

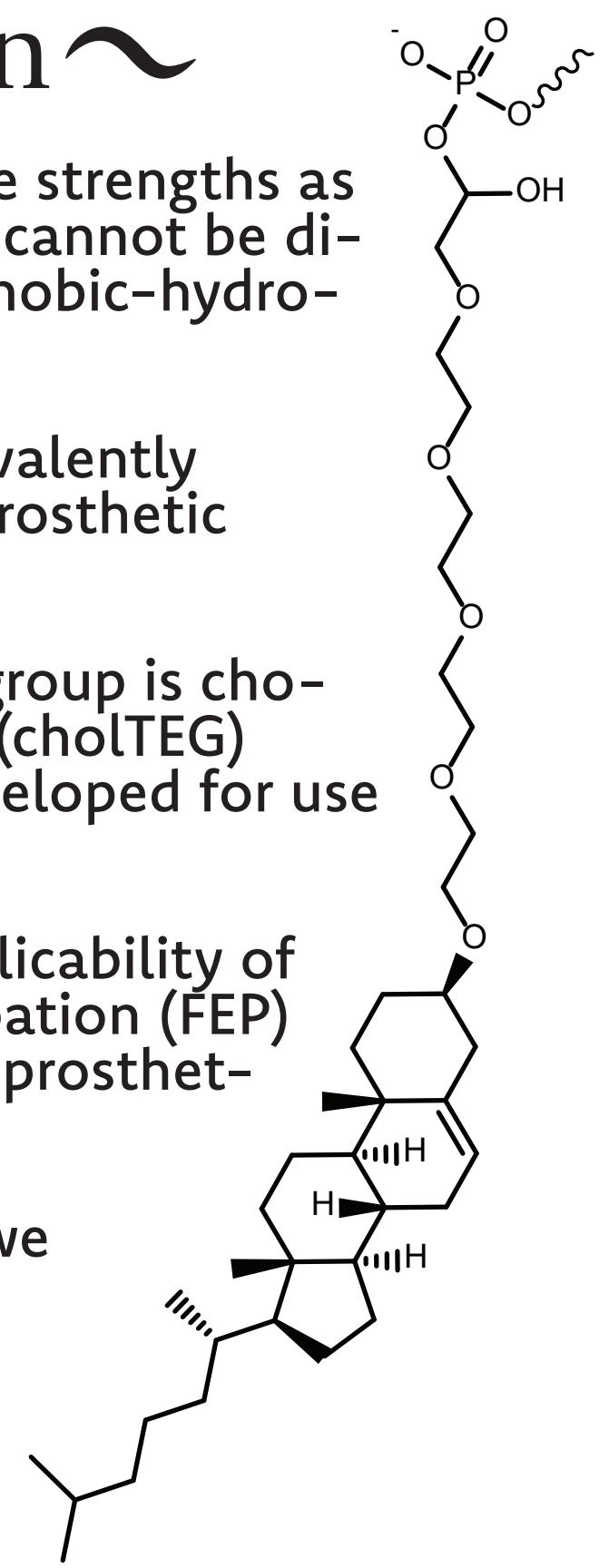
Optimizing DNA-Membrane Interfaces: A Novel Application of Free Energy Perturbation

Ezry Santiago-McRae, Dr. Grace Brannigan

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~Motivation~

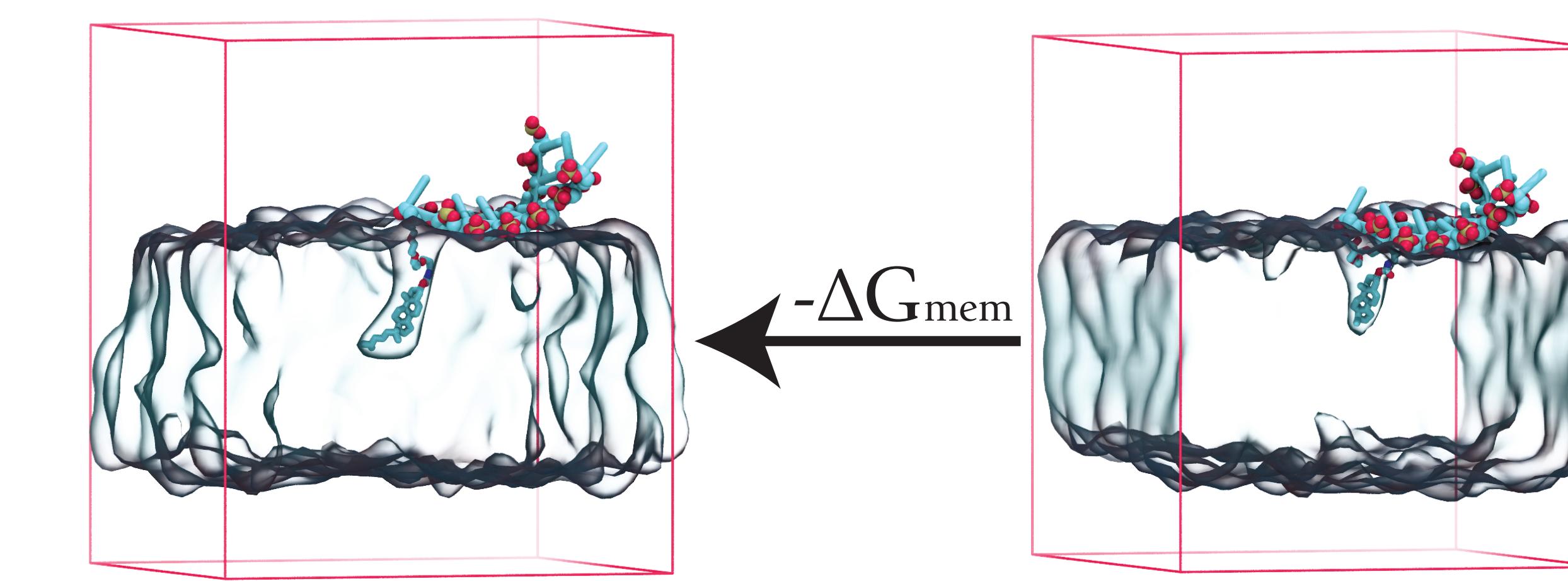
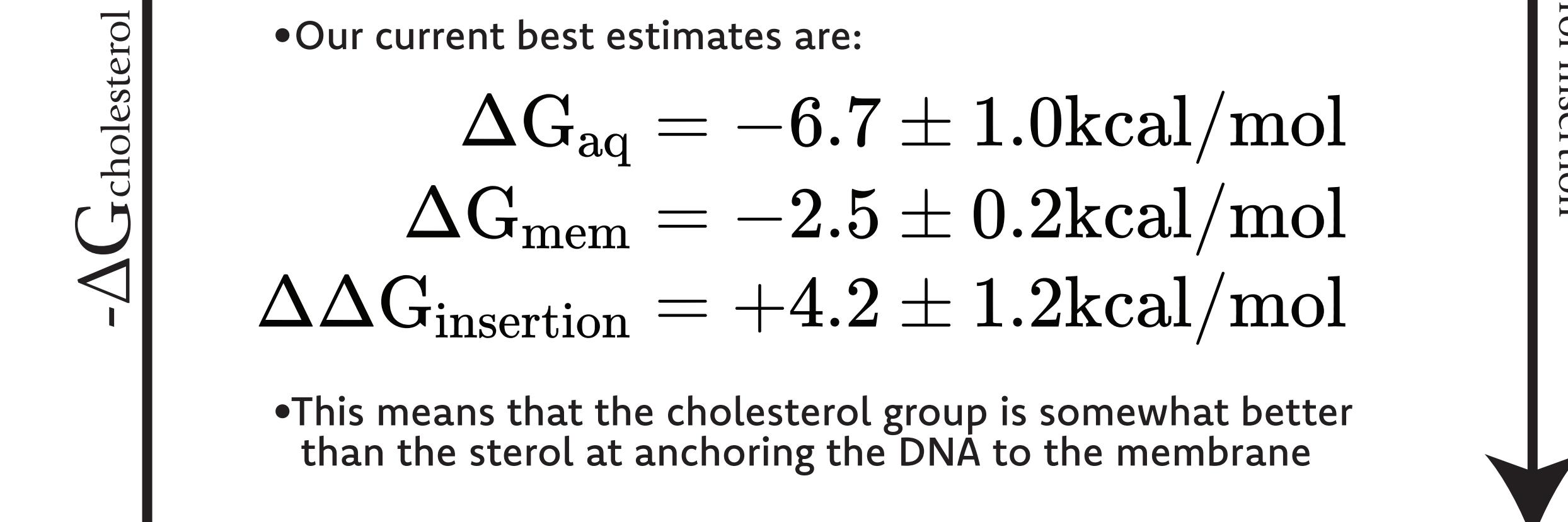
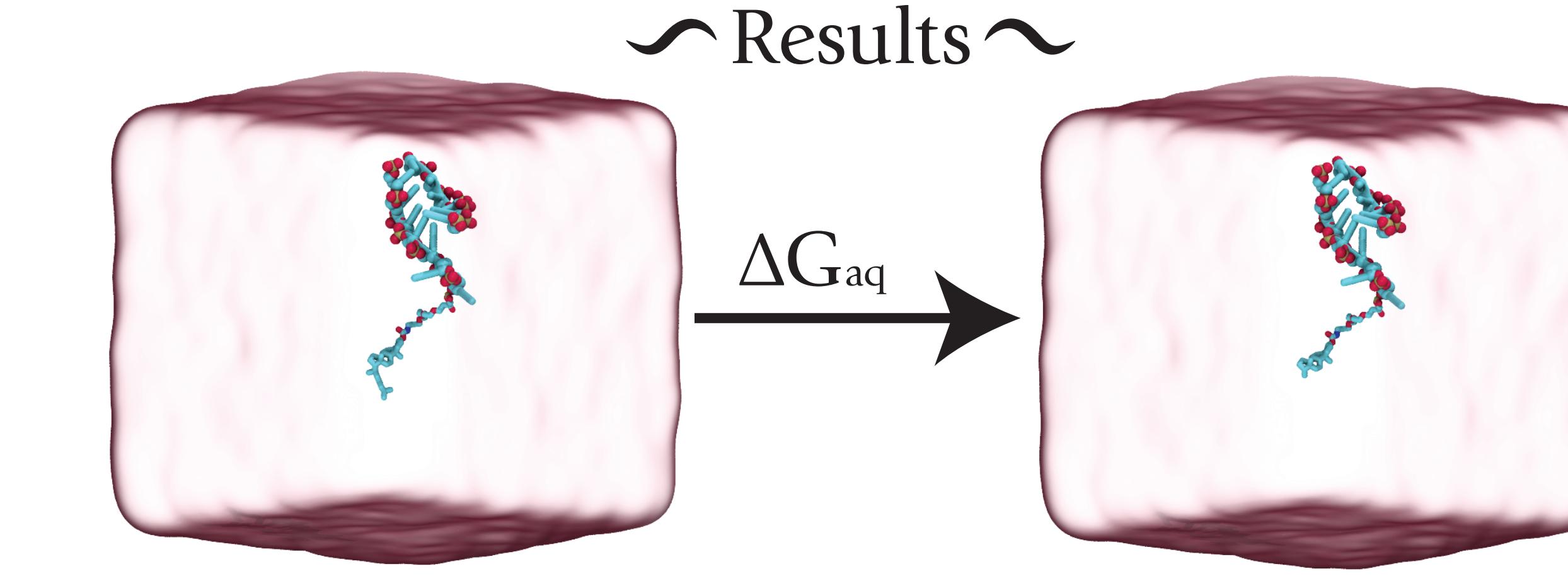
- Both DNA and polar lipids have strengths as nanoengineering materials but cannot be directly combined due to hydrophobic-hydrophilic incompatibility [1]
- This is usually addressed by covalently adding a hydrophobic tag or “prosthetic group” to the DNA [1]
- The most common prosthetic group is cholesterol tetra(ethylene-glycol) (choLEG) (right) which was originally developed for use in gene-silencing research [2]
- Here, we demonstrate the applicability of Alchemical Free Energy Perturbation (FEP) methods to optimization of prosthetic group design.
- As a proof-of-concept, we compare choLEG with a similar sterolTEG (left)



~Methods~

- We wish to compare the free energies of insertion of the two prosthetic groups.
- Gibbs free energy is given by:
$$\Delta G = -T\Delta S + P\Delta V + \Delta E$$
- Pressure, volume, temperature, and internal energy are easy to calculate from simulation, but entropy is not.
- Because pressure and volume are nearly constant, we treat Gibbs and Helmholtz free energy as interchangeable here.
- Free energy perturbations (FEP) avoid this by applying the Zwanzig equation [3]:
$$\Delta G = -RT \sum_{a \rightarrow b}^1 \ln \langle \exp[-\beta(E_{\lambda_{i+1}} - E_\lambda)] \rangle_{\lambda_i}$$
- In this method one system is simulated while periodically calculating the potential energy function of another other system. [4]

$$-\Delta G_{\text{cholesterol insertion}}$$



~Results~

~Discussion~

- We have demonstrated the applicability of FEP to the comparison of prosthetic groups
- Our results are in close agreement with the XLogP3 partition coefficient estimates:

$$\log e * \Delta\Delta G/kT = 3.1 \text{ vs. } 8.7 - 5.5 = 3.2 [5, 6]$$

~Future Aims~

- Improve statistical robustness by decorrelating samples
- Improve computational efficiency
- Begin work on a transmembrane structure and other prosthetic groups

Acknowledgements

Doctoral Committee Members:

- Dr. Grace Brannigan, Primary Advisor
Dr. Jinglin Fu, Secondary Advisor
Dr. Julie Griepenburg
Dr. Jérôme Hénin

Collaborators and Lab Members:

- Dr. Tom Joseph
Dr. Mark Arcario

Jesse Sandberg, MS
Connor Pitman
Jahmal Ennis
Noureen Abdelrahman

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