The narrow escape problem in a circular domain with radial piecewise constant diffusivity

Matthieu Mangeat and Heiko Rieger

Center for Biophysics & Department for Theoretical Physics, Universität des Saarlandes,
D-66123 Saarbrücken, Deutschland

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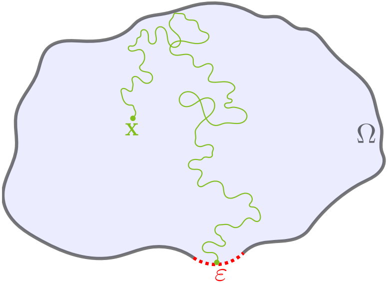
Narrow escape problem (NEP)

- Mean first passage time (MFPT) of Brownian motion (local diffusivity : $D(\mathbf{x})$) from a starting point ($\mathbf{x}$) to a small absorbing window (width : ε).
- Widely studied in last decades.
- Applications to chemical reaction kinetics, **intracellular transport**...



- Mathematical problem to solve :

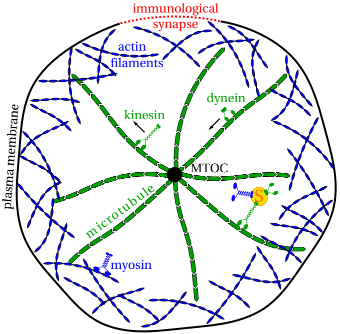
$$\nabla \cdot D(\mathbf{x}) \nabla t(\mathbf{x}) = -1$$
$$t(\mathbf{x} \in \partial\Omega_\varepsilon) = 0$$
$$\mathbf{n} \cdot \nabla t(\mathbf{x} \in \partial\Omega \backslash \partial\Omega_\varepsilon) = 0$$

- Numerical evaluation of the MFPT :
  - PDE solver (e.g. FreeFem++)
  - Kinetic Monte Carlo (stochastic)

S. Redner, A Guide to First-Passage Processes, Cambridge University Press (2001)
O. Bénichou and R. Voituriez, Phys. Rev. Lett. **100**, 168105 (2008)
F. Hecht, J. Numer. Math. **20**, 251 (2013)
K. Schwarz and H. Rieger, Journal of Computational Physics **237**, 396 (2013)

NEP in living cells

- NEP : intracellular cargo transport to immunological synapse located on cell membrane.
- Cargo : particle such as protein, vesicle, mitochondria, ...
- Spatial cytoskeleton organization with centrosome :



- Filaments :
  - polarized microtubules (radially distributed) $\rightarrow$ MTOC
  - actin filaments (randomly distributed), form actin cortex
- Molecular motor assisted motion (bind cargo & filaments)
  - dynein (periphery $\rightarrow$ center)
  - kinesin (center $\rightarrow$ periphery)
  - myosin (lateral transport)
- Stochastic alternation between two modes :
  - ballistic transport on filaments
  - cytoplasmic diffusion / stationary state ($D = 0$)

A. E. Hafner and H. Rieger, Biophysical Journal **118**, 1420 (2018)
P. C. Bressloff and J. M. Newby, Rev. Mod. Phys. **85**, 135 (2013)

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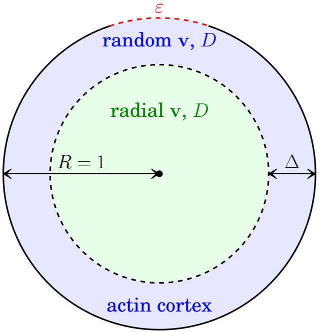

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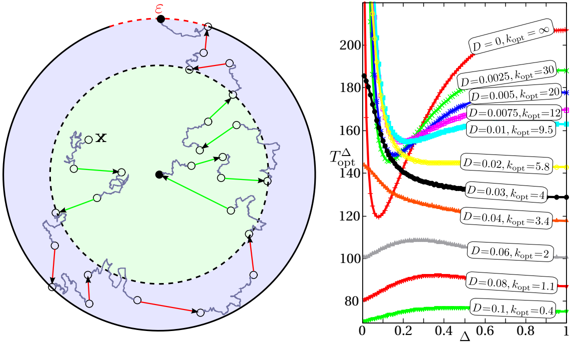
P. C. Bressloff and J. M. Newby, Rev. Mod. Phys. **85**, 135 (2013)

- Optimization of MFPT $\equiv$ **efficient intermittent search strategy**.

Efficient intermittent search strategies

- Small width of the actin cortex optimizes the MFPT for $D < 0.02$.
- Optimization more pronounced for small diffusivities.
- Random walk accelerated close to the boundary.



K. Schwarz, Y. Schröder, B. Qu, M. Hoth and H. Rieger, Phys. Rev. Lett. **117**, 068101 (2016)
A. E. Hafner and H. Rieger, Phys. Biol. **13**, 066003 (2016)

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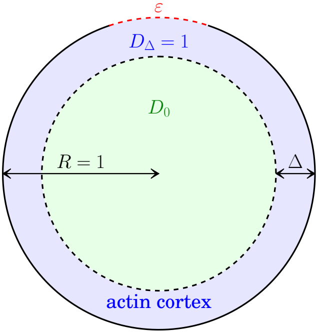
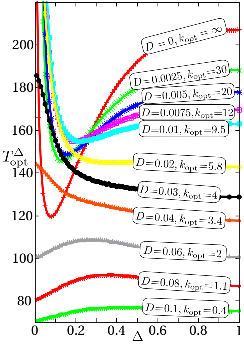




Model studied here :

- Ballistic motion neglected
- Two-shell geometry :

$$D_\Delta > D_0$$

- Three parameters :

$$\varepsilon,\ \Delta,\ D_\Delta/D_0$$

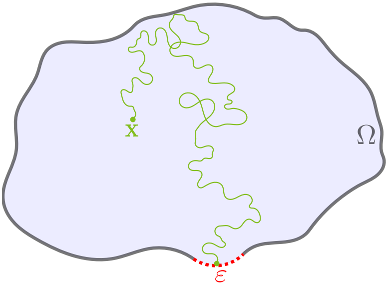
- **circular domain with radial piecewise constant diffusivity**

K. Schwarz, Y. Schröder, B. Qu, M. Hoth and H. Rieger, Phys. Rev. Lett. **117**, 068101 (2016)

A. E. Hafner and H. Rieger, Phys. Biol. **13**, 066003 (2016)

- What happens if the ballistic transport is neglected ?

Method : How to get narrow escape expressions ($\varepsilon \ll 1$) ?



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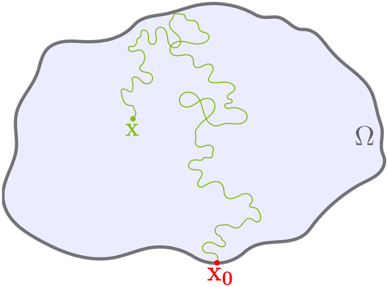
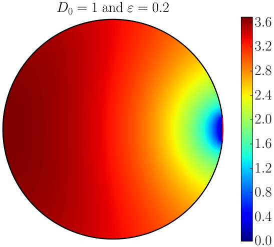


$$D\nabla^2 t(\mathbf{x}) = -1$$
$$t(\mathbf{x} \in \partial\Omega_\varepsilon) = 0$$
$$\mathbf{n}\cdot\nabla t(\mathbf{x} \in \partial\Omega \backslash \partial\Omega_\varepsilon) = 0$$

$$t(\mathbf{x}) = \frac{|\Omega|}{\pi D}\left[-\ln\frac{\varepsilon}{4} + \pi R(\mathbf{x_0}|\mathbf{x_0}) - \pi G(\mathbf{x}|\mathbf{x_0})\right]$$
$$\nabla^2 G(\mathbf{x}|\mathbf{x_0}) = \frac{1}{|\Omega|}, \quad \int_\Omega d\mathbf{x}\; G(\mathbf{x}|\mathbf{x_0}) = 0$$
$$G(\mathbf{x}\to\mathbf{x_0}|\mathbf{x_0}) = -\frac{1}{\pi}\ln\frac{|\mathbf{x}-\mathbf{x_0}|}{R} + R(\mathbf{x_0}|\mathbf{x_0})$$
$$\mathbf{n}\cdot\nabla G(\mathbf{x}\in\partial\Omega|\mathbf{x_0}) = 0$$

M. J. Ward and J. B. Keller, SIAM J. Appl. Math. **53**, 770 (1993)
S. Pillay, M. J. Ward, A. Peirce and T. Kolokolnikov, Multiscale Model. Simul. **8**, 803 (2010)

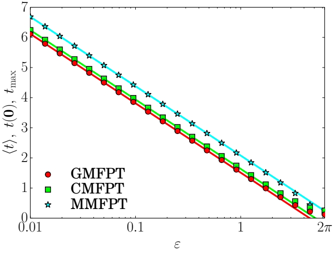
Known result : disk geometry ($D_\Delta = D_0$ or $\Delta = 1$)



- Narrow escape expression

$$t(\mathbf{x}) \underset{\varepsilon \ll 1}{\simeq} \ln \frac{4|\mathbf{x} - \mathbf{x_0}|}{\varepsilon} + \frac{1 - |\mathbf{x}|^2}{4}$$

A. Singer, Z. Schuss and D. Holcman, J. Stat. Phys. **122**, 465 (2006)



- Global mean first passage time (GMFPT)

$$\langle t \rangle \underset{\varepsilon \ll 1}{\simeq} -\ln \frac{\varepsilon}{4} + \frac{1}{8}$$

- Mean first passage time starting at the center (CMFPT)

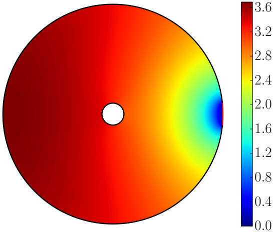
$$t(\mathbf{0}) \underset{\varepsilon \ll 1}{\simeq} -\ln \frac{\varepsilon}{4} + \frac{1}{4}$$

- Maximal mean first passage time (MMFPT)

$$t_{\max} \underset{\varepsilon \ll 1}{\simeq} -\ln \frac{\varepsilon}{4} + \ln 2$$

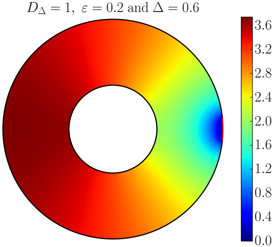
Annulus geometry ($D_0 = 0$)

$D_\Delta = 1$, $\varepsilon = 0.2$ and $\Delta = 0.9$



M. Mangeat and H. Rieger, J. Phys. A : Math. Theor. **42**, 424002 (2019)

Annulus geometry ($D_0 = 0$)



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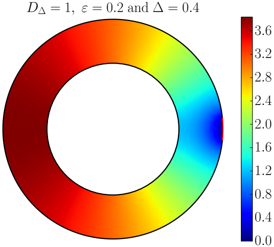

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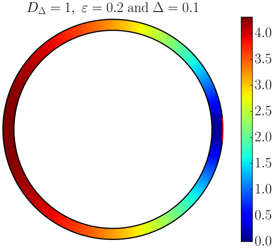

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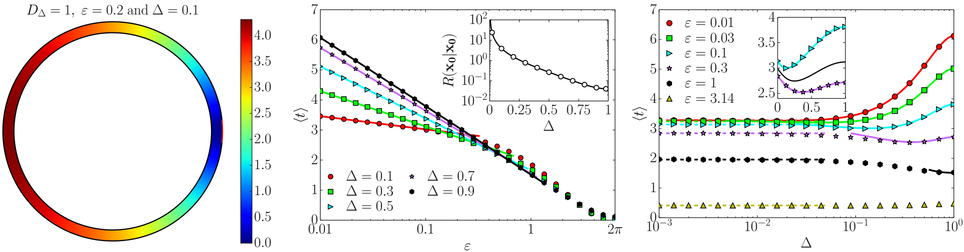


- Narrow escape expression ($\varepsilon \ll 1$) :

$$\langle t \rangle \underset{\varepsilon \ll 1}{\simeq} \Delta(2-\Delta)\left[-\ln\frac{\varepsilon}{4} + \frac{3}{8} + 2\sum_{n=1}^{\infty}\frac{(1-\Delta)^{2n}}{n\left[1-(1-\Delta)^{2n}\right]}\right] - \frac{1}{4} - \frac{(1-\Delta)^4\ln(1-\Delta)}{2\Delta(2-\Delta)}.$$

- Pseudo-one dimensional expression ($\Delta \ln \varepsilon \ll 1$) :

$$\langle t \rangle \underset{\Delta \ll 1}{\simeq} \frac{(2\pi-\varepsilon)^3}{24\pi}.$$

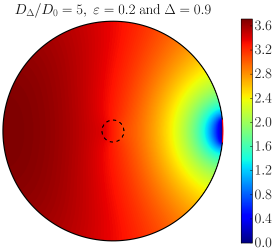
- General expression for $\Delta \ll 1$ and $\varepsilon \ll 1$:

$$\langle t \rangle \simeq -2\Delta \ln \varepsilon + \frac{\pi^2}{3} + \mathcal{O}(\Delta, \varepsilon).$$

- MFPT optimized for $\varepsilon < 1$ due to the inner hardcore repulsion.

M. Mangeat and H. Rieger, J. Phys. A : Math. Theor. **42**, 424002 (2019)

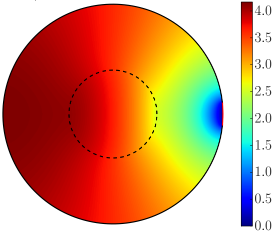
Two-shell geometry (fixed $D_\Delta/D_0 > 1$)



M. Mangeat and H. Rieger, J. Phys. A : Math. Theor. **42**, 424002 (2019)

Two-shell geometry (fixed $D_\Delta/D_0 > 1$)

$D_\Delta/D_0 = 5, \ \varepsilon = 0.2$ and $\Delta = 0.6$



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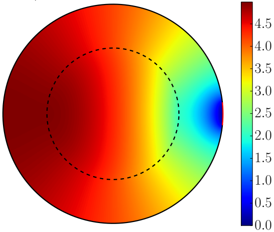
Two-shell geometry (fixed $D_\Delta/D_0 > 1$)

$D_\Delta/D_0 = 5,\ \varepsilon = 0.2$ and $\Delta = 0.4$



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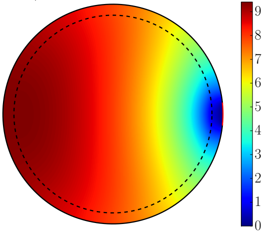

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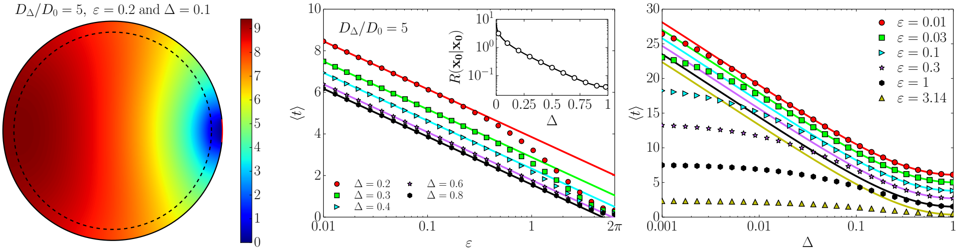


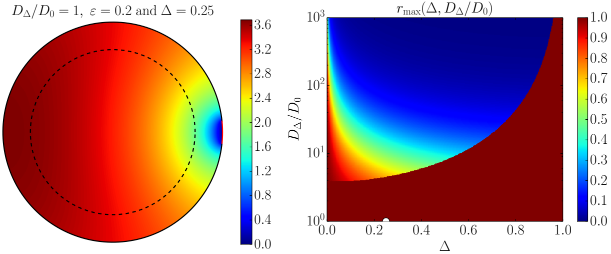
- Narrow escape expression ($\varepsilon \ll 1$) :

$$\langle t \rangle \underset{\varepsilon \ll 1}{\simeq} -\ln\frac{\varepsilon}{4} + \frac{1}{8} + \frac{D_\Delta - D_0}{8D_0}(1-\Delta)^4 + 2\sum_{n=1}^{\infty} \frac{(D_\Delta - D_0)(1-\Delta)^{2n}}{n\left\{2D_0 + (D_\Delta - D_0)\left[1-(1-\Delta)^{2n}\right]\right\}}$$

- GMFPT decreasing function of ε at fixed Δ and D_Δ/D_0.
- GMFPT decreasing function of Δ at fixed ε and D_Δ/D_0.
- GMFPT go to a constant in the $\Delta \to 0$ limit.

M. Mangeat and H. Rieger, J. Phys. A : Math. Theor. **42**, 424002 (2019)

Two-shell geometry (fixed $\Delta < 1$)



- Distance between starting position of MMFPT and center ($r_{\max}$) versus D_Δ/D_0 :
  - $D_\Delta/D_0 \in [1, D_c]$: like the disk geometry ($r_{\max} = 1$)
  - $D_\Delta/D_0 = D_c$: MMFPT starting position located in the inner shell ($r_{\max} < 1 - \Delta$)
  - $D_\Delta/D_0 \gg D_c$: MMFPT starting position goes continuously to the center ($r_{\max} \to 0$)

- $r_{\max}$ is a decreasing and discontinuous function of D_Δ/D_0.

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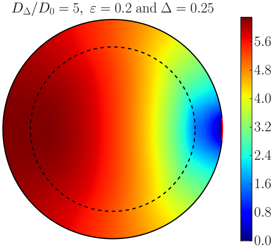

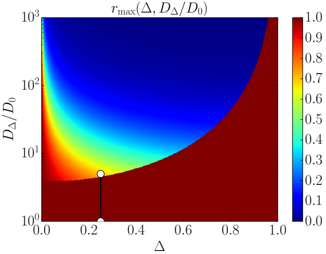

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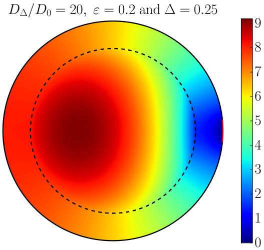

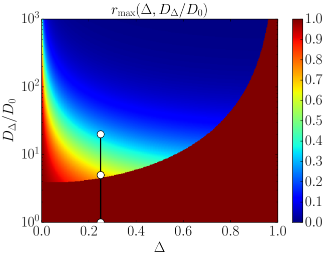

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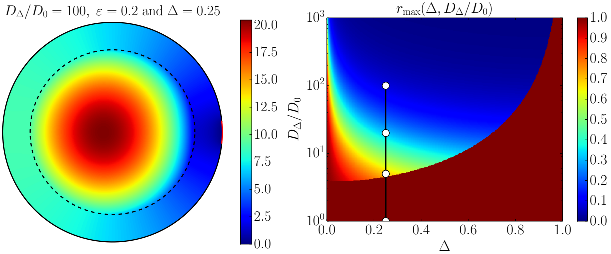

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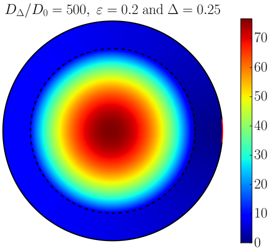

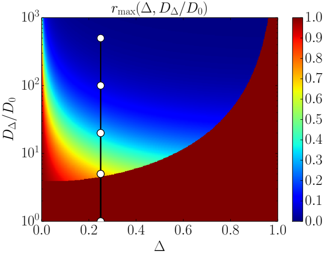

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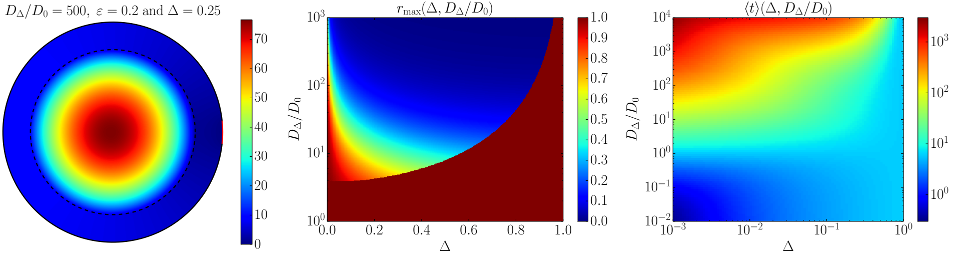

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- $r_{\max}$ is a decreasing and discontinuous function of D_Δ/D_0.
- GMFPT increasing function of D_Δ/D_0 at fixed ε and Δ.
- GMFPT is a monotonous function of all parameters : **no optimization**.

M. Mangeat and H. Rieger, J. Phys. A : Math. Theor. **42**, 424002 (2019)

- Analytical expression of MFPT obtained for circular domains in the narrow escape limit.
- For annulus geometry, the MFPT is optimized with the outer shell width Δ, due to hardcore repulsion.
- For two-shell geometry, the MFPT depends monotonouly on the outer shell width Δ.
- For two-shell geometry, the distance between the starting position and the center which maximizes the MFPT depends discontinuously on D_Δ/D_0.
- The MFPT can be optimized only when a mechanism enforce the particle to stay close to the surface : annulus geometry, intermittent search strategies, surface-mediated diffusion...

K. Schwarz, Y. Schröder, B. Qu, M. Hoth and H. Rieger, Phys. Rev. Lett. **117**, 068101 (2016)

A. E. Hafner and H. Rieger, Phys. Biol. **13**, 066003 (2016)

O. Bénichou, D. S. Grebenkov, P. E. Levitz, C. Loverdo, R. Voituriez, Phys. Rev. Lett. **105**, 150606 (2010)

- Make the boundary between the inner and outer shell semi-permeable.
- Introduce asymmetric reflection and transmission probabilities for the inner boundary.

Thank you for your attention !

List of publications :

- K. Schwarz, Y. Schröder, B. Qu, M. Hoth and H. Rieger, *Optimality of Spatially Inhomogeneous Search Strategies*, Phys. Rev. Lett. **117**, 068101 (2016)
- K. Schwarz, Y. Schröder and H. Rieger, *Numerical analysis of homogeneous and inhomogeneous intermittent search strategies*, Phys. Rev. E **94**, 042133 (2016)
- A. E. Hafner and H. Rieger, *Spatial organization of the cytoskeleton enhances cargo delivery to specific target areas on the plasma membrane of spherical cells*, Phys. Biol. **13**, 066003 (2016)
- A. E. Hafner and H. Rieger, *Spatial Cytoskeleton Organization Supports Targeted Intracellular Transport*, Biophysical Journal **118**, 1420 (2018)
- M. Mangeat and H. Rieger, *The narrow escape problem in a circular domain with radial piecewise constant diffusivity*, J. Phys. A : Math. Theor. **42**, 424002 (2019)