Reduction of dimensionality in biological search

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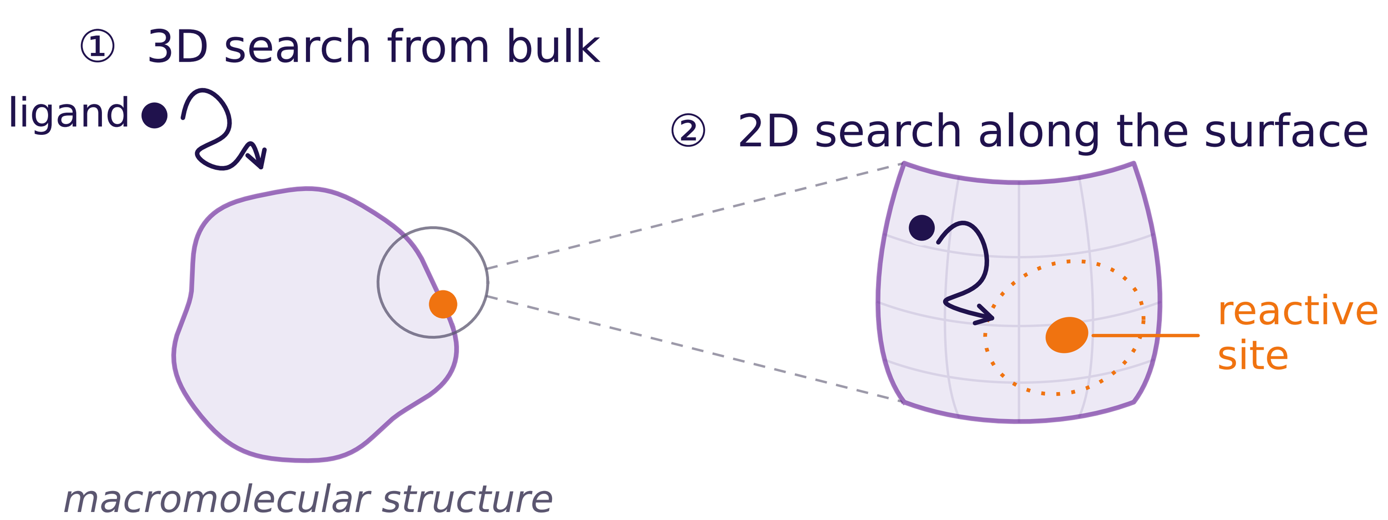
Background

How do **sparse searchers** find **precise targets** in crowded environments?

→ Diffusion from bulk is **not** efficient enough on its own.

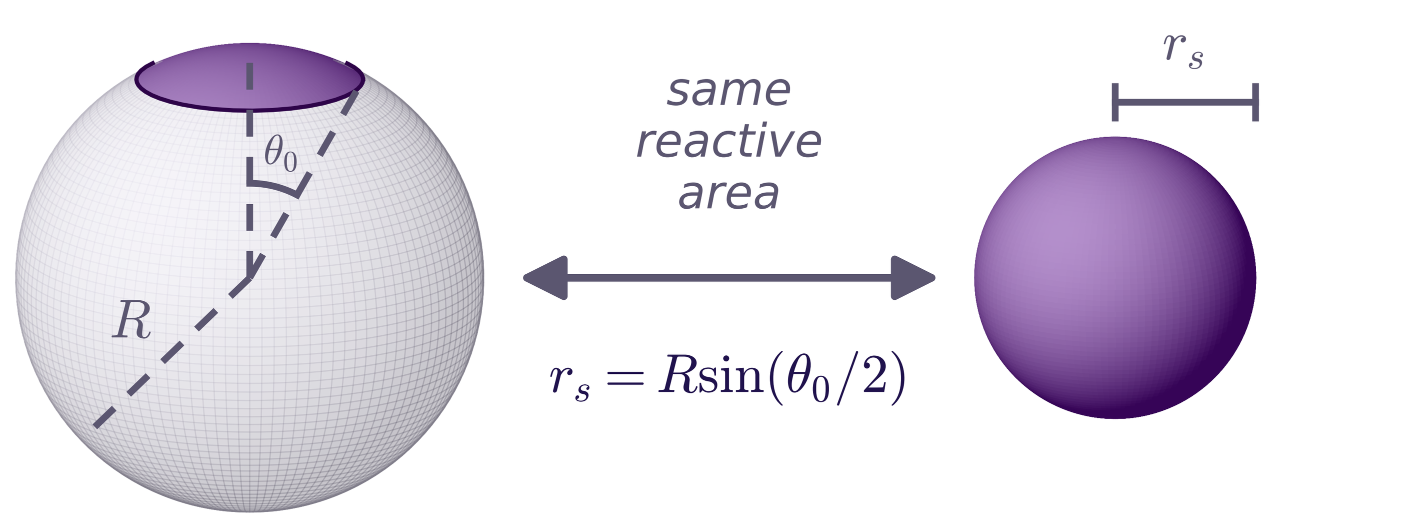
Geometry and dimensionality of a search space can have a large effect on searcher efficacy.

→ **Nonspecific surface binding** may allow a macromolecular structure to act as an **antenna**:



At fixed reactive area, does embedding the target in a larger passive body improve capture?

Model



reactive embedded patch | fully reactive particle

Axisymmetric Laplacian with mixed boundary conditions

$$\Delta u(r,\theta) = 0 \qquad \begin{cases} u(R,\theta) = 0, & \theta \le \theta_0 \text{ (reactive cap)} \\ \partial_r u|_{r=R} = 0, & \theta > \theta_0 \text{ (passive body)} \end{cases} \qquad \lim_{r\to\infty} u = u_0$$

Solution has the form $u(r,\theta) = u_0\left[1 + \sum_{n=0}^{\infty} B_n \left(\frac{R}{r}\right)^{n+1} P_n(\cos\theta)\right]$

where P_n are the Legendre polynomials with dimensionless coefficients B_n

Solution and simulation

Analysis

Solving for coefficients B_n requires satisfying the dual series

$$\sum_{n=0}^{\infty} B_n P_n(\cos\theta) = -1 \quad (\theta \le \theta_0) \qquad \text{and} \qquad \sum_{n=0}^{\infty} (n+1)\, B_n P_n(\cos\theta) = 0 \quad (\theta > \theta_0)$$

$$\text{Ansatz:} \qquad B_n = \frac{2n+1}{2(n+1)} \int_0^{\theta_0} H(t)\cos\left((n+\tfrac{1}{2})t\right)\,\mathrm{d}t, \qquad H(t) \in C^1[0,\theta_0]$$

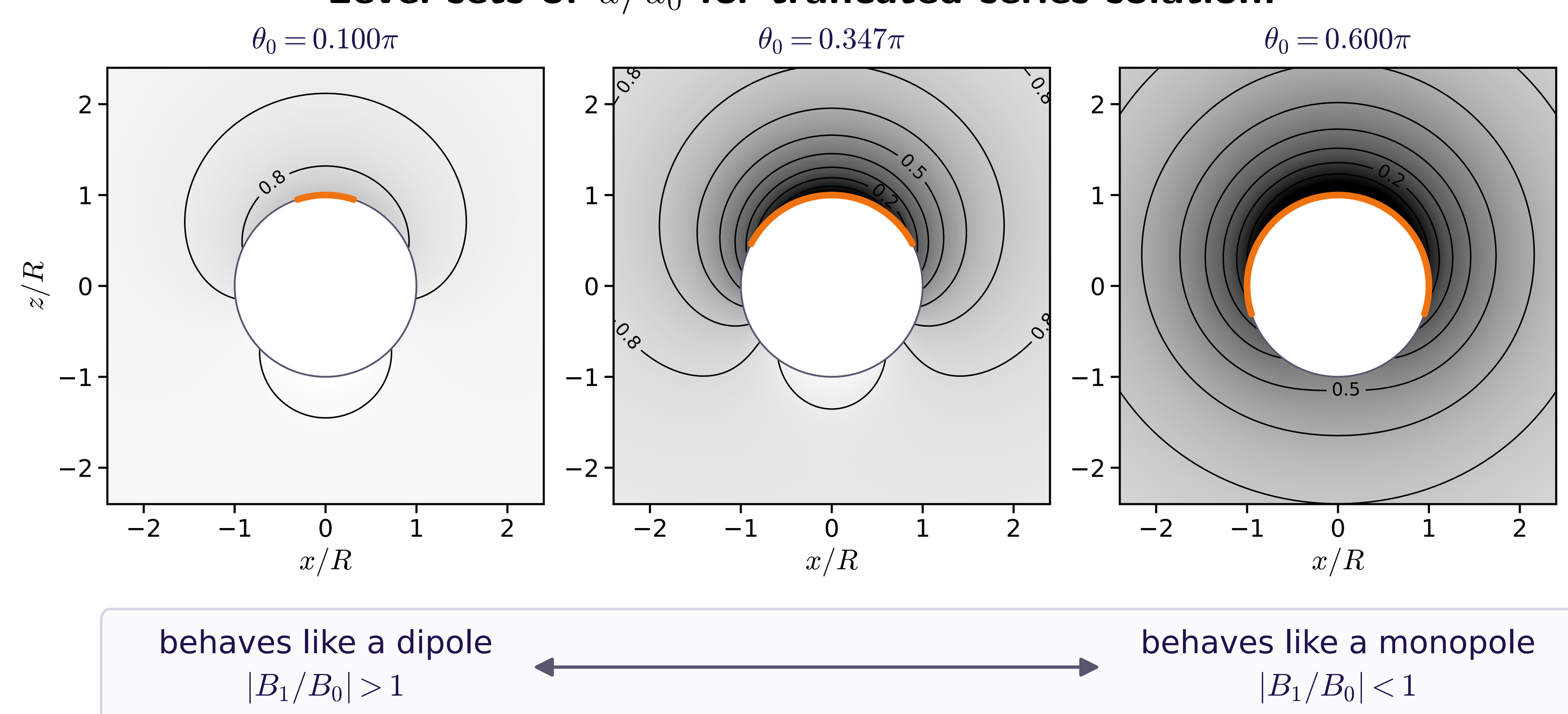
→ Neumann condition outside of patch satisfied automatically by ansatz

→ Dirichelet condition then reduces to Fredholm equation of the second kind on patch:

$$H(s) = -\frac{2}{\pi}\cos\frac{s}{2} + \frac{1}{\pi}\int_0^{\theta_0} M(s,t)\,H(t)\,\mathrm{d}t$$

We can then numerically solve for the coefficients, which decay as $|B_n| \sim n^{-1}$. Truncating at $n = 2$ gives a heuristic sense of the far-field effects.

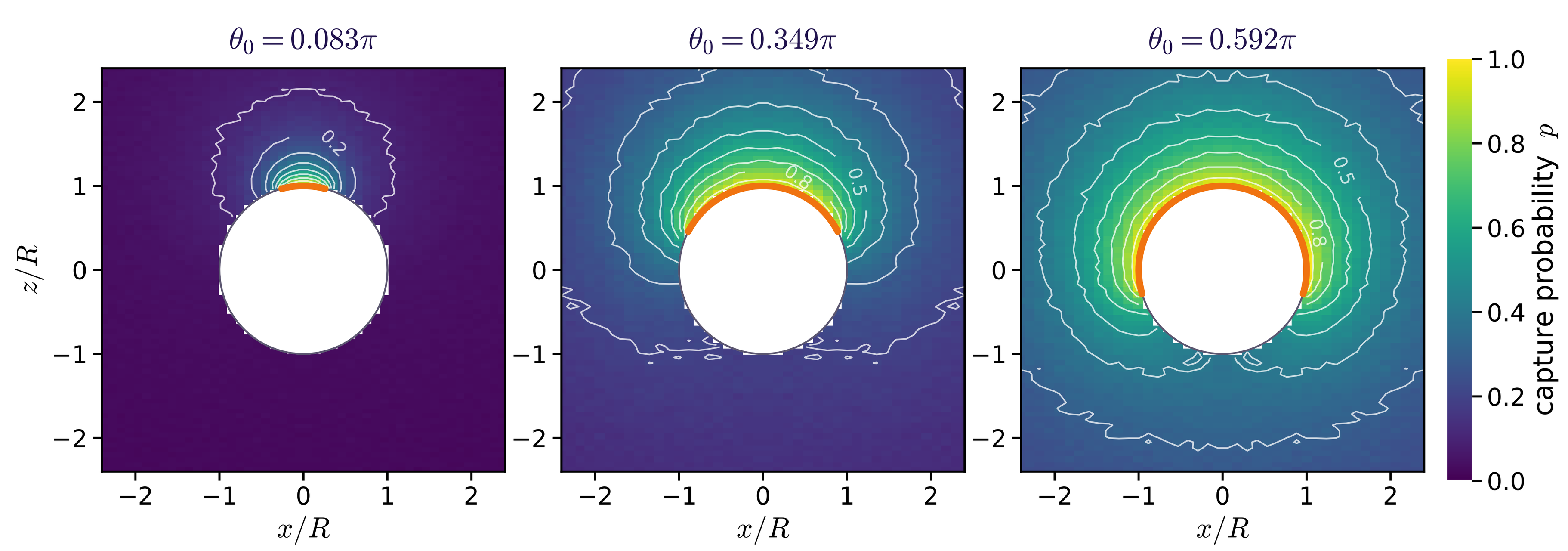
Level sets of u/u_0 for truncated series solution.



Far field effect (measured by $|B_1/B_0|$) shows transition ($|B_1/B_0|$=1) at $\theta_0 \approx 0.3467\pi$.

Simulations

Monte Carlo simulations show similar behavior and transition.

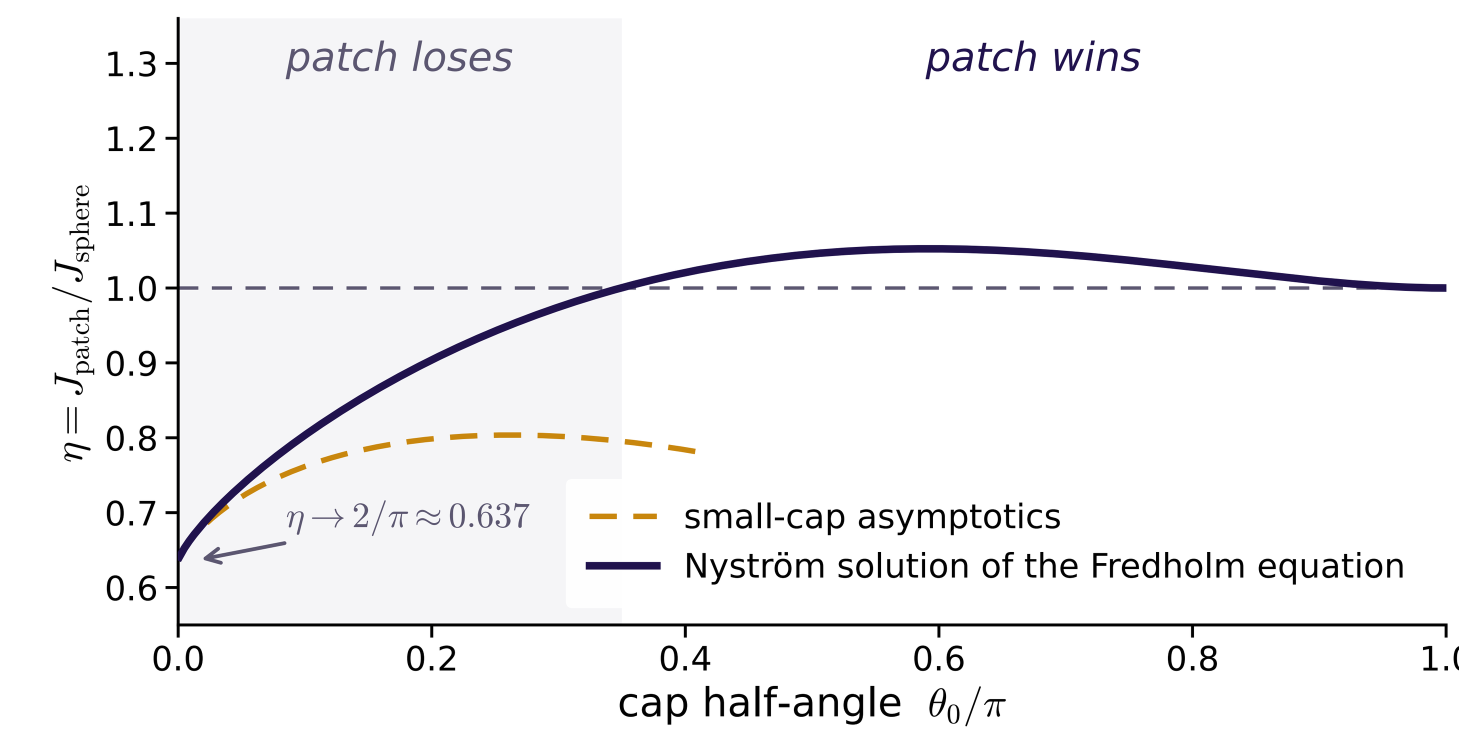


→ Capture probability is related to density distribution plotted above by $p = 1 - u/u_0$

Results

We compute the association rate using the steady-state flux to the target, with diffusion coefficient κ.

$$\eta(\theta_0) = \frac{J_{\text{patch}}}{J_{\text{sphere}}} = \frac{-4\pi\kappa u_0 R\, B_0}{4\pi\kappa u_0 R\sin(\theta_0/2)} = \frac{-B_0(\theta_0)}{\sin(\theta_0/2)}$$



$$\eta(\theta_0) \ge 1 \quad \text{for } \theta_0 > 0.3491\pi.$$

In the limit $\theta_0 \to 0$ we recover the classical case of a disc on a reflecting plane.

→ Patch size for $\theta_0 > 0.35\pi$ is large... how to make biological sense of this?

→ Search as a two-step process:

!!! NOT a 3D search from bulk straight onto the precise reaction site

→ 2D diffusion on surface to small reaction site: gives the reaction site an **"effective radius"** defined by capture probability for a 2D searcher

→ 3D diffusion to the surface is then coupled to the 2D search via this effective radius

Next questions

→ To what extent do biological proteins take advantage of this principle?

→ Some evidence from protein-protein associations ("binding funnel")

→ What about larger structures (e.g. condensates?)

→ When is nonspecific binding an advantageous strategy, if there are multiple patches embedded in one structure? Or if only some structures have reaction sites?

→ What about the 2D search step? Can we find a plausible model for surface search, e.g. on a condensate, that produces an effective radius in a sensible range?

→ Why do these two different characterizations, $|B_1/B_0|$ and η, recover nearly the same transition point at around 0.35π? (they differ by $0.0024\pi \approx 0.43°$)

References

Adam & Delbrück, *PNAS* (1968) • Berg et al., *Biochemistry* (1981) • Berg, *Biophys. J.* (1985) • Hołyst et al., *PRE* (2000) • Sneddon, *Mixed BVPs in Potential Theory* (1966).