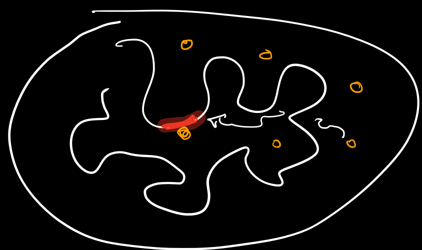
Protein-DNA kinetics

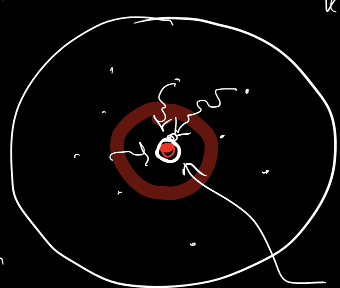


t_s time takes for a protein to find its site

$$t_s = (k_{on} \cdot [S])^{-1}$$

- Diffusion: binnde

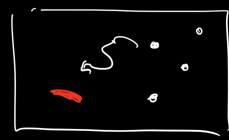
k_{on} - ?



Marian Smoluchowski (1917) Lviv

target of radius r_0

Bimolecular reaction



t_{search} for a protein to find its target

$$[P] + [S] \xrightarrow{k_{on}} [P \cdot S]$$

k_{on} - units? related to t_{search}

$$\frac{d[PS]}{dt} = k_{on}[P][S] \qquad k_{on} - [M^{-1} s^{-1}]$$

$$t = (k_{on} [\text{concentration}])^{-1}$$

[P] [S]

Rate of getting a site occupied $= \frac{d[PS]/[S]}{dt} = k_{on}[P]$

Rate of protein finding a target $= \frac{d[PS]/[P]}{dt} = k_{on}[S]$

$$\underset{[P]}{C(\infty)}\, k_{on} = \{\text{total flux through the surface of the target}\} = I$$

$C(\infty) = \text{const}$

$C(r_0) = 0$

$C(\infty) = \text{const}$

$$\Delta C(r) = 0$$

concentration of the protein

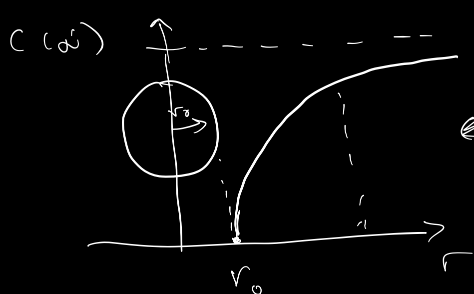
$$\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \frac{\partial}{\partial r} C(r)\right) = 0$$

$= 0$, const

$$r^2 \frac{\partial C(r)}{\partial r} = A$$

$$C(r) = A\frac{1}{r} + B$$

$$\boxed{C(r) = \left(1 - \frac{r_0}{r}\right) C(\infty)}$$



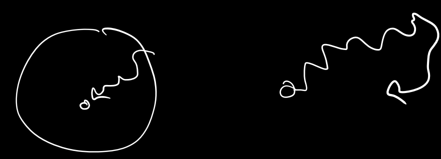
~1 nm, 1 μm

← no effect beyond $r \approx 2r_0$

no local crowding!

$c(\infty)\, k_{on} = \overset{\text{total}}{\text{flux}} \equiv I = 4\pi r_0^2 \cdot J$

J ↑ flux



$$J = -D \nabla c(r)\Big|_{r=r_0}$$

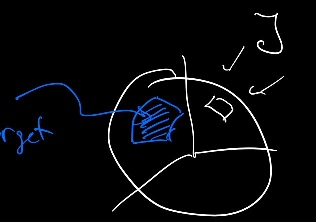
$$= D \frac{r_0}{r_0^2} c(\infty)$$

$$c(\infty)\, k_{on} = 4\pi r_0^2 D \frac{1}{r_0} c(\infty) = 4\pi D r_0 c(\infty)$$

$$\boxed{k_{on} = 4\pi D r_0 \, a}$$

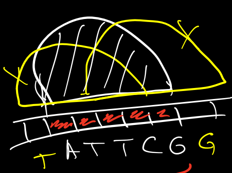
← Smoluchowski rate

a — fraction of the surface of the target that is reactive



$I = 4\pi r_0^2 J a$

Estimate k_{on} for protein-DNA interactions

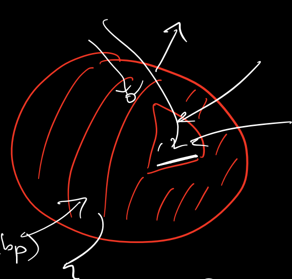


r_0 - ?

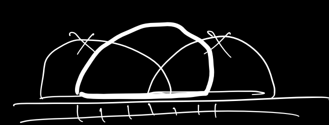
$D \sim 3 \cdot 10^{-7} \frac{cm^2}{s}$

r_0 = site size ?

$r_0 = 0.34\,nm \cdot L\,(bp)$



$a = 1/L$



$r_0 a = 0.34 \cdot L/L = 1\,bp$

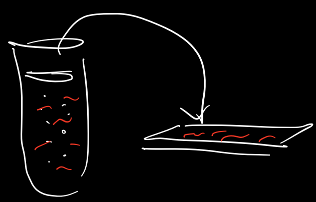
$$\boxed{k_{on}^{Smol}} = 10 \cdot 3 \cdot 10^{-7} \frac{cm^2}{s} \cdot 1\,bp = 10 \cdot 3 \cdot 10^{-7} \frac{cm^3}{s} \cdot \frac{1}{3} 10^{-7}$$

$1\,bp = \frac{1}{3}\,nm = \frac{1}{3} \cdot 10^{-7}\,cm$

$$= 10^{-13} \frac{cm^3}{s} = 10^{-13} \frac{cm^3}{s} 10^{-3} \frac{l}{cm^3} = 10^{-16} \frac{l}{s} \times 6 \cdot 10^{23} \frac{1}{l} \frac{l}{M}$$

$$= \boxed{10^7\, M^{-1} \cdot s^{-1}}$$ ← speed limit

100 – 1000 fold



Art Riggs (1970)

$$k_{on}^{exp} = 10^{9} - 10^{10}\ M^{-1} s^{-1}$$

proteins Bind DNA

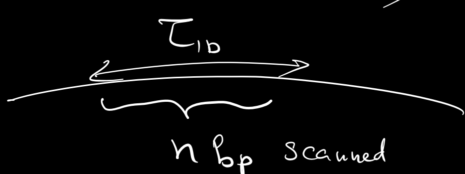
100 - 1000 times faster!

o Facilitated diffusion!

Max DelBruck : changing dimentionality could help... Otto Peter Berg & von Hippel

· 1D+3D diffusion

$$t_s = \left\{ \begin{matrix}\#\text{ of} \\ \text{rounds}\end{matrix} \text{ of } \begin{matrix}3D+1D \\ \text{diffusion}\end{matrix} \right\} \times (\tau_{1D} + \tau_{3D})$$



prob to find the site on one round $= \dfrac{n}{M}$

$n \ll M$

$$\left\langle \begin{matrix}\#\text{ of rounds} \\ \text{till success}\end{matrix} \right\rangle = \frac{M}{n}$$

$$t_s = \frac{M}{n}(\tau_{1D} + \tau_{3D})$$

$$n^2 = 2D_{1D}\tau_{1D}$$

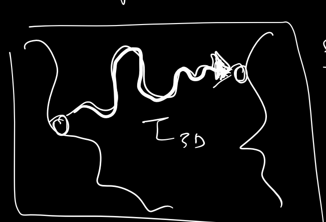
size protein

$$= \frac{M}{\sqrt{2D_{1D}\tau_{1D}}}(\tau_{1D} + \tau_{3D})$$

determined by protein-DNA non-specific Binding energy!

depends on [DNA] & D_{3D}

$$E_{ns} \approx L \cdot 1\,kT$$



$$t_s = \frac{M}{\sqrt{2D\tau_{1D}}}\left(\tau_{1D} + \tau_{3D}\right) \longrightarrow \text{optimal? over } \tau_{1D}$$

$$0 = \frac{dt_s}{d\tau_{1D}} = \frac{M}{\sqrt{2D}} \cdot \frac{d}{d\tau_{1D}}\left[\sqrt{\tau_{1D}} + \frac{\tau_{3D}}{\sqrt{\tau_{1D}}}\right] =$$

$$\sim \frac{1}{\sqrt{\tau_{1D}}} + \frac{\tau_{3D}}{\tau_{1D}^{3/2}} = 0$$

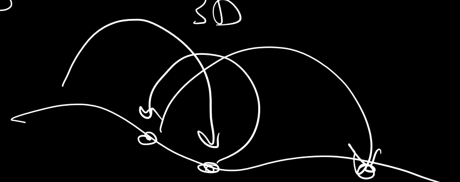
$$\boxed{\tau_{1D}^{opt} = \tau_{3D}}$$ ← very general...

$$\boxed{t_s^{optimal} = \frac{M}{n} 2\tau_{3D}}$$ ← optimal 3D + 1D search

o How much faster is this 1D+3D?

3D only: $n = 1$ $\tau_{1D} = 0$

$$\boxed{t_s^{3D} = M\tau_{3D}}$$



1D only $\tau_{3D} = 0$ $n = M$

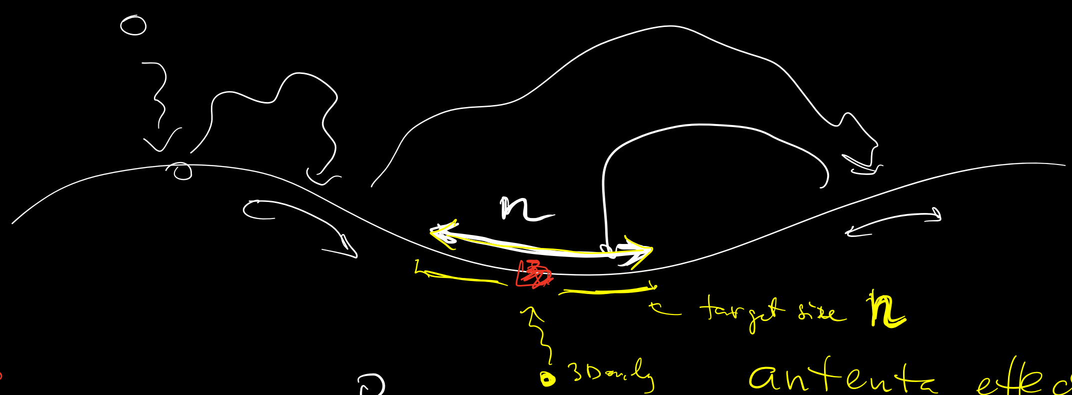
$M^2 = 2D_{1D}\tau_{1D}$ $\tau_{1D} = \frac{M^2}{2D_{1D}}$

$$\boxed{t_s^{1D} = \frac{M}{M} \cdot \frac{M^2}{2D_{1D}} \sim M^2}$$

$$\boxed{\frac{t_s^{3D}}{t_s^{opt}} = \frac{M\tau_{3D}}{2M/n \cdot \tau_{3D}} = \frac{n}{2}}$$ ← acceleration due to 1D + 3D

↑ why?

Recall Smoluchowski $k_{on} = 4\pi D_{3D} r_0 \cdot a$



antenna effect

$n^{exp} \simeq 200 - 1000$ bp

×2 ← reflects that the protein spends 1/2 of its time on remote places on DNA

$$D_{1D}^{exp} \simeq 10^{6} \frac{bp^2}{s}$$

if $\tau_{1D} \simeq 1$ sec $\quad n \simeq 10^{3}$ bp