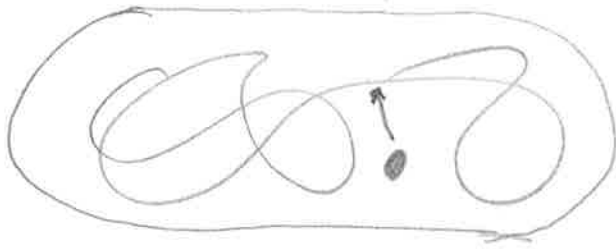


Target search on DNA



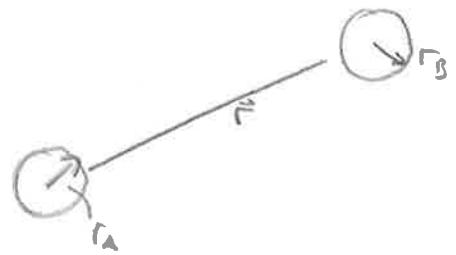
- 5×10^6 bp in μm^3
- specific binding site
- low copy numbers TF (10 copies of lac repressor)

diffusion in 3D

- general (problem of) diffusion limited rates
- upper limit on any enzymatic reaction

$$\sim k [S] [E]$$

\uparrow substrate \uparrow enzyme



- relative diffusion constant

$$D = D_A + D_B \quad \left[\frac{\mu\text{m}^2}{\text{s}} \right]$$

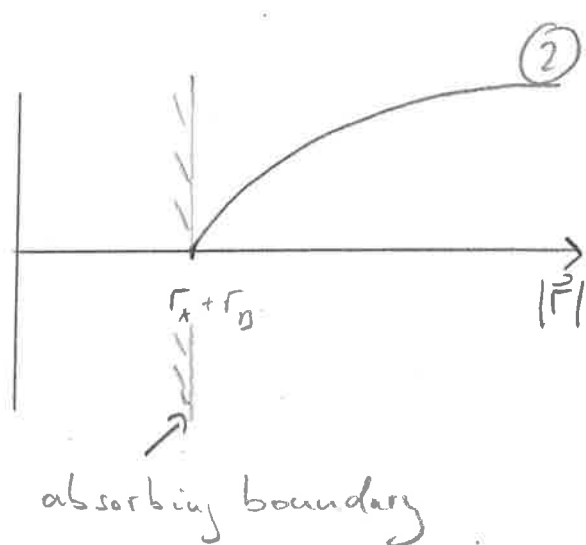
- radii are important (they hit each other if $|r| < r_A + r_B$)

• k has units $\frac{\text{length}^3}{\text{s}} \Rightarrow k \sim D(r_A + r_B)$

→ diffusion limited rate of perfectly absorbing spheres

$$k = 4\pi (D_A + D_B) (r_A + r_B)$$

Absorbing sphere



- isotropic \rightarrow only $|\vec{r}|$ matters
- we are looking for a steady constant flux solution

$$C = Dr^2 \frac{\partial P(r)}{\partial r} \Rightarrow \frac{\partial P}{\partial r} = \frac{C}{Dr^2}$$

$$\Rightarrow P(r) = X \left(1 - \frac{r_A + r_B}{r} \right)$$

- the gradient at the boundary is $\frac{X}{r_A + r_B}$
- multiplying by the surface area, we have

$$R = 4\pi (r_A + r_B)^2 \frac{D}{r_A + r_B} = 4\pi D (r_A + r_B)$$

- this rate is an upper bound, geometric constraints reduce it. (orientation, smaller binding surfaces)
- electrostatic attraction makes these problems often less severe

Diffusion limited binding site search

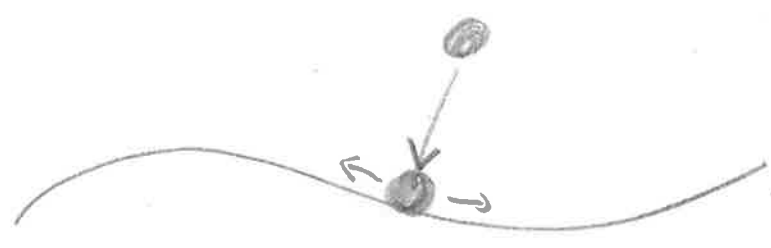
- DNA doesn't move much: $D_{DNA} + D_{TF} \approx D_{TF} \approx 100 \frac{\mu m^2}{s}$
(in vitro, in vivo $\frac{1}{3}$)

- reactive length: one basepair precision
 $\Rightarrow r = 0.3 nm$

$$K = 4\pi \times 100 \times 0.3 \times 10^{-3} \frac{mm^3}{s} \approx 0.4 \frac{mm^3}{s} \approx 2 \times 10^8 M^{-1}s^{-1}$$

- measurements in vitro: $k \approx 10^{10} / Ms$
- ~ 100 fold discrepancy that puzzled Qbio folks
 \rightarrow discovery of new mechanism and search paradigms

Combined 1D/3D search

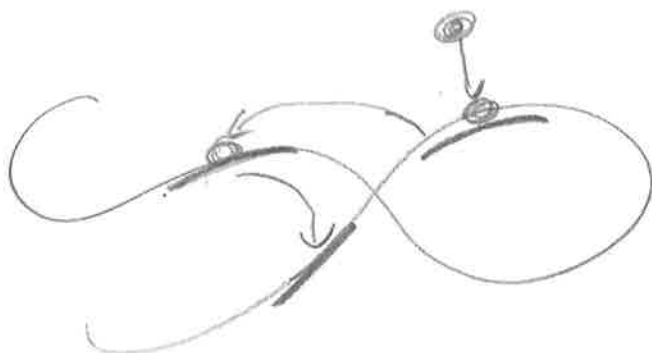


- TF binds unspecifically to DNA
- scans local sequence for binding site

- distance searched
- $l \approx \sqrt{2D_{1D}t}$ (max extend 2 fold higher)
- initially fast search, but increasingly redundant
- $D_{1D} \approx 10^5 - 10^6 \frac{bp^2}{s} = 0.01 - 0.1 \frac{\mu m^2}{s}$
- much slower than 3D
- $10^6 \sim \sqrt{2D_{1D}t} \Rightarrow t \approx 10^6 s \rightarrow$ way too long

What if search was combined 1D/3D?

(4)



• time to find site

k ← number cycles until success

$$t_s = \sum_{i=1}^k (\tau_{i,1D} + \tau_{i,3D})$$

↑ time on DNA ↑ time in solution

$\bar{l} = \frac{L}{\bar{e}}$ ← genome length

← length searched in one round.

$$\bar{e} = \sqrt{2D_{1D} \bar{\tau}_{1D}}$$

$$\Rightarrow t_s = \bar{l} (\bar{\tau}_{1D} + \bar{\tau}_{3D}) = \frac{L}{\sqrt{2D_{1D} \bar{\tau}_{1D}}} (\bar{\tau}_{1D} + \bar{\tau}_{3D})$$
$$= \frac{L}{\sqrt{2D_{1D}}} \left(\sqrt{\bar{\tau}_{1D}} + \sqrt{\frac{\bar{\tau}_{3D}}{\bar{\tau}_{1D}}} \right)$$

$$\frac{\partial t_s}{\partial \bar{\tau}_{1D}} = \frac{L}{2\sqrt{2D_{1D}}} \left(\frac{1}{\sqrt{\bar{\tau}_{1D}}} - \frac{\sqrt{\bar{\tau}_{3D}}}{\bar{\tau}_{1D}^{3/2}} \right) = 0$$

$$\Rightarrow \boxed{\bar{\tau}_{1D} = \bar{\tau}_{3D}} \Rightarrow \text{equal time!} \nabla$$

Why is there an optimum?

(5)

$\tau_{10} \rightarrow 0 \rightarrow$ pure 3D search

$\tau_{10} \rightarrow \infty \rightarrow$ pure 1D search

Intersegment transfer

- optimal is 50/50, but TFs are often unspecifically associated with DNA > 90%
- possible explanation: intersegment transfer



- distant DNA pieces come close in 3D
- direct transfers from one to another reduce redundancy of local search
- DNA contacts have a length distribution of $r \sim s^{-3/2}$