

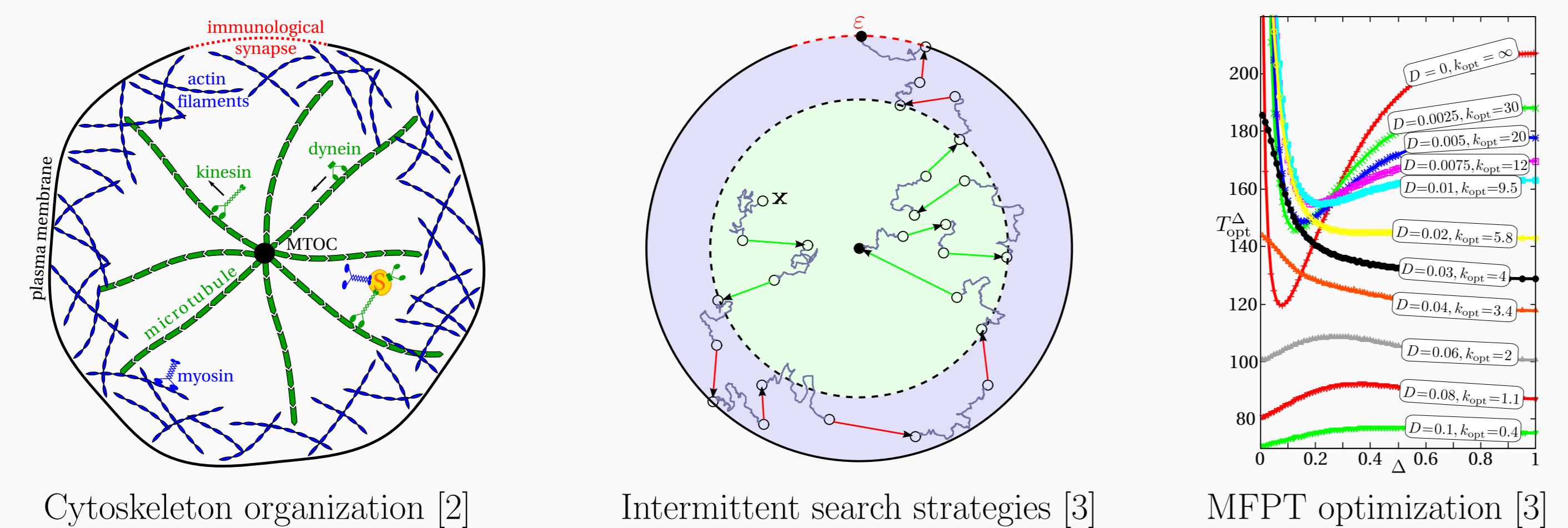
Introduction

Intracellular transport of cargo-particles towards a specific area on cell membrane (e.g immunological synapse in T cells) is crucial for the correct functioning of cells. The cytoskeleton is organized in a two-shell geometry which separates the microtubules radiating from the centrosome and the actin filaments near the cell membrane. The particles perform an intermittent search, alternating randomly between a cytoplasmic diffusive transport and a ballistic transport on filaments assisted by molecular motors [1]. The transport time can be minimized for thin cortex due to an accelerated effective diffusivity close to the cell membrane [2, 3]. For small escape area, this intracellular transport constitutes the narrow escape problem (NEP).

NEPs are widely studied in various biological and chemical contexts, and consist in calculating the mean-first passage time (MFPT) to reach a small absorbing window [4]. In two dimensions, the MFPT is proportional to the logarithm of the escape region perimeter and its subleading order depends on the full domain geometry. We ask whether the MFPT optimization in two-shell circular domains can also be achieved by passive Brownian particles. We consider a Brownian motion with different diffusion constants in the two shells and a potential barrier between the two and investigate the NEP to reach a small window on the external boundary. We derive asymptotic expressions for the MFPT in the thin cortex and small escape region limits [5] confirmed by numerical calculations using the finite element method [6] and stochastic simulations.

Intracellular transport and intermittent search strategies

▶ Intracellular transport of cargo particles (e.g. proteins, vesicle, mitochondria) to immunological synapse:



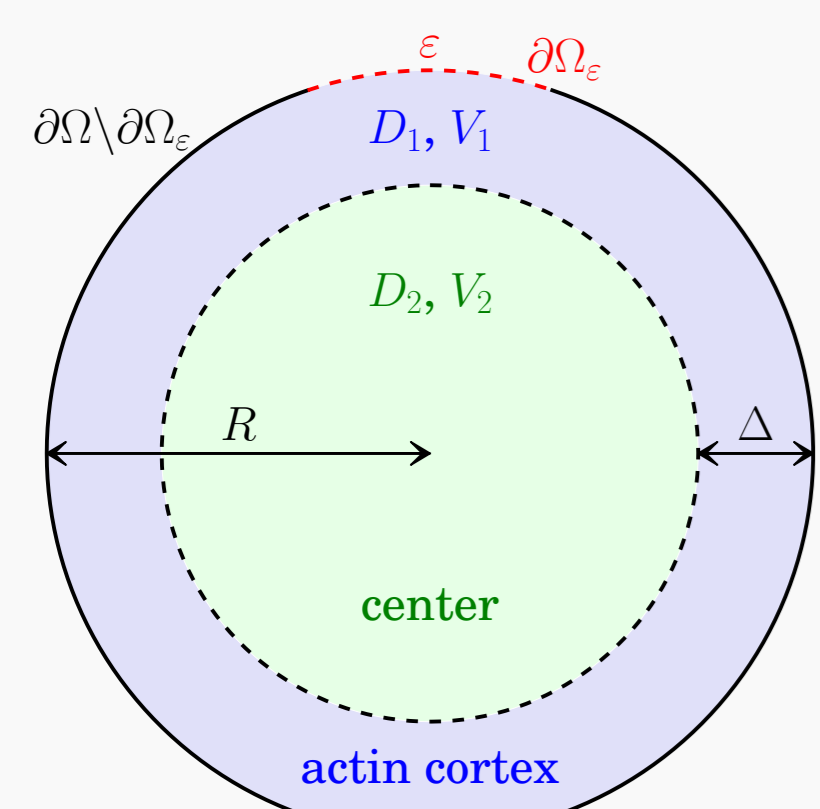
▶ Spatial cytoskeleton organization: microtubules (kinesin/dynein) vs actin filaments (myosin).
 ▶ Efficient intermittent search strategies: small width of actin cortex optimizes the transport and random walk is accelerated in the actin cortex.

The model for passive Brownian particles

▶ MFPT for a Brownian particle starting at position \mathbf{x} with diffusivity $D(\mathbf{x})$ in potential $V(\mathbf{x})$ satisfies

$$\nabla_{\mathbf{x}} \cdot [D(\mathbf{x}) \exp(-\beta V(\mathbf{x})) \nabla_{\mathbf{x}} t(\mathbf{x})] = -\exp(-\beta V(\mathbf{x})).$$

▶ Two-shell circular domains with piecewise constant diffusivity and potential:



▶ Bulk equations for MFPT:

$$D_1 \nabla_{\mathbf{x}}^2 t_1(\mathbf{x}) = -1, \quad \mathbf{x} \in \Omega_1$$

$$D_2 \nabla_{\mathbf{x}}^2 t_2(\mathbf{x}) = -1, \quad \mathbf{x} \in \Omega_2$$

▶ Boundary conditions between the two shells ($|\mathbf{x}| = R - \Delta$):

$$t_1(\mathbf{x}) = t_2(\mathbf{x})$$

$$D_1 \exp(-\beta V_1) \mathbf{n} \cdot \nabla_{\mathbf{x}} t_1(\mathbf{x}) = D_2 \exp(-\beta V_2) \mathbf{n} \cdot \nabla_{\mathbf{x}} t_2(\mathbf{x})$$

▶ External boundary condition ($|\mathbf{x}| = R$):

$$t_1(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Omega_{\varepsilon}$$

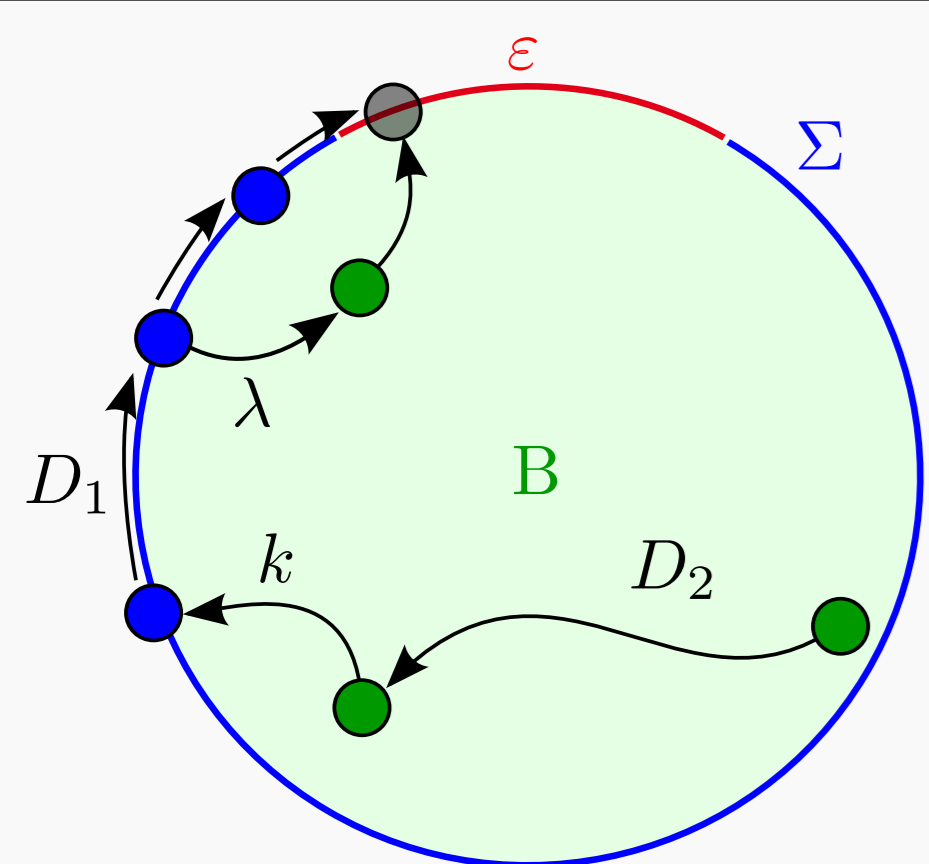
$$\mathbf{n} \cdot \nabla_{\mathbf{x}} t_1(\mathbf{x}) = 0, \quad \mathbf{x} \in \partial\Omega \setminus \partial\Omega_{\varepsilon}.$$

▶ Average MFPT:

$$T = \frac{D_1}{R^2} \langle t \rangle = \frac{D_1}{R^2} \int_{\Omega} d\mathbf{x} P_s(\mathbf{x}) t(\mathbf{x}) \quad \text{with} \quad P_s(\mathbf{x}) = \frac{\exp(-\beta V(\mathbf{x}))}{\int_{\Omega} d\mathbf{x} \exp(-\beta V(\mathbf{x}))}.$$

▶ Parameters: $\chi = 1 - \Delta/R$, $\Delta V = V_2 - V_1$, D_1/D_2 and ε .

Thin cortex limit ($\Delta \ll R$)



▶ MFPT equations for the surface-mediated diffusion problem [7]:

$$D_2 \nabla_{\mathbf{x}}^2 t_B(r, \theta) = -1,$$

$$\frac{D_1}{R^2} \Delta_{\theta} t_{\Sigma}(\theta) - \frac{\lambda}{k} \partial_r t_B(R, \theta) = -1,$$

$$t_{\Sigma}(\theta) - t_B(R, \theta) = \frac{1}{k} \partial_r t_B(R, \theta).$$

▶ λ desorption rate and k absorption rate.

▶ Equivalence with two-shell geometry:

$$\lim_{(k, \lambda) \rightarrow +\infty} \frac{k D_2}{\lambda} = \lim_{\Delta \rightarrow 0} \Delta \exp(\beta \Delta V) = \kappa.$$

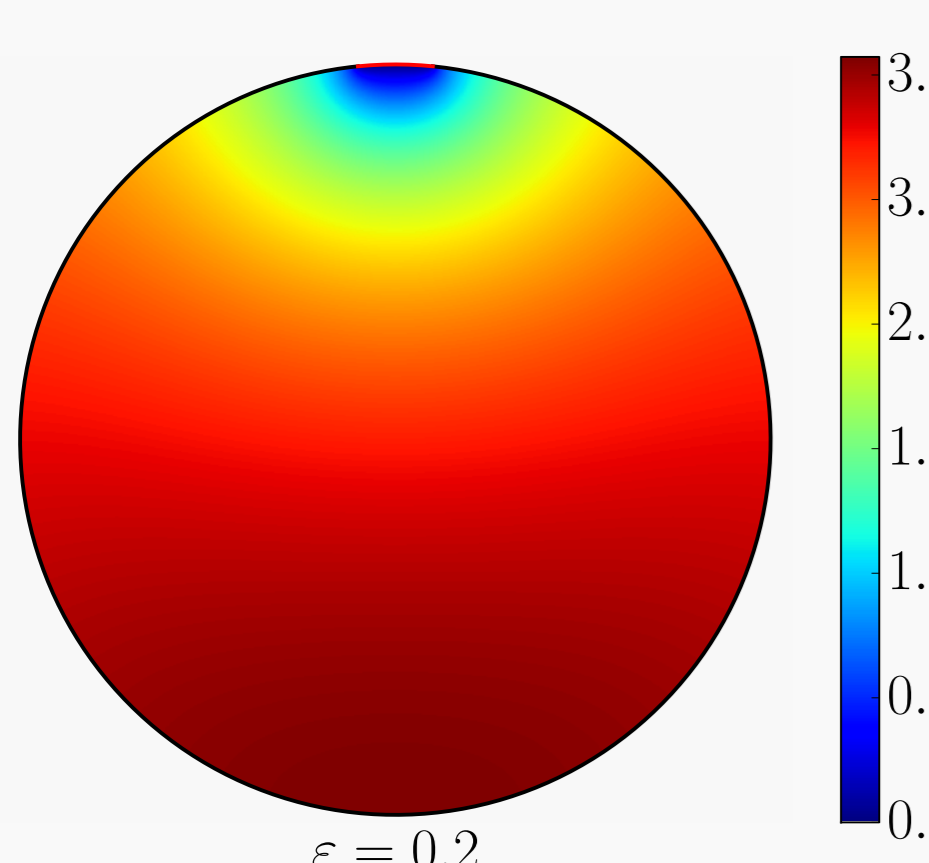
▶ $\exp(-\beta \Delta V) = 0$: $\kappa = +\infty$

$$\lim_{\Delta \rightarrow 0} t(\mathbf{x}) = \frac{R^2}{2D_1} (\theta - \varepsilon/2)(2\pi - \varepsilon/2 - \theta)$$

▶ $\Delta V < +\infty$: $\kappa = 0$

$$\lim_{\Delta \rightarrow 0} t(\mathbf{x}) = \frac{D_1}{D_2} \lim_{\Delta \rightarrow R} t(\mathbf{x})$$

Disk geometry ($D_1 = D_2$ and $\Delta V = 0$)



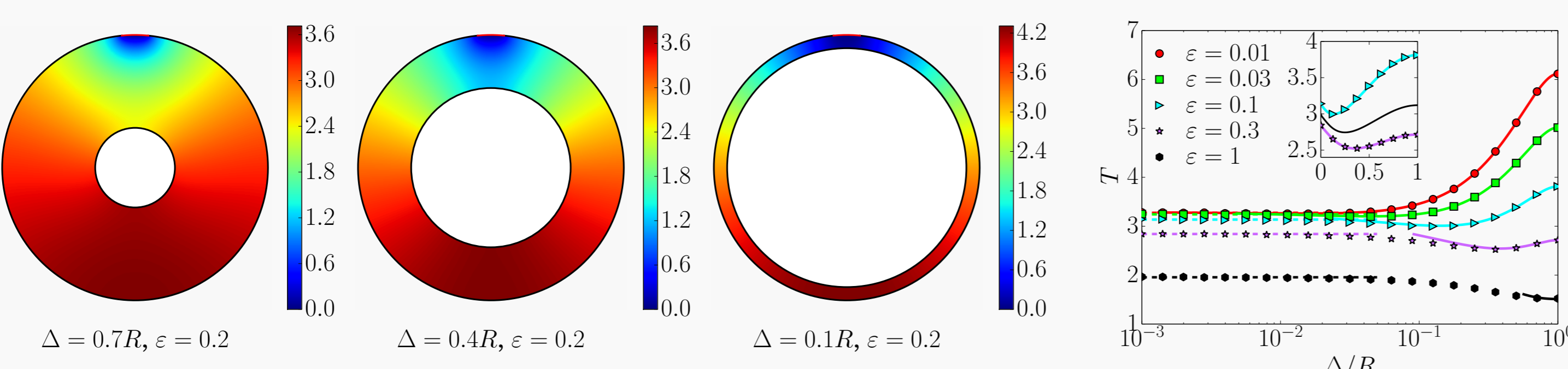
▶ Narrow escape limit ($\varepsilon \ll 1$) [8]:

$$\frac{D_1 t(\mathbf{x})}{R^2} \simeq \ln \frac{4|\mathbf{x} - \mathbf{x}_0|}{\varepsilon R} + \frac{R^2 - |\mathbf{x}|^2}{4R^2}, \quad T \simeq -\ln \frac{\varepsilon}{4} + \frac{1}{8}.$$

▶ Exact solution in complex plane ($z = y/R + ix/R$) [9]:

$$\frac{D_1 t(z)}{R^2} = \frac{1 - |z|^2}{4} + \ln \left| \frac{1 - z + \sqrt{[1 - z \exp(-i\varepsilon/2)][1 - z \exp(i\varepsilon/2)]}}{2 \sin(\varepsilon/4)} \right|.$$

Annulus geometry ($\Delta V \rightarrow \infty$)



▶ Narrow escape limit ($\varepsilon \ll 1$):

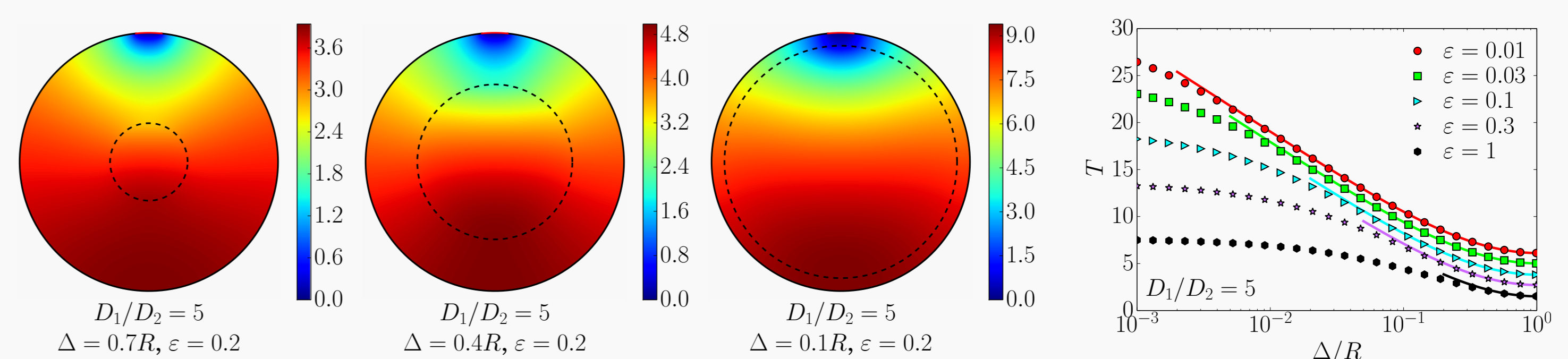
$$T \simeq (1 - \chi^2) \left[-\ln \frac{\varepsilon}{4} - 2 \sum_{k=1}^{\infty} \ln(1 - \chi^{2k}) \right] + \frac{1}{8} - \frac{3\chi^2}{8} - \frac{\chi^4 \ln \chi}{2(1 - \chi^2)}.$$

▶ Thin cortex limit ($\Delta \rightarrow 0$):

$$T \simeq (2\pi - \varepsilon)^3 / 24\pi.$$

▶ MFPT optimization due to the inner hardcore repulsion.

Heterogeneous diffusion in two-shell geometry ($\Delta V = 0$)



▶ Narrow escape limit ($\varepsilon \ll 1$):

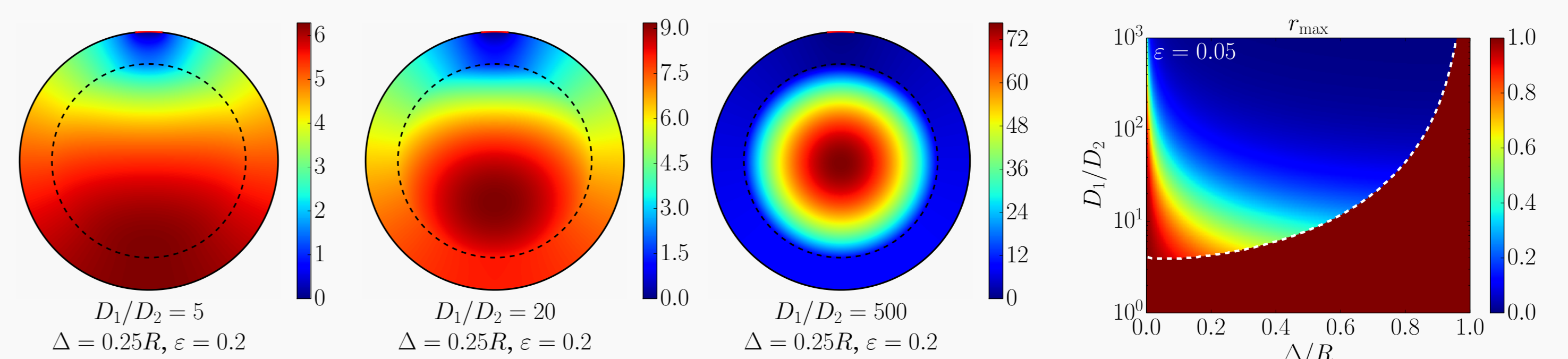
$$T \simeq -\ln \frac{\varepsilon}{4} - 2 \sum_{k=1}^{\infty} \left[\frac{D_1 - D_2}{D_1 + D_2} \right]^k \ln(1 - \chi^{2k}) + \frac{1}{8} + \frac{D_1 - D_2}{8D_2} \chi^4.$$

▶ Thin cortex limit ($\Delta \rightarrow 0$):

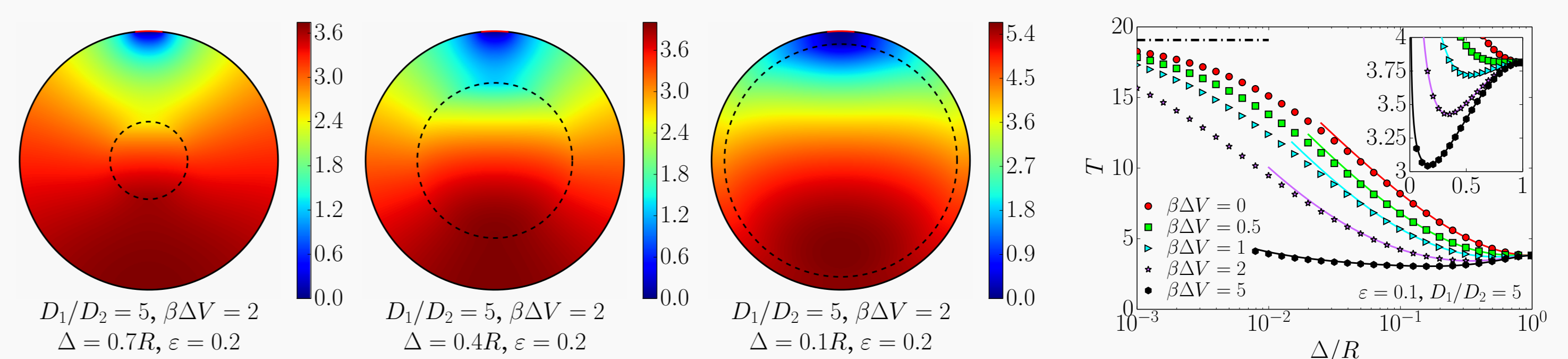
$$T \simeq \frac{D_1}{D_2} \left(-\ln \frac{\varepsilon}{4} + \frac{1}{8} \right).$$

▶ T is monotonous with Δ : no optimization for $D_1 > D_2$! A mechanism forcing the particles to stay close to the surface is needed.

▶ Distance to center of starting position of maximal MFPT (r_{\max}) decreases discontinuously with D_1/D_2 :



Potential difference and MFPT optimization

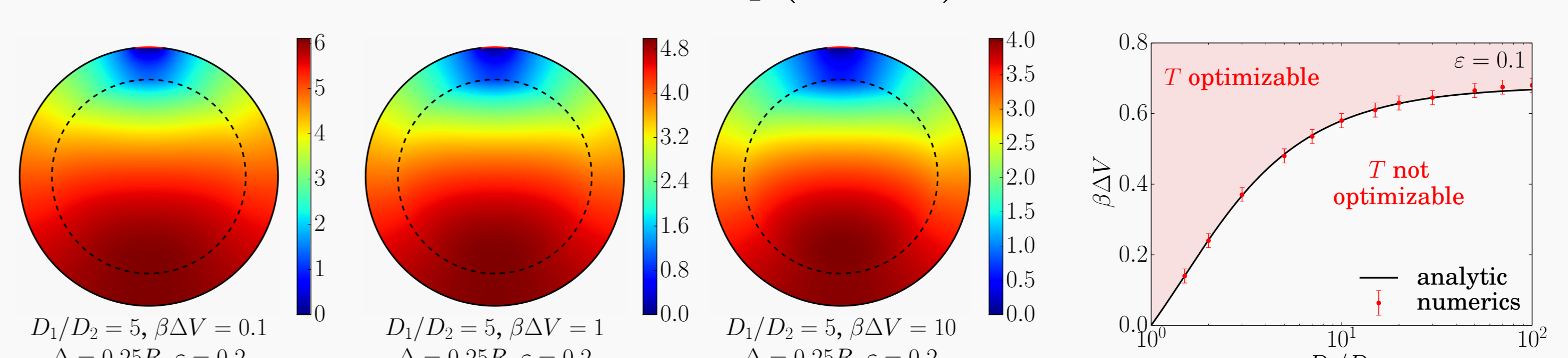


▶ Narrow escape limit ($\varepsilon \ll 1$):

$$T \simeq \left\{ 1 - \chi^2 [1 - \exp(-\beta \Delta V)] \right\} \left\{ -\ln \frac{\varepsilon}{4} - 2 \sum_{k=1}^{\infty} \left[\frac{D_1 - D_2 \exp(-\beta \Delta V)}{D_1 + D_2 \exp(-\beta \Delta V)} \right]^k \ln(1 - \chi^{2k}) \right\} + \frac{1}{8} + \frac{(D_1 - D_2) \chi^2 \exp(-\beta \Delta V) - 3D_2 [1 - \exp(-\beta \Delta V)] (1 - \chi^2)}{8D_2 \{1 - \chi^2 [1 - \exp(-\beta \Delta V)]\}} \chi^2 - \frac{[1 - \exp(-\beta \Delta V)]^2 \chi^4 \ln \chi}{2 \{1 - \chi^2 [1 - \exp(-\beta \Delta V)]\}}.$$

▶ Thin cortex limit ($\Delta \rightarrow 0$):

$$T \simeq \frac{D_1}{D_2} \left(-\ln \frac{\varepsilon}{4} + \frac{1}{8} \right).$$



▶ MFPT is optimizable if and only if the minimal value is smaller than the disk geometry value ($\chi = 0$).

▶ T can be optimized for $D_1 > D_2$ if the potential barrier satisfies:

$$\beta \Delta V \gtrsim \frac{2(D_1 - D_2)}{(D_1 + D_2) \left(-\ln \frac{\varepsilon}{4} + \frac{3}{8} \right)}.$$

▶ T is minimum for $\Delta = 0$ when $D_1 < D_2$.

Conclusion and perspectives

- ▶ MFPT optimization can be observed for passive Brownian particles in two-shell geometries.
- ▶ We can also analyze $t(\mathbf{0})$, the MFPT for particles starting at the center.
- ▶ All these results can be reproduced for 3d NEP, and the same conclusions can be made.
- ▶ Main perspective: get analytical results for NE problem with ballistic transport (i.e. active particles).

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