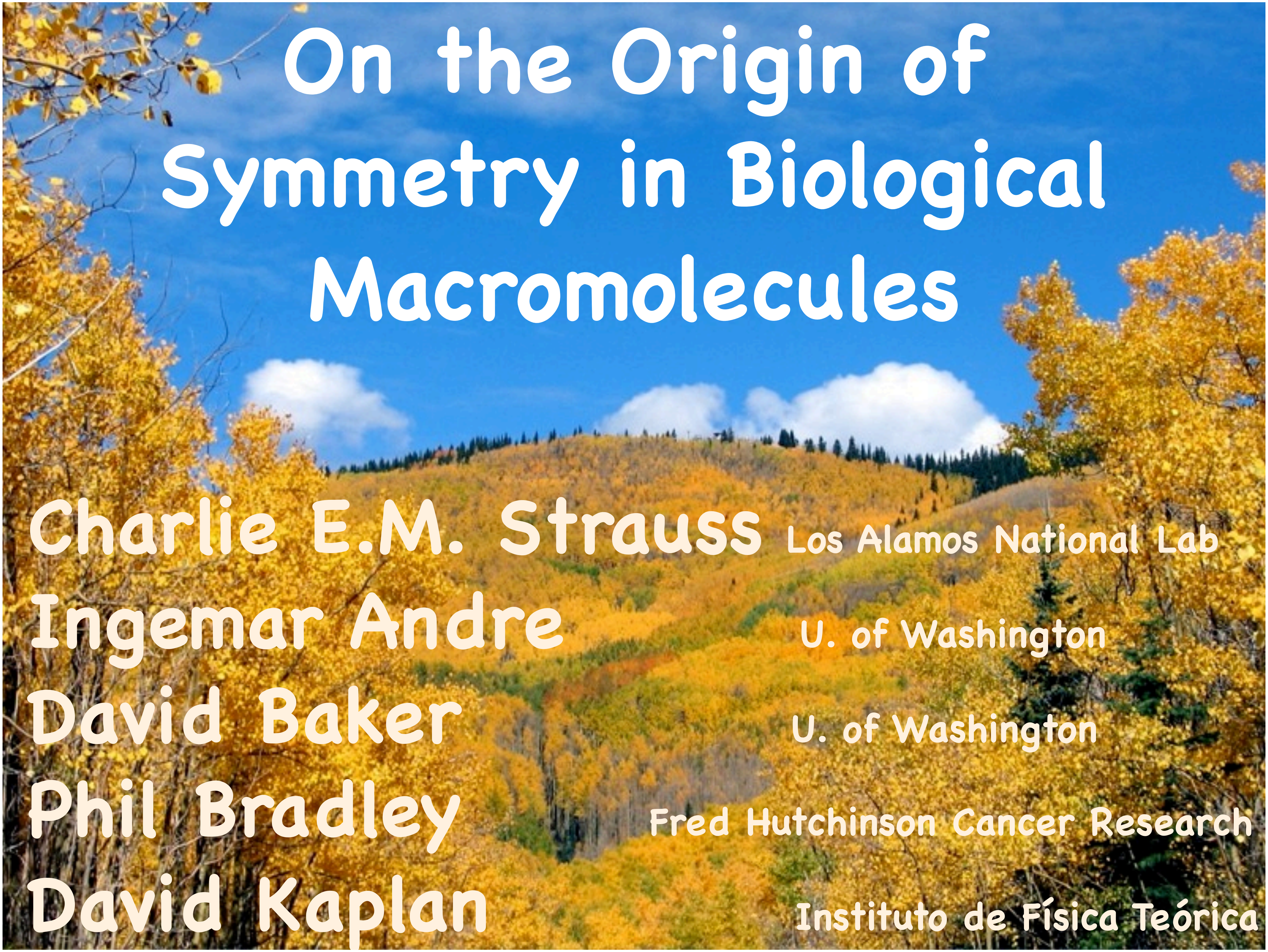


On the Origin of Symmetry in Biological Macromolecules

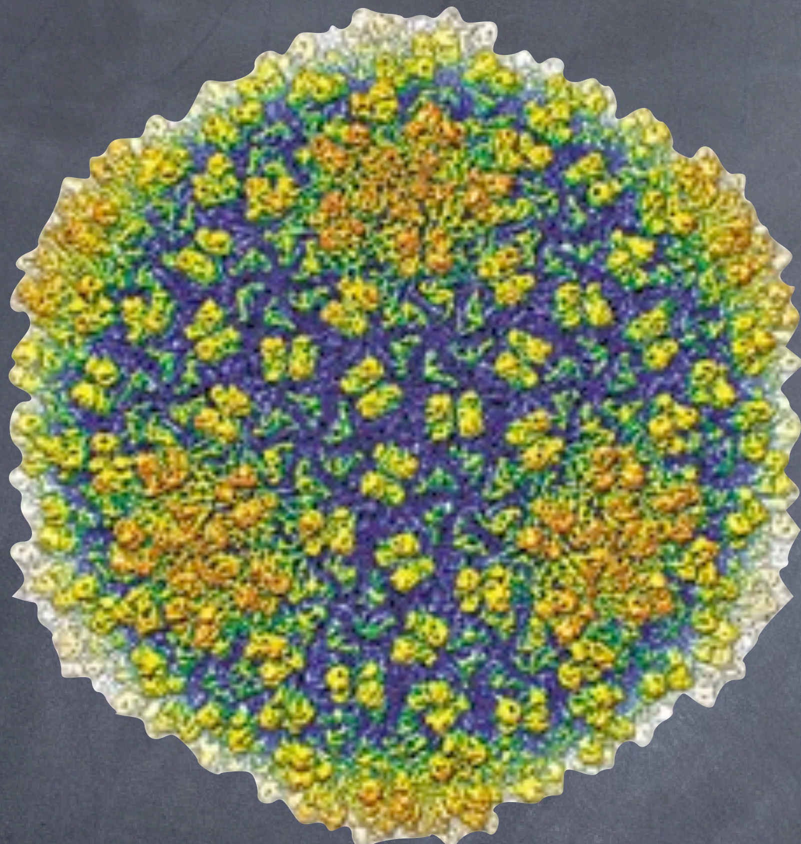
Charlie E.M. Strauss Los Alamos National Lab

Ingemar Andre U. of Washington

David Baker U. of Washington

Phil Bradley Fred Hutchinson Cancer Research

David Kaplan Instituto de Física Teórica



When proteins structures were first solved many were surprised that the subunits of the macroscopic symmetric structures turned out to be asymmetric.

Monomer Proteins are Rare

E. Coli (Goodsel + Olson 2000)

- Only 1/5th of proteins are monomers
- Most frequent form is symmetric homo dimer

Why?

Evolution “creates” symmetry because it....

- ...benefits the organism
- ...is a side effect
- ...sensitizes evolution

The sad secret of arguments about evolutionary history

(Can't truly quantitatively say how much any effect really mattered)

Our Pre-evolutionary hypothesis

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- Evolutionary selection can't favor anything that is not formed long enough to convey a fitness advantage.
  - only low binding energies are competent

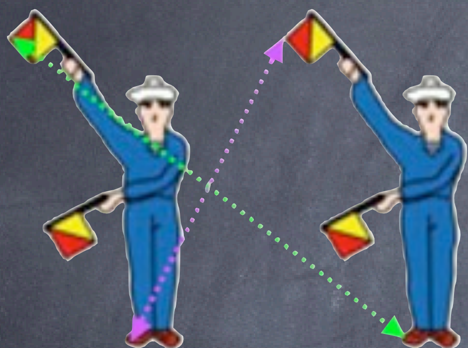
Our Pre-evolutionary hypothesis

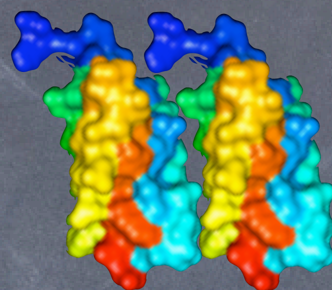
- Evolutionary selection can't favor anything that is not formed long enough to convey a fitness advantage.
  - only low binding energies are competent
- The sub-population of low energy random homo-dimer is overwhelmingly symmetric.
  - Quantitatively sufficient to account for the prevalence of dimer symmetry in the Protein Data Base.

Measuring "nearly" symmetric

C2 symmetry: atom pairs obey:

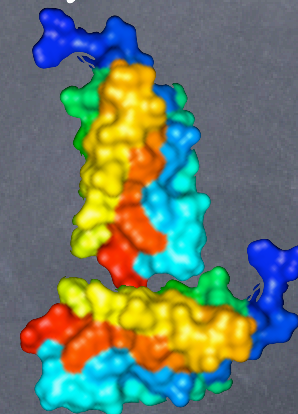
Distance(A->B') = Distance (B->A')

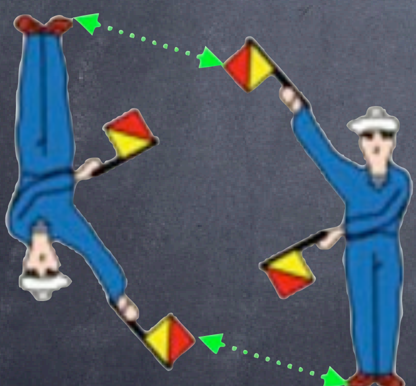


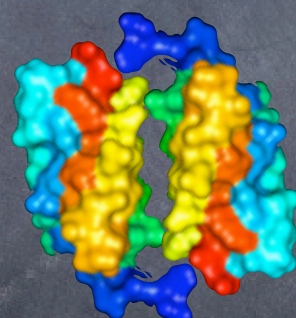


Asymmetric

$|A\text{-}B'| \neq |A'\text{-}B|$

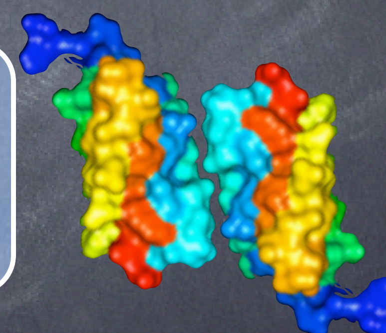






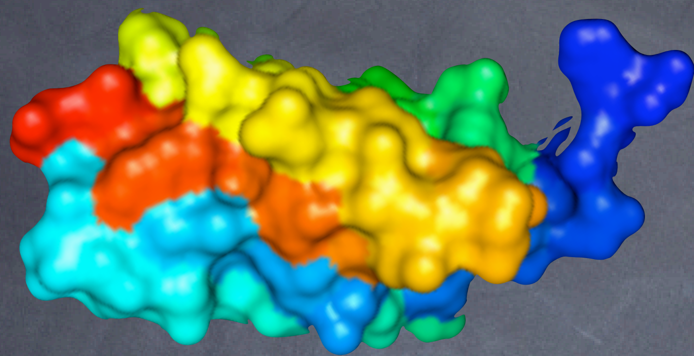
Symmetric

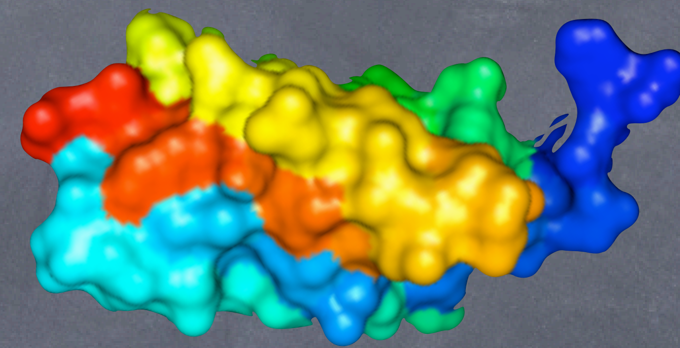
$|A\text{-}B'| = |A'\text{-}B|$



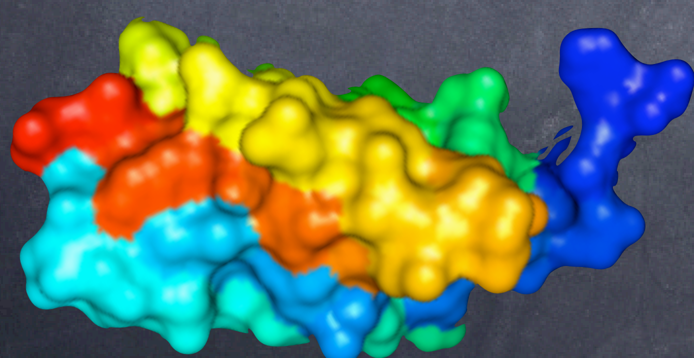
$$S_{dev} \equiv \left| dist(A,B') - dist(B,A') \right|$$

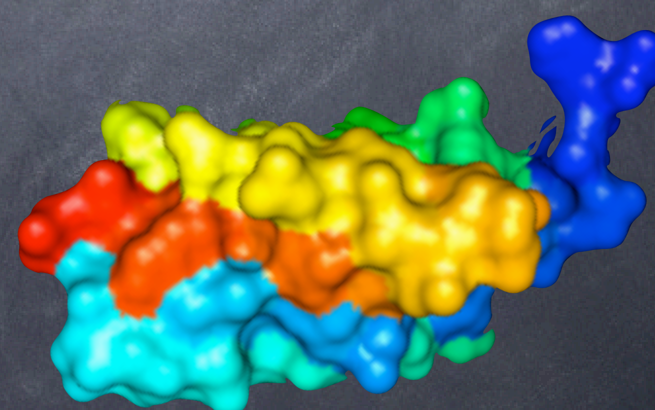
$$S_{dev} \equiv \frac{1}{N}\sum_{N}|dist(A,B') - dist(A',B)|$$





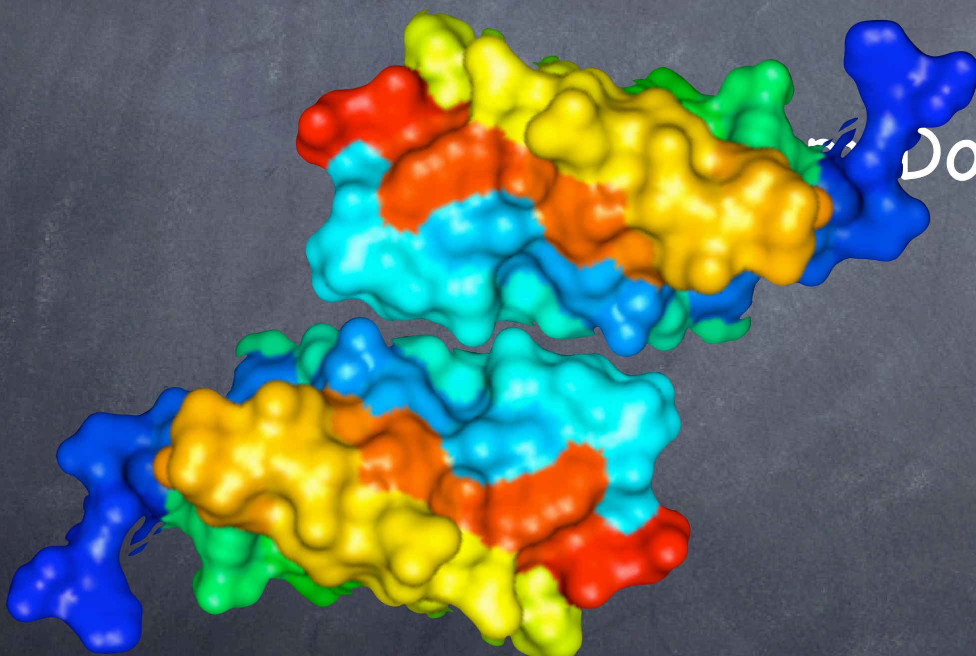
Random Docking

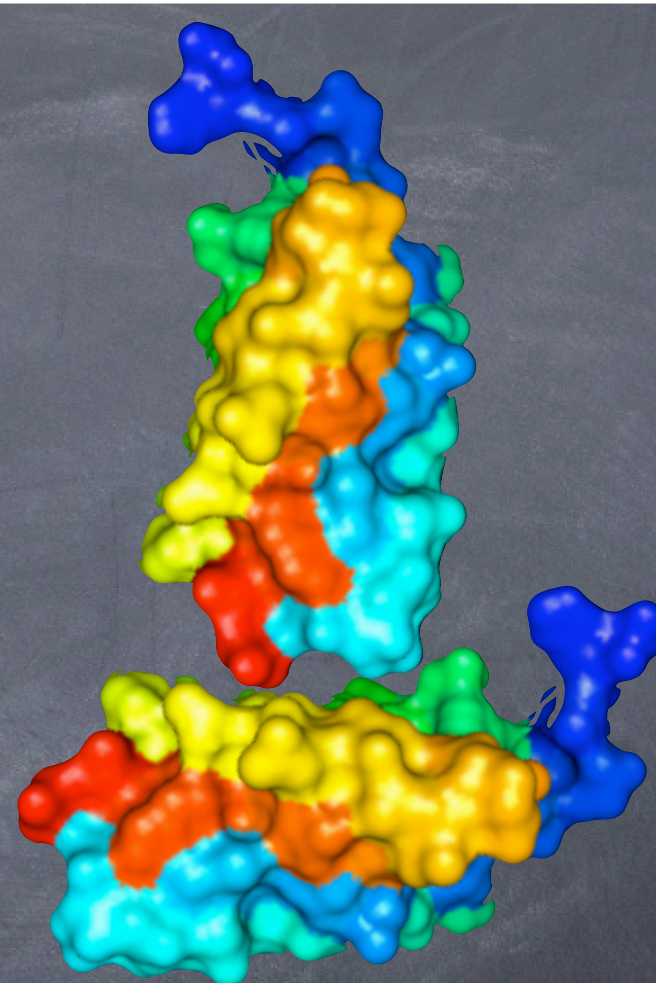




$$S_{dev} \equiv \frac{1}{N}\sum_{N}|dist(A,B') - dist(A',B)|$$

Sdev=0
Symmetric



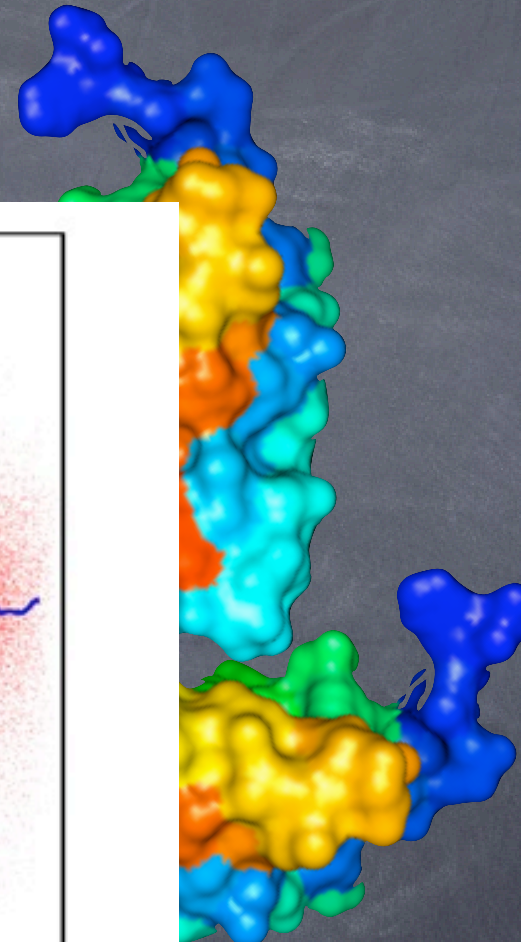


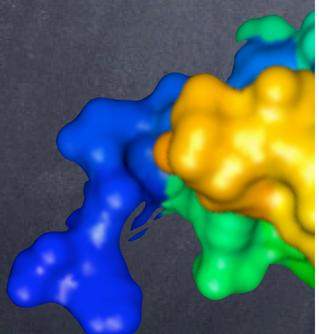
Sdev >> 0
Asymmetric

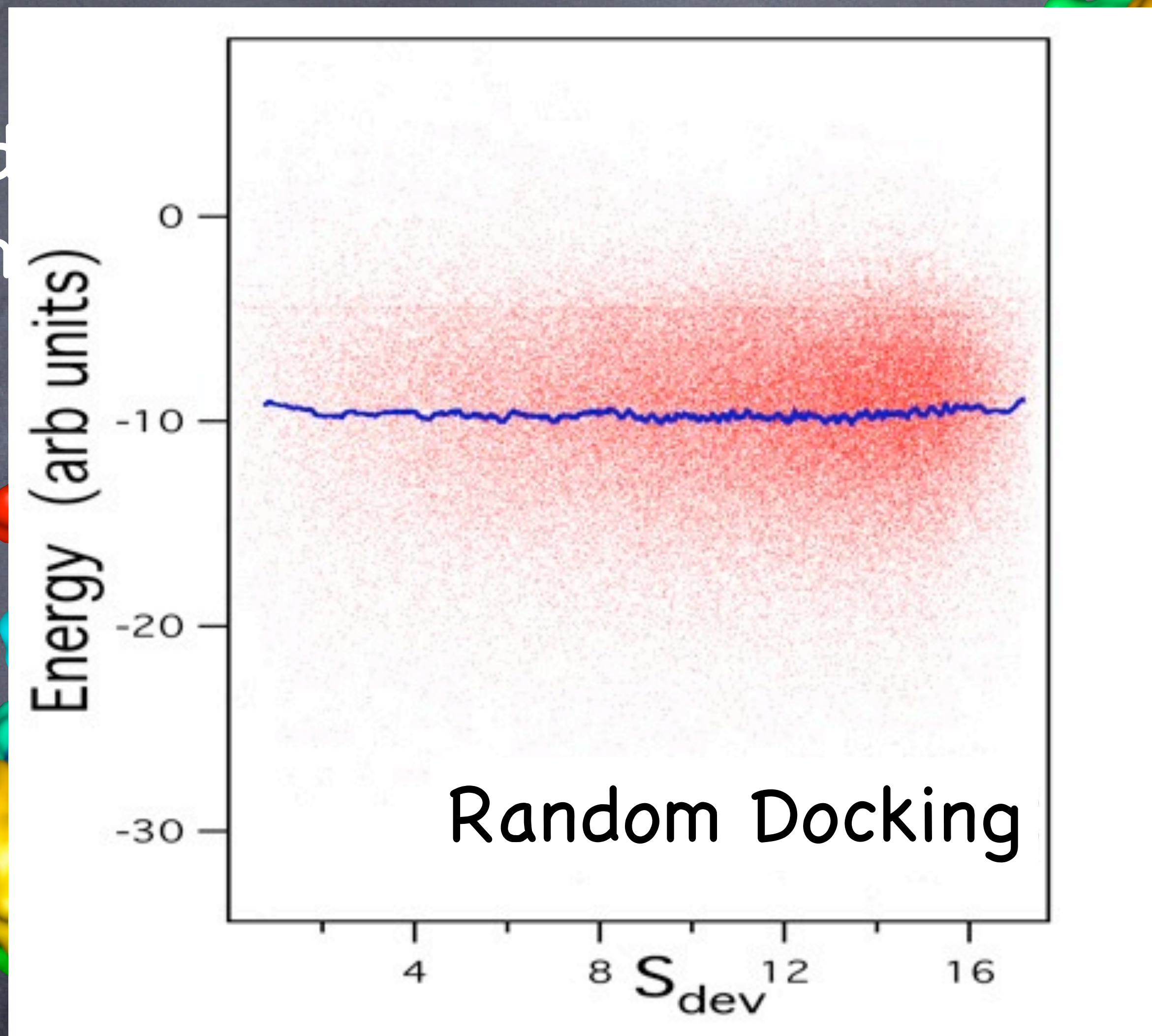
$$S_{dev} \equiv \frac{1}{N} \sum_{N} |dist(A, B') - dist(A', B)|$$

Sd

Sym







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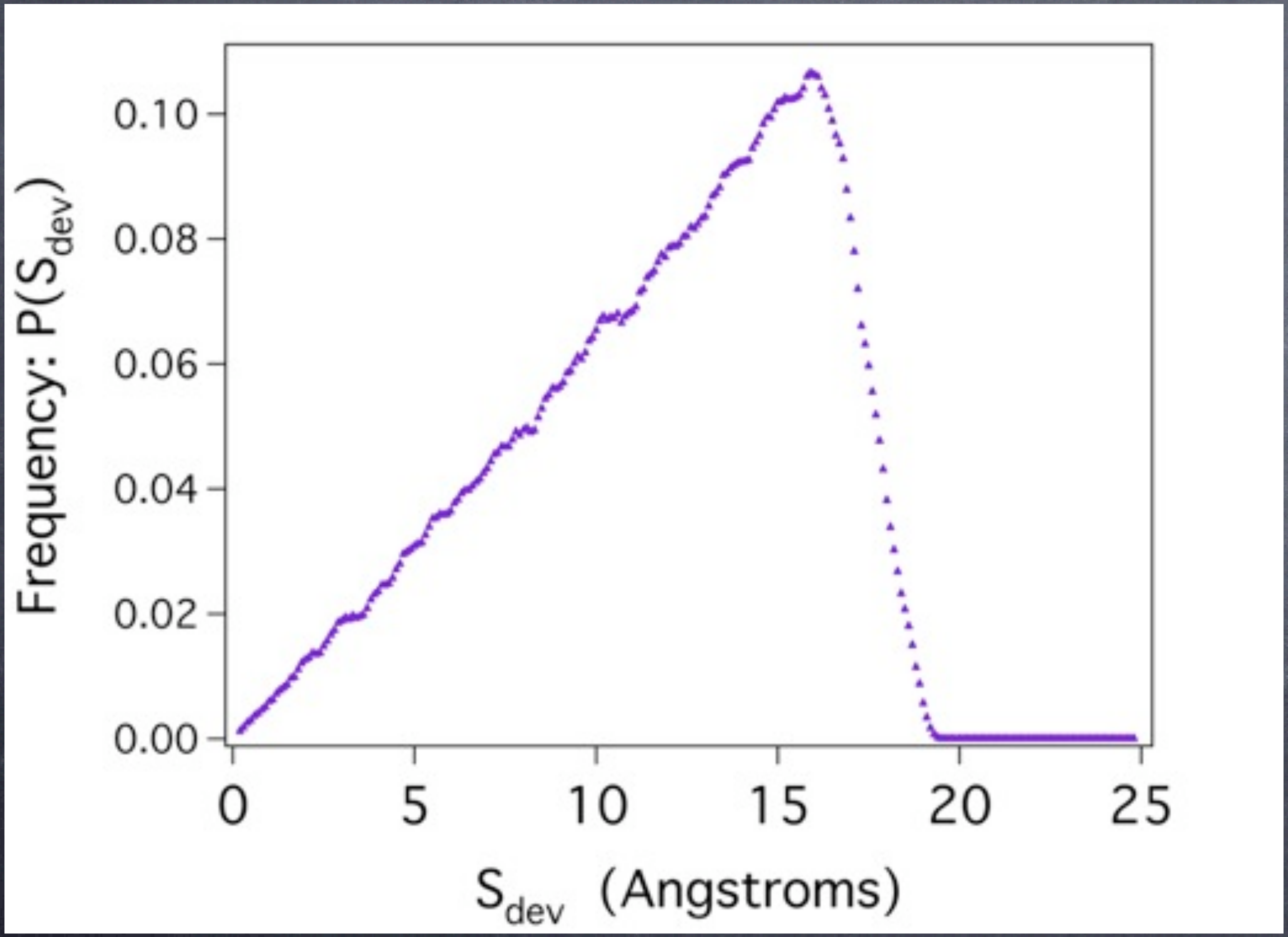
tric

Randomly Docked Homodimers

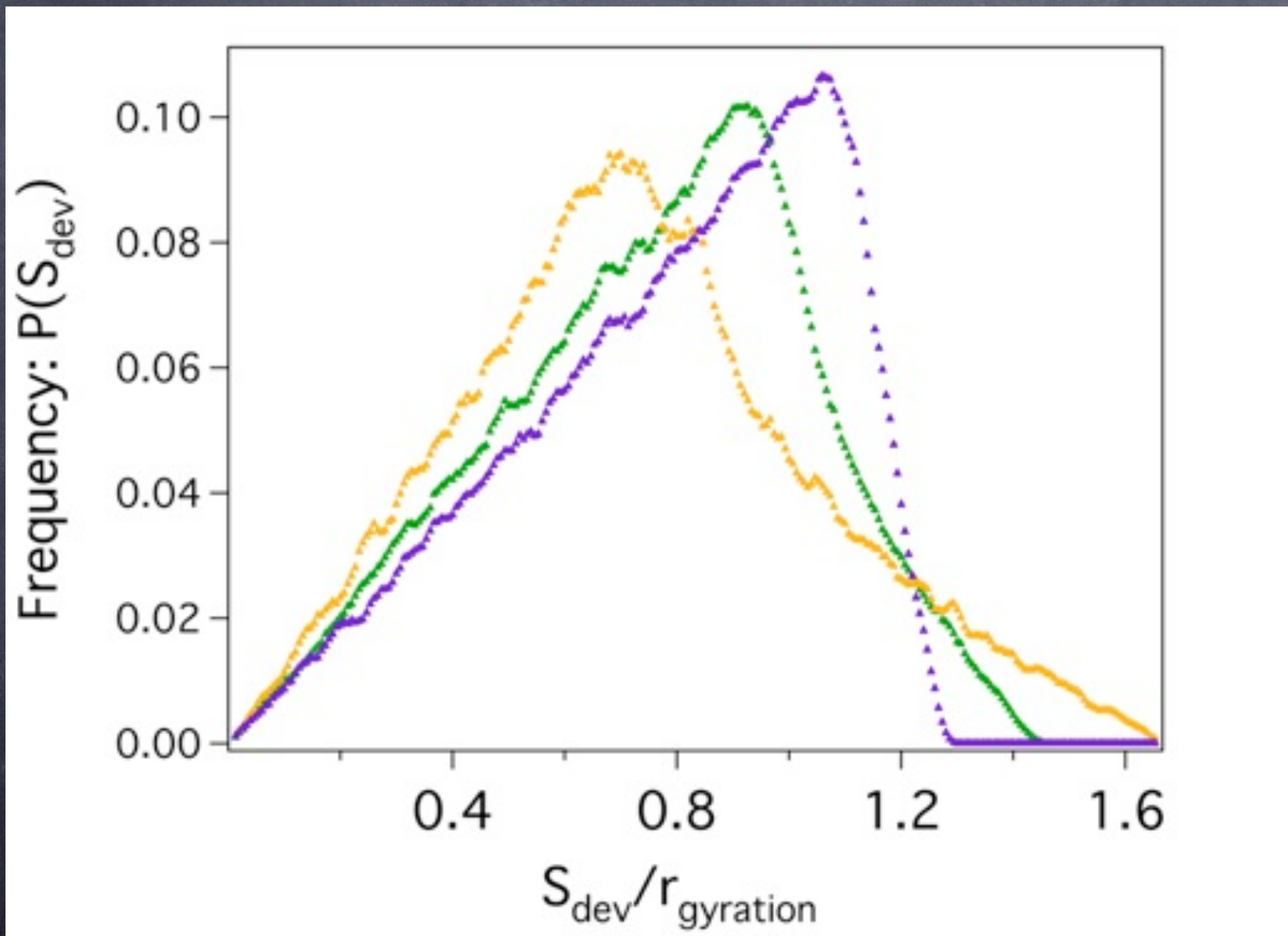
Perfect symmetry has vanishingly small probability



More ⟵ Symmetry ⟶ Less

Randomly Docked Homodimers

Perfect symmetry has vanishingly small probability



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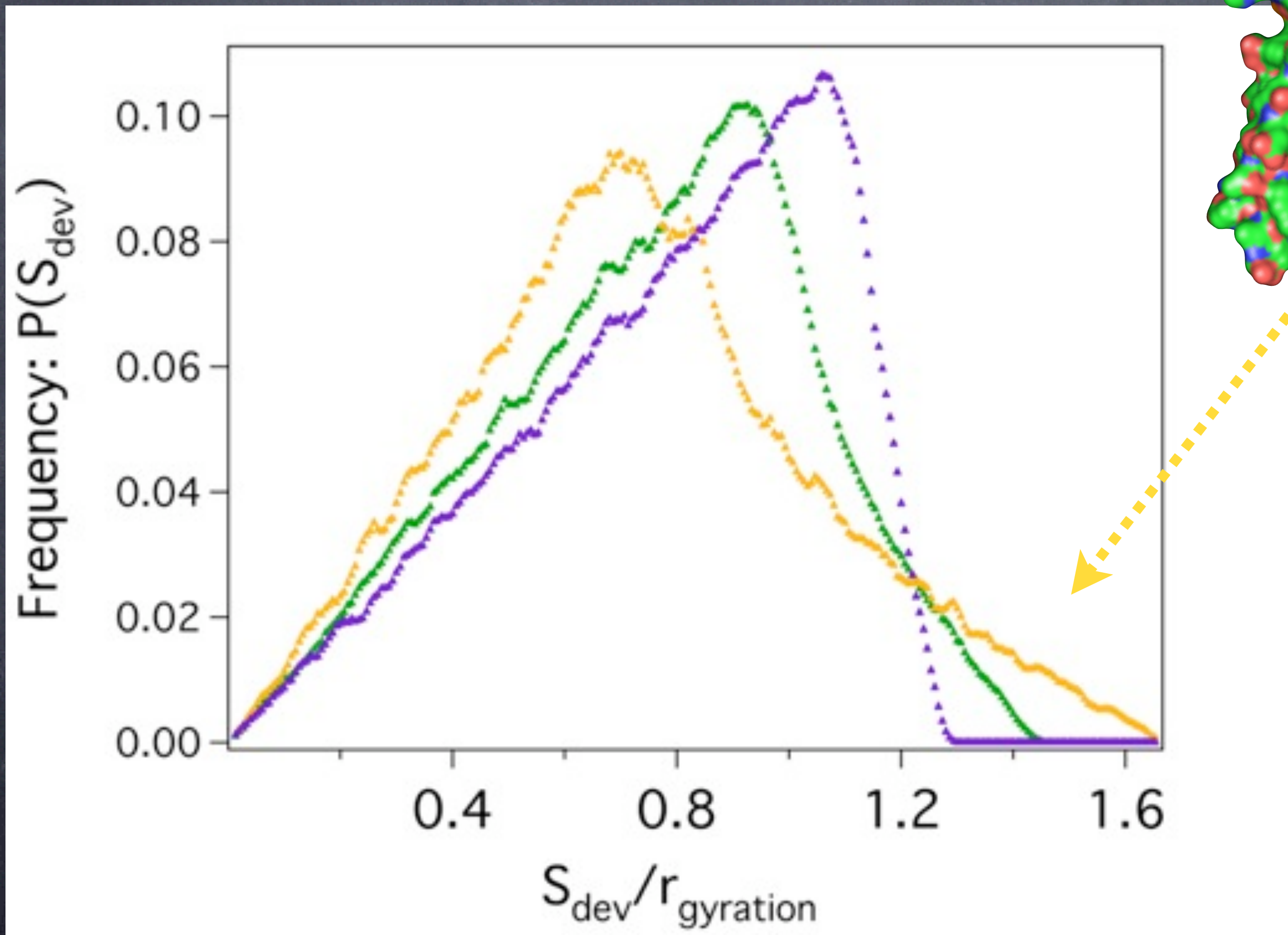

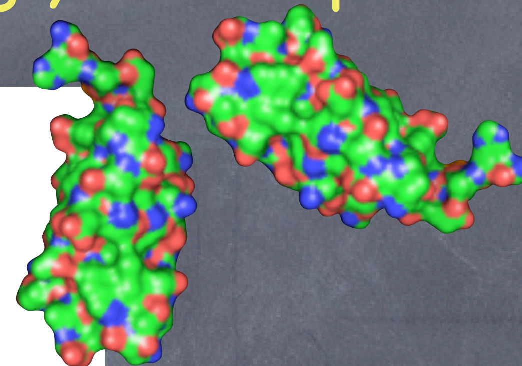

More ← Symmetry → Less

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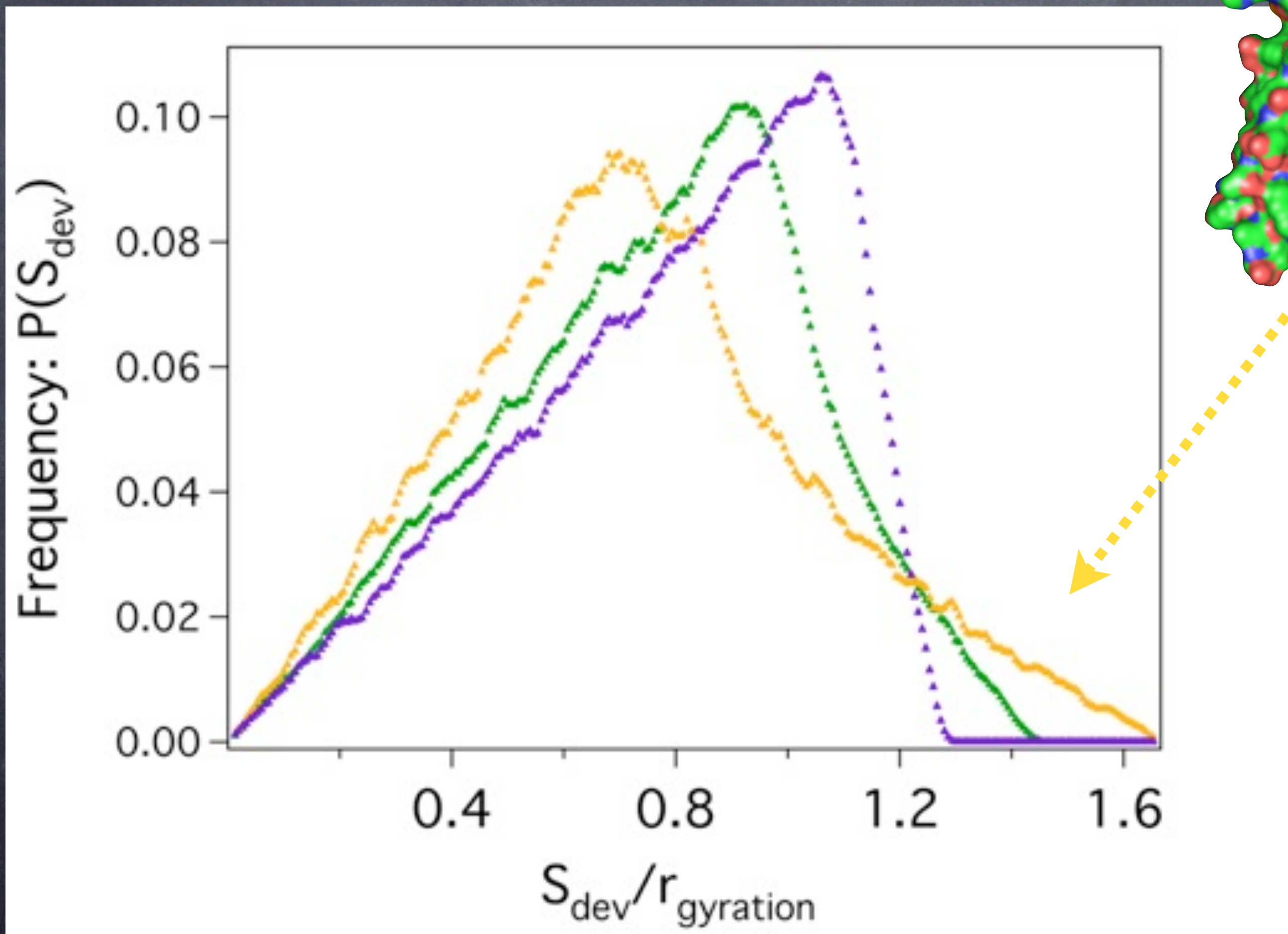
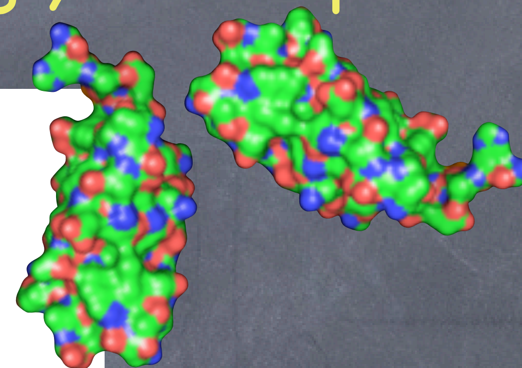
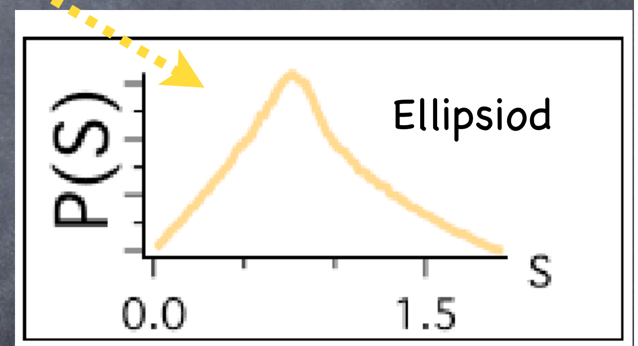




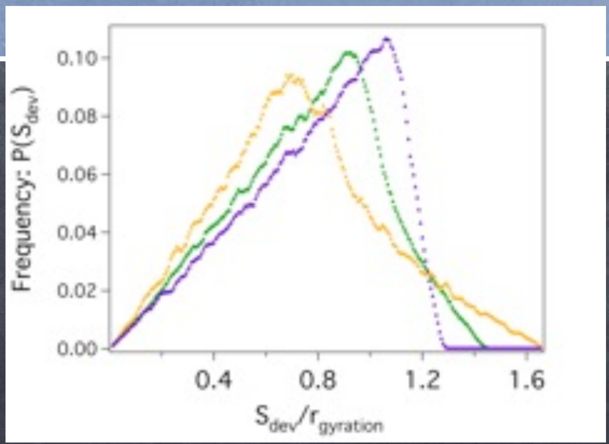


More ← Symmetry → Less

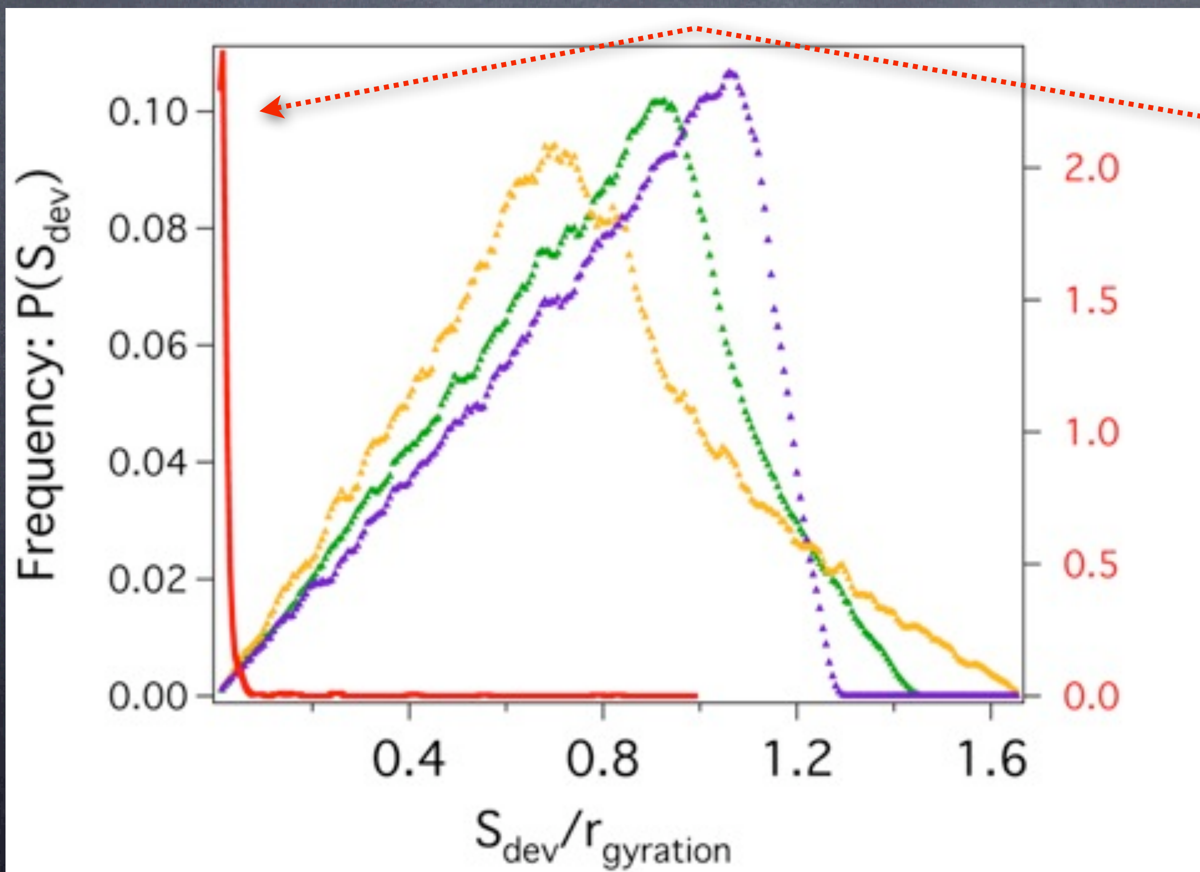
Density of States

- Sdev density of states asymptotically linear:

$$P(S_{dev}) \approx const * \frac{S_{dev}}{R_g^2}$$



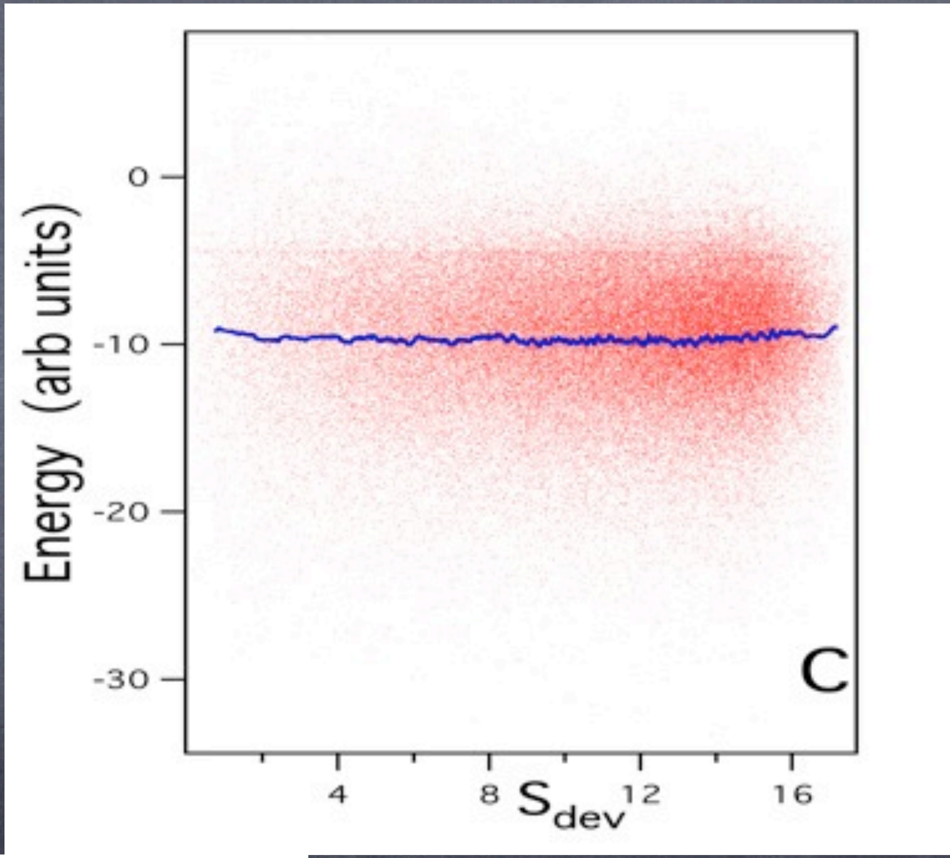
Natural Homodimers are **far** more symmetric than random complexes

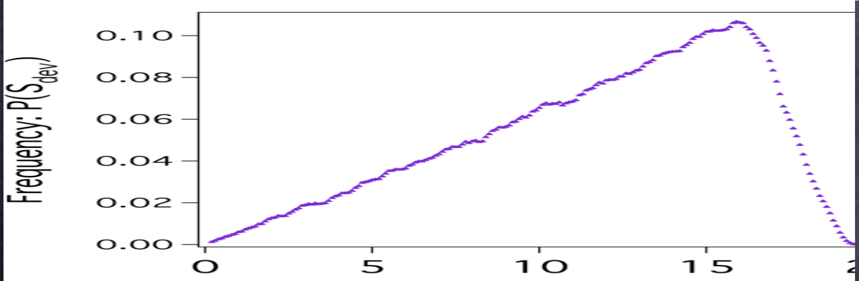


Distribution of 796 Natural Homodimers

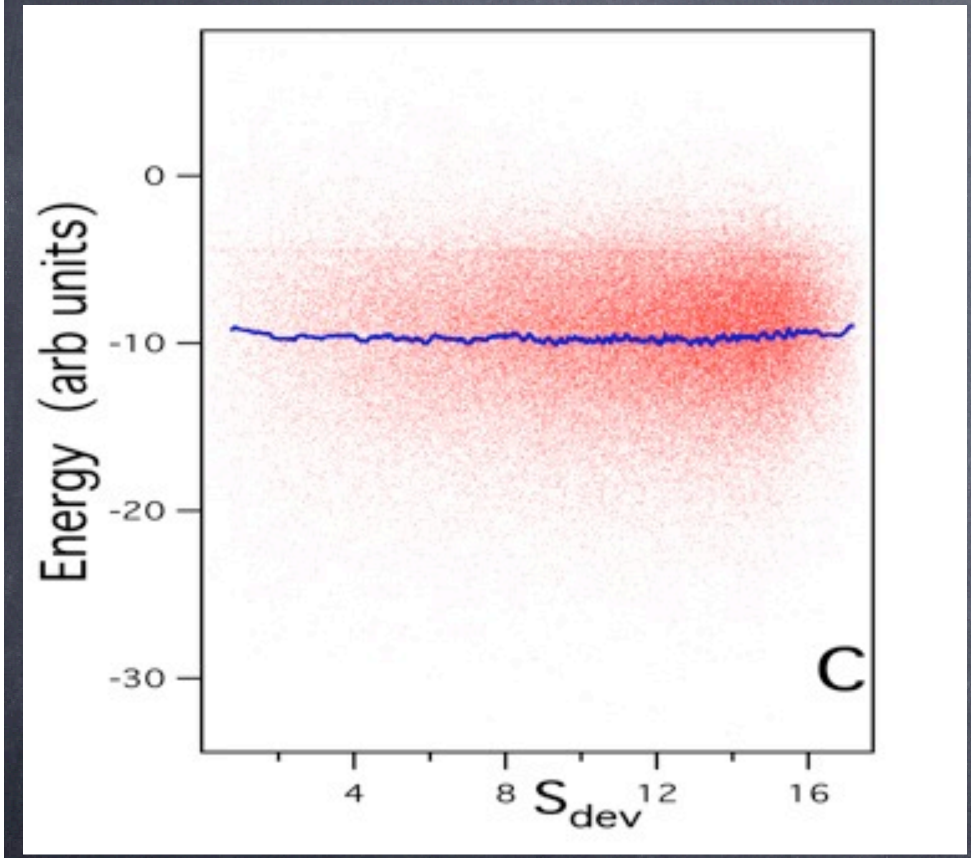
How does Symmetry Affect Binding Energy?

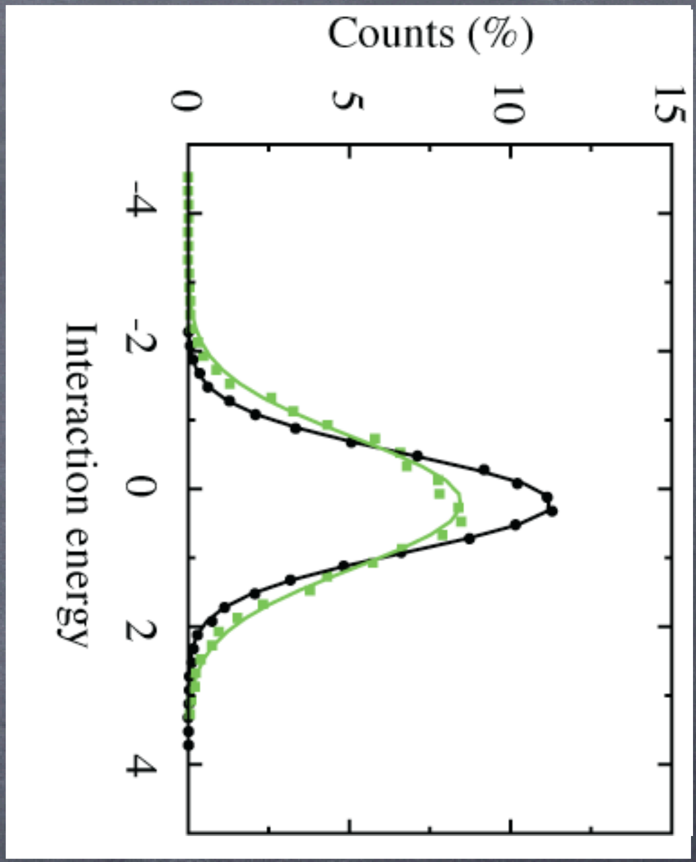
Docking Energy Distribution





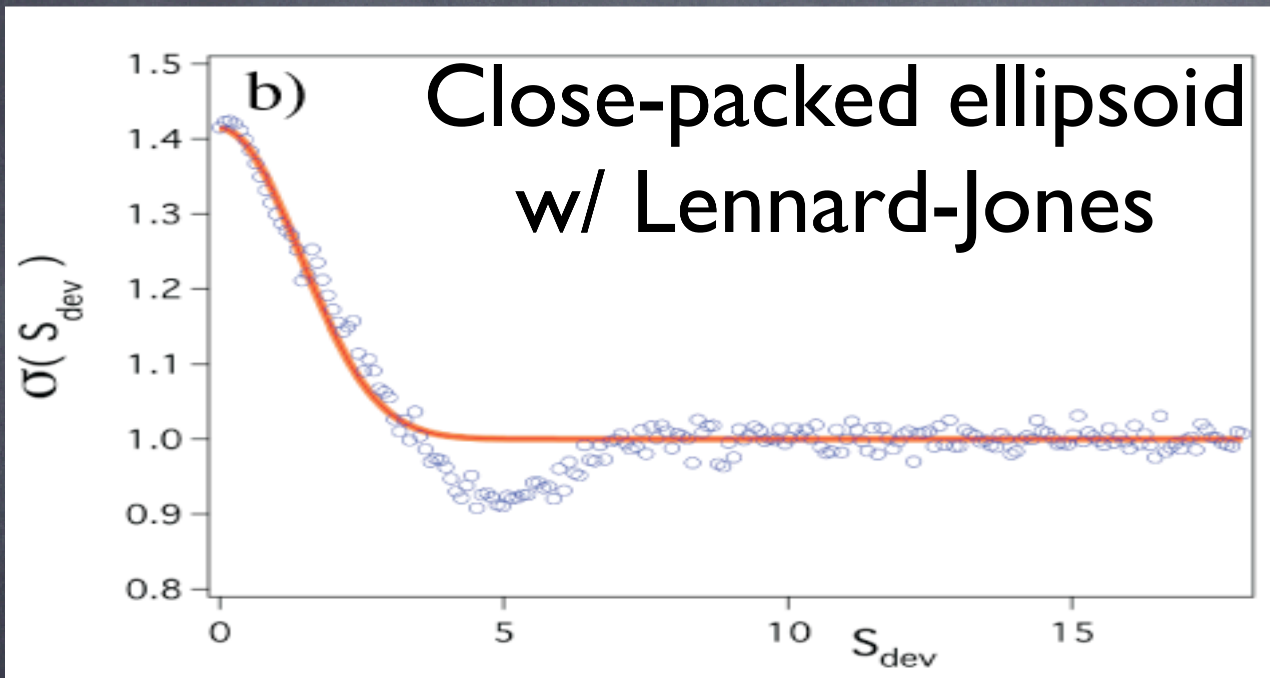
Docking Energy Distribution

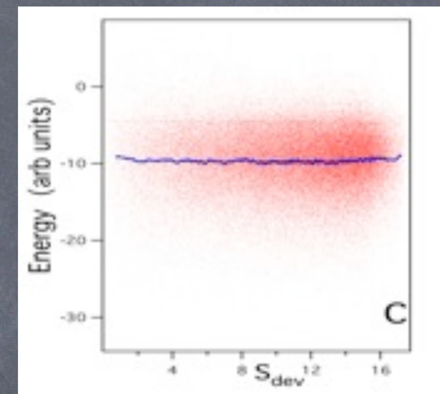




- Symmetric case has same mean but wider variance

Variance of the Energy



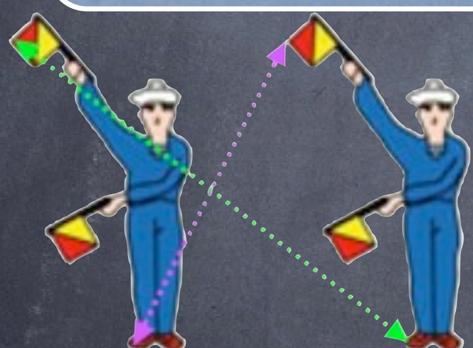
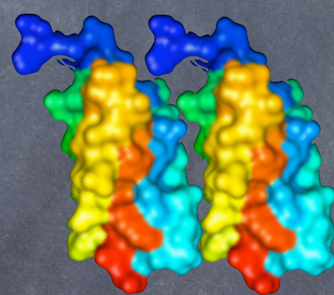


$$\sigma^2_{asym} \times \begin{cases} 1 & for \quad S_{dev} \gg Van\ der\ Waals\ radius \\ 1+\rho & for \quad S_{dev} < R_{VdW} \\ 2 & for \quad S_{dev} == 0 \end{cases}$$

Symmetric Conformations: half as many independent interactions but each occurs twice

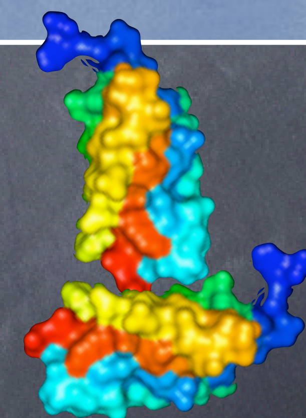
Betting Twice as Much Half as Often, Doubles the Variance

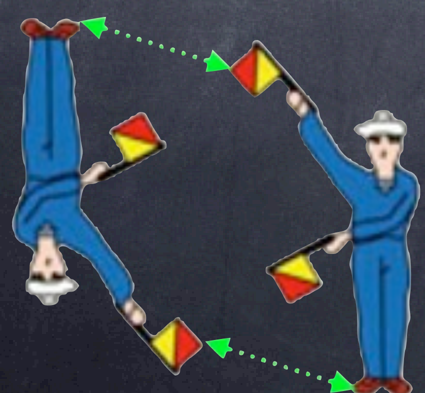
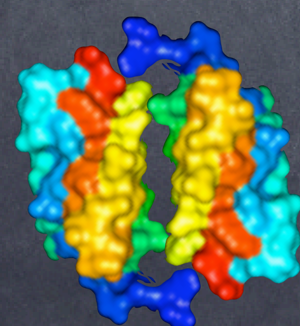
$$E(A,B') + E(A',B)$$

Asymmetric

$|A-B'| \neq |A'-B|$



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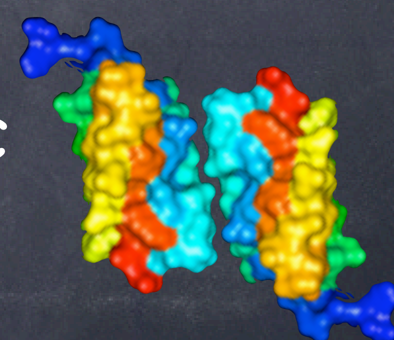

The Joint Distribution

$$P(E, S_{dev}) = P(E|S_{dev})P(S_{dev})$$

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Density of States
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$$P(S_{dev}) \approx const * \frac{S_{dev}}{R_g^2}$$

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Energy Distribution given Sdev × Density of States of Sdev

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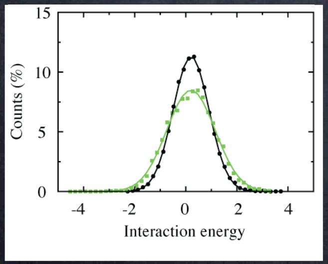
Energy Distribution given Sdev × Density of States of Sdev

$$P(E|S_{dev}) = \frac{1}{\sigma(S_{dev})\sqrt{2\pi}} exp(\frac{-E^2}{2\sigma(S_{dev})^2})$$



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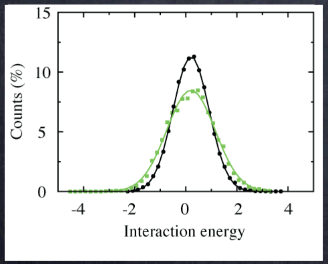
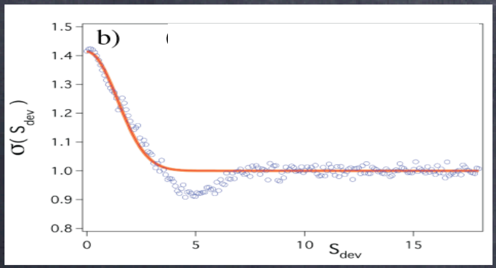




$$P(S_{dev}) \approx const * \frac{S_{dev}}{R_g^2}$$

“Function Competence”

- Unless a dimer is formed a significant fraction of the time, it can’t perform any action useful to the organism
  - Evolutionary Selection will be blind to dimers with binding energies much greater than the entropic barrier, **E’**

$$P(S_{dev}|E < E')$$

“Function Competence”

- Unless a dimer is formed a significant fraction of the time, it can’t perform any action useful to the organism
  - Evolutionary Selection will be blind to dimers with binding energies much greater than the entropic barrier, **E’**

$$P(S_{dev}|E < E') = const \times \int_{-\infty}^{E'} P(E, S_{dev})dE$$

Not a math test.

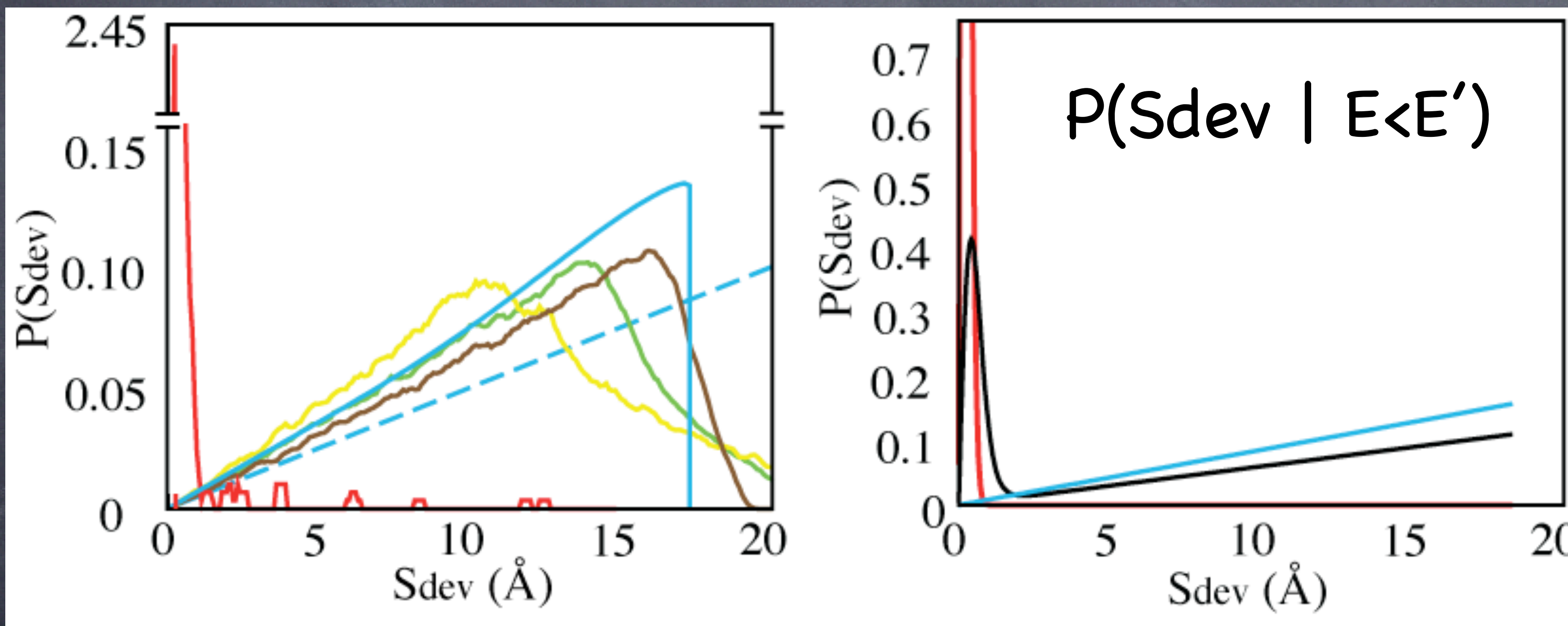
Symmetry distribution of function-competent dimers

$$P(S_{dev}|E < E') =$$

$$\boxed{\frac{const \times S_{dev}}{R_g^2 \sigma_0 \sqrt{1 + exp\left(\frac{-S_{dev}^2}{2L^2}\right)}} \int_{-\infty}^{E'} exp\left(\frac{-E^2}{2\sigma_0^2(1+exp\left(\frac{-S_{dev}^2}{2L^2}\right)}\right) dE}$$

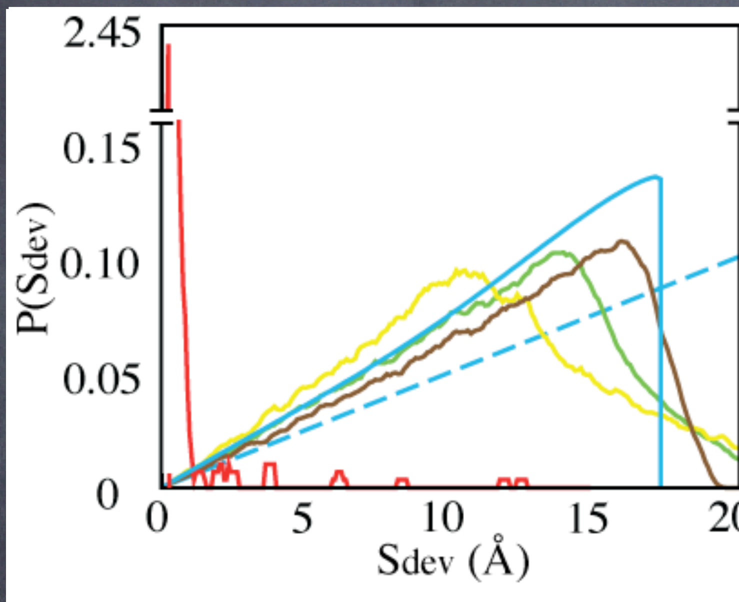
- Family of curves for different entropic energy barriers E′
  - almost no adjustable parameters

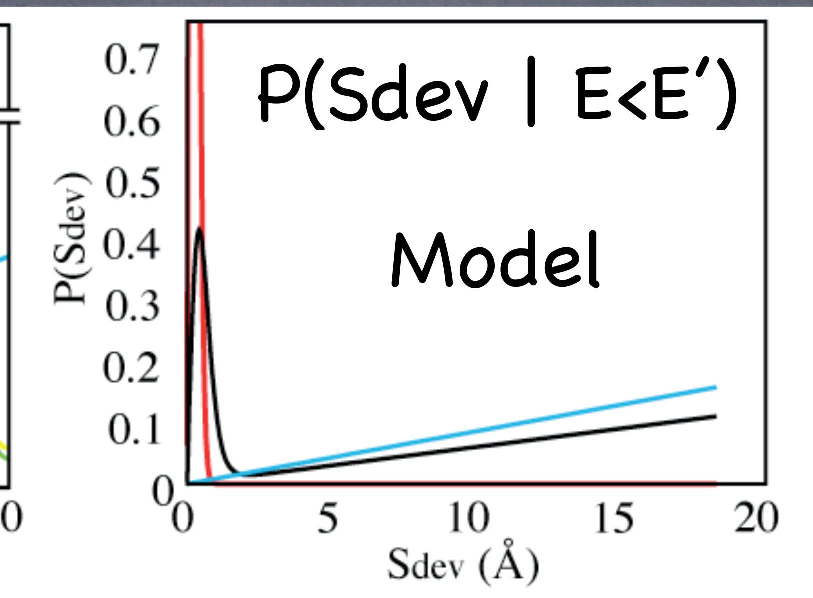
Distribution of Partial Symmetry

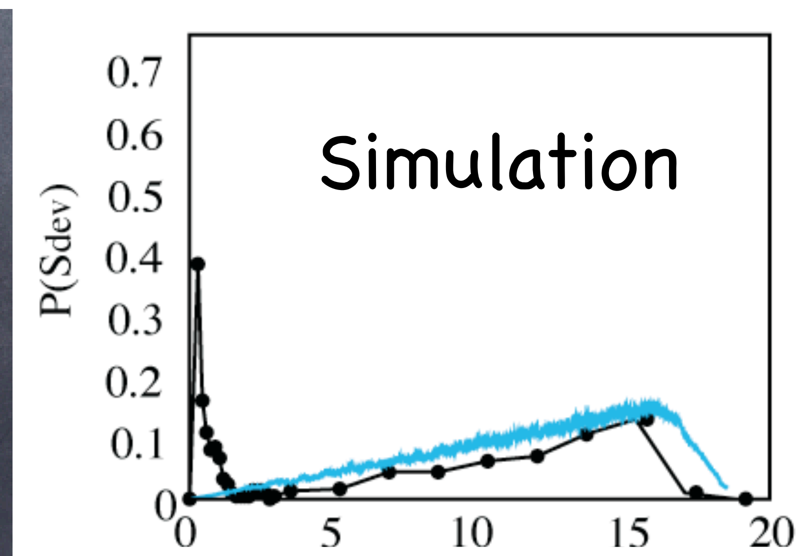


- As barrier rises, the distribution becomes more symmetric

Distribution of Symmetry



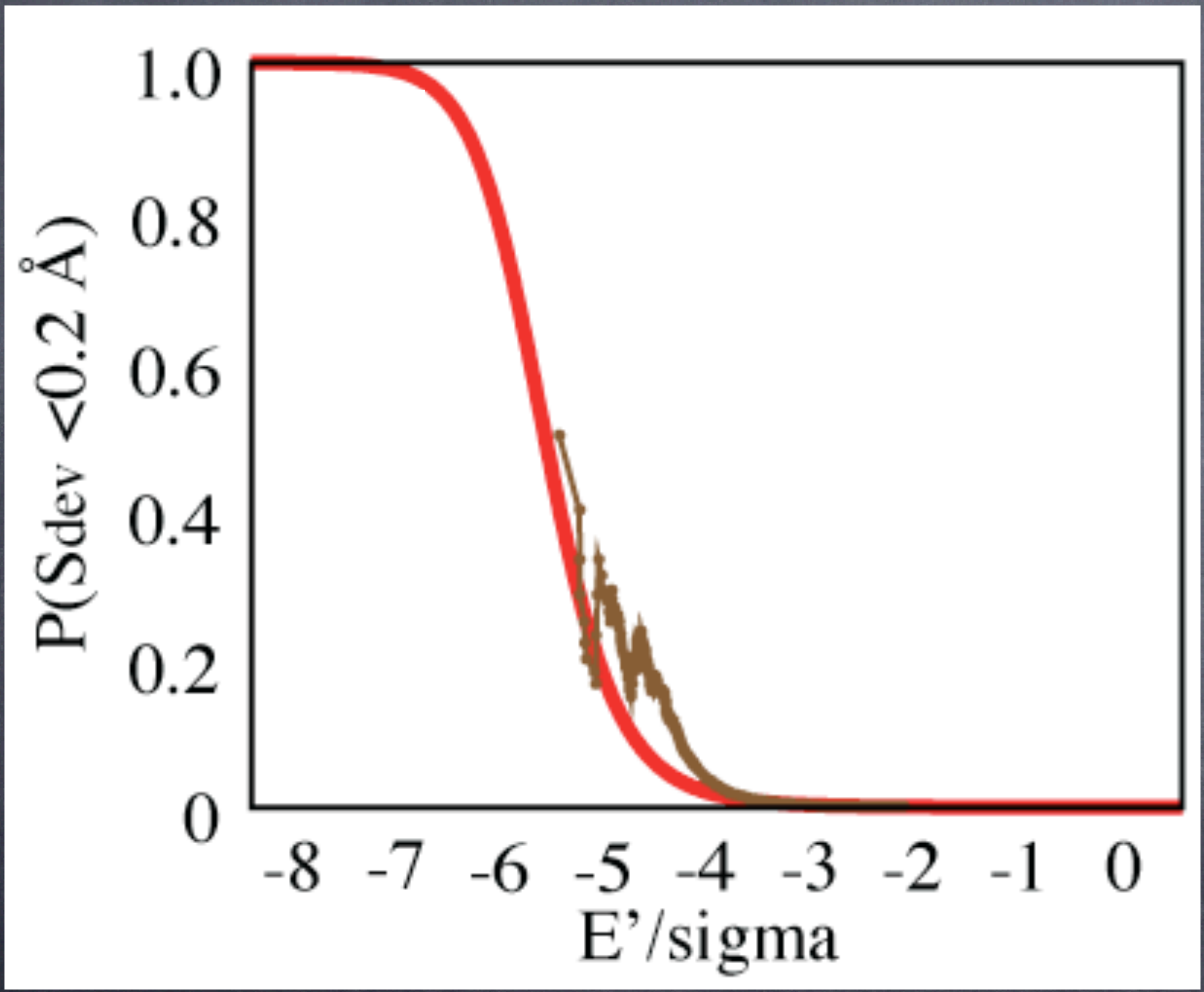




- As binding barrier rises, the distribution becomes more symmetric

Symmetry "Phase Transition"

Probability dimer is symmetric



- Strongest binders are nearly 100% symmetric
- nearly all <u>function-competent</u> complexes will be symmetric!

Stronger <--Binding Energy--> Weaker

Conclusions

- Symmetry is merely a thermodynamic side-effect
  - **not** because of a specific functional advantage
- Effect is always present and magnitude is sufficient to quantitatively explain observed symmetry bias.
- Energy tail outcompetes declining density of states.