Modeling Diffusion and Capture.

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NIST,

Pollen grains on the stamen of a flower.

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Support:

NSF DMS - 1516753
Diffusion in heterogeneous and dynamic environments.

\[ dX_t = DdW_t; \]
\[ < X >^2 = D < dt > \]
\[ \text{square mean displacement} = D \times \text{time} \]

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?
The cell nucleus - genetic material passes from the interior/exterior through small pores called Nuclear Pore Complexes (NPCs).

- Nucleus ~10% of cell volume.
- Roughly N = 2000 surface pores which occupy 2% of the surface area.

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

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?
• 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

\[ p(x, t) \] — probability that particle starting at \( x = (x, y) \) is free at time \( t \)

\[
x_{n-1} \quad x_n \quad x_{n+1}
\]

\[
ę = y_{n+1} \quad x_n = n\Delta x
\]

\[
y = y_n \quad y_n = n\Delta y
\]

\[
y = y_{n-1}
\]

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

\[
\Delta x = \Delta y \to 0 \quad \frac{\Delta x^2}{4\Delta t} = D
\]

\[
\frac{\partial p}{\partial t} = D \Delta p \equiv D \left[ \frac{\partial^2 p}{\partial x^2} + \frac{\partial^2 p}{\partial y^2} \right]
\]

\[
p(x, 0) = \delta(x - x_0)
\]
The probability of absorption II

In N dimensional free space:

$$p(x, t) = \left( \frac{1}{\sqrt{4\pi Dt}} \right)^N e^{-|x-x_0|/(4Dt)}$$

Diffusion Kernel

Reflecting (or Neumann).

\[ \nabla p \cdot \hat{n} = 0 \text{ on } \partial \Omega \]

Absorbing (or Dirichlet).

\[ p = 0 \text{ on } \partial \Omega \]

Partially Absorbing (or Robin)

\[ \nabla p \cdot \hat{n} + \kappa p = 0 \text{ on } \partial \Omega \]

\[ \kappa \ll 1 \quad \text{Mostly Reflecting} \]
\[ \kappa \gg 1 \quad \text{Mostly Absorbing} \]
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:

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

$\phi = 1$ on $\partial \Omega$ for capture
$\phi = 0$ on $\partial \Omega$ for escape

This is sometimes called harmonic measure.
The importance of dimension in diffusion and capture problems
Consider a delta-function release at $x=R$.

$$u_t = Du_{xx} \quad x > 0, \ t > 0$$
$$u(x, 0) = \delta(x - R) \quad x > 0$$
$$u(0, t) = 0 \quad t > 0$$

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

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

Probability of capture: $\phi(R) = 1$

Capture Time

$p(t)$

$\sim t^{-3/2}e^{-R^2/4Dt}$
Capture in 2D

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

Capture Time

\[
q(\tau, 3) \sim \frac{2}{\tau [\ln \tau]^2}
\]

Probability of capture:

\[
\phi(R) = 1
\]
Consider a \( d \)-function release at \( r=R \) and a spherical trap of radius \( a \).

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

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

\[
u(a, t) = 0 \quad t > 0
\]

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

Capture Time

\[
q(\tau, \delta) = \left(1 - \frac{1}{\delta}\right) \frac{e^{\frac{(\delta-1)^2}{4\tau}}}{2\sqrt{\pi} \tau^{3/2}}
\]

\( \sim \tau^{-3/2} e^{-\tau} \)

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.

\[ u(\mathbf{x}) - \text{The probability that particle is captured starting at } \mathbf{x} \in \mathbb{R}^3. \]

\[ \begin{align*}
\Delta u &= 0, \quad \text{outside sphere.} \\
u &= 1, \quad \text{on absorbing pores.} \\
\partial_n u &= 0, \quad \text{on reflecting surface} \\
u(\mathbf{x}) &= \frac{C}{|\mathbf{x}|} + O\left(\frac{1}{|\mathbf{x}|^2}\right), \quad |\mathbf{x}| \to \infty
\end{align*} \]

\[ C - \text{The capacitance of the target. } C = 1 \text{ for all absorbing.} \]

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

\[ J = D \int_{\partial \Omega_a} \partial_n u \, dS = 4\pi DC \]

Goal: Calculate \( C \) for many pores distributed over the surface.
- $N$ small non overlapping pores.
- Common radius $\sigma$.

Using physical intuition, postulated that the flux satisfies

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

**Key result:**

$J \propto$ total pore perimeter.

**Limitations**

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

The sensing is near optimal provided pores are numerous and separated.
Important Ingredient - Single Pore on a flat plane.

\[
\begin{align*}
\Delta w &= 0, \quad z > 0; \\
w &= 1, \quad z = 0, \quad x^2 + y^2 \leq \sigma^2; \\
\partial_n w &= 0, \quad z = 0, \quad x^2 + y^2 > \sigma^2.
\end{align*}
\]

Capacitance: \[C = \frac{2\sigma}{\pi}, \quad J = 4D\sigma.\]

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

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’**

\[ u = 0 \quad \partial_n u = 0 \quad \partial_n u + \kappa u = 0 \]

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

**Exact Planar capture time distribution**

\[
F(t) = \frac{\kappa}{\sqrt{\pi t}} e^{-\frac{x_0^2}{4t}} - \kappa^2 e^{\kappa (\kappa t + x_0)} \text{erfc} \left( \frac{2\kappa t + x_0}{2\sqrt{t}} \right)
\]
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’**

\[
\begin{align*}
\mathbf{u} &= 0 \\
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\partial_n \mathbf{u} + \kappa \mathbf{u} &= 0
\end{align*}
\]

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

**Main Question**: How should the leakage parameter \( \kappa \) be chosen?

- Depends on the absorbing area fraction.
- Depends on the particular receptor clustering.
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’**

\[ u = 0 \quad \partial_n u = 0 \]

\[ \partial_n u + \kappa u = 0 \]

Using the Berg-Purcell Flux: \( J = 4DN\sigma \)

\[ \kappa = \frac{4D}{\pi\sigma} f \]

- \( f \) – absorbing fraction,
- \( \sigma \) – individual pore size

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

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’**

\[ u = 0 \quad \partial_n u = 0 \quad \partial_n u + \kappa u = 0 \]

\[ \kappa = \frac{4D f}{\pi \sigma} \chi(f), \quad \chi(f) = \frac{1 + A \sqrt{f} - B f^2}{(1 - f)^2} \]

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


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

\[ J = 4DN\sigma \left[ 1 + \frac{\sigma}{\pi} \log 2\sigma + \frac{\sigma}{\pi} \left( -\frac{3}{2} + \frac{2}{N} \mathcal{H}(y_1, \ldots, y_N) \right) + \cdots \right]^{-1} \]

\[ \mathcal{H} = \sum_{j \neq k} g(|y_j - y_k|), \quad g(d) = \frac{1}{d} + \frac{1}{2} \log \left[ \frac{d}{2 + d} \right] \]

- 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.

Result requires an explicit surface Green’s Function.
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.

Surface Green’s Function of Sphere.

\[
\begin{align*}
\Delta G &= 0, \quad |x| > 1; \\
\partial_n G &= \delta(x - x_0), \quad |x| = 1.
\end{align*}
\]

\[
G(x; x_0) = \frac{1}{2\pi} \left[ \frac{1}{|x - x_0|} - \frac{1}{2} \log \left( \frac{1 - x \cdot x_0 + |x - x_0|}{|x| - x \cdot x_0} \right) \right]
\]

Problem: Find global minimizers of

\[ \mathcal{H} = \sum_{j \neq k} g(|y_j - y_k|), \quad g(d) = \frac{1}{d} + \frac{1}{2} \log \left[ \frac{d}{2 + d} \right] \]

- 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 \((\theta, \phi)\)
Better

Fibonacci Spirals
Best (so far...)
Boundary Homogenization Result

Assuming a uniform distribution on points on sphere.

\[ H = \sum_{j \neq k} g(|y_j - y_k|), \quad g(d) = \frac{1}{d} + \frac{1}{2} \log \left( \frac{d}{2 + d} \right) \]

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

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

\scriptsize

Later: Numerical verification for realistic N (thousands).

\[ u = 1, \quad \text{absorbing pores.} \]
\[ \partial_n u = 0, \quad \text{reflecting surface.} \]
\[ \partial_n u + \kappa u = 0, \quad \text{all over.} \]
The Equivalent 2D problem.

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

$$\left\{ \begin{array} { l l l } 
\Delta v_h = 0, & |x| > 1; \\
\sigma \partial_n v_h + \kappa(\ell) v_h = 0, & |x| = 1 
\end{array} \right.$$  

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

Window/Pore size

$Lindsay, Tzou, Kolokolnikov$

PRE, 91(3), 2015.
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.

$$u = 0 \quad \partial_n u = 0$$
Numerical Solution of the Capacitance Problem

\[ u(x) - \text{The probability that particle is captured starting at } x \in \mathbb{R}^3. \]

\[ \begin{align*}
\Delta u &= 0, \quad \text{outside sphere.} \\
u &= 1, \quad \text{on absorbing pores.} \\
\partial_n u &= 0, \quad \text{on reflecting surface} \\
u(x) &= \frac{C}{|x|} + \mathcal{O} \left( \frac{1}{|x|^2} \right), \quad |x| \to \infty
\end{align*} \]

Popular Particle Based Solutions.

Particle at \( X(t) \) at time \( t \):

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

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

Step 1: Project Onto Surface

\[ u = \frac{e^{\frac{-r^2 - (z-z_0)^2}{4Dt}} - e^{\frac{-r^2 - (z+z_0)^2}{4Dt}}}{8\pi^{3/2}(Dt)^{3/2}} \]

Step 2: Check if particle Has Been Absorbed

Step 3: Diffuse Particle Off Surface
Integral equation over the support of the pores.

Boundary Integral solution of the Capacitance Problem

\[ p(y) = \int_{x \in \partial \Omega} G(x; y)q(x)dS. \]

Surface Potential \[ \begin{align*}
G(x; y) &= \frac{1}{2\pi} \left[ \frac{1}{|x - y|} - \frac{1}{2} \log \left( \frac{1 - x \cdot y + |x - y|}{|x| - x \cdot y} \right) \right] \\
G(x; y) &= \frac{1}{2\pi} \frac{1}{|x - y|}
\end{align*} \]

Neumann to Dirichlet Map

Pores on a plane \hspace{2cm} Pores on a sphere

Integral equation over the support of the pores.

Sphere Case

Planar Case
Boundary Integral solution of the Capacitance Problem

\[ p(y) = \int_{x \in \partial \Omega} G(x; y) q(x) dS. \]

Neumann to Dirichlet Map

**Main Difficulty:**
Flux has an (integrable) singularity on the edge of 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:

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

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

\[ Z_{00} = \frac{1}{\sqrt{2\pi}}, \]

\[ Z_{1-1} = \frac{2}{\sqrt{\pi}} r \cos(\theta), \quad Z_{11} = \frac{2}{\sqrt{\pi}} r \sin(\theta), \]

\[ Z_{2-2} = \sqrt{\frac{6}{\pi}} r^2 \cos(2\theta), \quad Z_{20} = \sqrt{\frac{3}{\pi}} (2r^2 - 1), \quad Z_{22} = \sqrt{\frac{6}{\pi}} r^2 \sin(2\theta). \]
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

\[ p(y) = \int_{x \in \partial \Omega} G(x; y) q(x) dS. \]

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 \( J = \int_{\partial \Omega} q(x) dS. \)

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

Disadvantages
- Relies on explicit Green’s Function.
- Circular pore geometry assumed.
Numerical Results Sphere:

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

\[ J = 4DN\sigma \left[ 1 + \frac{\sigma}{\pi} \log 2\sigma + \frac{\sigma}{\pi} \left( -\frac{3}{2} + \frac{2}{N} \mathcal{H}(y_1, \ldots, y_N) \right) \right]^{-1} \]

Relative Error - One Pore

Agreement - Platonic Solids

Relative error resolved to 1 part in \(10^8\)!
Accuracy as function of pore separation.

Two Planar Pores


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

<table>
<thead>
<tr>
<th>N</th>
<th>(\varepsilon_{\text{rel}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>1.02%</td>
</tr>
<tr>
<td>101</td>
<td>0.90%</td>
</tr>
<tr>
<td>201</td>
<td>0.76%</td>
</tr>
<tr>
<td>501</td>
<td>0.58%</td>
</tr>
<tr>
<td>1001</td>
<td>0.37%</td>
</tr>
<tr>
<td>2001</td>
<td>0.34%</td>
</tr>
</tbody>
</table>

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

\[
\begin{aligned}
D \left[ \frac{\partial^2 w}{\partial r^2} + \frac{1}{r} \frac{\partial w}{\partial r} + \frac{1}{r^2} \frac{\partial^2 w}{\partial \theta^2} \right] + \omega \frac{\partial w}{\partial \theta} &= -1, \quad r < 1; \\
\partial_r w &= 0, \quad r = 1; \quad w = 0, \quad \text{on } \Gamma_a \quad \partial_\nu w = 0, \quad \text{on } \Gamma_r
\end{aligned}
\]

Optimal radius for a given speed of rotation.

Tzou & Kolokolnikov
SIAM MMS 2015
Ongoing Work II: Trap Cooperation Strategies I

Absorbing Boundaries

Random Motion

$x = x_1(t)$

$x = x_2(t)$

Out-of Phase

In Phase

Advection

$y = y(t)$
\( \omega \) - 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 \( \chi(\omega) < 0 \)

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


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Michael Ward (UBC)

Preprints at: [www.nd.edu/~alinda1](http://www.nd.edu/~alindsa1)

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