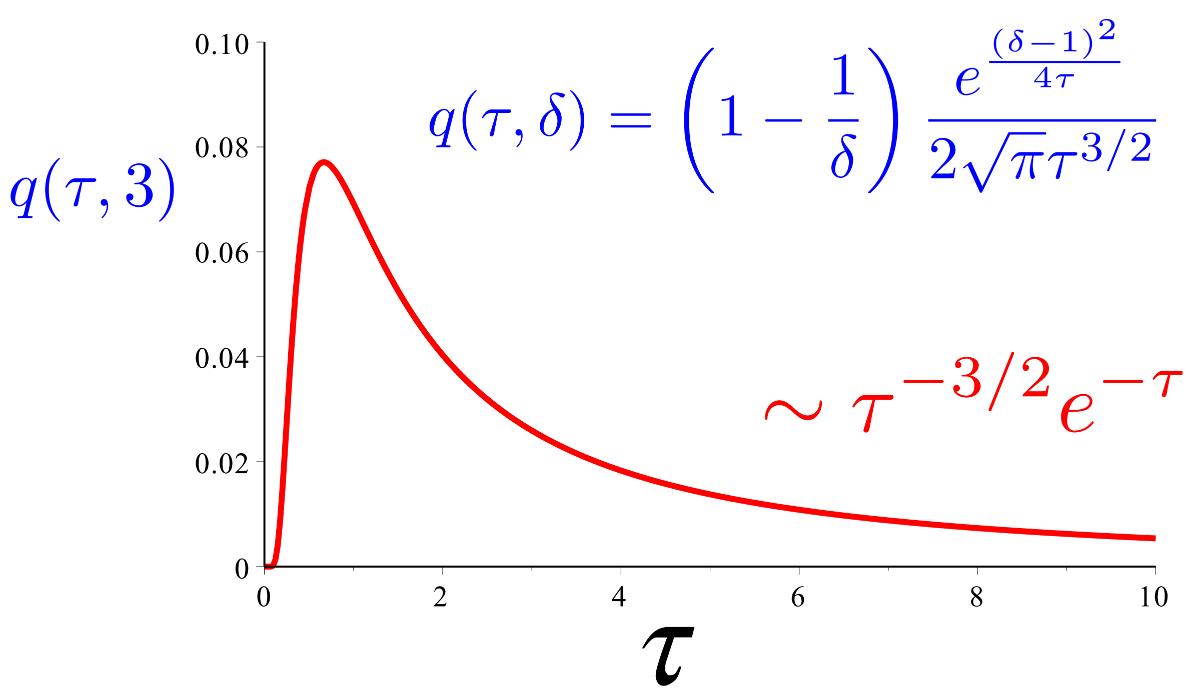
$$u_t = D\left[u_{rr} + \frac{2}{r}u_r\right] \qquad r>0,\ t>0$$

$$u(r,0) = \frac{1}{4\pi R^2}\delta(r-R) \quad r>a$$

$$u(a,t)=0 \quad t>0$$

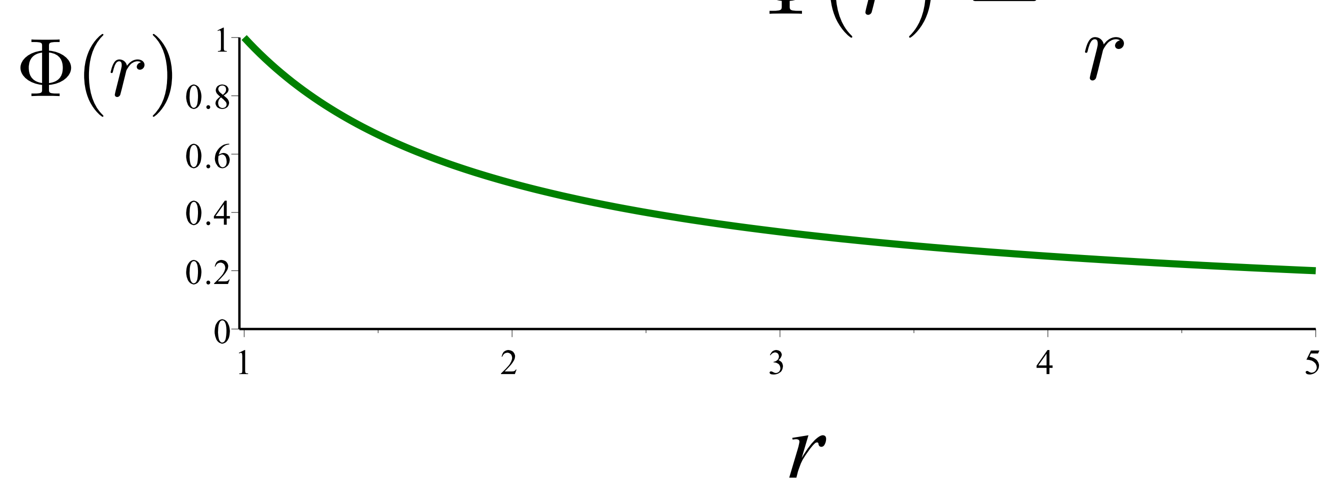
FPT: $p(t) = \dfrac{a^2}{d}q(\tau,\delta) \quad \delta = \dfrac{R}{a} \quad \tau = \dfrac{a^2 t}{d}$

Capture Time

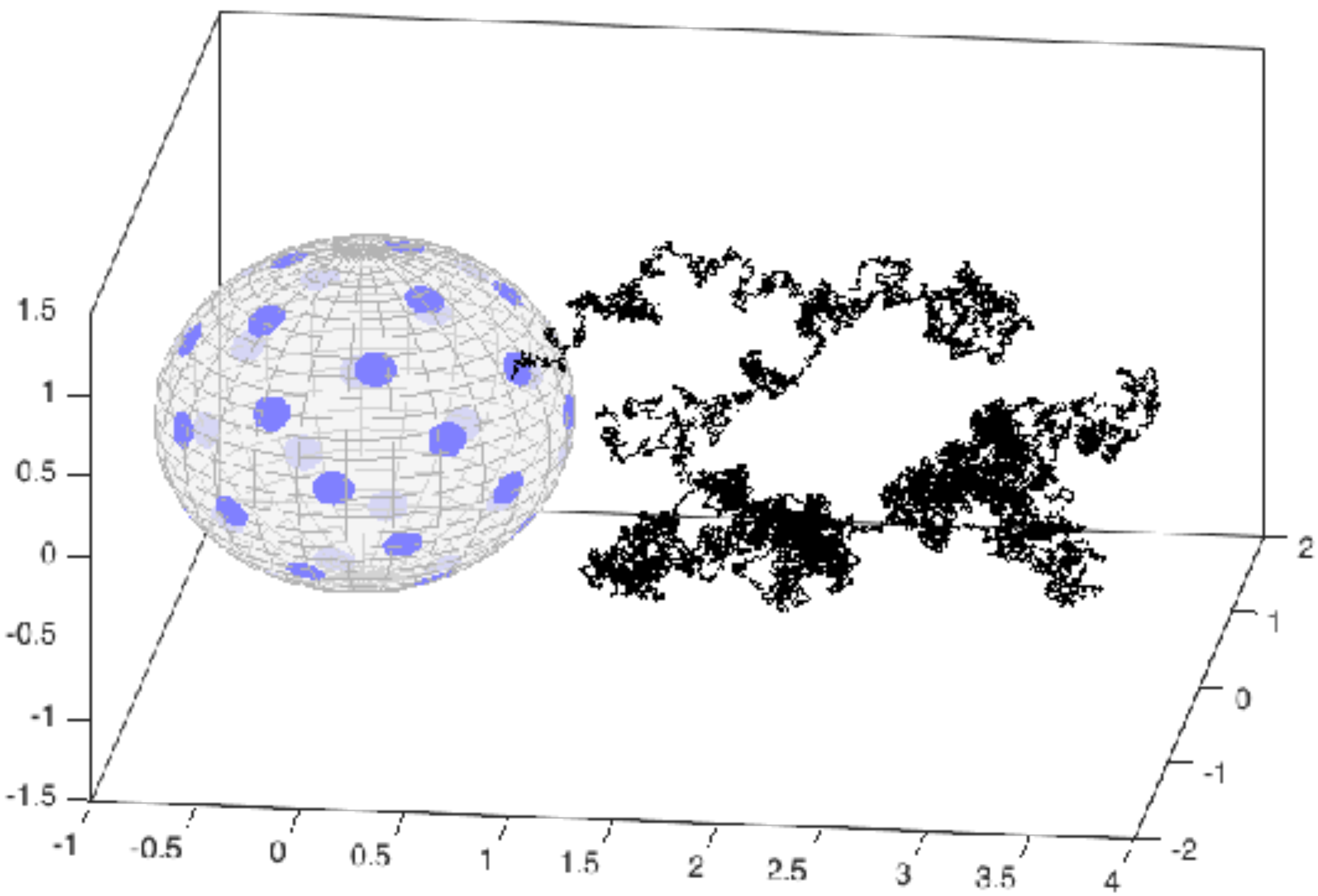


Probability of capture:

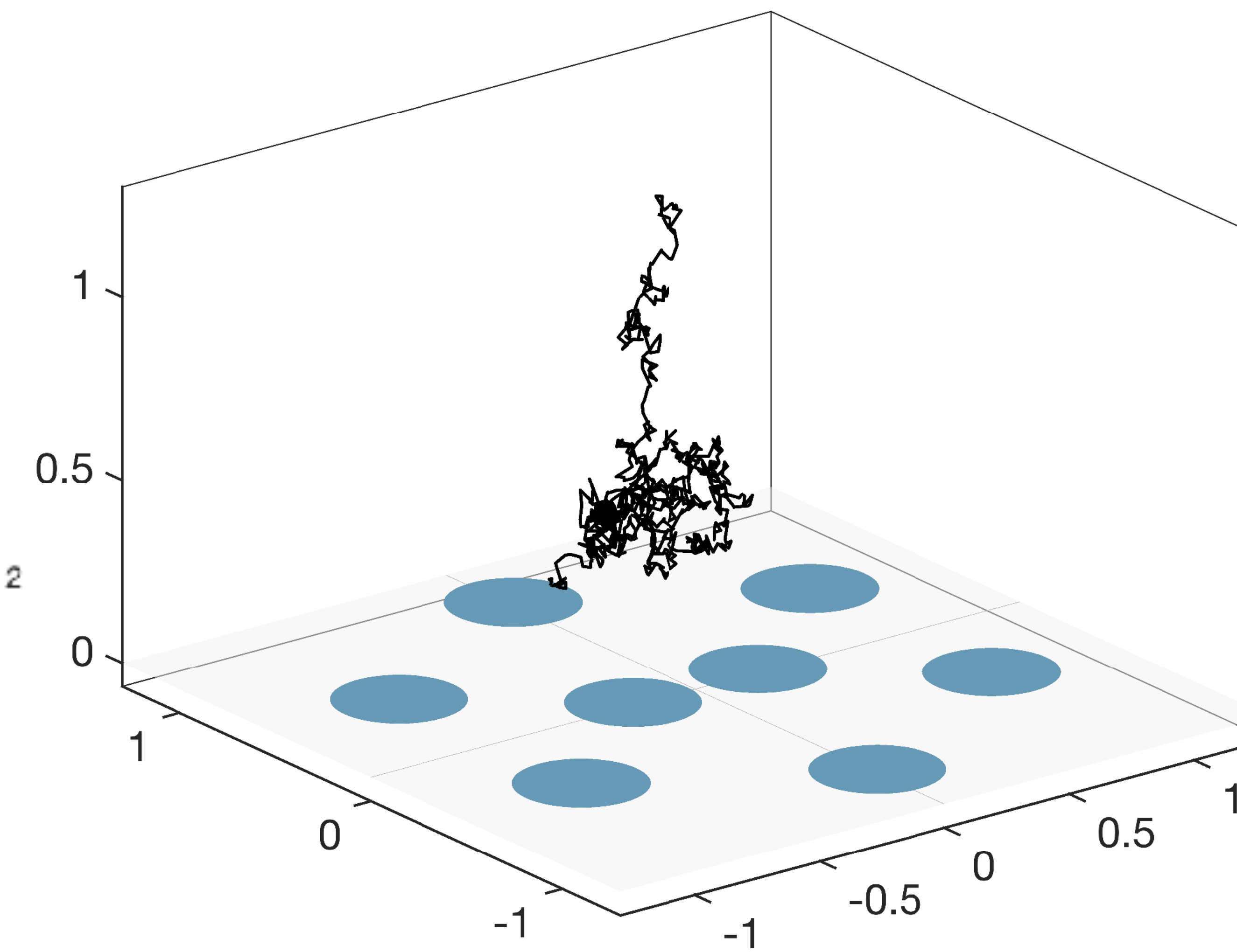
$$\Phi(r) = \frac{a}{r}$$



Problem: 3D Diffusion to a surface with small absorbing pores.



Problem 1: Pores on sphere.



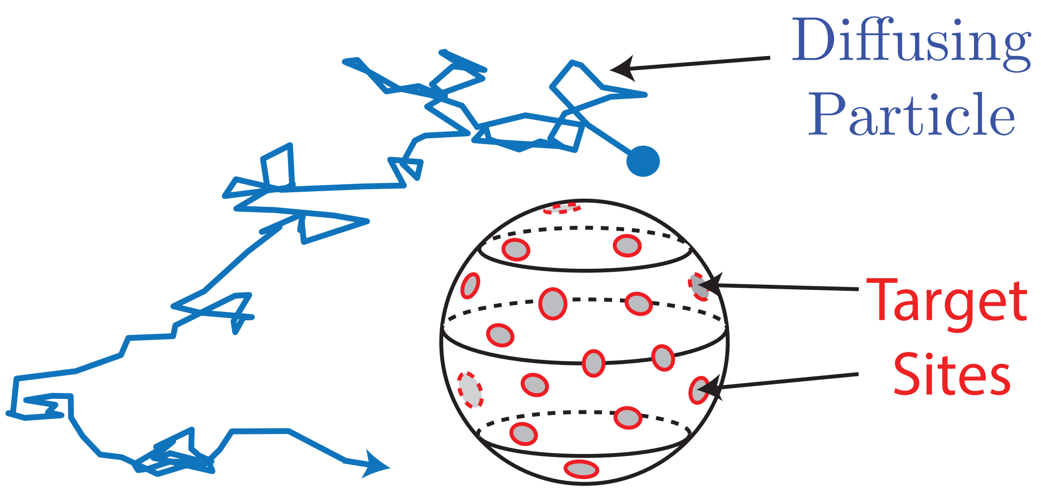
Problem 2: Pores on infinite plane.

Describe the rate of capture at the pores.

Diffusion to a structured 3D target with small absorbing pores.

$u(\mathbf{x})$ – The probability that particle is captured starting at $\mathbf{x} \in \mathbb{R}^3$.

$$\begin{cases} \Delta u = 0, & \text{outside sphere.} \\ u = 1, & \text{on absorbing pores.} \\ \partial_n u = 0, & \text{on reflecting surface} \\ u(\mathbf{x}) = \dfrac{C}{|\mathbf{x}|} + \mathcal{O}\left(\dfrac{1}{|\mathbf{x}|^2}\right), & |\mathbf{x}| \to \infty \end{cases}$$



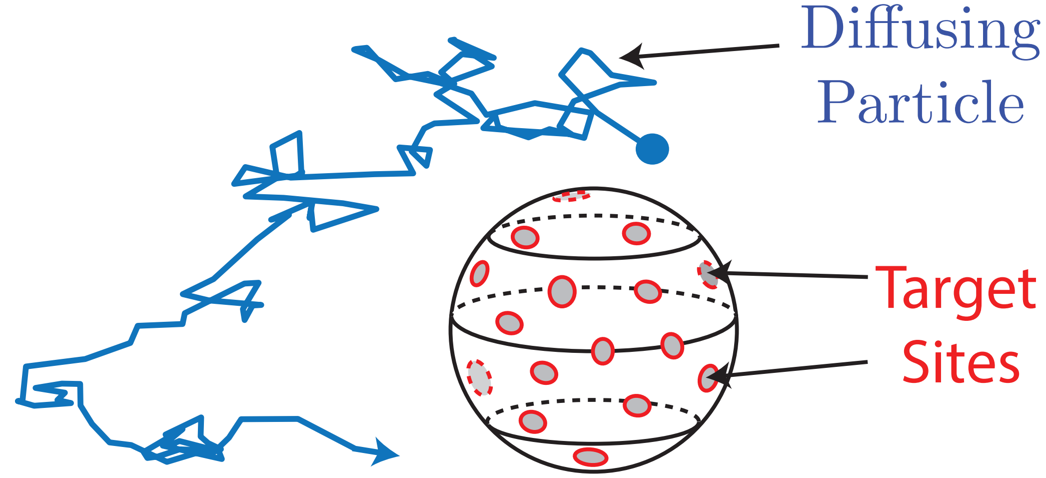
C – The capacitance of the target. $C = 1$ for all absorbing.

The flux into the target is given by (from the divergence theorem)

$$\boxed{J = D \int_{\partial\Omega_a} \partial_n u \, dS = 4\pi D C}$$

<u>Goal: Calculate C for many pores distributed over the surface.</u>

Berg & Purcell - Physics of Chemoreception 1977 (~1500 citations)



- N small non overlapping pores.
- Common radius σ.

Using physical intuition, postulated that the flux satisfies

$$\boxed{J = 4\pi D \frac{N\sigma}{N\sigma + \pi} = {\color{red}4DN\sigma} + \mathcal{O}(\sigma^2), \qquad \sigma \to 0}$$

Key result:

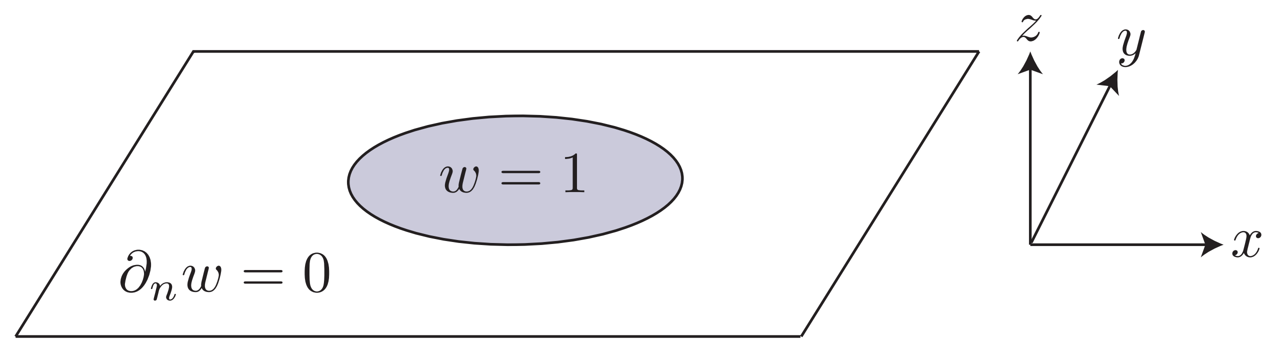
$J \propto$ total pore perimeter. $\implies$ The sensing is near optimal provided pores are numerous and separated.

Limitations

- Derived by interpolating between all absorbing and N independent pores.
- No information on influence of receptor spatial arrangements.

Important Ingredient - Single Pore on a flat plane.

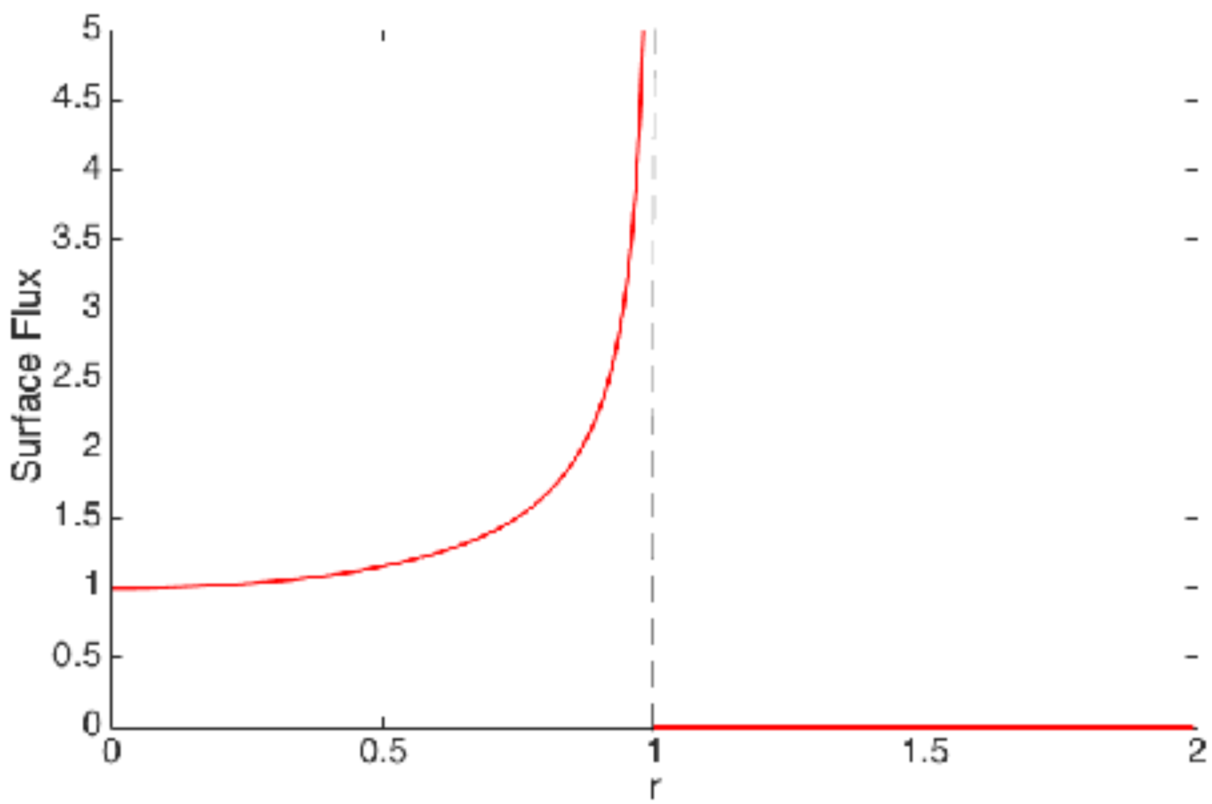
$$\begin{cases} \Delta w = 0, & z > 0; \\ w = 1, & z = 0, \quad x^2 + y^2 \le \sigma^2; \\ \partial_n w = 0, & z = 0, \quad x^2 + y^2 > \sigma^2. \end{cases}$$



Capacitance: $C = \dfrac{2\sigma}{\pi}, \quad J = 4D\sigma.$

Ref: Sneddon, Mixed Boundary Value Problems, 1966.

Surface Flux: $$\left.\frac{\partial w}{\partial z}\right|_{z=0} = \begin{cases} 0, & x^2 + y^2 > \sigma^2; \\ \dfrac{1}{\sqrt{\sigma^2 - x^2 - y^2}}, & x^2 + y^2 < \sigma^2. \end{cases}$$



Integrable singularity at meeting of Dirichlet and Neumann parts.

Most flux is though pore edge than center.

Naive numerical approaches will fail.

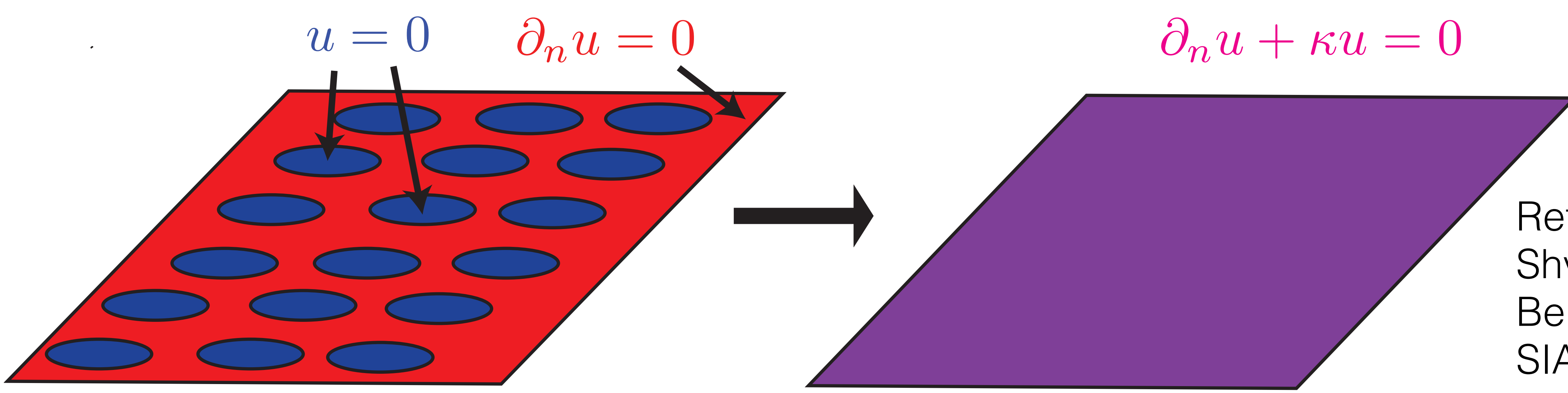
Rain Drain Analogy - perimeter that matters in the biologically realistic limit!

Source: shutterstock.com

Literature since Berg & Purcell - How does clustering influence the capture rate?

- Exact analysis very difficult - classical potential theory utilizes separation of variables which is tricky for mixed boundary values problems

Boundary Homogenization or ‘effective medium theory’



Ref: Muratov, Shvartsmam, Berezhkovskii, SIAM MMS 2006.

Exact Planar capture time distribution

$$F(t) = \frac{\kappa}{\sqrt{\pi t}} e^{-\frac{x_0^2}{4t}} - \kappa^2 e^{\kappa(\kappa t + x_0)} \mathrm{erfc}\left(\frac{2\kappa t + x_0}{2\sqrt{t}}\right)$$

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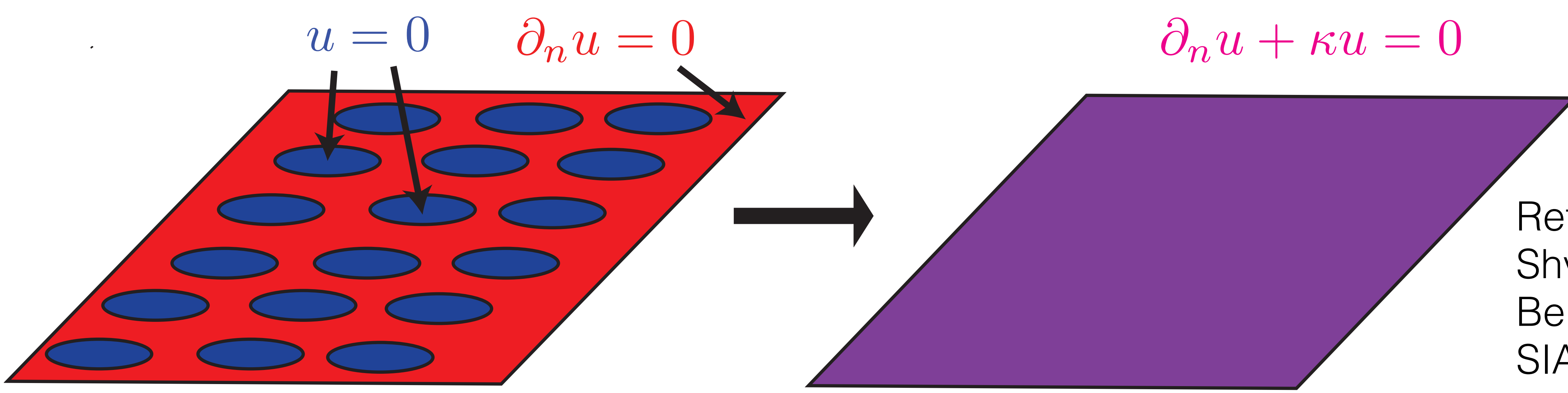
Boundary Homogenization or ‘effective medium theory’



Ref: Muratov, Shvartsmam, Berezhkovskii, SIAM MMS 2006.

Main Question: How should the leakage parameter κ be chosen?

- Depends on the absorbing area fraction.

- Depends on the particular receptor clustering.

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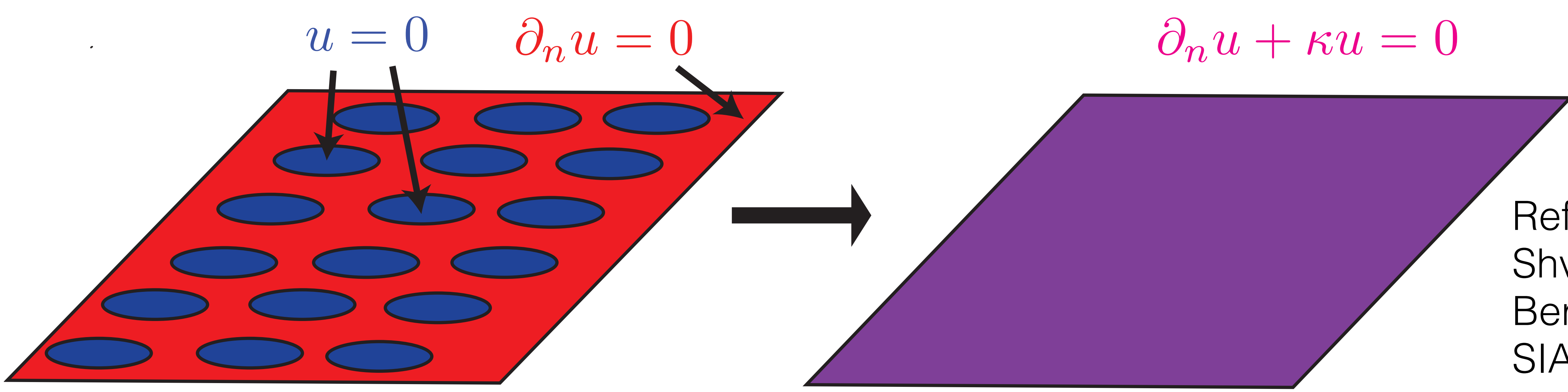
Boundary Homogenization or 'effective medium theory'



Ref: Muratov, Shvartsmam, Berezhkovskii, SIAM MMS 2006.

Using the Berg-Purcell Flux: $J = 4DN\sigma$ $\implies$

$$\kappa = \frac{4D}{\pi\sigma} f$$

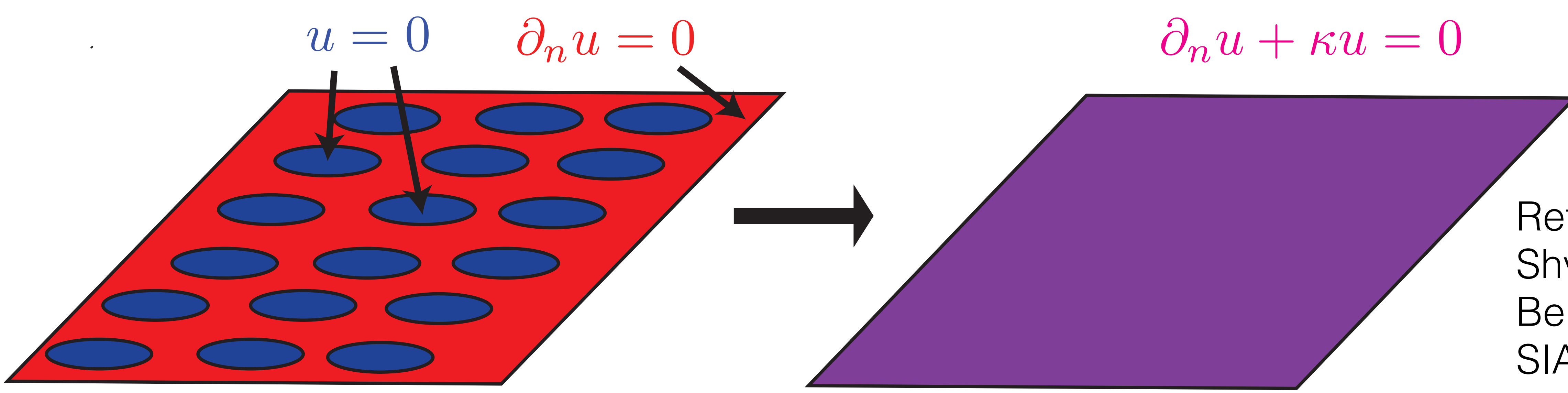
Ref: Shoup, Szabo BioPhys J. 1982.

f – absorbing fraction, σ – individual pore size

Literature since Berg & Purcell - How does clustering influence the capture rate?

- Exact analysis very difficult - classical potential theory utilizes separation of variables which is tricky for mixed boundary values problems

Boundary Homogenization or 'effective medium theory'



Ref: Muratov, Shvartsmam, Berezhkovskii, SIAM MMS 2006.

$$\kappa = \frac{4Df}{\pi\sigma}\chi(f), \quad \chi(f) = \frac{1 + A\sqrt{f} - Bf^2}{(1-f)^2}$$

Ref: Berezhkovskii 2008, 2013, 2016.

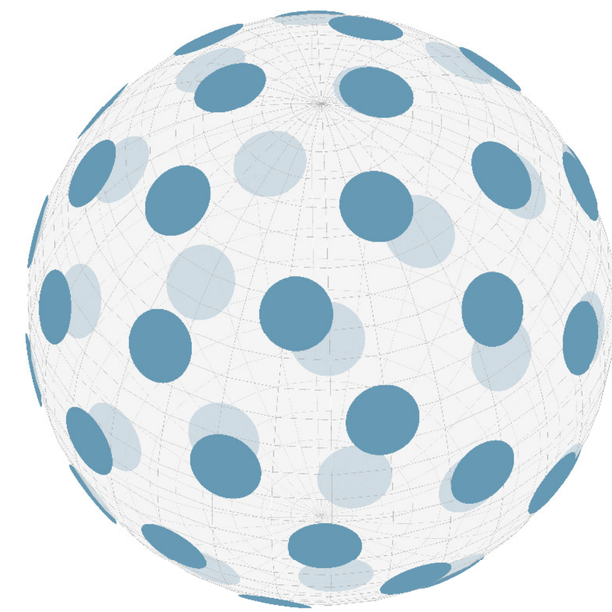
Particle simulations fit parameters. A = 1.62, 1.75, 1.37 and B = 1.36, 2.02, 2.59, for triangular, square and hexagonal lattices.

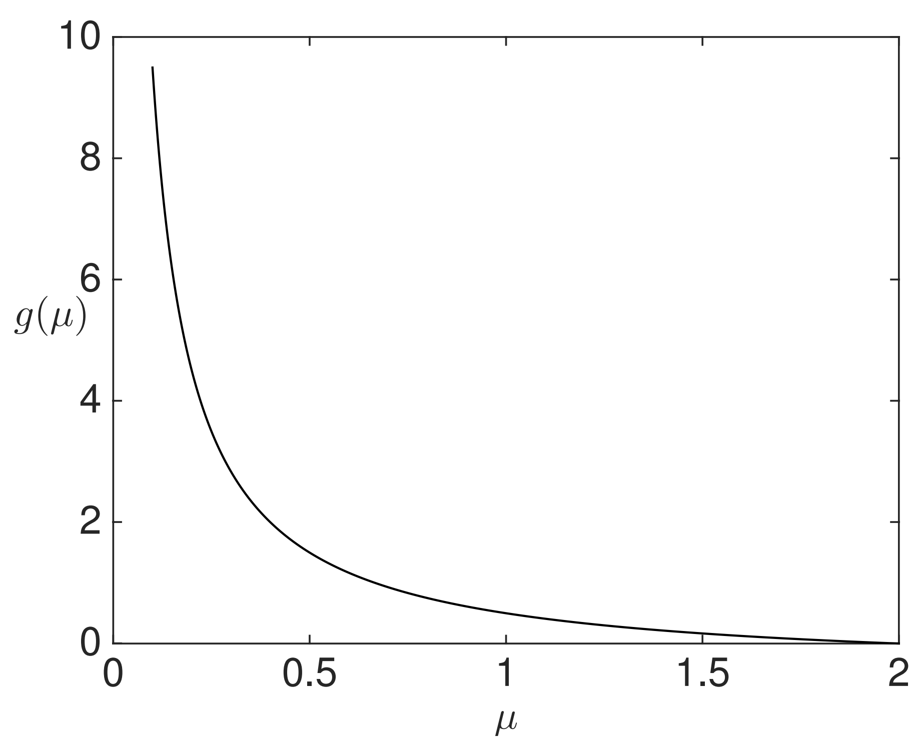
Lindsay, Ward, Bernoff - SIAM MMS, Vol. 15, No. 1 (2017)

- From a detailed singular perturbation analysis with N pores of common radius.

$$J = 4DN\sigma\left[\underbrace{1}_{\text{B\&P Result}} + \underbrace{\frac{\sigma}{\pi}\log 2\sigma}_{\text{Effect of Spherical Geometry}} + \frac{\sigma}{\pi}\left(-\frac{3}{2} + \underbrace{\frac{2}{N}\mathcal{H}(\mathbf{y}_1,\ldots,\mathbf{y}_N)}_{\text{Interpore Interaction Term}}\right) + \cdots\right]^{-1}$$

$$\mathcal{H} = \sum_{j\neq k} g(|\mathbf{y}_j - \mathbf{y}_k|), \qquad g(d) = \frac{1}{d} + \frac{1}{2}\log\left[\frac{d}{2+d}\right]$$



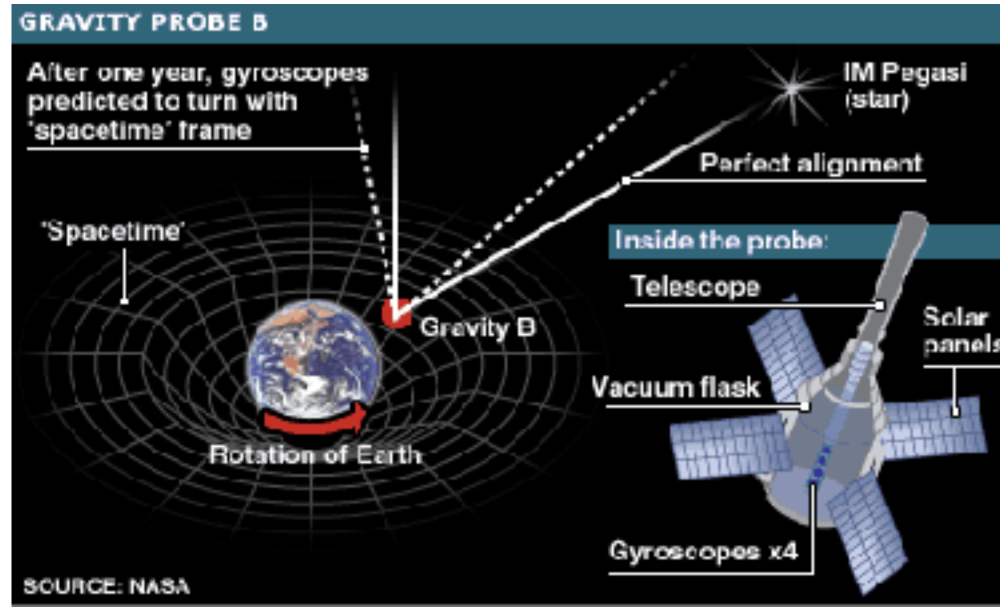


- Flux is maximized when $\mathcal{H}$ is minimized.
- $g'(\mu) < 0, \quad 0 < \mu < 2.$
- $g''(\mu) < 0, \quad 0 < \mu < 2.$
- Suggests optimal configuration should be roughly equidistributed.

<u>Result requires an explicit surface Green's Function.</u>

Gravity Probe B

- Launched in 2004 to verify predictions of General Relativity.
- Four Gyros measured the precessions over the period of a year.
- Gyroscopes the most perfect spheres ever manufactured at time.



A gyro for GP-B

Surface Green's Function of Sphere.

$$
\begin{aligned}
\Delta G &= 0, \qquad |\mathbf{x}| > 1; \\
\partial_n G &= \delta(\mathbf{x} - \mathbf{x}_0), \qquad |\mathbf{x}| = 1.
\end{aligned}
$$

Ref: Nemenman and Silbergleit, J. Appl. Phys., 86 (1999), pp. 614–624.

$$
G(\mathbf{x}; \mathbf{x}_0) = \frac{1}{2\pi}\left[\frac{1}{|\mathbf{x} - \mathbf{x}_0|} - \frac{1}{2}\log\left(\frac{1 - \mathbf{x}\cdot\mathbf{x}_0 + |\mathbf{x} - \mathbf{x}_0|}{|\mathbf{x}| - \mathbf{x}\cdot\mathbf{x}_0}\right)\right]
$$

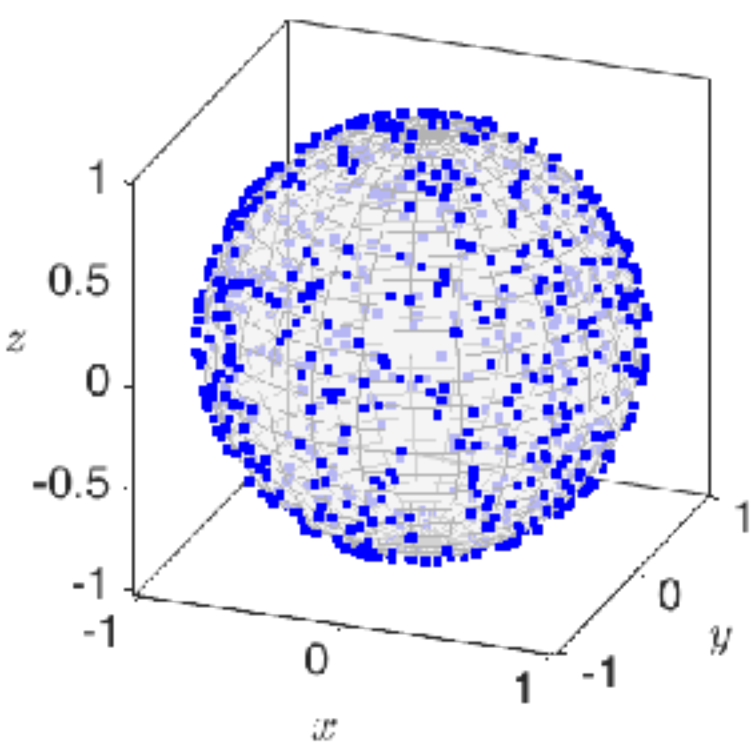
Problem: Find global minimizers of

$$\mathcal{H} = \sum_{j \neq k} g(|\mathbf{y}_j - \mathbf{y}_k|), \qquad g(d) = \frac{1}{d} + \frac{1}{2}\log\left[\frac{d}{2+d}\right]$$

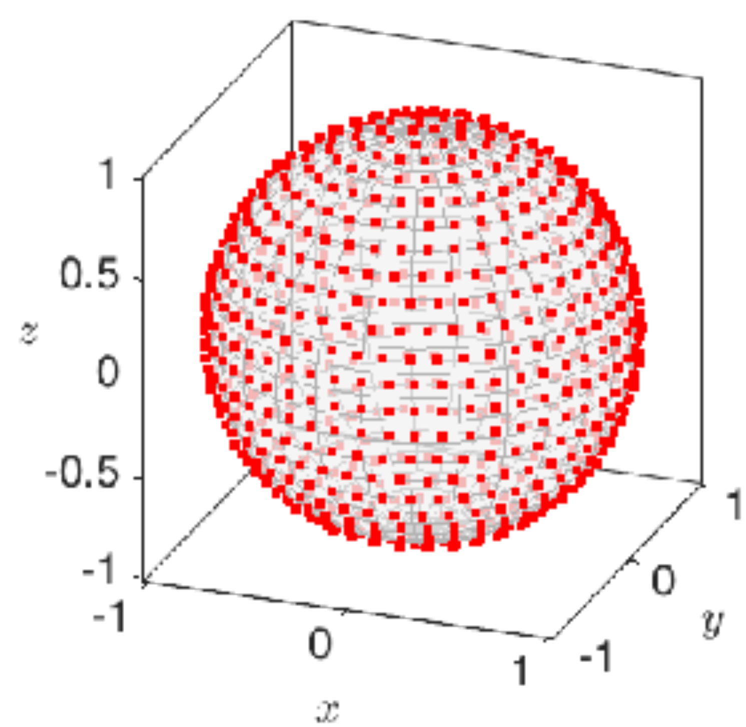
- Difficult as number of local optimizers increases drastically as N increases.
- How does $\mathcal{H}_{\text{min}}$ behave as $N \to \infty$?
- Finding optimal "equispaced" coverings of the sphere an old problem.

Smale's 7th problem

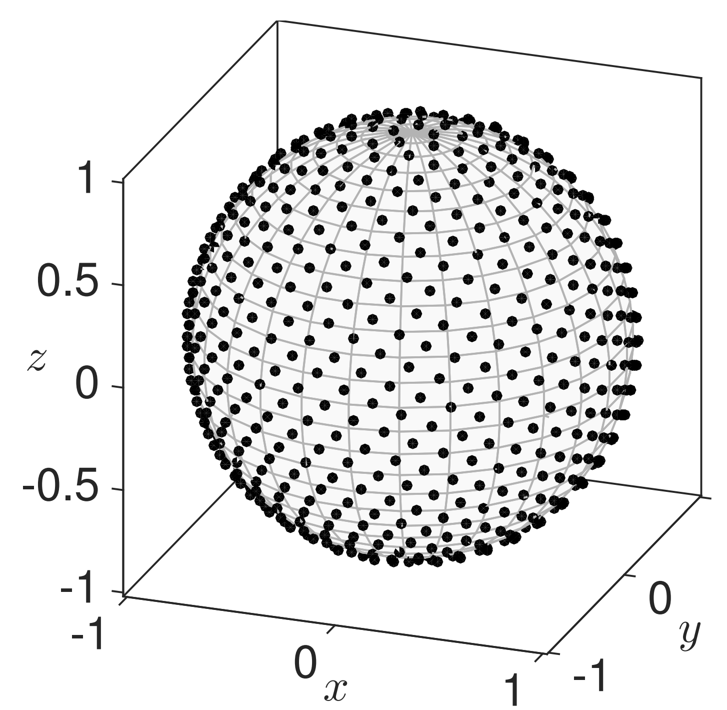
Three coverings of $N = 800$ points.



Uniform Random
Not Great



Equispaced in (θ, ϕ)
Better



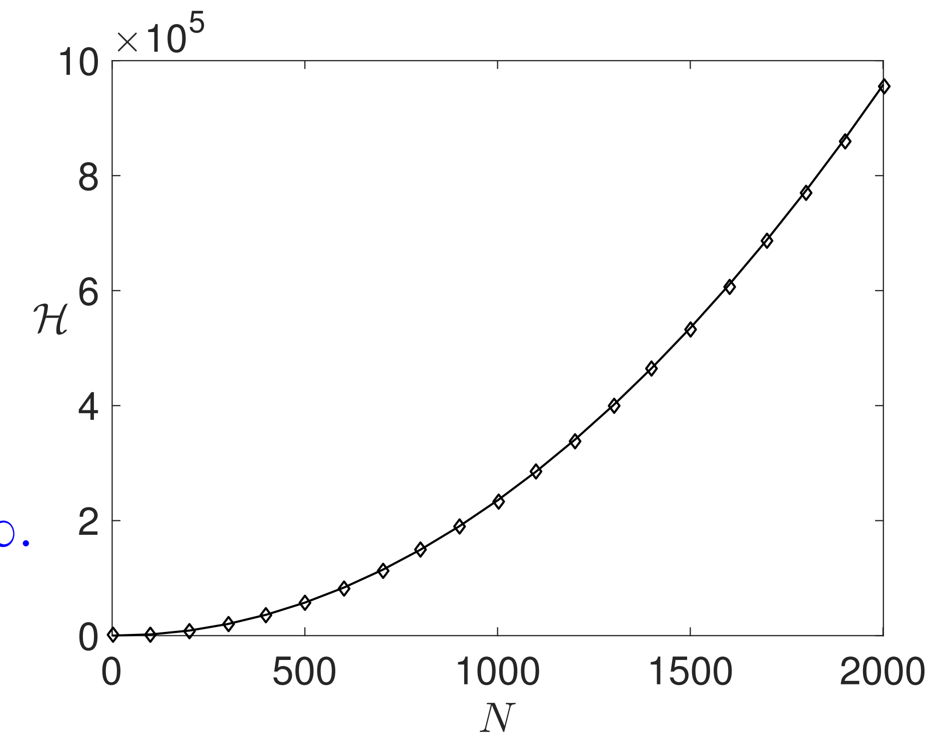
Fibonacci Spirals
Best (so far...)

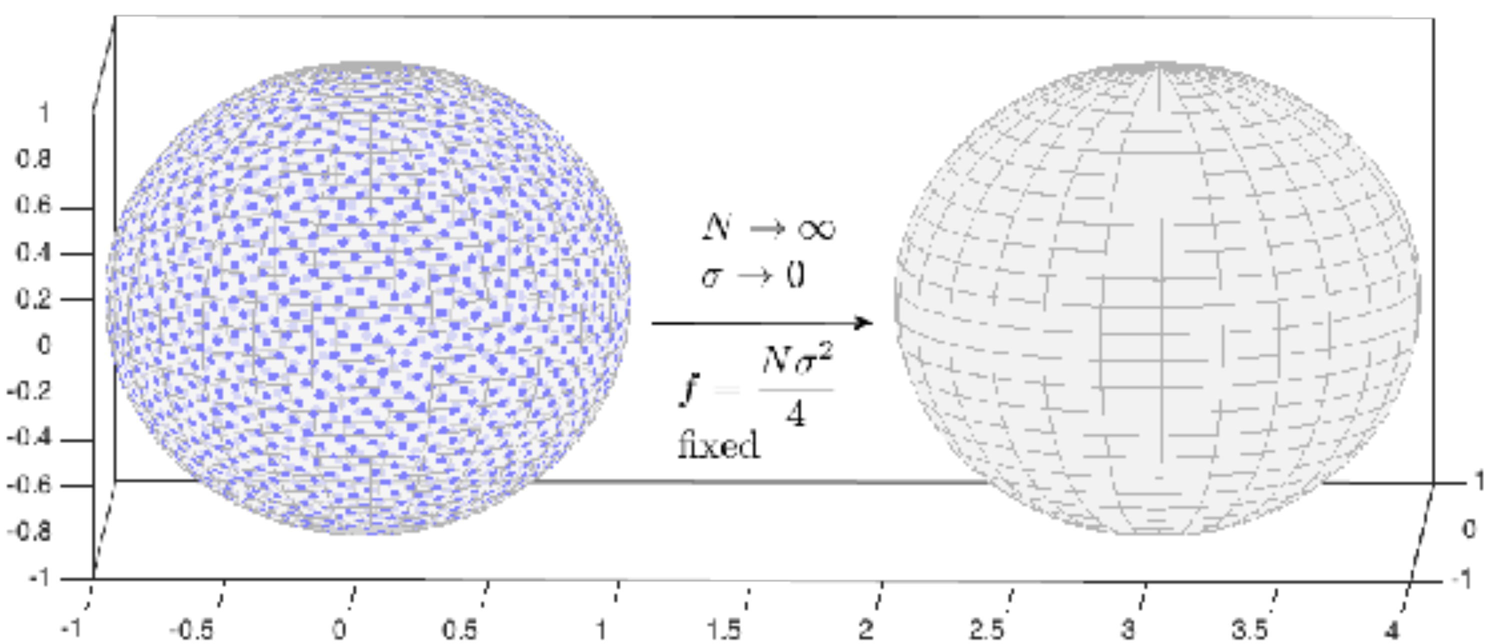
Boundary Homogenization Result

Assuming a uniform distribution on points on sphere.

$$\mathcal{H} = \sum_{j \neq k} g(|\mathbf{y}_j - \mathbf{y}_k|), \qquad g(d) = \frac{1}{d} + \frac{1}{2} \log\left[\frac{d}{2+d}\right]$$

$$\mathcal{H} = \frac{N^2}{4} - \frac{N^{\frac{3}{2}}}{2} + \frac{N}{8}\log N + \frac{N}{8} + \frac{N^{\frac{1}{2}}}{4} + \mathcal{O}(\log N) \quad N \to \infty.$$





$$u = 1, \quad \text{absorbing pores.}$$

$$\partial_n u = 0, \quad \text{reflecting surface.}$$

$$\partial_n u + \kappa\, u = 0, \ \text{all over.}$$

$$\boxed{\kappa = \frac{4f}{\pi\sigma}\left[1 - \frac{4}{\pi}\sqrt{f} + \frac{\sigma}{\pi}\log[\beta\sqrt{f}] + \frac{\sigma^2}{4\pi\sqrt{f}}\right]^{-1}}$$

Later: Numerical verification for realistic N (thousands).

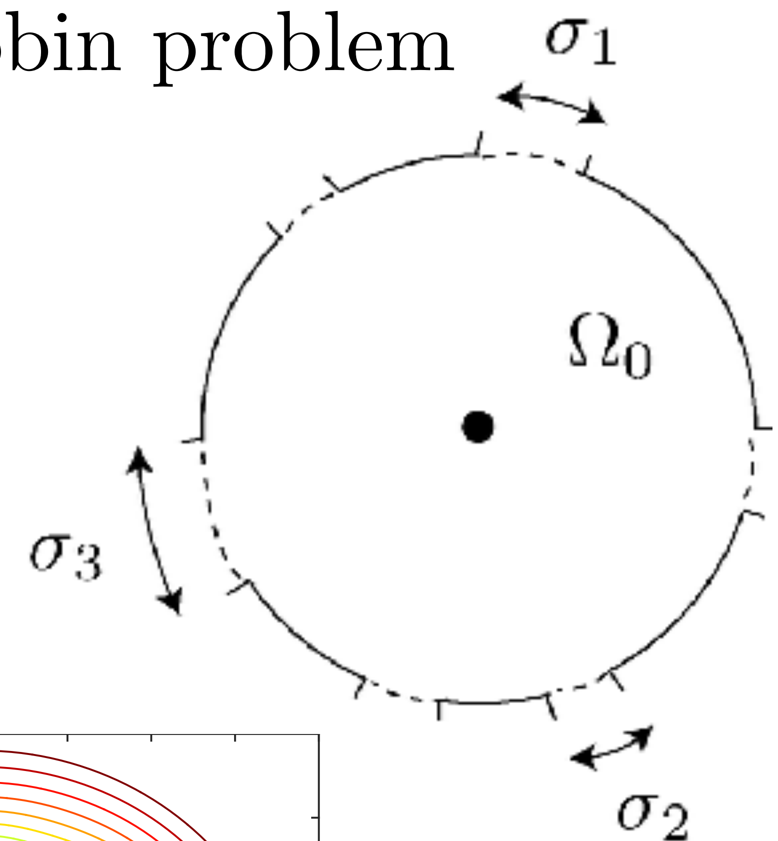
The Equivalent 2D problem.

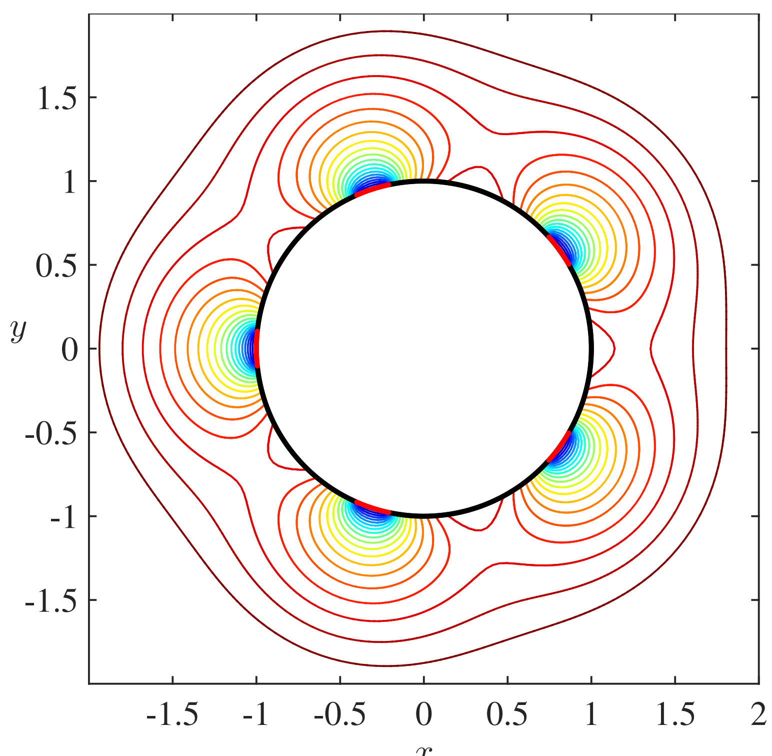
Fixed $\ell = \sigma N$, and $N \to \infty$, gives effective Robin problem

$$\begin{cases} \Delta v_h = 0, & |\mathbf{x}| > 1; \\ \sigma \partial_n v_h + \kappa(\ell)\, v_h = 0, & |\mathbf{x}| = 1 \end{cases}$$

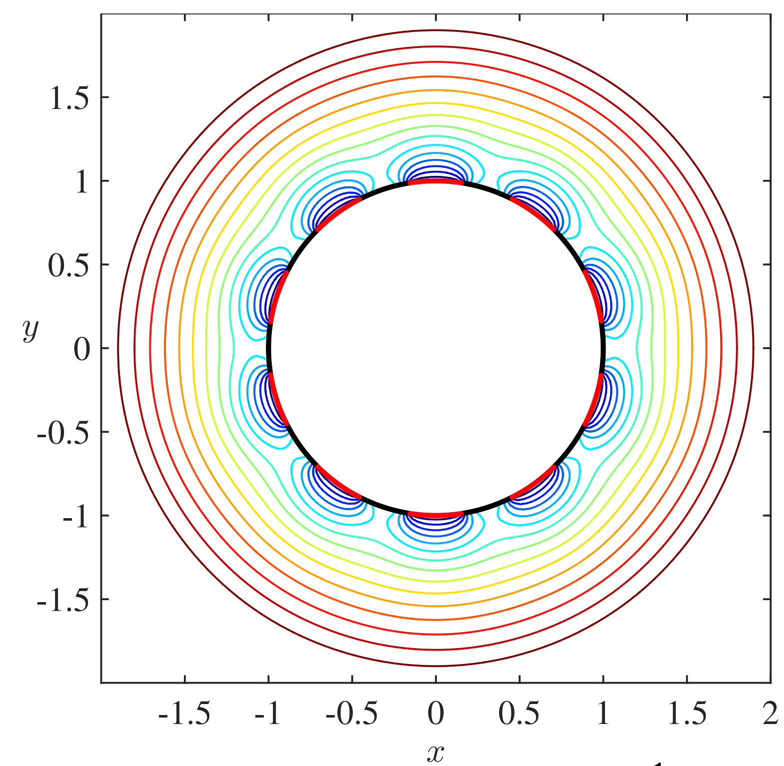
Window/Pore size

$$\kappa(\ell) = \frac{-\pi \ell}{\log \frac{\pi \ell}{2}}$$





$N = 5$ & $\ell = \dfrac{1}{6}$



$N = 10$ & $\ell = \dfrac{1}{2}$

Lindsay, Tzou, Kolokolnikov
PRE, 91(3), 2015.

Planar Homogenization Problem

For N pores of radius a:

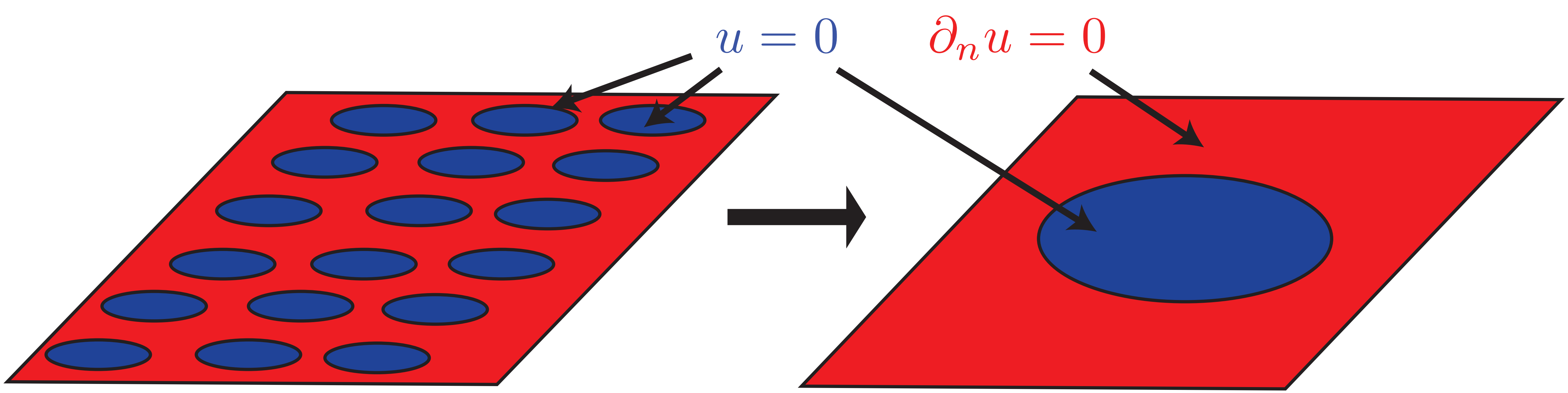
$$J_{\text{pore}} = 4aN - \frac{1}{\pi}\sum_{i\neq j}\frac{8a^2}{d_{ij}} + \frac{1}{\pi^2}\sum_{j\neq k}\sum_{i\neq j}\frac{16a^3}{d_{ij}d_{jk}}$$

Berg & Purcell 1977

Bernoff & Lindsay 2017

When the distance between pores, $d_{ij} \gg a$.

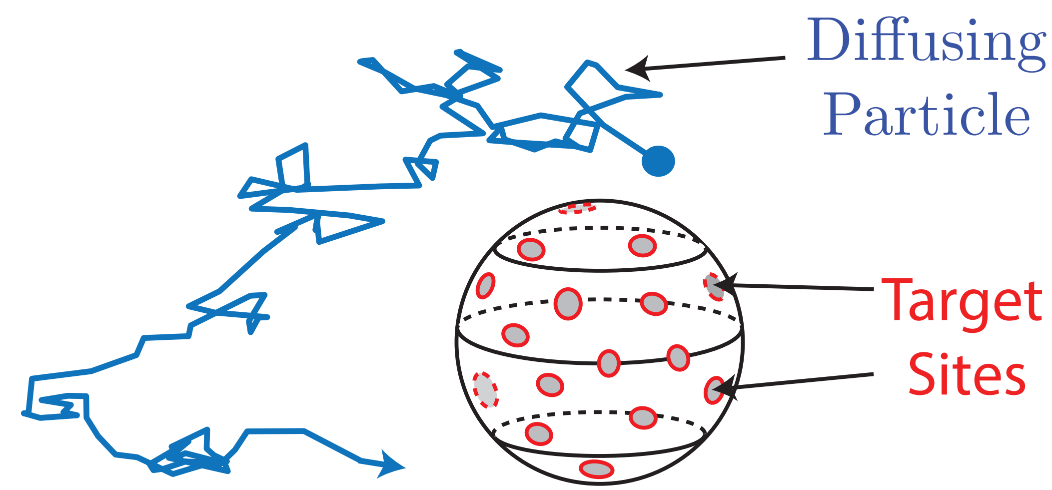
This tells us how to replace many pores with one.



Numerical Solution of the Capacitance Problem

$u(\mathbf{x})$ – The probability that particle is captured starting at $\mathbf{x} \in \mathbb{R}^3$.

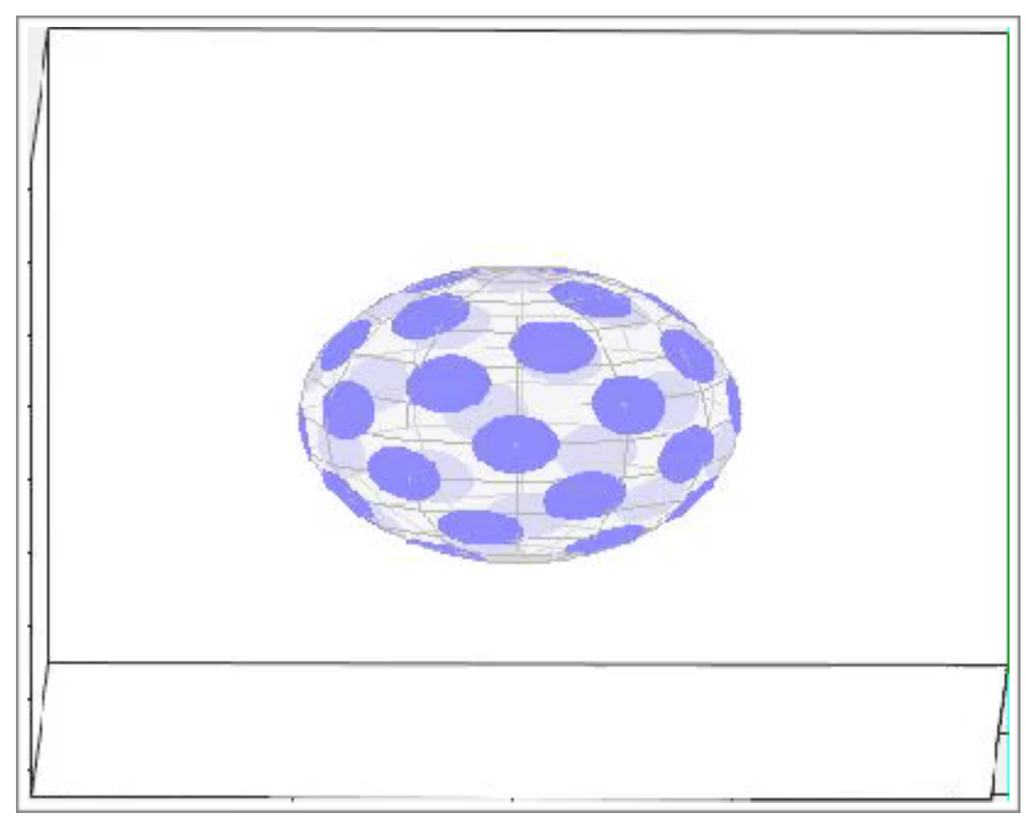
$$\begin{cases} \Delta u = 0, & \text{outside sphere.} \\ u = 1, & \text{on absorbing pores.} \\ \partial_n u = 0, & \text{on reflecting surface} \\ u(\mathbf{x}) = \dfrac{C}{|\mathbf{x}|} + \mathcal{O}\left(\dfrac{1}{|\mathbf{x}|^2}\right), & |\mathbf{x}| \to \infty \end{cases}$$



Popular Particle Based Solutions.

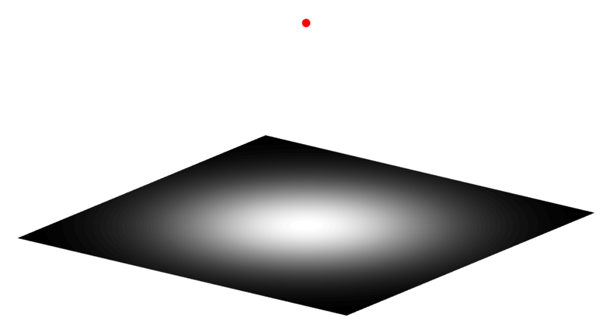
Particle at $\mathbf{X}(t)$ at time t:

1. Draw randoms $\mathbf{Z} \in N(0,1)^3$.
2. Iterate $\mathbf{X}(t+dt) = \mathbf{X}(t) + 8D\sqrt{dt}\,\mathbf{Z}$.
3. if absorbing surface encountered, then stop.
4. if $|\mathbf{X}(t+dt)| > R$, then particle escapes.
5. else repeat



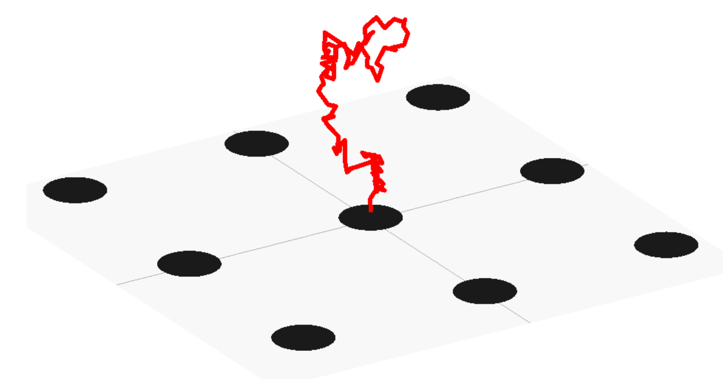
Kinetic Monte Carlo for periodic domain.

Step 1: Project Onto Surface

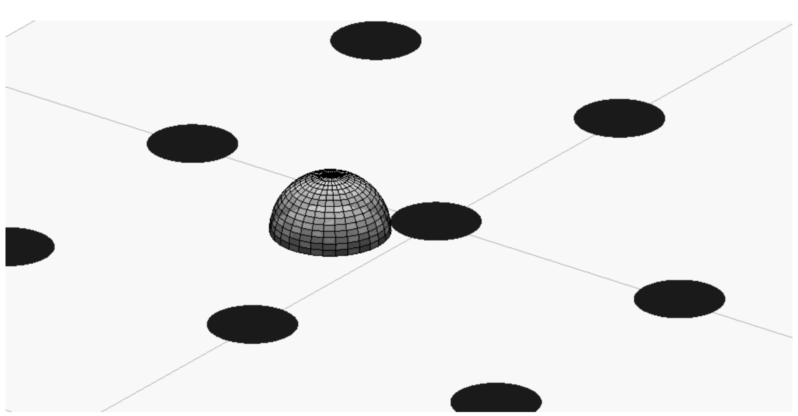


$$u = \frac{e^{\frac{-r^2-(z-z0)^2}{4Dt}} - e^{\frac{-r^2-(z+z0)^2}{4Dt}}}{8\pi^{3/2}(Dt)^{3/2}}$$

Step 2: Check if particle Has Been Absorbed

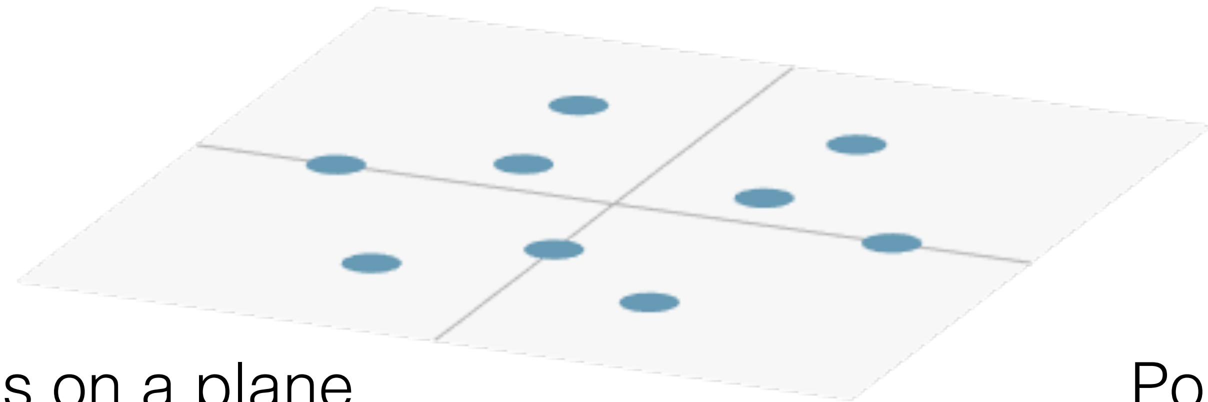


Step 3: Diffuse Particle Off Surface



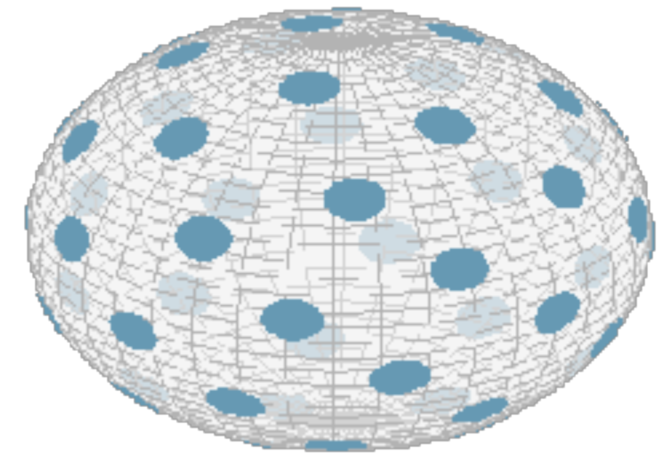
$$F(t) = 2\sqrt{\pi}t^{\frac{1}{2}} \sum_{n=1}^{\infty} e^{-(n+\frac{1}{2})^2 \frac{\pi^2}{t}}$$

Boundary Integral solution of the Capacitance Problem



Pores on a plane

Pores on a sphere



$$p(\mathbf{y}) = \int_{\mathbf{x}\in\partial\Omega_a} G(\mathbf{x};\mathbf{y})q(\mathbf{x})dS.$$

Surface Potential

Green's function

Surface Flux

Neumann to Dirichlet Map

Integral equation over the support of the pores.

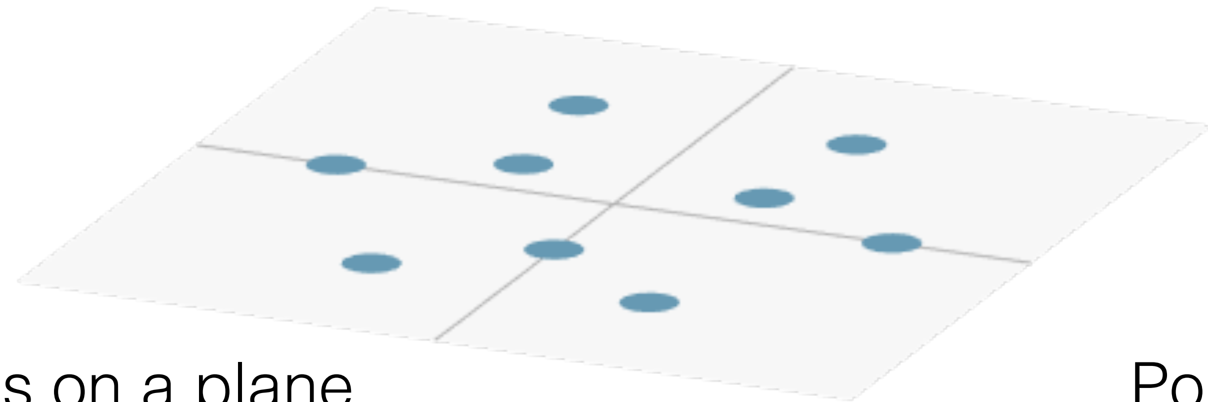
$$G(\mathbf{x};\mathbf{y}) = \frac{1}{2\pi}\left[\frac{1}{|\mathbf{x}-\mathbf{y}|} - \frac{1}{2}\log\left(\frac{1-\mathbf{x}\cdot\mathbf{y}+|\mathbf{x}-\mathbf{y}|}{|\mathbf{x}|-\mathbf{x}\cdot\mathbf{y}}\right)\right]$$

Sphere Case

$$G(\mathbf{x};\mathbf{y}) = \frac{1}{2\pi}\frac{1}{|\mathbf{x}-\mathbf{y}|}$$

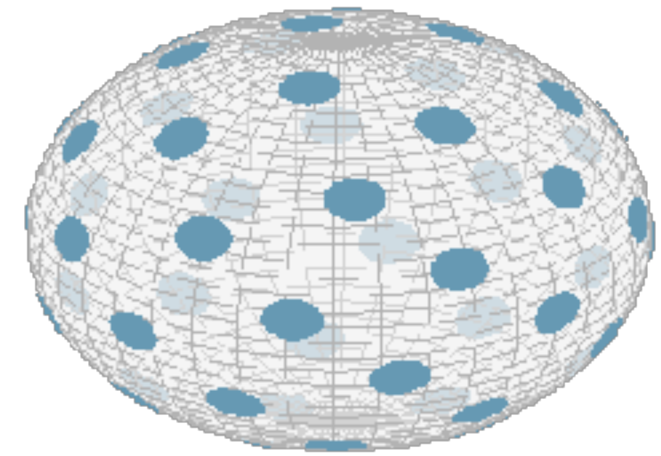
Planar Case

Boundary Integral solution of the Capacitance Problem



Pores on a plane

Pores on a sphere



$$p(\mathbf{y}) = \int_{\mathbf{x}\in\partial\Omega_a} G(\mathbf{x};\mathbf{y})q(\mathbf{x})dS.$$

Neumann to Dirichlet Map

Surface Potential

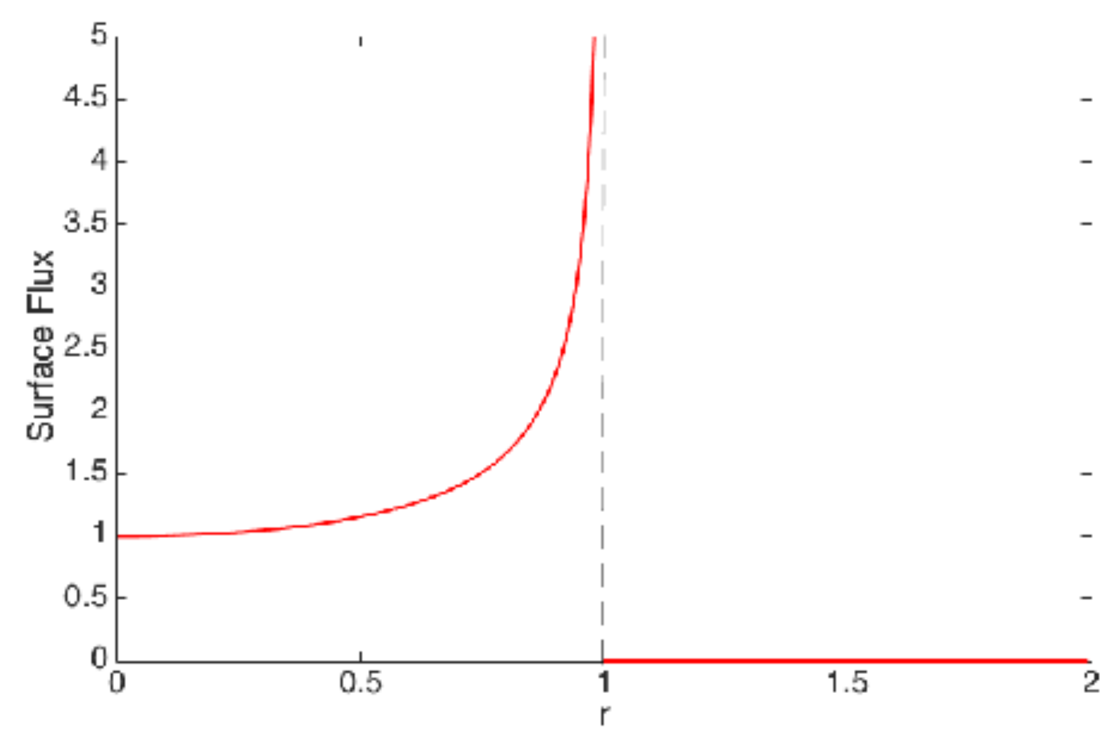
Green's function

Surface Flux

Integral equation over the support of the pores.

Main Difficulty:
Flux has an (integrable) singularity on the edge of each each pore.

Solution:
Expand surface potential and flux in basis which mimics the known singularity on boundary of pores.



The Zernike Polynomials.

At each pore, expand flux and potential:

Surface Potential

$$p(r,\theta) = \sum_{m,j} b_{m,j} Z_{m,j}(r,\theta),$$

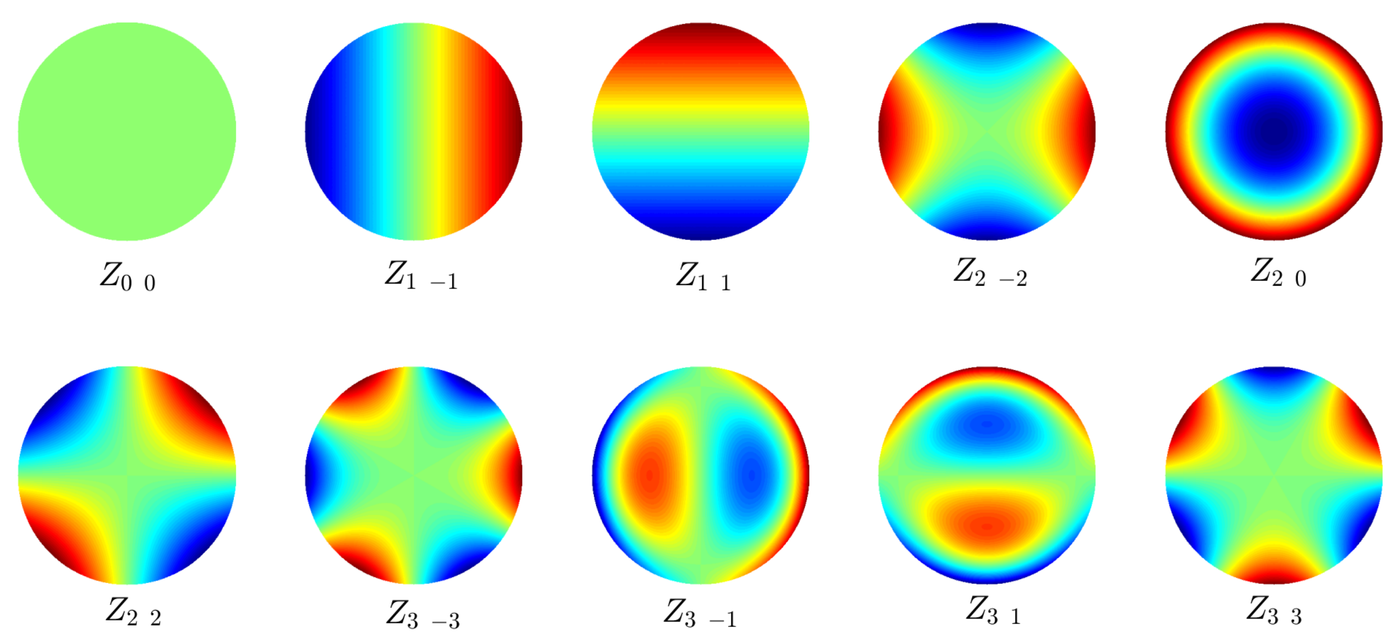
Surface Flux

$$q(r,\theta) = \sum_{m,j} \frac{c_{m,j}}{\sqrt{1-r^2}} Z_{m,j}(r,\theta), \quad \text{where} \quad Z_{mj}(\xi,t) = \begin{cases} P_{mj}(\xi)\sin(jt) & j>0, \\ P_{m0}(\xi) & j=0, \\ P_{m|j|}(\xi)\cos(jt) & j<0, \end{cases}$$

$$Z_{0\,0} = \frac{1}{\sqrt{2\pi}},$$

$$Z_{1\,-1} = \frac{2}{\sqrt{\pi}} r\cos(\theta), \quad Z_{1\,1} = \frac{2}{\sqrt{\pi}} r\sin(\theta),$$

$$Z_{2\,-2} = \sqrt{\frac{6}{\pi}} r^2\cos(2\theta), \quad Z_{2\,0} = \sqrt{\frac{3}{\pi}}\left(2r^2-1\right), \quad Z_{2\,2} = \sqrt{\frac{6}{\pi}} r^2\sin(2\theta).$$



Frits Zernike (1888-1966)

- Dutch Physicist.
- 1953 Physics Nobel Prize for phase-contrast microscope. Imaging translucent samples by change in light phase, not intensity.
- Zernike Polynomial derived in 1934 and form a complete basis for square integrable functions with circular support.
- Used extensively in beam optics for analyzing waveforms entering through circular apertures.
- Quantifying and correcting ocular aberrations (e.g. astigmatism) in optometry.

Boundary Integral solution Procedure

$$p(\mathbf{y}) = \int_{\mathbf{x}\in\partial\Omega_a} G(\mathbf{x};\mathbf{y})q(\mathbf{x})dS.$$

Surface Potential

Green's function

Surface Flux

Neumann to Dirichlet Map

1. Expand flux and potential with M Zernike modes at the N pores.
2. Gives N*(M+1)*(M+2)/2 unknowns for the system.
3. Form dense system for unknowns by projecting the flux onto Zernike modes.
4. Solve linear system and calculate the flux $J = \int_{\partial\Omega_a} q(\mathbf{x})dS.$

<u>Advantages</u>

- Spectral accuracy.
- Runs very quickly for low modes.

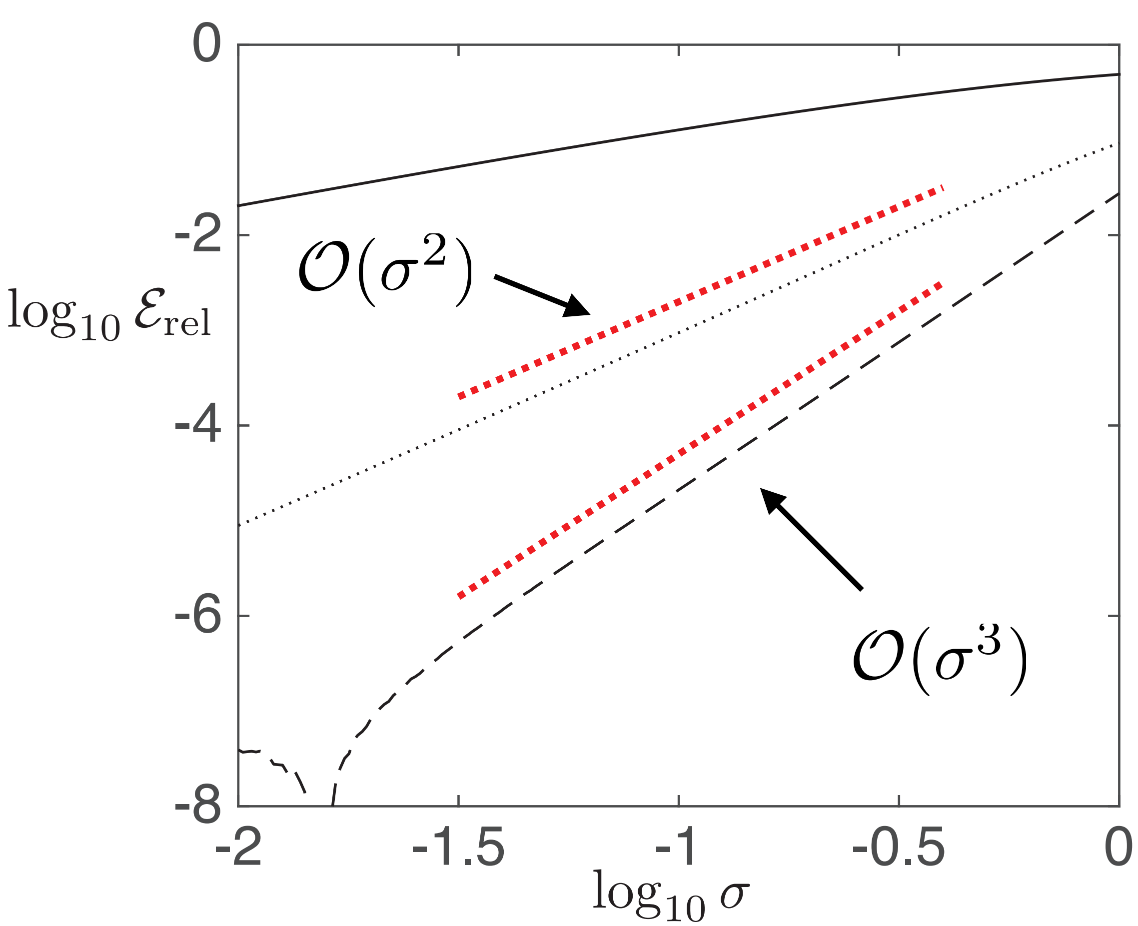
<u>Disadvantages</u>

- Relies on explicit Green's Function.
- Circular pore geometry assumed.

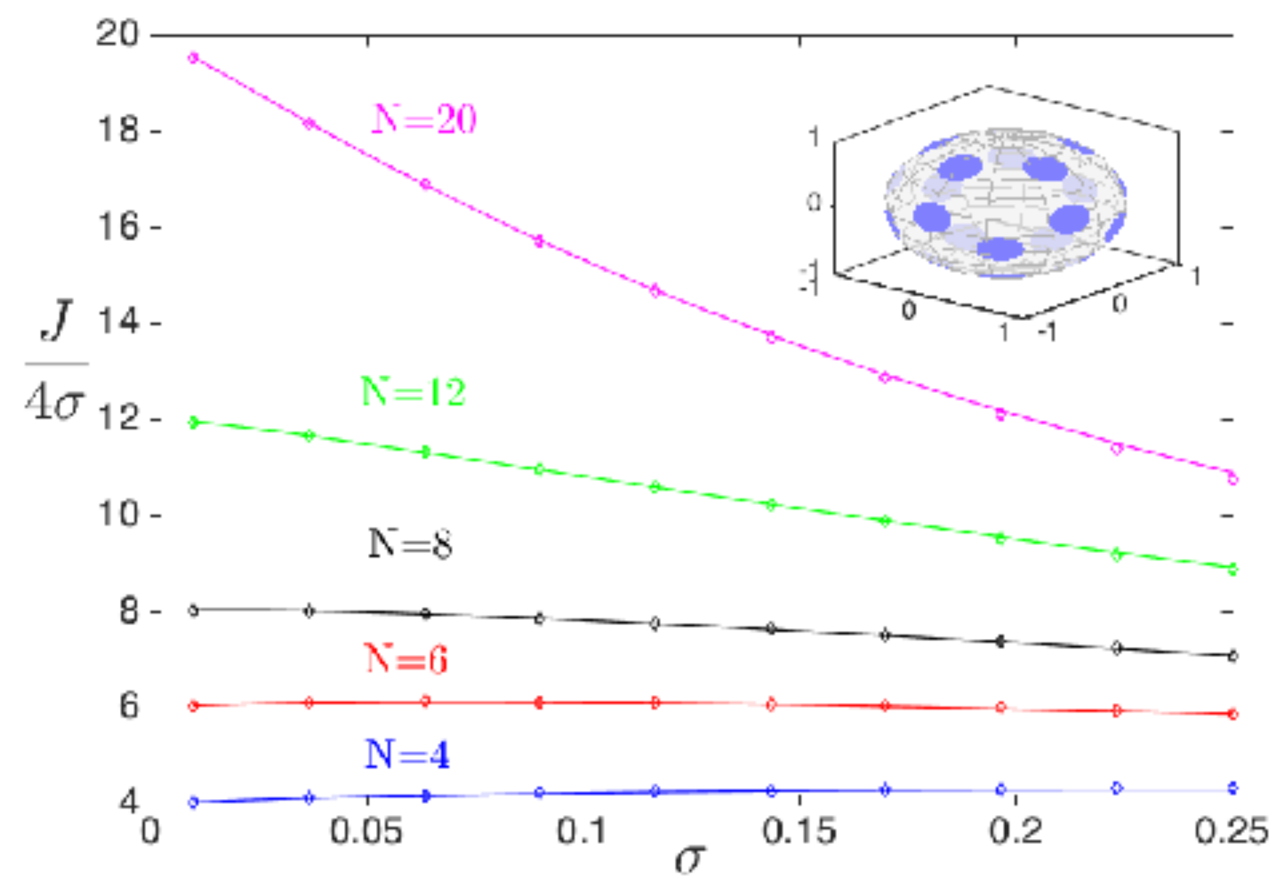
Numerical Results Sphere:

<u>N=1:</u> $$J = 4D\sigma\left[1 + \frac{\sigma}{\pi}\left(\log 2\sigma - \frac{3}{2}\right) - \frac{\sigma^2}{\pi^2}\left(\frac{\pi^2+21}{36}\right) + \cdots\right], \quad \text{as} \quad \sigma \to 0.$$

<u>N>1:</u> $$J = 4DN\sigma\left[1 + \frac{\sigma}{\pi}\log 2\sigma + \frac{\sigma}{\pi}\left(-\frac{3}{2} + \frac{2}{N}\mathcal{H}(\mathbf{y}_1, \ldots, \mathbf{y}_N)\right)\right]^{-1}$$



<u>Relative Error - One Pore</u>

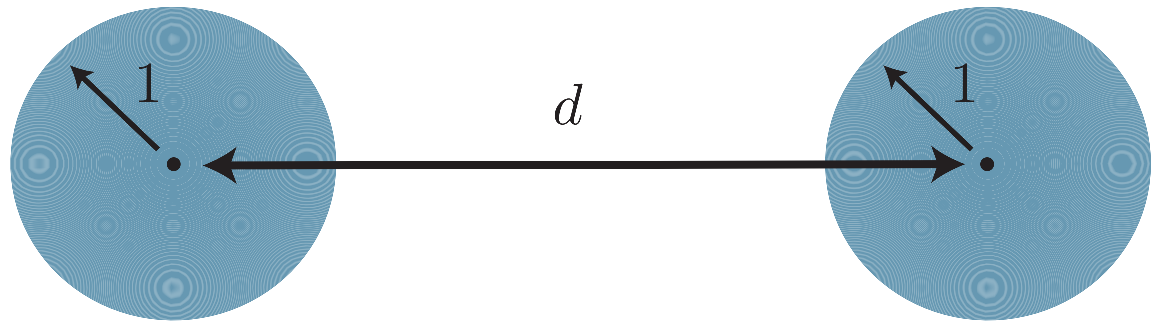


<u>Agreement - Platonic Solids</u>

Relative error resolved to 1 part in 10^8!

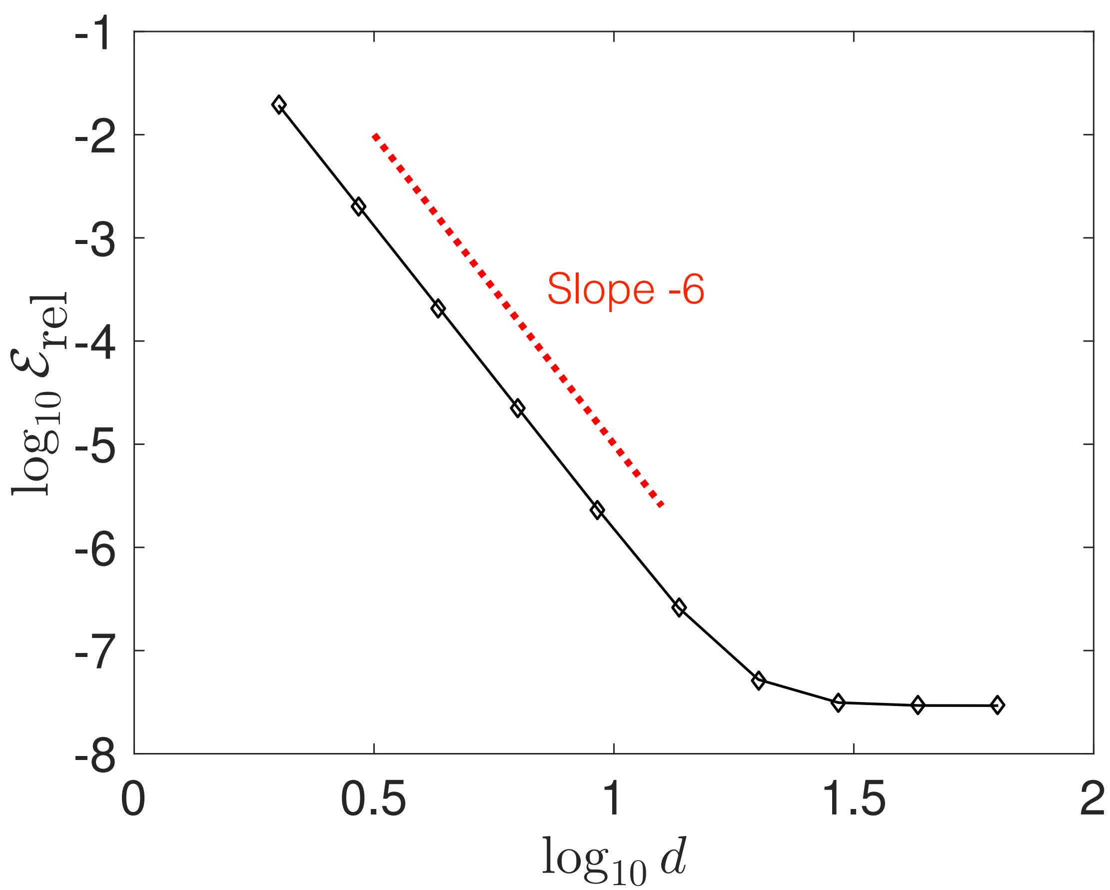
Accuracy as function of pore separation.

Two Planar Pores

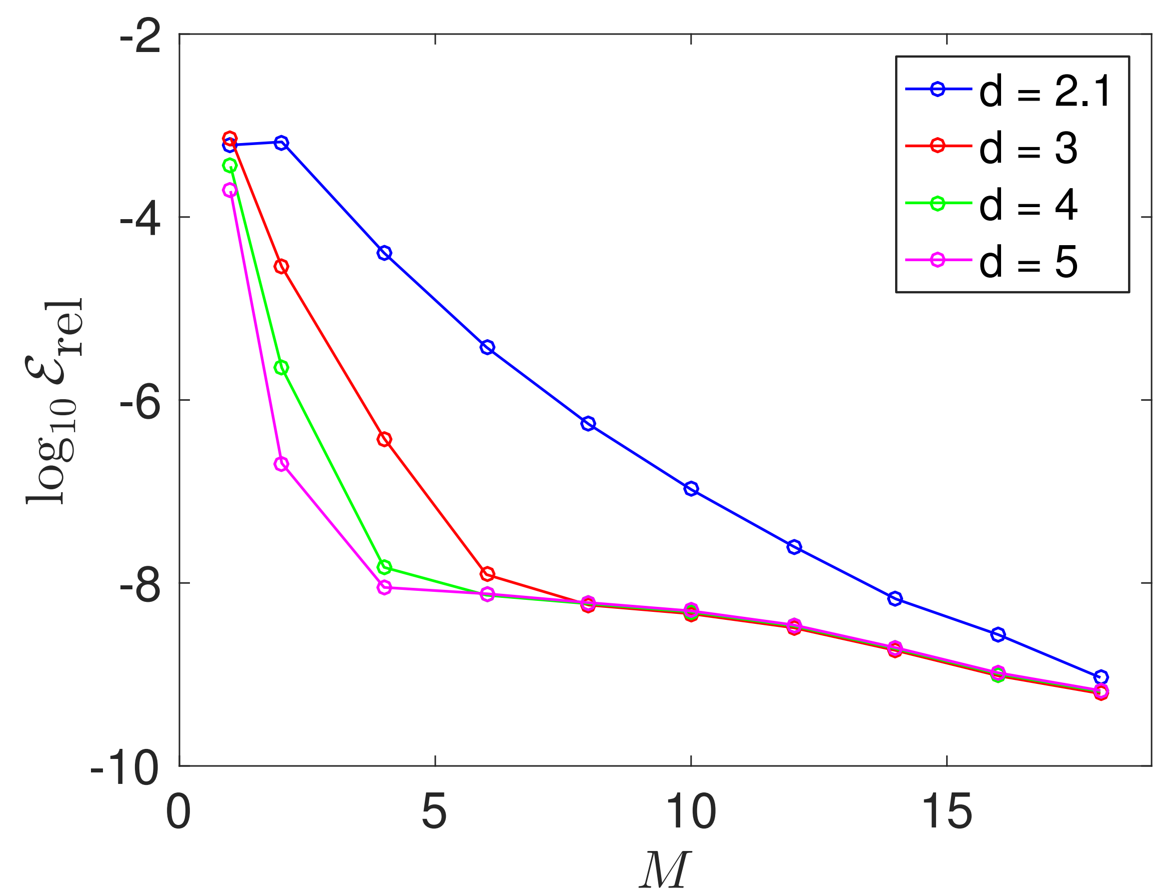


Ref: Strieder,
J. Chem, Phys, 2012.

$$J = 8D\left[1 - \frac{2}{\pi d} + \frac{4}{\pi^2 d^2} - \frac{2(12+\pi^2)}{3\pi^3 d^3} + \frac{16(3+\pi^2)}{3\pi^4 d^4} - \frac{4(120+70\pi^2+3\pi^4)}{15\pi^5 d^5}\right] + \mathcal{O}(d^{-6}), \quad d \to \infty.$$



Convergence of numerics with exact solution

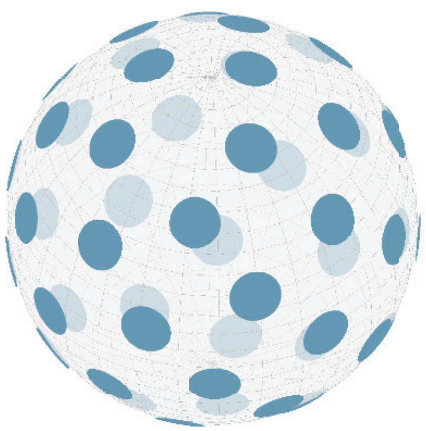


Zernike Modes Taken

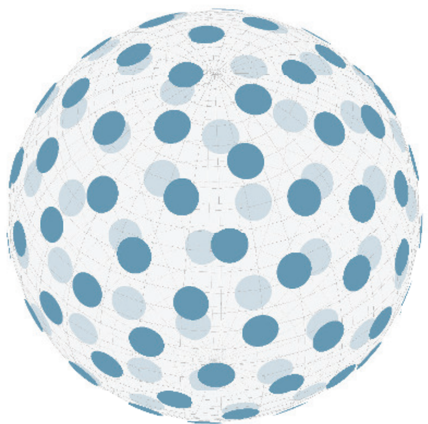
Validation of the homogenized sphere condition.

$$J_h = 4\pi D \left[1 + \frac{\pi\sigma}{4f}\left(1 - \frac{4}{\pi}\sqrt{f} + \frac{f}{\pi}\log(4e^{-1}\sqrt{f}) + \frac{\sigma^2}{2\pi\sqrt{f}}\right)\right]^{-1}.$$

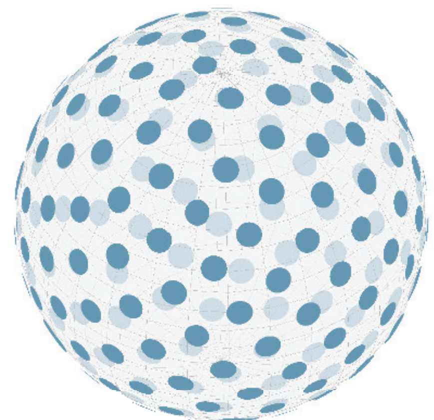
Fibonacci Spiral Points and 2% absorbing fraction.



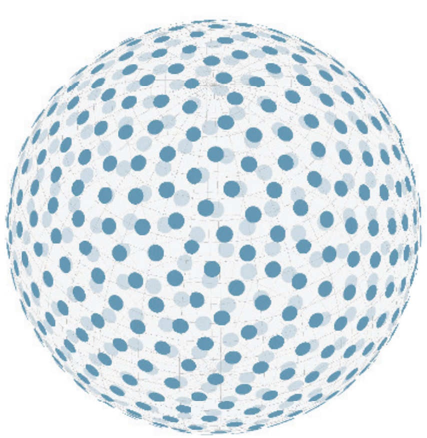
$N = 51$



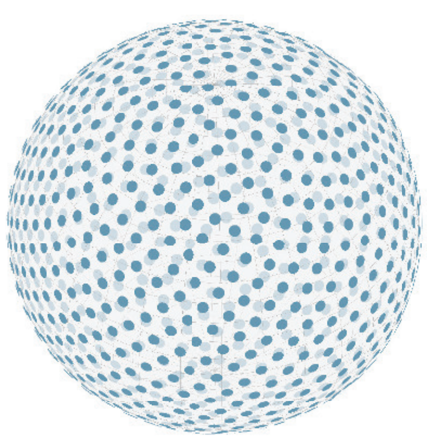
$N = 101$



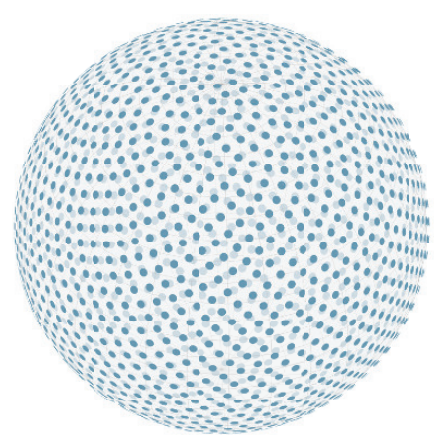
$N = 201$



$N = 501$



$N = 1001$

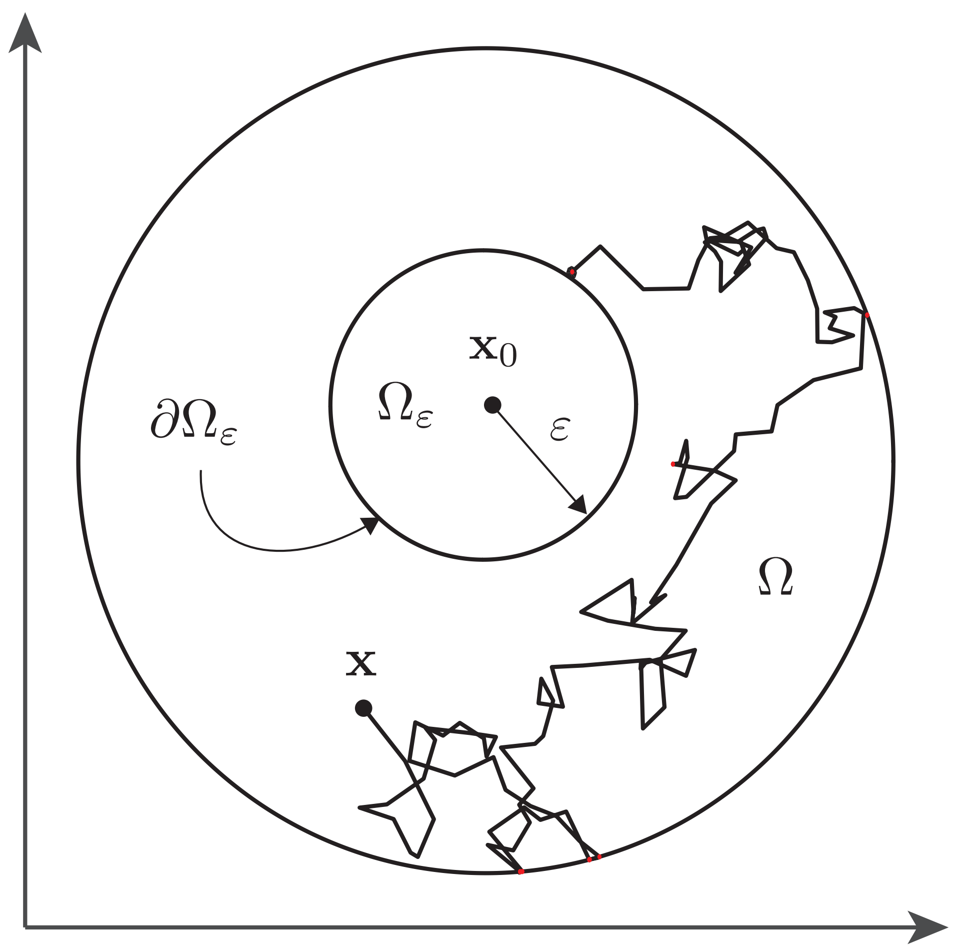


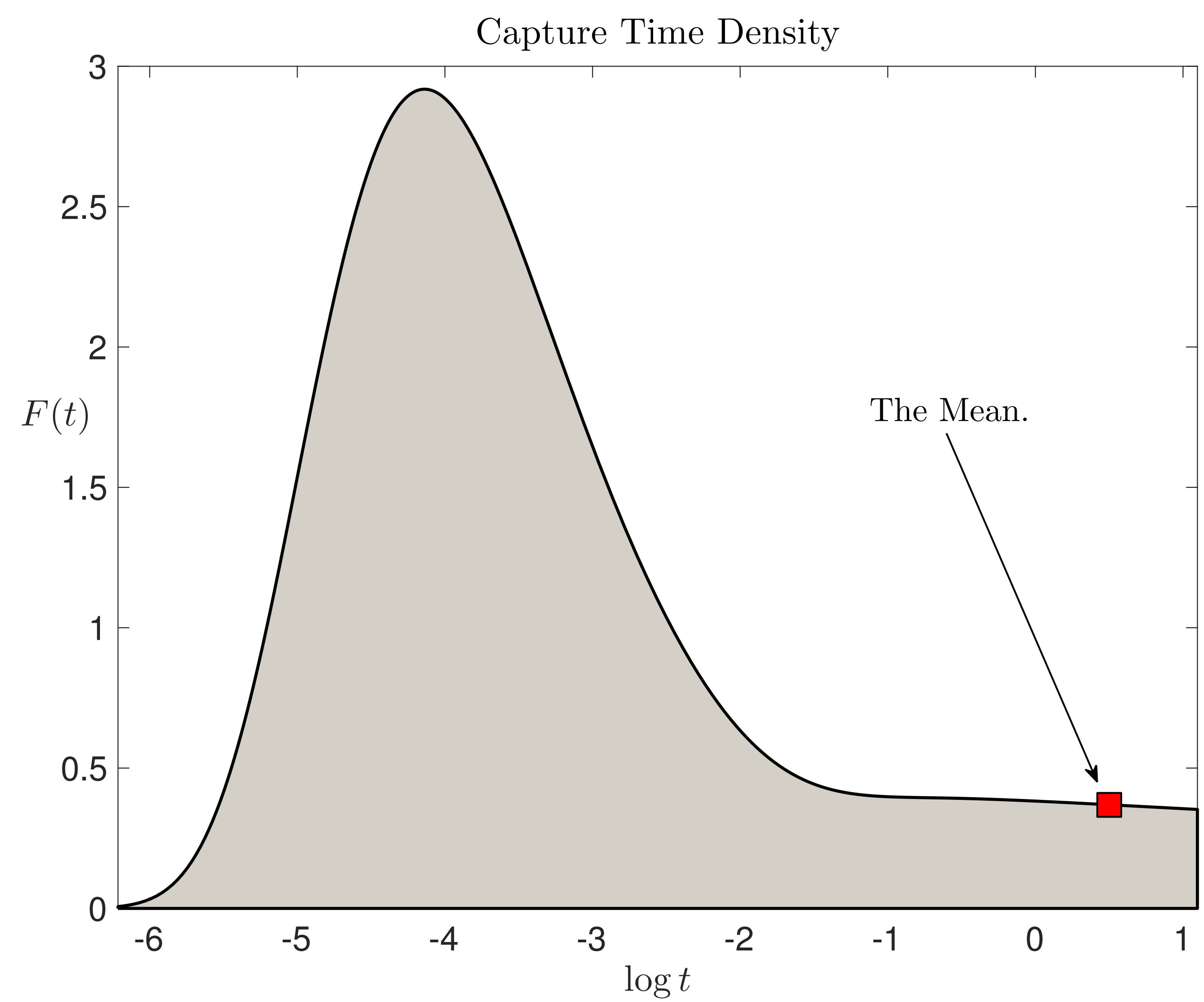
$N = 2001$

N	$\mathcal{E}_{\text{rel}}$
51	1.02%
101	0.90%
201	0.76%
501	0.58%
1001	0.37%
2001	0.34%

Homogenized Formula accurately predicts the flux to the target in biologically realistic examples!!

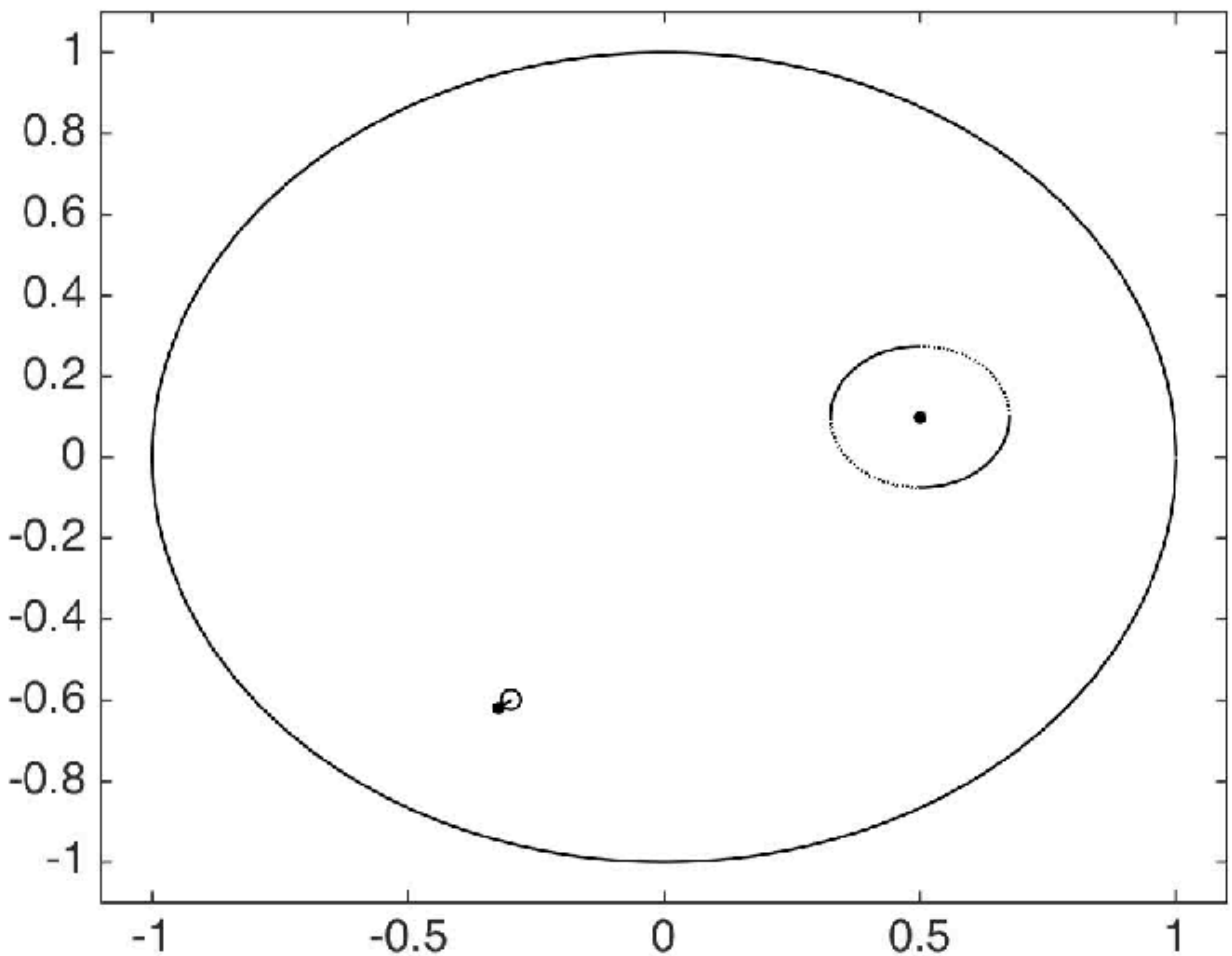
Ongoing Work: The full First Passage Time (FPT) distribution.





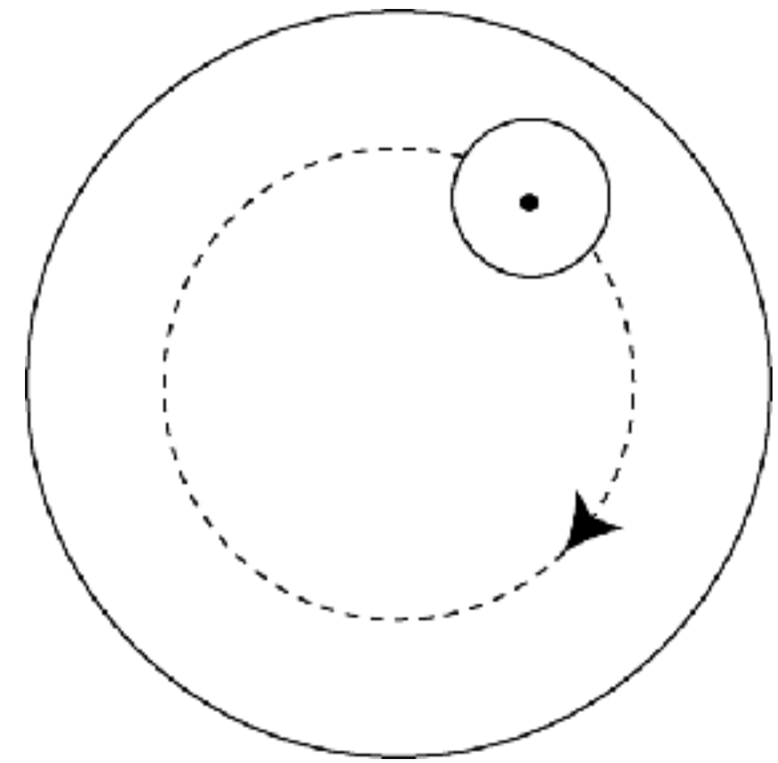
The MFPT overestimates typical capture times.
Important to get the full capture time distribution

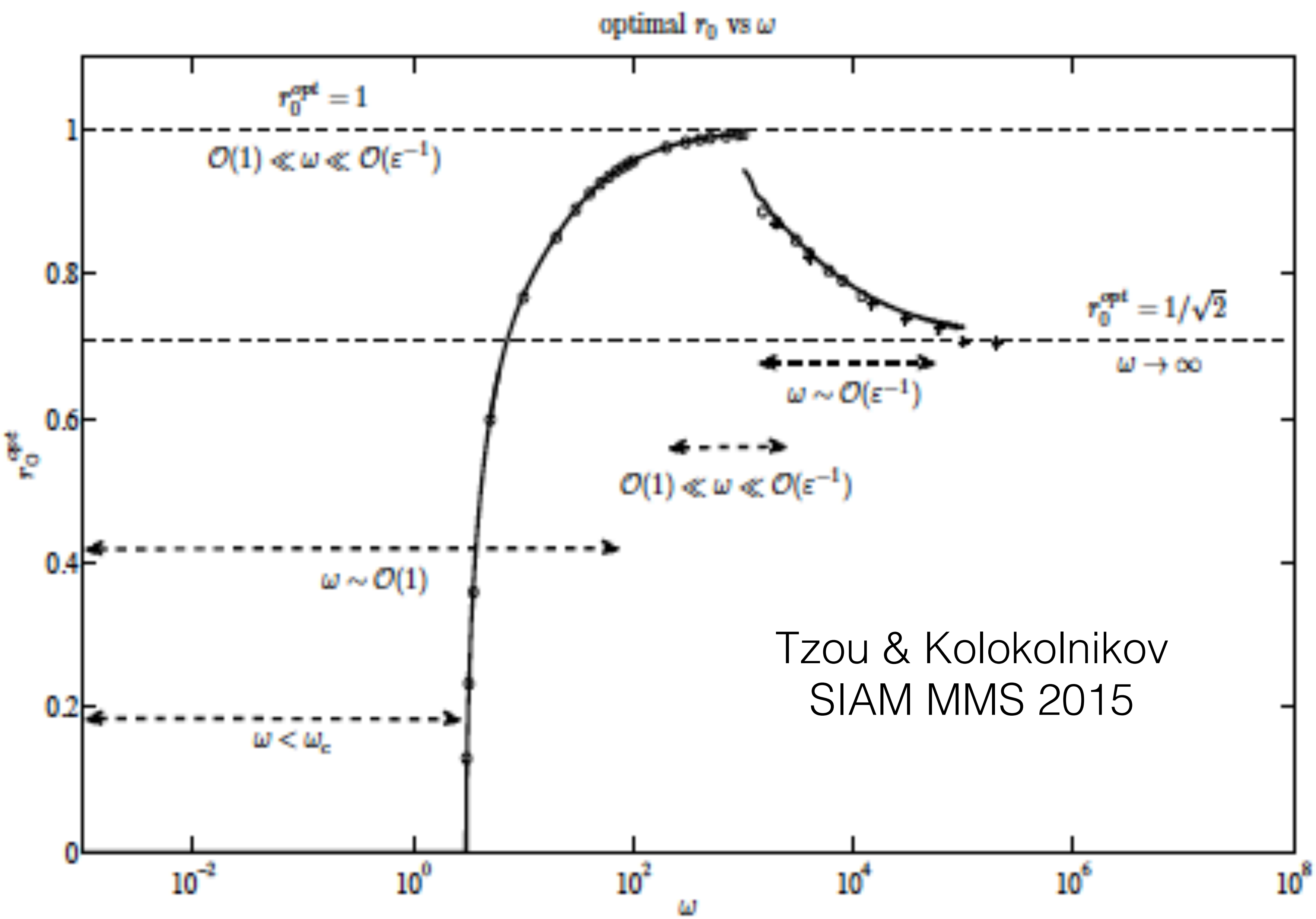
Ongoing Work II: Formulation of Capture problems in a dynamical setting.



Rotating Trap

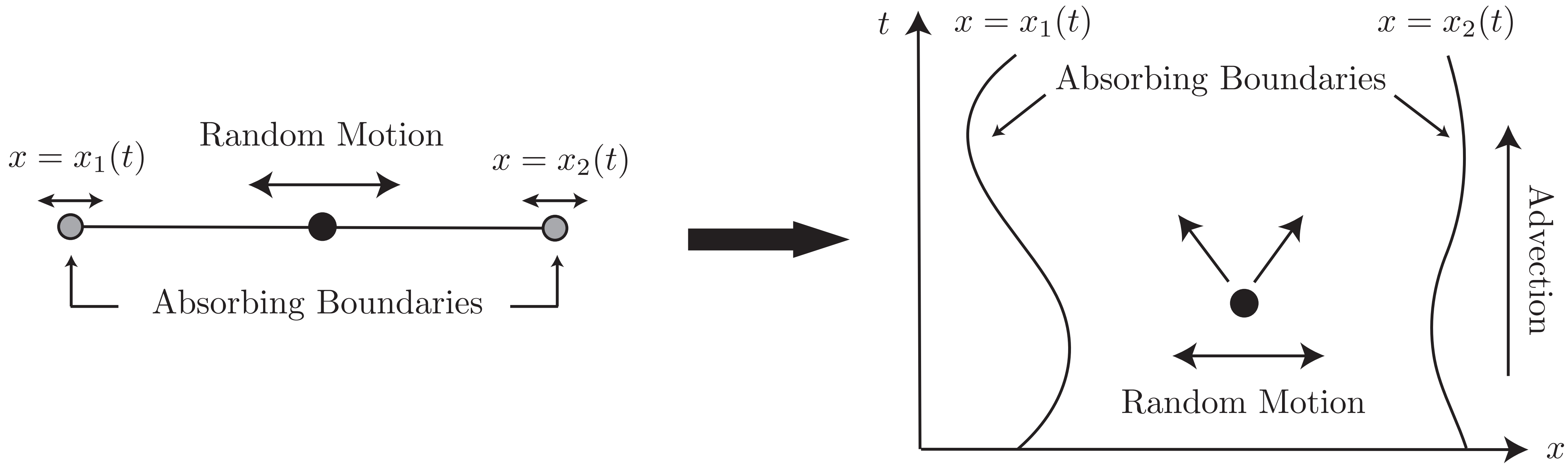
$$\begin{cases} D\Big[\dfrac{\partial^2 w}{\partial r^2} + \dfrac{1}{r}\dfrac{\partial w}{\partial r} + \dfrac{1}{r^2}\dfrac{\partial^2 w}{\partial \theta^2}\Big] + \omega\dfrac{\partial w}{\partial \theta} = -1, \qquad r < 1; \\ \partial_r w = 0, \quad r = 1; \qquad w = 0, \quad \text{on } \Gamma_a \qquad \partial_\nu w = 0, \quad \text{on } \Gamma_r \end{cases}$$

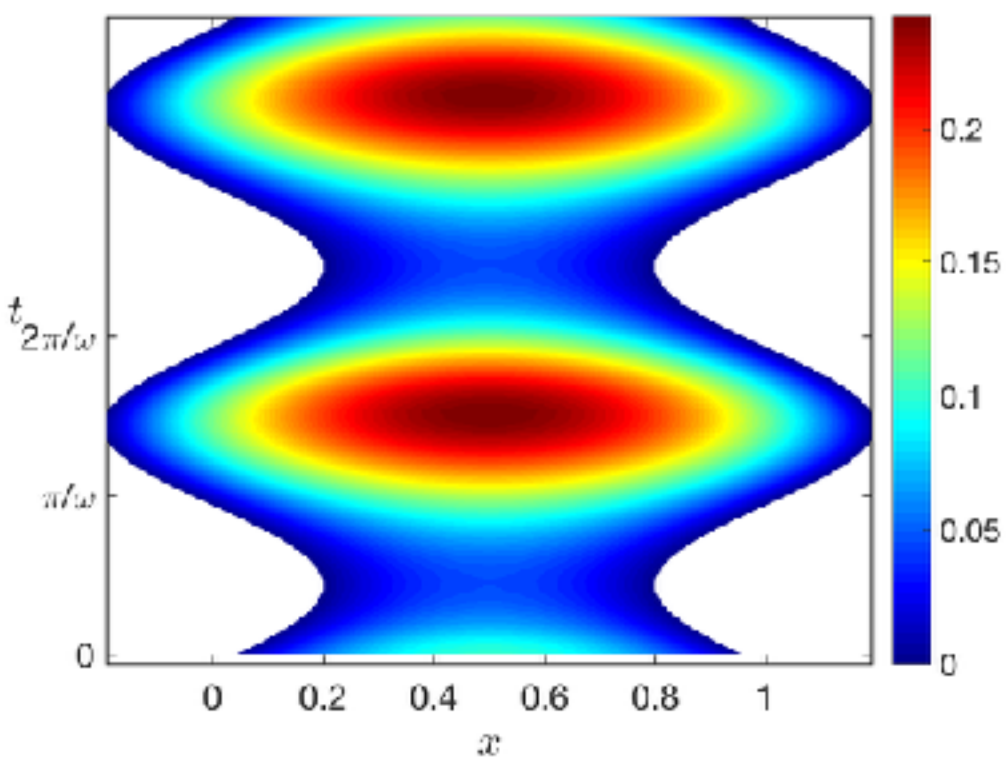




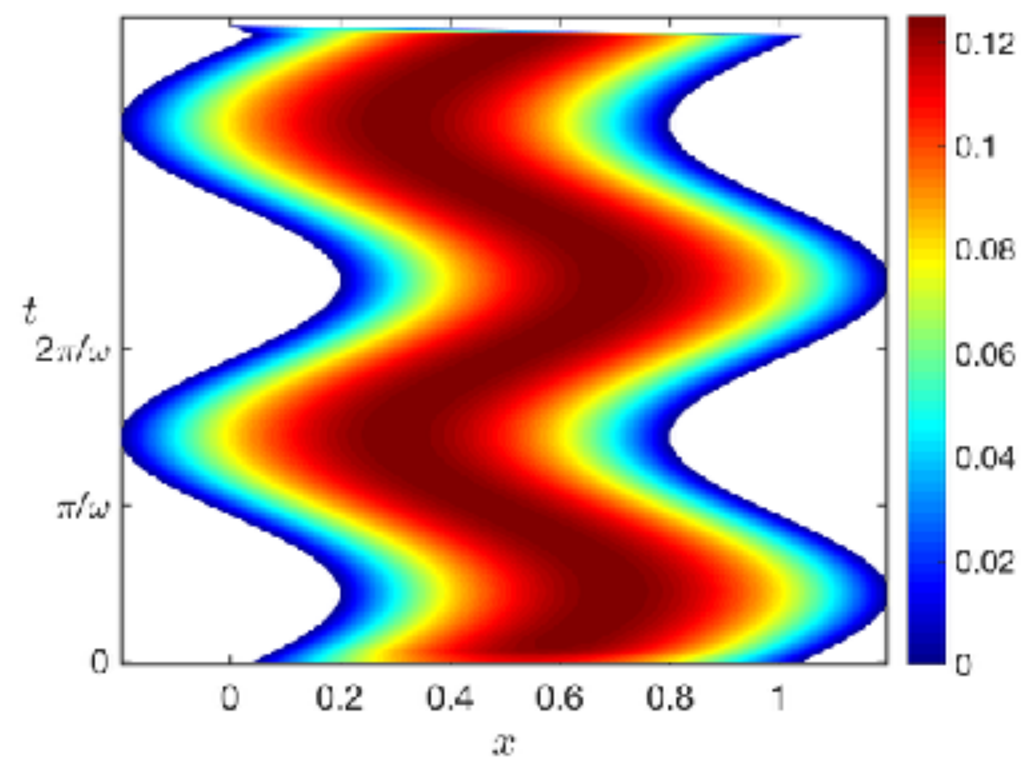
Optimal radius for a given speed of rotation.

Ongoing Work II: Trap Cooperation Strategies I





Out-of Phase



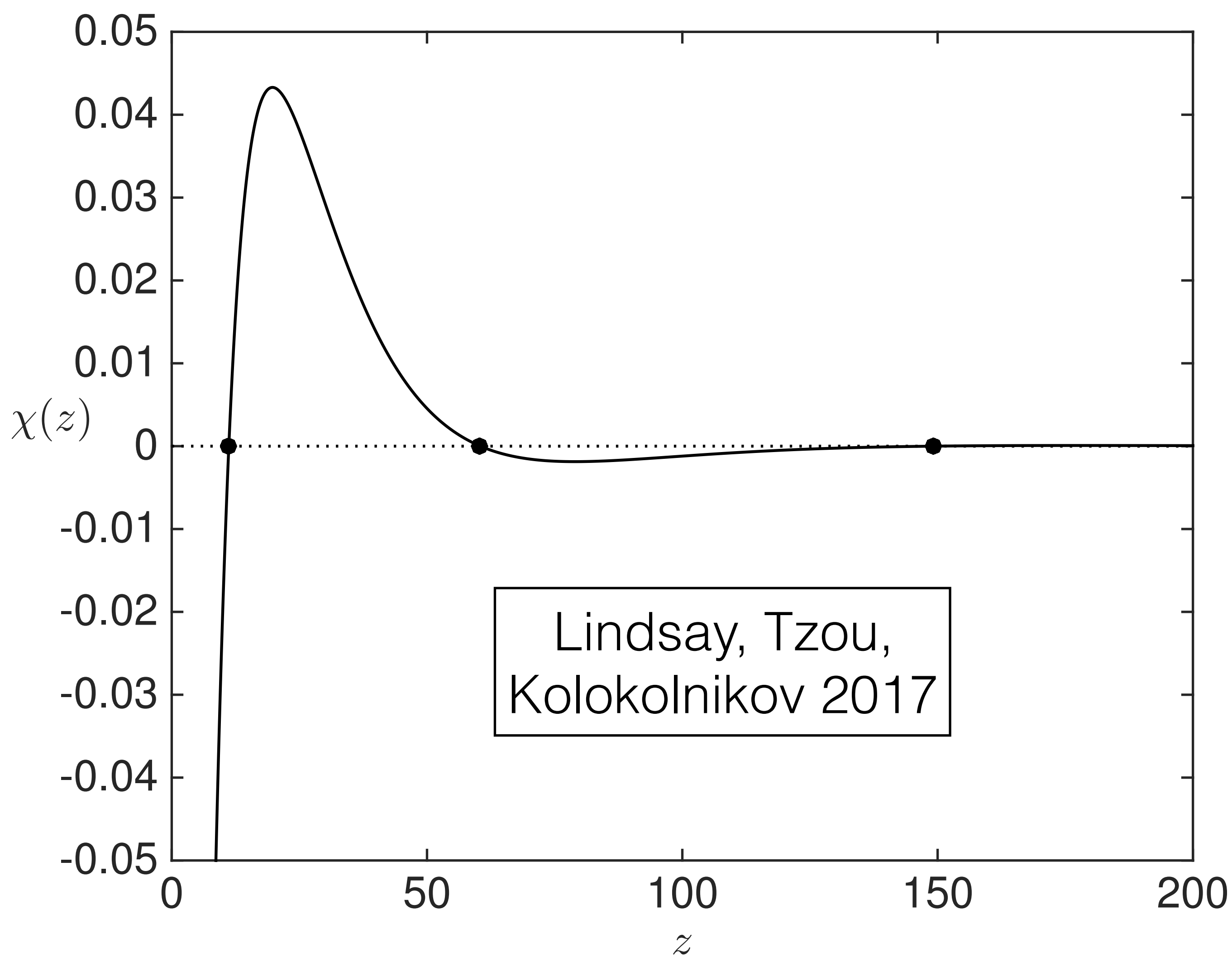
In Phase

Ongoing Work: Trap Cooperation Strategies II

ω - common trap frequency

$$\chi(z) = \frac{\cosh\sqrt{\frac{z}{2}}\sin\sqrt{\frac{z}{2}} + \sinh\sqrt{\frac{z}{2}}\cos\sqrt{\frac{z}{2}}}{\cos\sqrt{2z} - \cosh\sqrt{2z}}.$$

Trap interaction strength.



In phase minimizes MFPT when

$$\chi(\omega) > 0$$

Out-of-phase minimizes MFPT when

$$\chi(\omega) < 0$$

Conclusions.

1. Showed explicitly how pore/receptor clustering influences diffusive sensing rates, resolving a long standing problem postulated by Berg & Purcell.

2. Derivation of macro scale capture laws from microscale clustering pattern.

3. These averaged features can be used to give insight and reduce challenging computational aspects of these multi scale problems.

4. Developed a precision numerical tools for studying receptor clustering.

Future Work.

1. Formulate and solve problems for capture in more general dynamic environments. (e.g. **moving domains**, **transient** and **growing pores**).

2. On top of this, get the **full distribution of capture times**! Is the homogenized boundary condition verified here valid for the time dependent problem?

Thank you for your attention!!

References:

- Lindsay & Bernoff, *Numerical approximation of diffusive capture rates by planar and spherical surfaces with absorbing pores,* Submitted SIAM J. Applied Math. 2017.

- Lindsay, Tzou, Kolokolnikov, *Optimization of first passage times by multiple cooperating mobile traps*, To Appear, SIAM MMS (2017).

- Lindsay, Bernoff, Ward, *First passage statistics for the capture of a Brownian particle by a structured spherical target with multiple surface traps*, SIAM MMS, **15**(1), pp. 74-109 (2017).

- Lindsay, Spoonmore, Tzou, *Hybrid Asymptotic-Numerical Approach for estimating first passage densities of the two-dimensional narrow capture problem*, PRE **94** 042418, (2016)

- Lindsay, Tzou, Kolokolnikov, *Narrow escape problem with a mixed trap and the effect of orientation.* PRE, Vol. 91, No. 3, (2015).

Collaborators:

Andrew Bernoff (Harvey Mudd)
Theo Kolokolnikov (Dalhousie)
Daniel Scmidt (Harvey Mudd)
Ryan Spoonmore (Notre Dame)
Justin Tzou, (UBC)
Michael Ward (UBC)

Preprints at: www.nd.edu/~alindsa1

Support:

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