Target search on DNA

- 5x10^6 bp in \( \mu m^2 \)
- Specific binding site
- Low copy number TF (10 copies of lac repressor)

**Diffusion in 3D**

- General problem: diffusion limited rates
- Upper limit on any enzymatic reaction

\[
\tilde{\kappa} \sim K [S][E]
\]

- Relative diffusion constant

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

- Radii are important (they limit each other if \( 1/15 < r_A + r_B \))

- \( \kappa \) has units \( \frac{length^3}{s} \)

\[
\kappa \sim D(r_A + r_B)
\]

\( \rightarrow \) Diffusion limited rate of perfectly absorbing spheres

\[
\kappa = 4\pi \left( D_A + D_B \right) (r_A + r_B)
\]
**Absorbing sphere**

- Isotropic \( \Rightarrow \) only \( \frac{1}{r^2} \) matters

- We are looking for a steady, constant flux solution

\[
C = D r^2 \frac{\partial P(r)}{\partial r} \Rightarrow \frac{\partial P}{\partial r} = \frac{C}{D r^2}
\]

\[
\Rightarrow P(r) = \frac{x}{r} \left( 1 - \frac{r_A + r_B}{r} \right)
\]

- The gradient at the boundary is \( \frac{x}{r_A + r_B} \)

- Multiplying by the surface area, we have

\[
12 = 4\pi (r_A + r_B)^2 \frac{D}{r_A + r_B} = 4\pi D (r_A + r_B)
\]

- This rate is an upper bound; geometric constraints reduce it.
  (Orientation, smaller binding surface)

- Electrostatic attraction makes these problems often less severe
Diffusion limited binding site search

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

- reactive length: one base pair precision
  \( r = 0.3 \, nm \)

  \[ K = \frac{4D_{\text{TF}} \times 100 \times 0.3 \times 10^{-9} \, \mu m^2 / s}{1} \approx 0.4 \, \mu m^2 / s \approx 2 \times 10^8 \, M^{-1} \cdot s^{-1} \]

- measurements in vitro: \( K \approx 10^{10} / M \)

- ~100-fold discrepancy that puzzled Abio Sols
  → discovery of new mechanism and search paradigms

Combined 1D/2D search

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

- distance searched

  \[ l = \sqrt{2D_{\text{tot}}t} \quad (\text{max extend 2-fold higher}) \]

- initially fast search, but increasingly redundant

- \( D_{1D} \approx 10^5 - 10^6 \, \frac{bp^2}{s} = 0.01 - 0.1 \, \mu m^2 / s \)

- much slower than 3D

  \[ 10^6 \approx \sqrt{2D_{1D}} \Rightarrow t \approx 10^6 \, s \quad \text{way too long} \]
What is search was combined 15/30?

- time to find sick
  \[ t_s = \sum_{i=1}^L (\tilde{\tau}_{i,10} + \tilde{\tau}_{i,30}) \]
  \[ \text{time on DNA} \quad \text{time in solution} \]

\[ \overline{12} = \frac{L}{\bar{e}} \]
\[ \text{genome length} \]
\[ \text{length searched in one round} \]

\[ e = \sqrt{2D_{10}} \sqrt{\tilde{\tau}_{10}} \]

\[ t_s = 12 (\sqrt{\tilde{\tau}_{10}} + \sqrt{\tilde{\tau}_{30}}) = \frac{L}{\sqrt{2D_{10} \tilde{\tau}_{10}}} \left( \sqrt{\tilde{\tau}_{10}} + \sqrt{\tilde{\tau}_{30}} \right) \]
\[ = \frac{L}{\sqrt{2D_{10}}} \left( \sqrt{\tilde{\tau}_{10}} + \sqrt{\tilde{\tau}_{30}} \right) \]

\[ \frac{\partial t_s}{\partial \tilde{\tau}_{10}} = \frac{L}{2 \sqrt{2D_{10}}} \left( \frac{1}{\sqrt{\tilde{\tau}_{10}}} + \frac{\sqrt{\tilde{\tau}_{30}}}{\tilde{\tau}_{10}} \right) = 0 \]

\[ \Rightarrow \overline{\tilde{\tau}_{10}} = \overline{\tilde{\tau}_{30}} \Rightarrow \text{equal time?} \]
Why is there an optimum?

\[ \tau \rightarrow 0 \quad \rightarrow \text{pure 3D search} \]

\[ \tau \rightarrow 0 \quad \rightarrow \text{pure 1D search} \]

**Intrasegment transfer**

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

\[ \infty \]

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