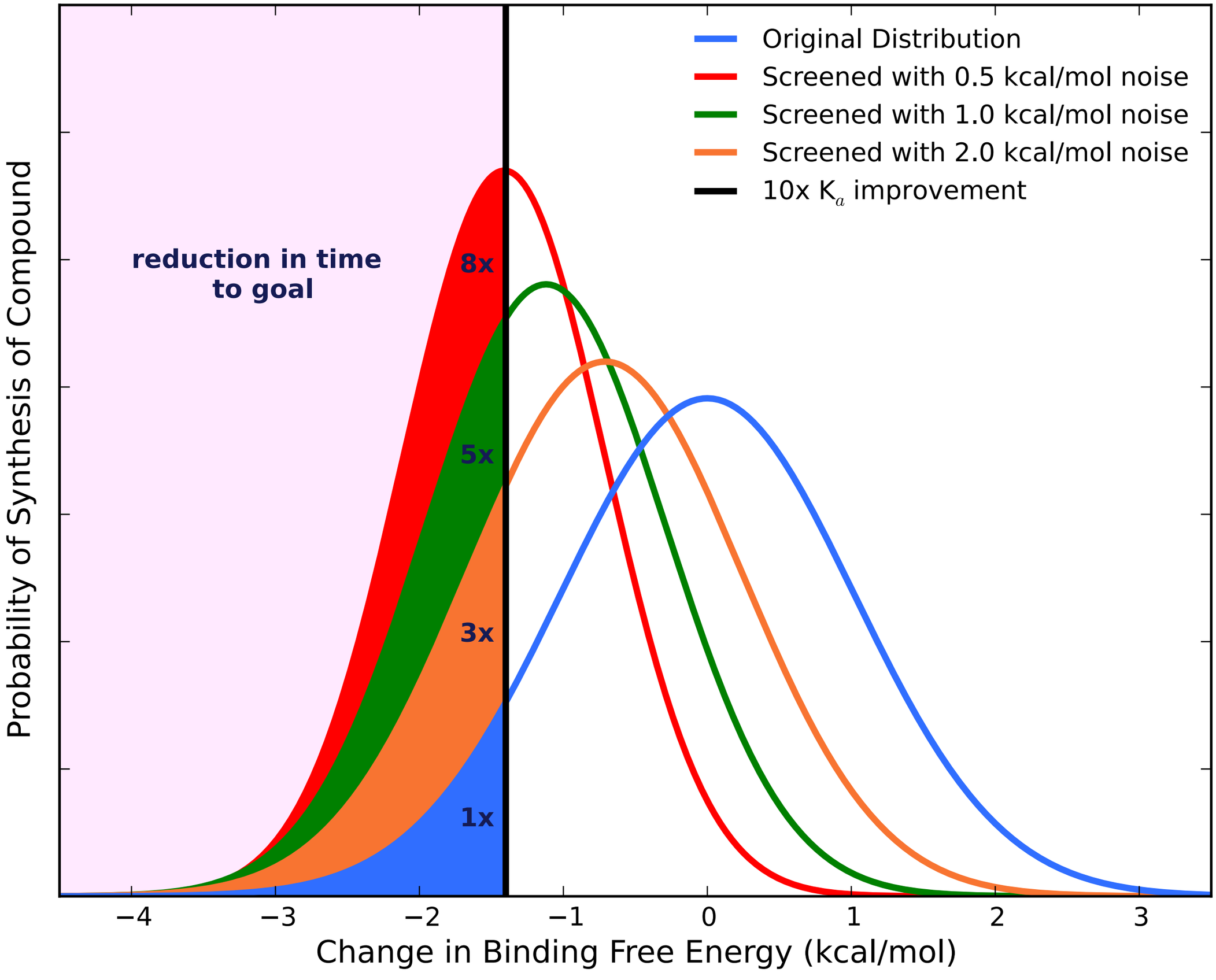
Original Distribution
Screened with 0.5 kcal/mol noise
Screened with 1.0 kcal/mol noise
Screened with 2.0 kcal/mol noise
10x K$_a$ improvement
reduction in time to goal
8x
5x
3x
1x
Probability of Synthesis of Compound
−4
−3
−2
−1
0
1
2
3
Change in Binding Free Energy (kcal/mol)

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

7

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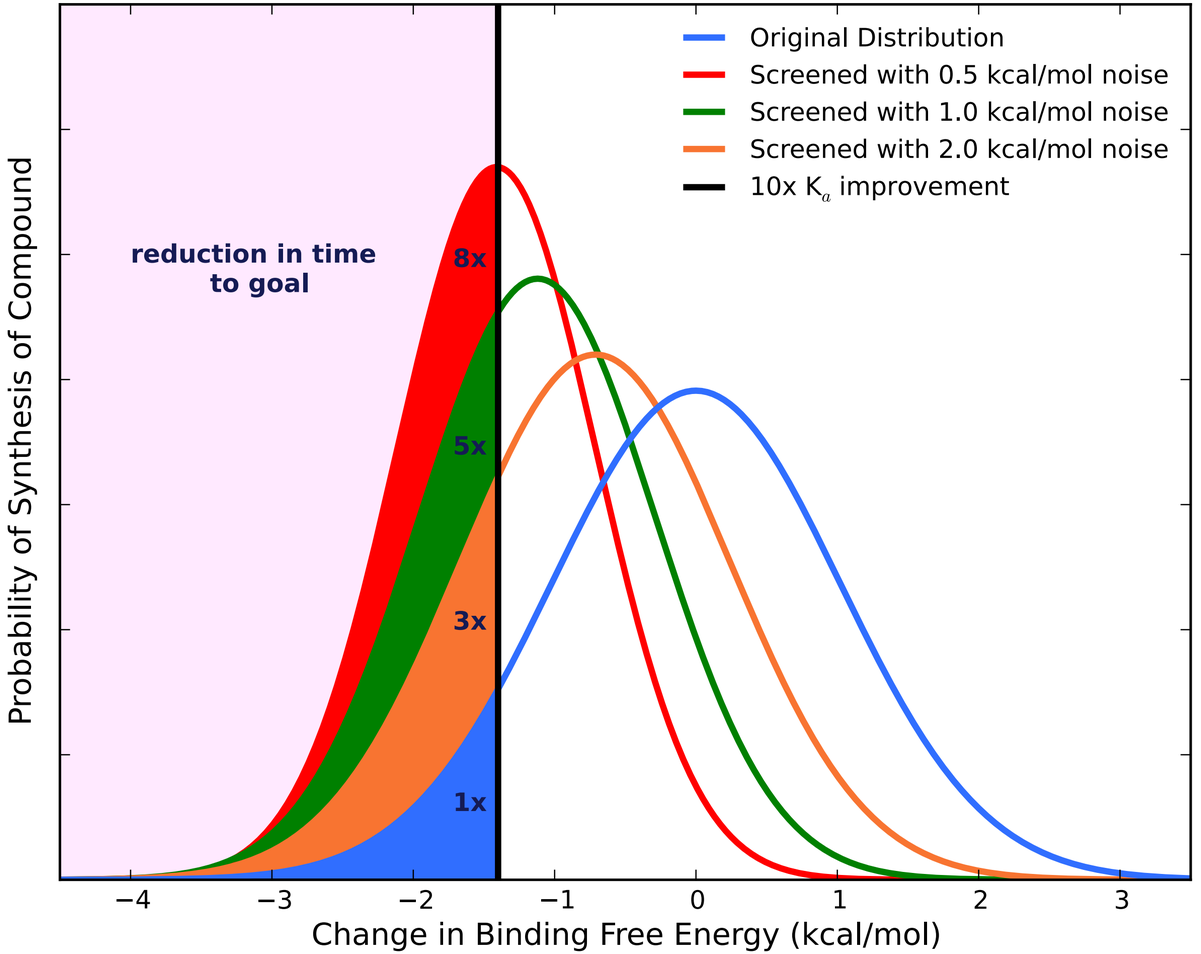
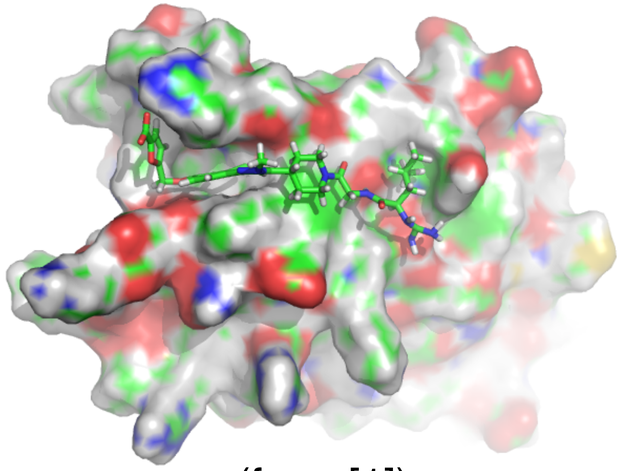


Shirts, Mobley, and Brown, “Free Energy Calculations in Structure-based Drug Design”, in “Structure Based Drug Design” by Merz et al., Cambridge University Press, 2010. See also Mobley & Klimovich, JCP 2013

Docking approximates binding ΔG

- $\Delta G = \Delta H + T\Delta S$

- Docking score ~ ΔH
- It sometimes involves
  - ad hoc ΔS based on the number of rotatable bonds
  - ΔG_{solv}
- Docking is based on “optimal” orientations



(from [1])