Unpacking this result: 

\[ \tau(r) = \frac{R_{\text{max}}^3}{3DR} - \frac{R_{\text{max}}^3}{3DR} - \frac{r^2}{6D} + \frac{R^2}{6D} \]

Even at separation of 2R, \( \tau \) is 50% of value at separation \( R_{\text{max}} \)!

Since \( R \approx 2 \) nm, once proteins become separated by \( \approx 10 \) nm or more, it will take them roughly the same (long) time to find each other again.
Unless the particles start very close to each other \((r \approx R)\) the average time to capture is almost independent of initial separation:

\[
T \approx \frac{R_{\text{max}}^3}{3DR} = \left(\frac{R_{\text{max}}}{6D}\right) \left(\frac{2R_{\text{max}}}{R}\right)
\]

Can think of
\[
\left(\frac{2R_{\text{max}}}{R}\right) \propto \frac{1}{\text{chance of collision during one random sweep}}
\]

additional factor required to get particles to meet

\[
T \approx \frac{R_{\text{max}}^3}{3DR}
\]

two proteins meeting in bacteria:

\(D_1 = 10 \, \mu m^2/s\)

\(R_1 = 1nm\)

\(R_2 = 1nm\)

\(D_2 = 10 \, \mu m^2/s\)

\(R_{\text{max}} = 1 \, \mu m\) for bacteria

\(D = 20 \, \mu m^2/s = D_1 + D_2\)

\(R = 2 nm = R_1 + R_2\)

\[
T = \left(8.3 \times 10^{-3} \, s\right) \left(1000\right) = 8.3 \, s
\]

What if we had \(n\) particles, all searching for 1 target? (radius \(r_2\))

\[
T \approx \left(\frac{R_{\text{max}}^2}{6D}\right) \left(\frac{2R_{\text{max}}}{nR}\right)
\]

likelihood of collision increases by factor \(n\)
\[ V = \frac{4}{3} \pi R_{\text{max}}^3 \]  

volume confining particles

\[ \tau = \frac{V}{4\pi DR_n} = \frac{1}{4\pi DR c} \]

where

\[ c = \frac{n}{V} \]

concentration of searching particles

rate of molecules reaching target

\[ k_0 = \frac{1}{\tau} = 4\pi DR c \]

units: s^{-1}

"Smoluchowski rate"

Sometimes also written as rate per concentration:

\[ k_{\text{mol}} = \frac{k_0}{c} = 4\pi DR \]

where \( c \) is measured in molar

\[ 1 \text{ M} = \frac{N_A}{L} = \frac{6.022 \times 10^{23}}{10^{-3} \text{ m}^3} \]
find maximum using \( \frac{dk}{d\phi} = 0 \) \( \Rightarrow \phi = \frac{1}{4} \) [quite realistic!]

\[ c = \frac{\phi}{V_{prot}} = 7 \text{ mM} \]

\( n = cV \approx 4 \times 10^6 \) proteins in the cell

[actual # for E. Coli \( \approx \) with \( V = 1 \mu m^3 \) for bacteria

\( n \) (total) \( = 3 \times 10^6 - 10^7 \) proteins depending on growth rate]

optimal \( k \approx 2.6 \times 10^6 \) s\(^{-1}\)

[For E.Coli, the genome takes up \( 5 \times 10^6 \text{ bp} \times (1 \text{ nm})^3 \) of volume, or \( \phi = 0.005 \) s, we can ignore it.]

[Of course, this is for one protein type, one target.]

In reality, many proteins of different types, each with different targets.

For each type, the concentration

\[ c \leq \text{ mM} \]

\( n \leq 10^6 \) for \( V = 1 \mu m^3 \)

For E. Coli: \( c \approx 10 \text{ nM} - 0.1 \text{ mM} \) \( \approx 10^{-10^5} \) copies/cell

[See also Ch. 2 of PBOC.]

Can we go even smaller?

Keep in mind that really

\[ \phi \approx \frac{n_{prot} V_{prot}}{V} + \frac{n_{bp} V_{bp}}{V} \]

where \( n_{prot} = \# \text{ proteins} \)

\( n_{bp} = \# \text{ bp of DNA} \) \( V_{bp} \approx 1 \text{ nm}^3 \)

\( \Rightarrow \) indep. of volume \( V \)!
For *E. Coli* w/ $5 \times 10^6$ bp the second term is negligible, but as we go smaller the contribution of the genome becomes more important.

What happens after molecules meet?

In order to get specific combinations of molecules + reactions to occur in the crowded cellular environment (where collisions with random proteins/DNA may occur on ms time scales), binding is controlled by shape + the chemistry of the molecular surfaces (more on that next lecture). This adds an extra step to the process: molecules must meet, and have the right shape/orientation to bind.

Simple three state picture: [focus on one target molecule]

1. $k_s = 4\pi DRc$
2. $k_b$
3. $k_d$

$\Rightarrow$ depends on how quickly searching molecule can find the right orientation when near target + bind $\Rightarrow$ can be 100 ns or longer just for rotational reorientation.
\[ k_u = \text{how quickly molecules drift apart without interactions keeping them close,} \]

\[ k_u \approx \left( \frac{R^2}{6D} \right) \] (diffusion time to drift \( R \) distance away) \(^{-1} \)

\[ \approx (8 \text{ ns})^{-1} \] very fast!

for \( R = 1 \text{ nm}, D = 20 \mu \text{m}^2/\text{s} \)