

Even modest accuracies in calculated binding free
energies can have significant benefits

Shirts, Mobley, and Brown, “Free Energy Calculations in Structure-based Drug Design”, in “Structure Based Drug Design” by Merz et al., Cambridge University Press, 2010. See also Mobley & Klimovich, JCP 2013

- Medicinal chemist suggests 100 derivatives or compounds per week
- Your job is to pick the top 10 to carry forward

Hypothetical pipeline:

Question: How many molecules do we have to make to gain a factor of 10 in affinity?

- 0.5 kcal/mol noise: Decreases # required by 8x
- 1.0 kcal/mol noise: Decreases by 5x
- 2 kcal/mol noise: Decreases by 3x



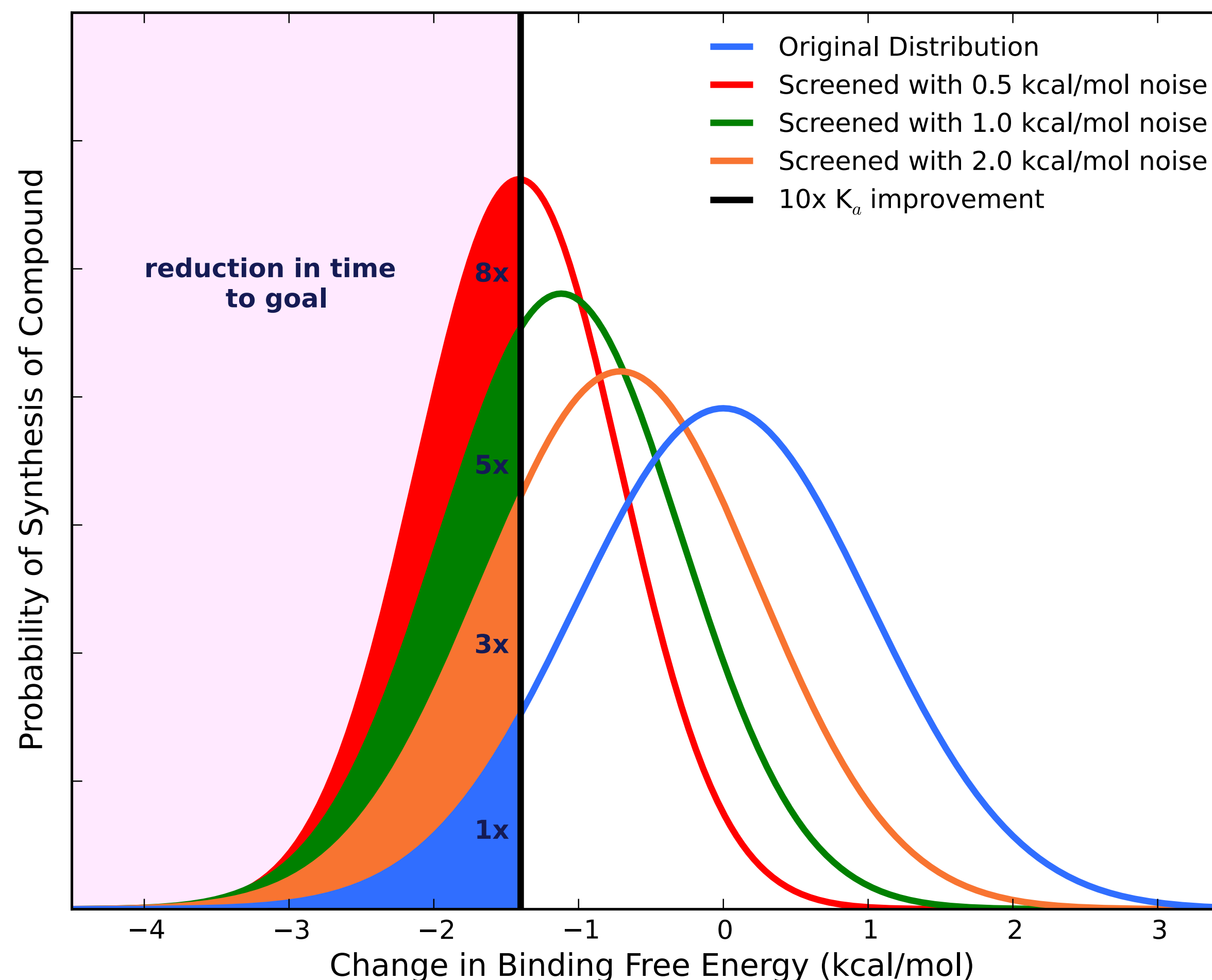
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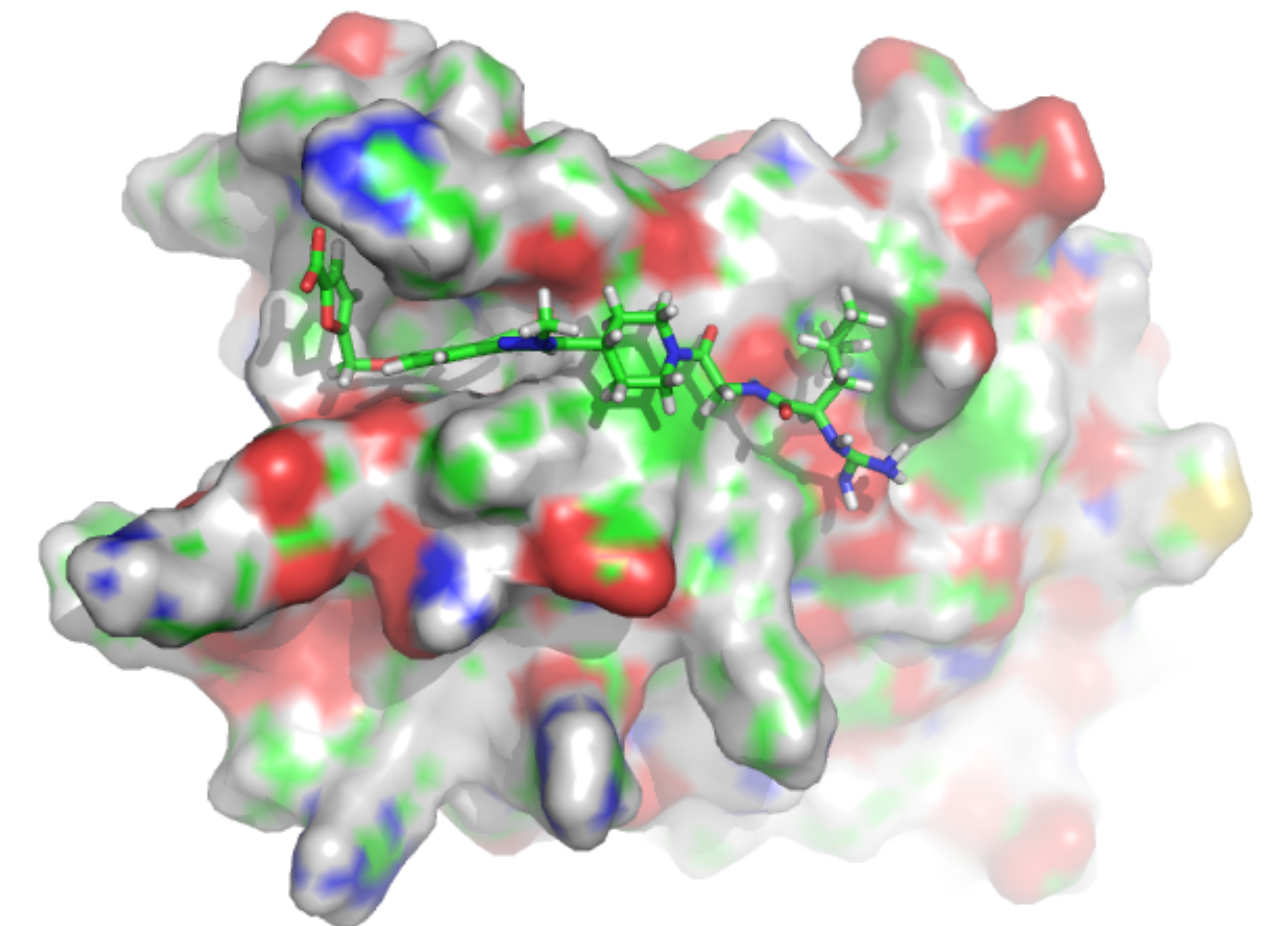
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Docking approximates binding ΔG

- $\Delta G = \Delta H + T\Delta S$
- Docking score $\sim \Delta H$
- It sometimes involves
 - ad hoc ΔS based on the number of rotatable bonds
 - ΔG_{solv}
- Docking is based on “optimal” orientations



(from [1])