SCHRÖDINGER®

Summary of the Course and Introduction of Advanced Techniques

In this course you learned how to:

- View and modify compounds in a virtual workspace
- Perform structure-based and ligand-based virtual screening
- Evaluate the results from virtual screening
- Find new hit compounds that can be tested
- Generate an SAR analysis and computed physical properties for compound ideation

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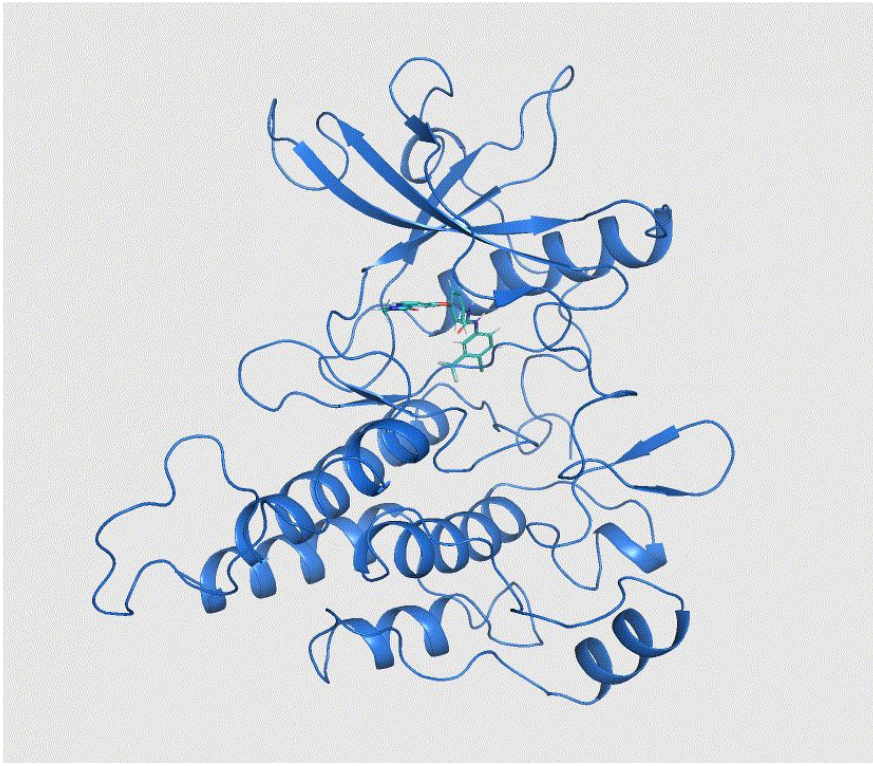
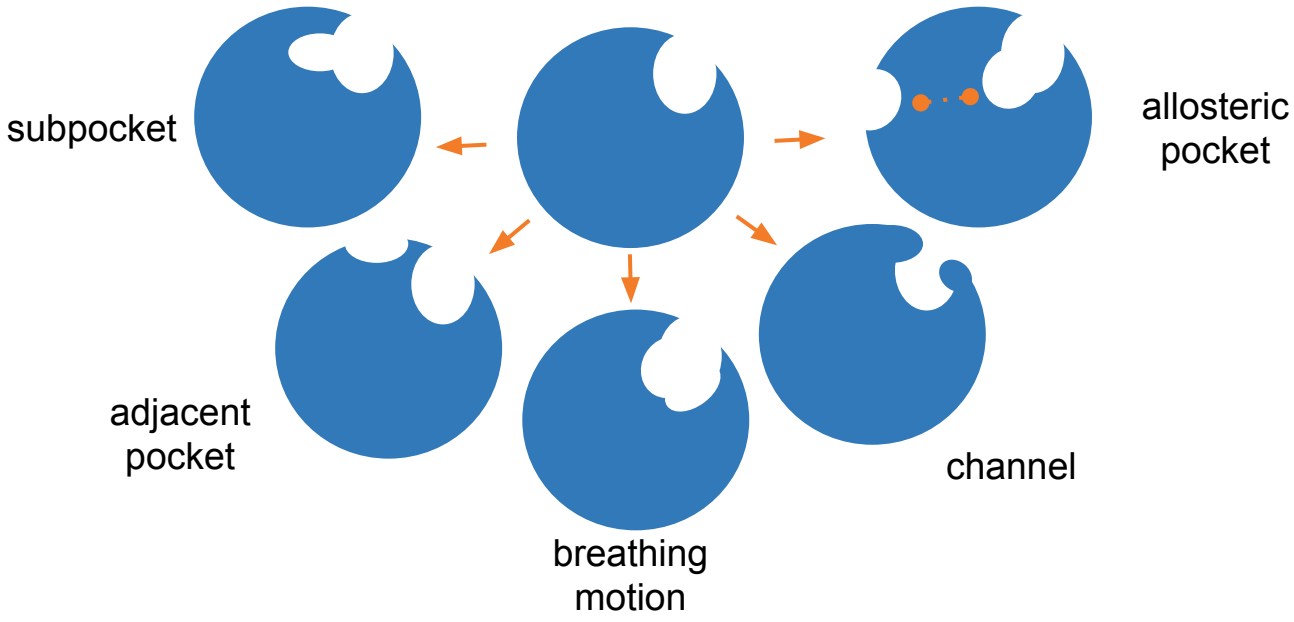
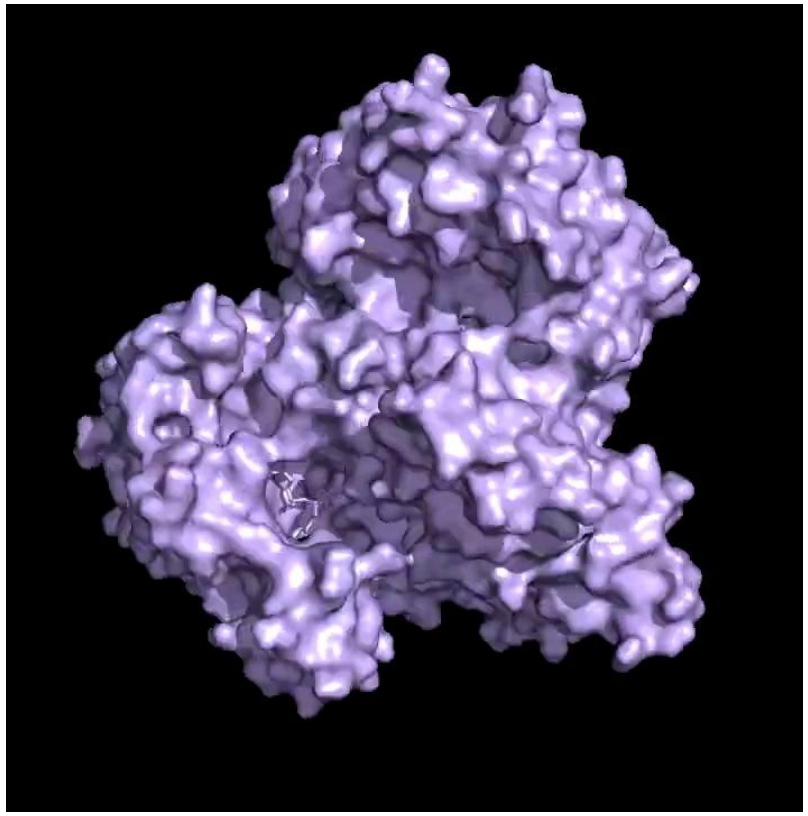
VEGFR2 Case Study Lessons Learned

- **Structural differences** between crystals of the same receptor were important to consider when planning virtual screening
- Structure-based virtual screens resulted in **comparable enrichment**
- Hits that are different from a crystal structure ligand usually do not return a **docking score** that correlates with binding affinity
- **Validating** screening methods is very important



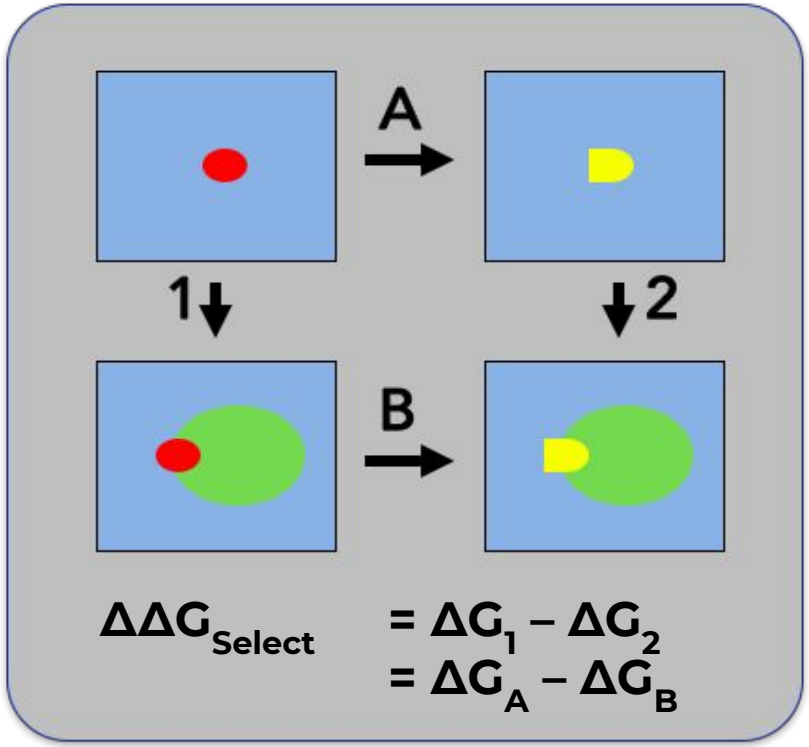
Physics-based methods allow you to see a clearer picture

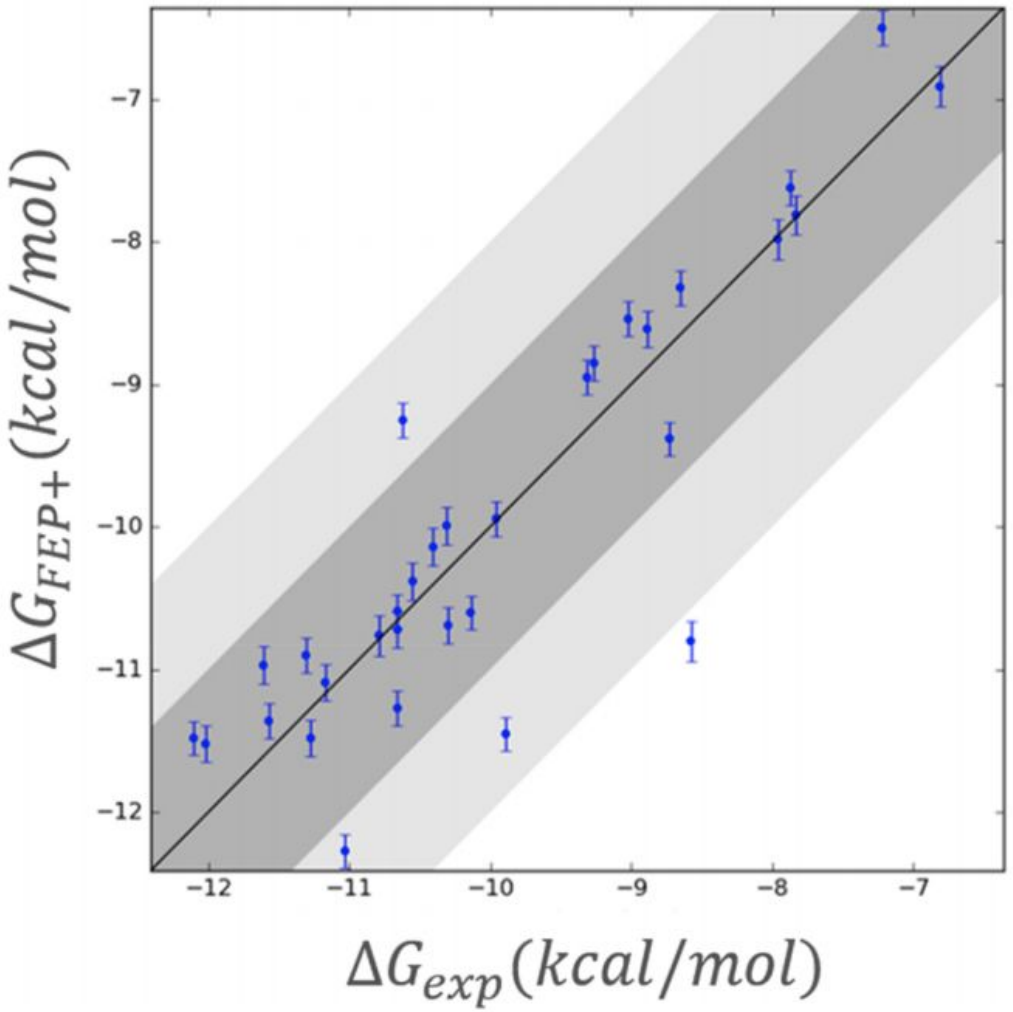




Stank et al, *Accounts of Chem. Res.* 2016.
Shan et al, *J. Am. Chem. Soc.* 2011, 133, 24, 9181-9183

Free energy perturbation can correlate with binding affinities

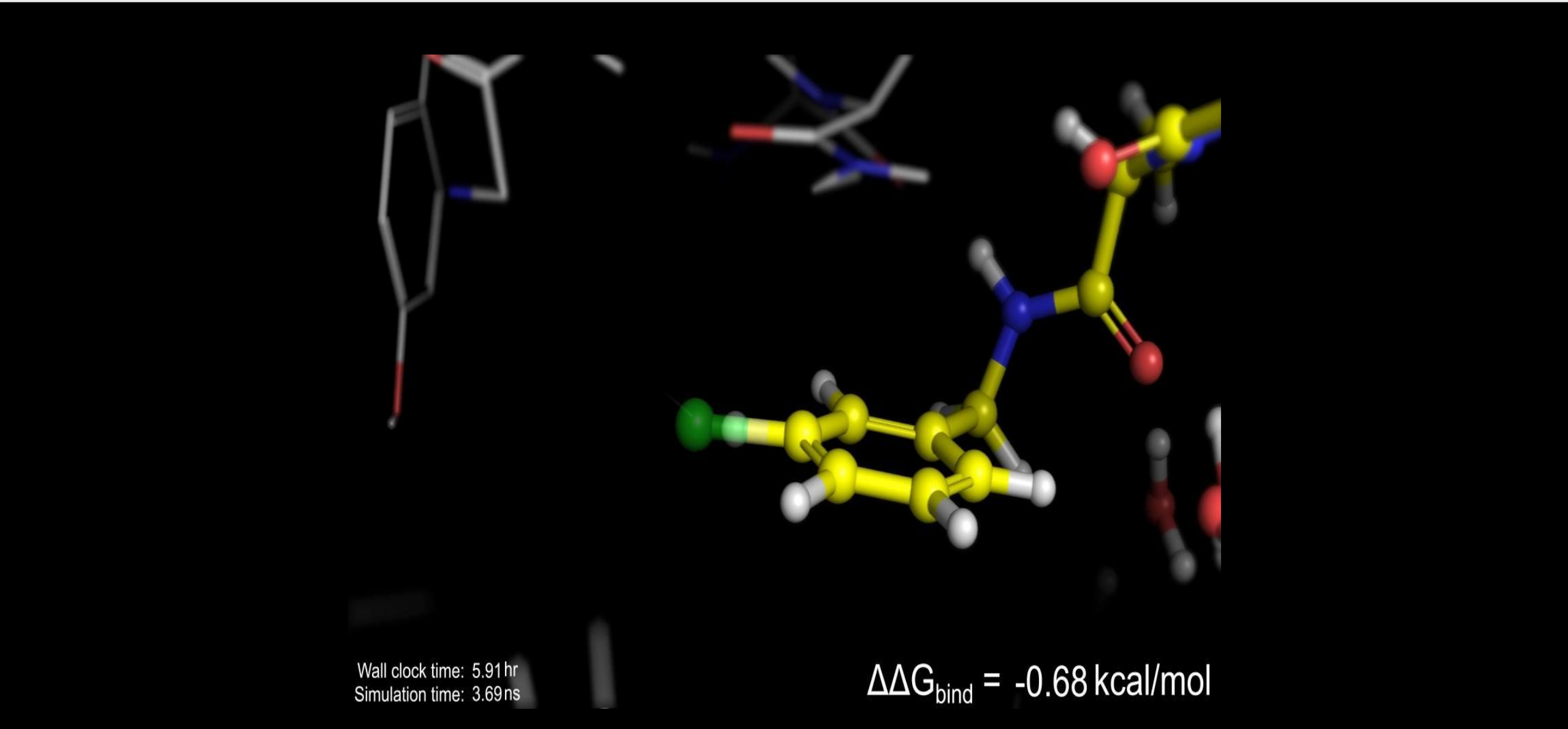




- FEP+ computes:
  - the difference between ligand 1→2 in solution (**A**)
  - the difference between ligand 1→2 in the binding site (**B**)

Saha et al. J. Chem. Theory Comput. 2018, 14, 5815−5822
Wang, L.; et al., J. Am. Chem. Soc., 2015, 137 (7), 2695–2703

FEP+ in action - modifying thrombin ligands



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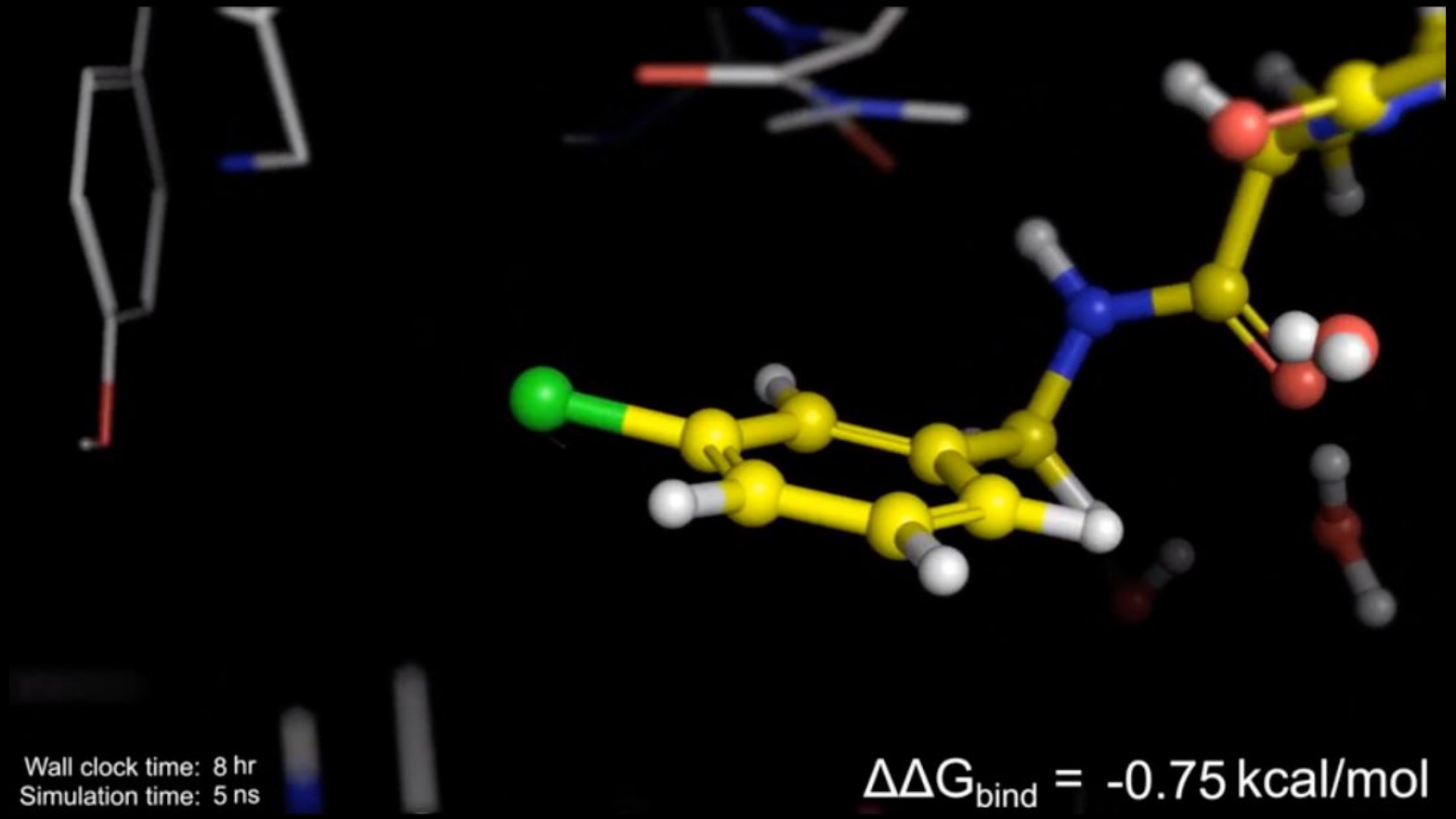

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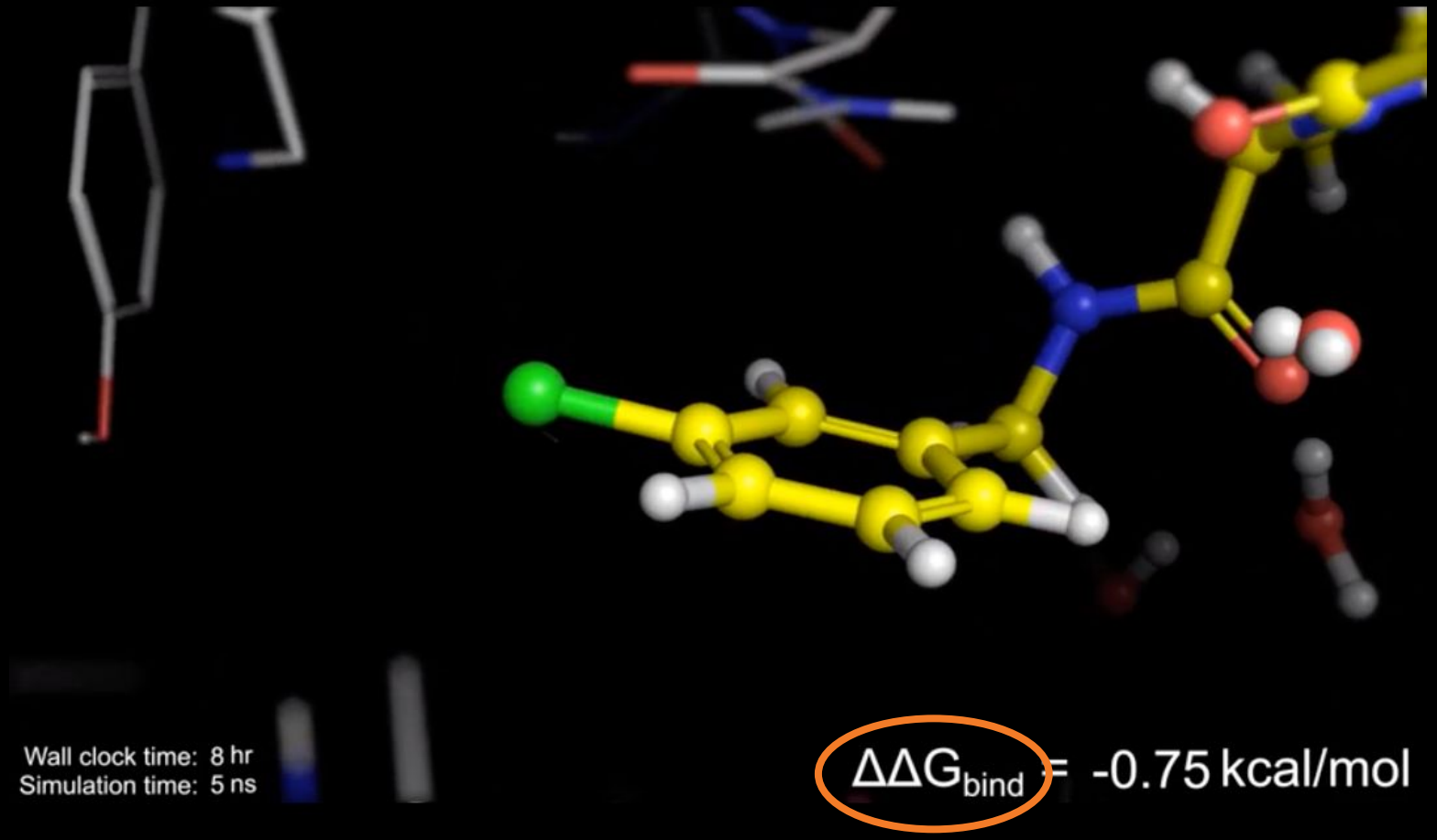
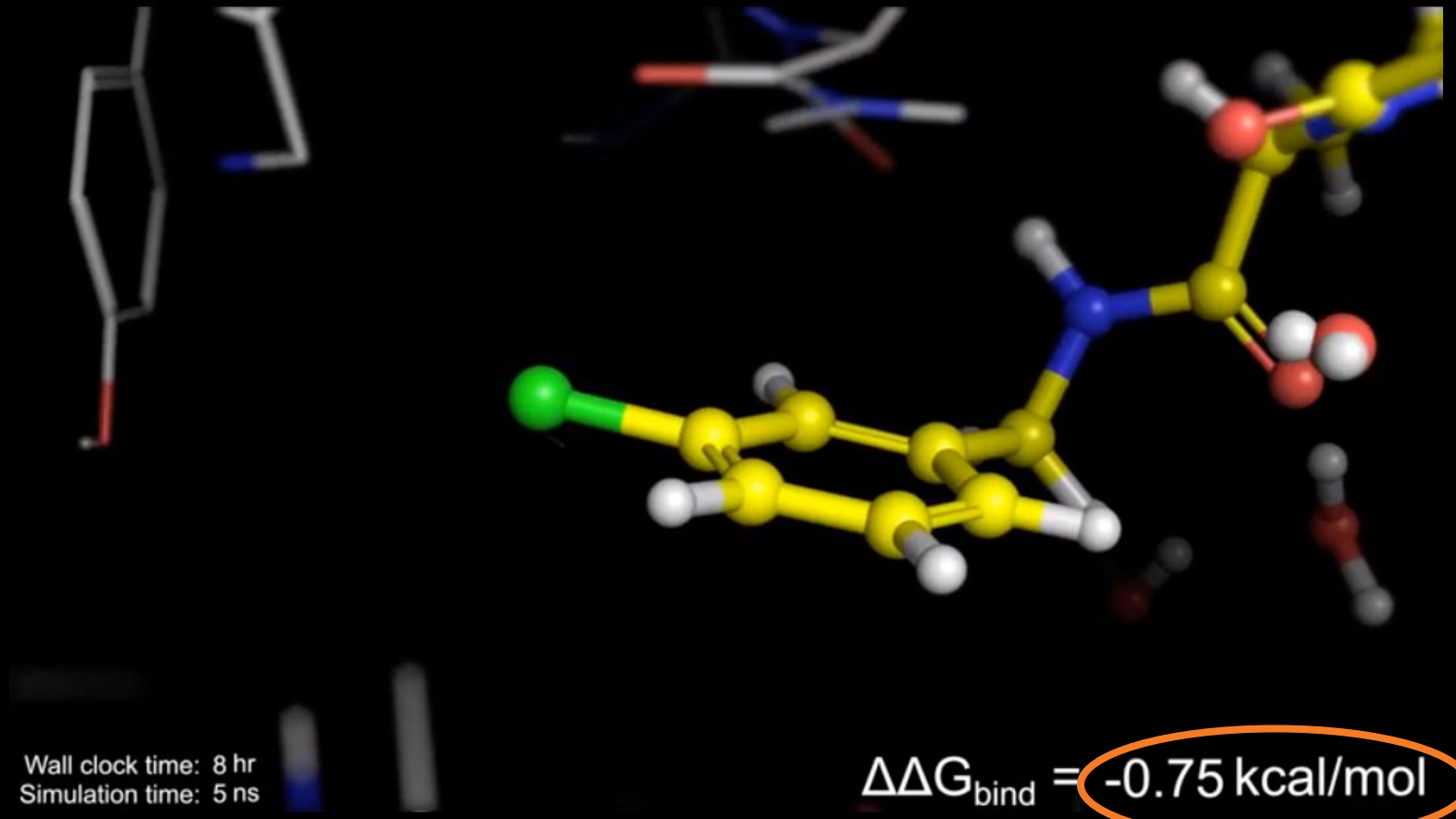


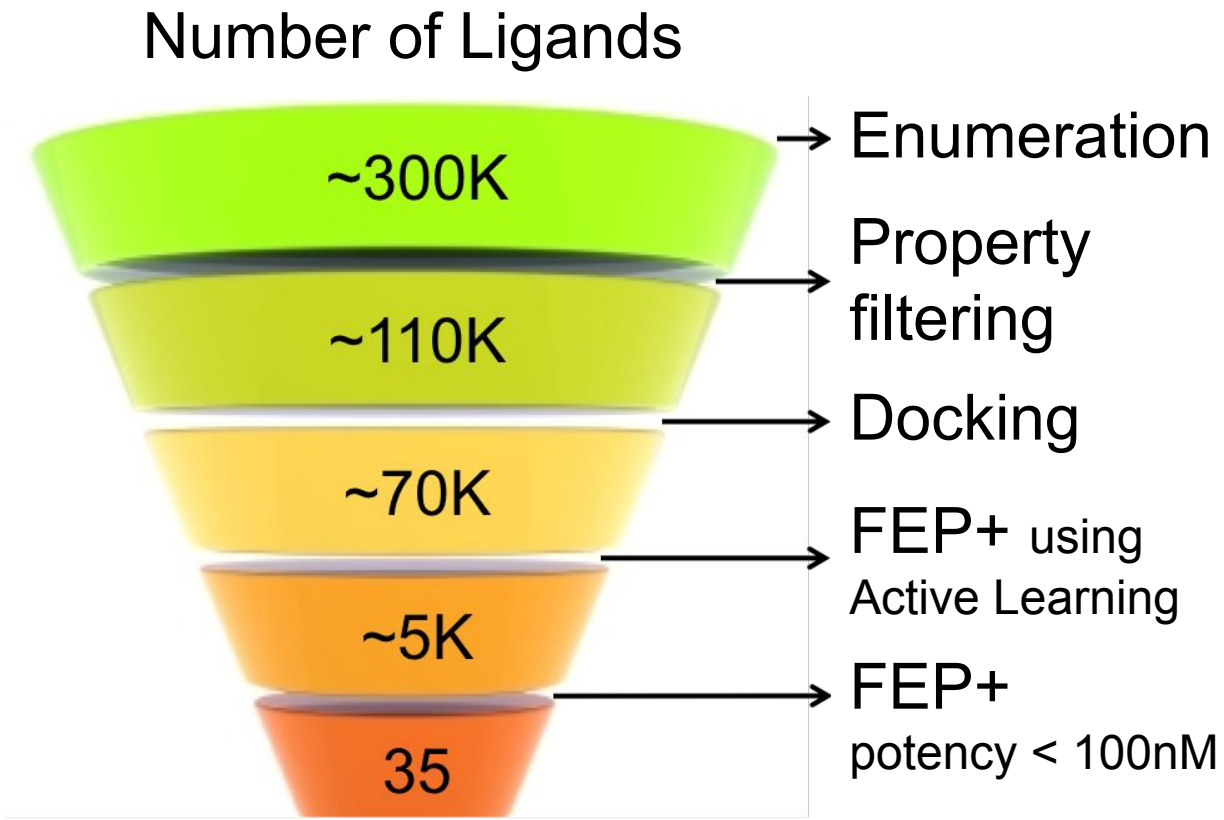
FEP+ in action - modifying thrombin ligands



You have a foundation for applying modeling to your research

FEP+ Checklist for Target and Compound Selection

- For retrospective testing, include some compounds with known binding affinity from a biological assay
- There is at least one high-quality crystallographic structure that corresponds to the biological assay
  - If a structure from a homology model has to be used, validate the model through retrospective FEP+ calculations
- The location of the binding site is well established
- The binding mode of the ligands is conserved across the series
- Any idea compounds explored are structurally-similar to one another and to known compounds



Konze, K. et al, J. Chem. Inf. Model. 2019, 59, 9, 3782–3793.

Thanks for joining us!

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