An Ensemble-Based SMD Workflow that Predicts the Residence Time of A_{2A} Receptor Ligands

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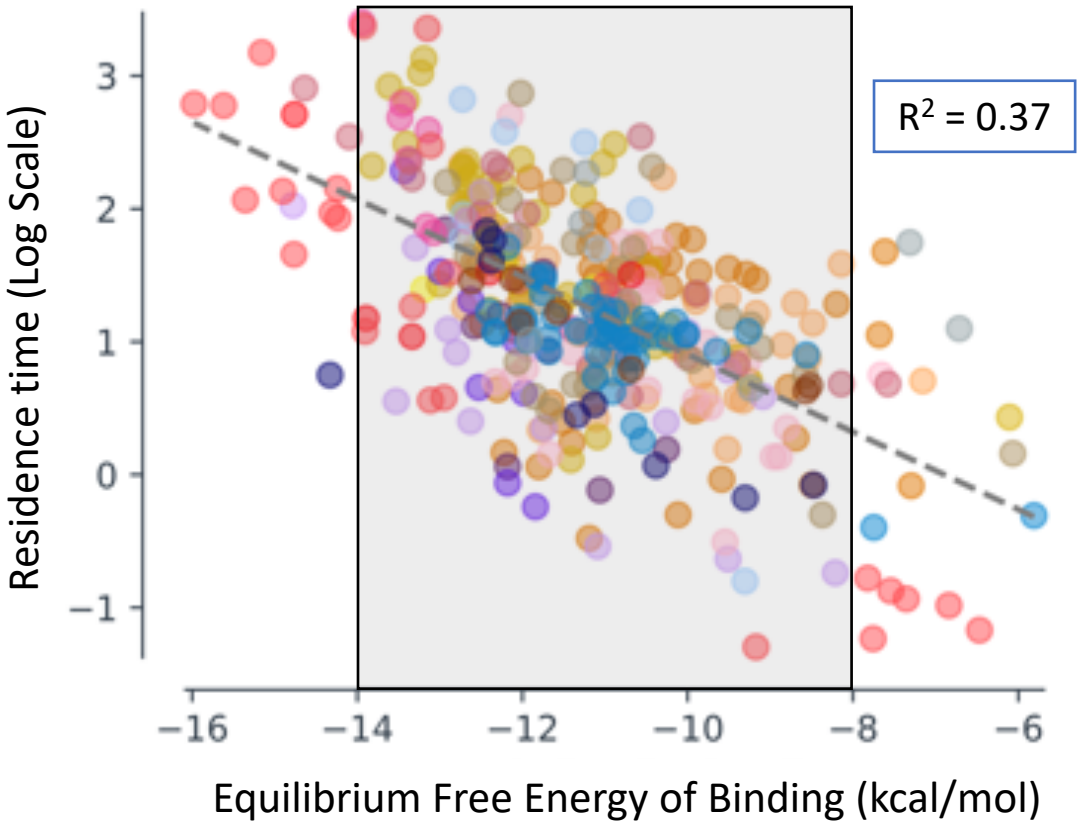
Residence time is important in drug discovery



There is a weak correlation between GPCR kinetic and equilibrium binding values

- nM binders have great variability in residence time
- *In vivo* efficacy GPCR ligands has been proven to be linked to residence time[1]
- Notable reviews suggest that residence time should be optimized in hit to lead and lead optimization phases of drug discovery[2]

1. Guo *et al*, Functional efficacy of adenosine A_{2A} receptor agonists is positively correlated to their receptor residence time. **2012** *British Journal of Pharmacology*
2. Schuetz *et al*, Kinetics for Drug Discovery: an industry-driven effort to target drug residence time. **2017** *Drug Discovery Today*

Aim: To develop a protocol, for drug discovery, that can predict drug-target residence time

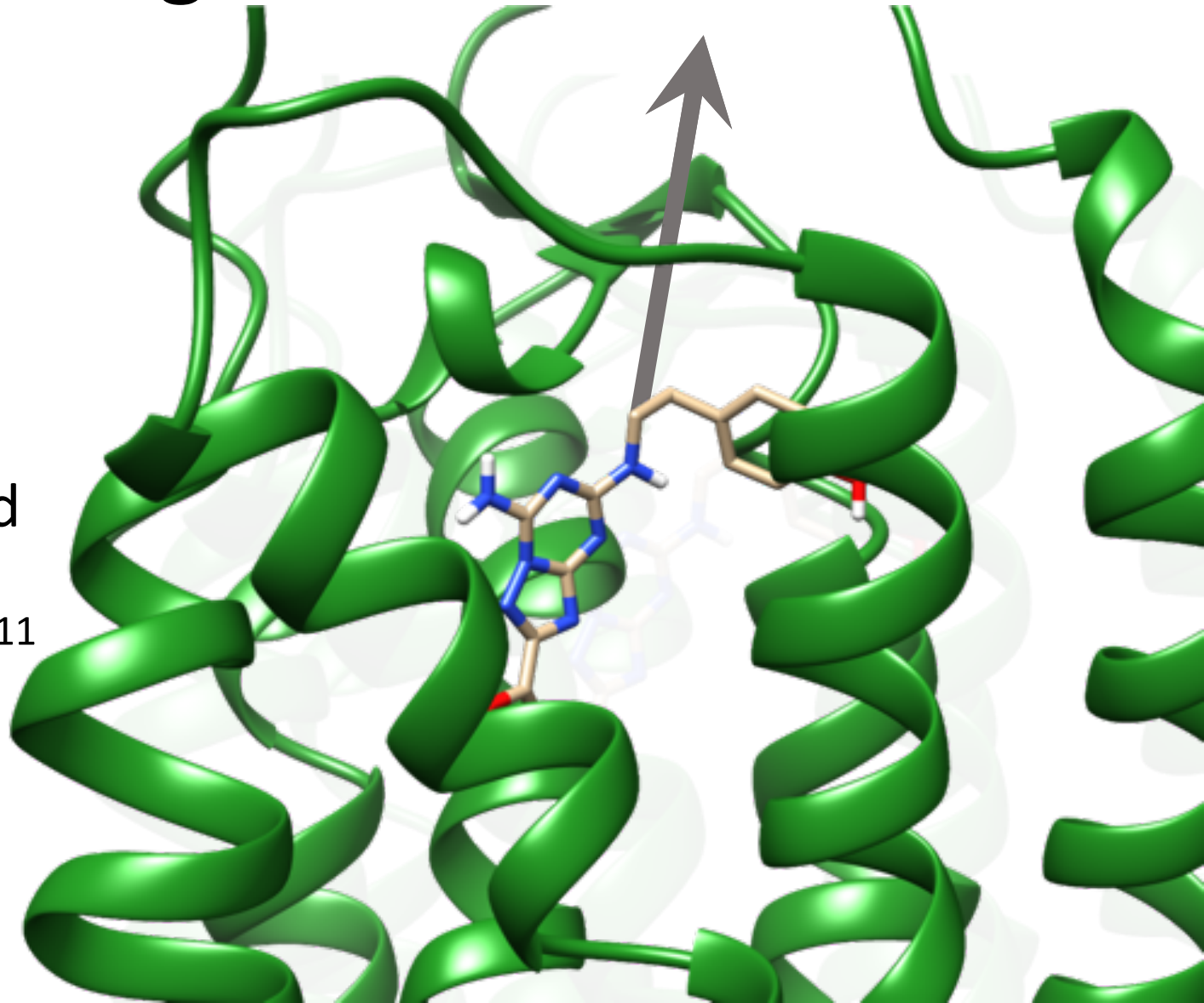
Adenosine A_{2A} Receptor

- Prototypical Class A GPCR
- 46 structures available
- Lots of historic site-directed mutagenesis equilibrium binding data
- Kinetic ligand binding data available

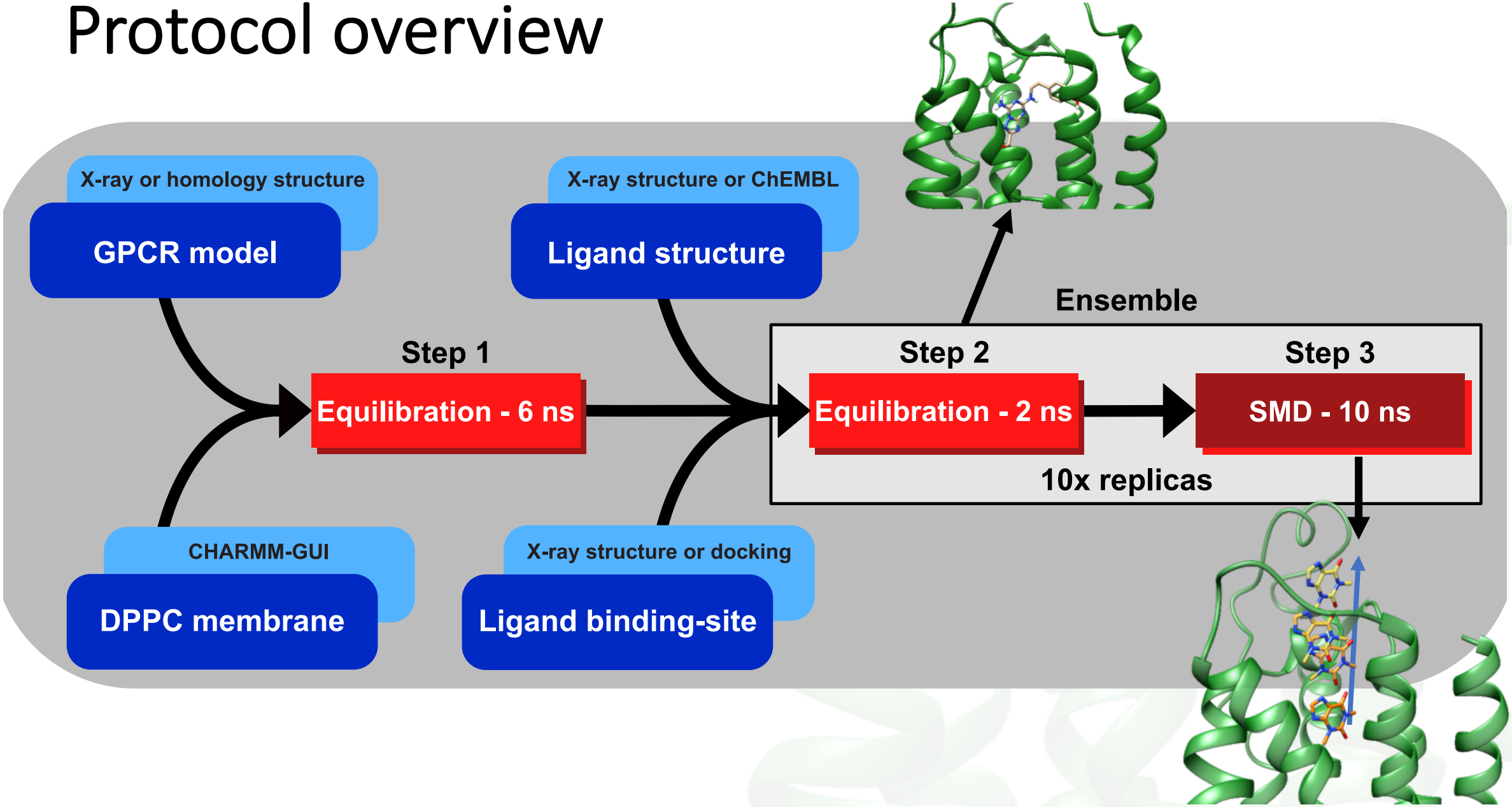
Steered MD forces the ligand to dissociate

- Ligand dissociation, for GPCR ligands, occurs on the minutes/hours timescale

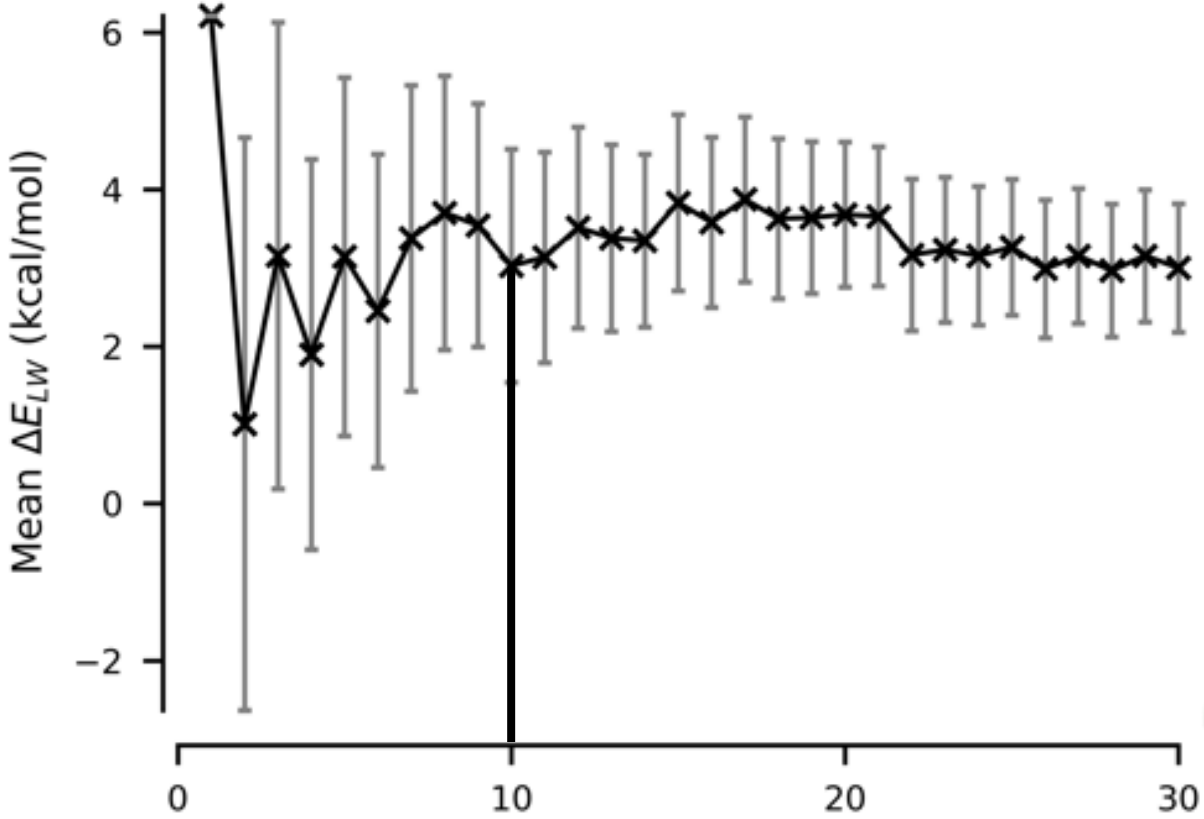
- Used constant velocity steered MD (1 Å/ns) to speed dissociation by an order of 10^{11}

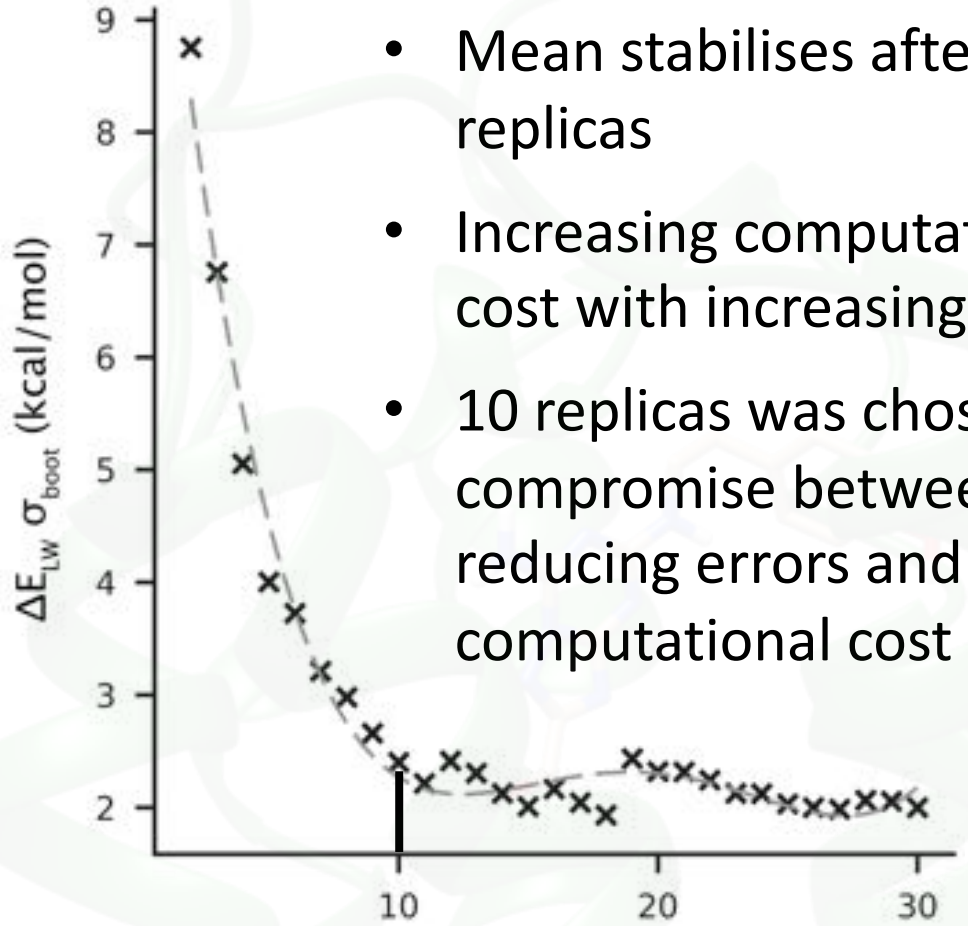


Protocol overview



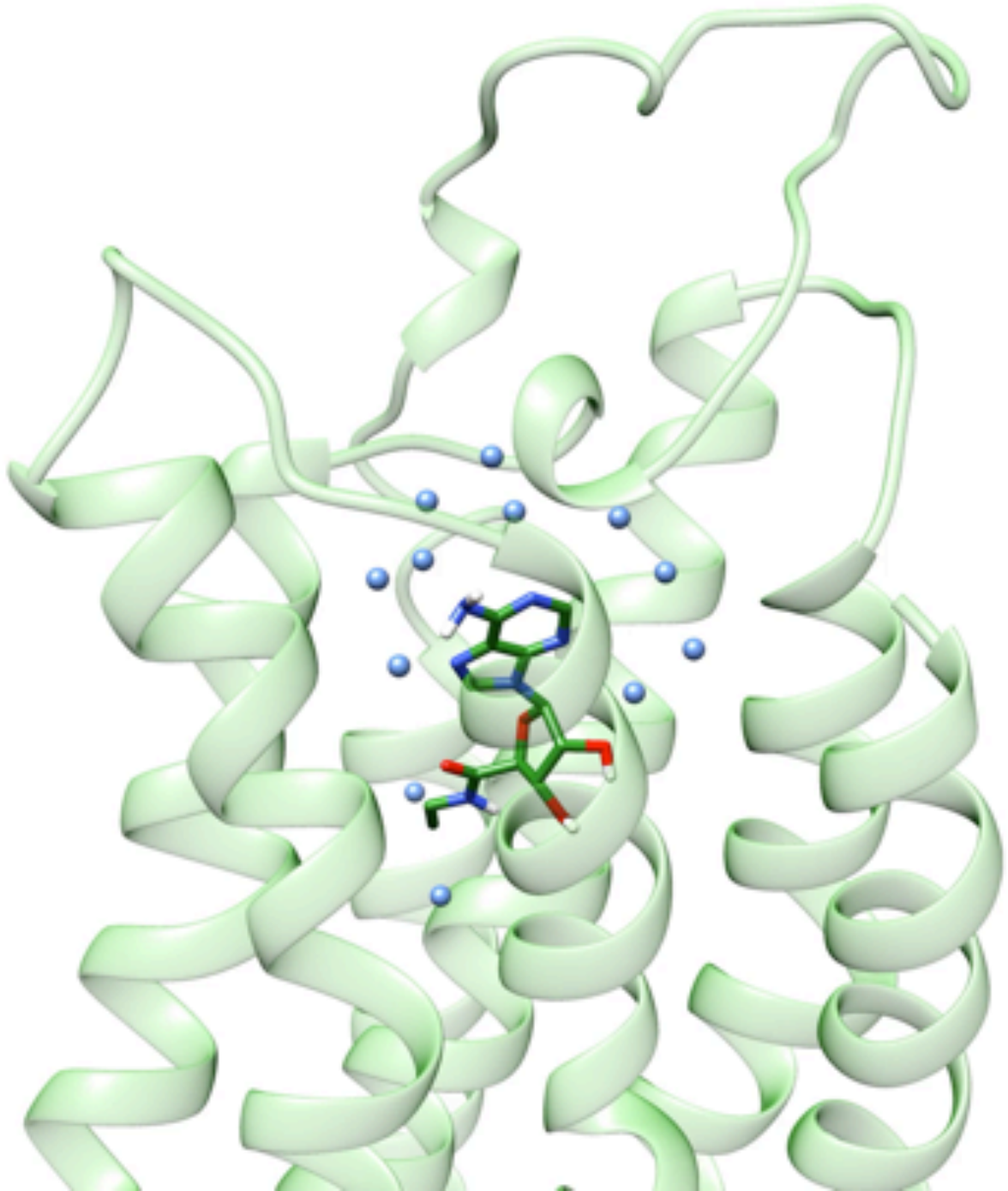
Increasing the number of replicas decreases error





- Mean stabilises after 3 replicas
- Increasing computational cost with increasing replicas
- 10 replicas was chosen as a compromise between reducing errors and computational cost

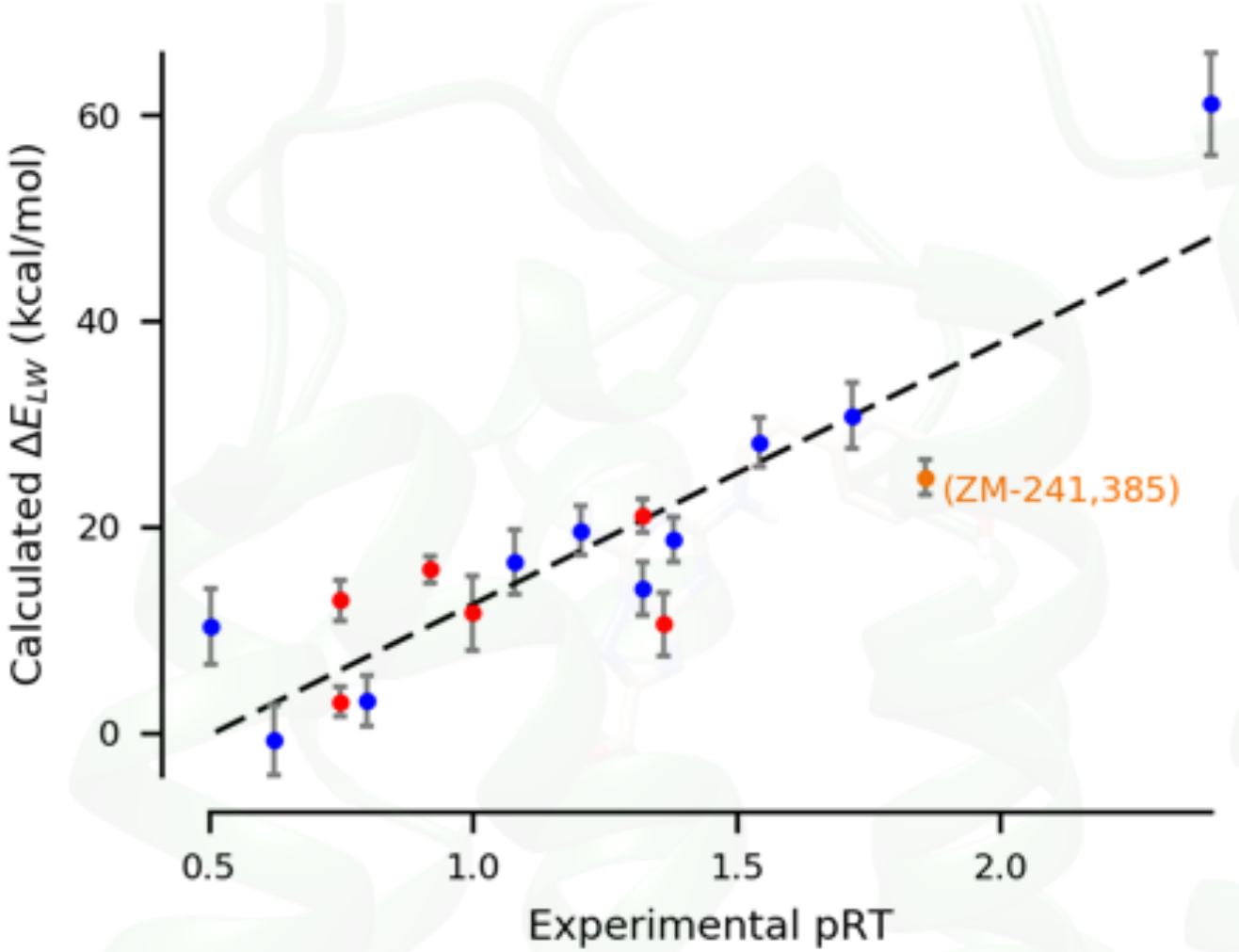
Dissociation of agonist from the A_{2A} receptor using SMD



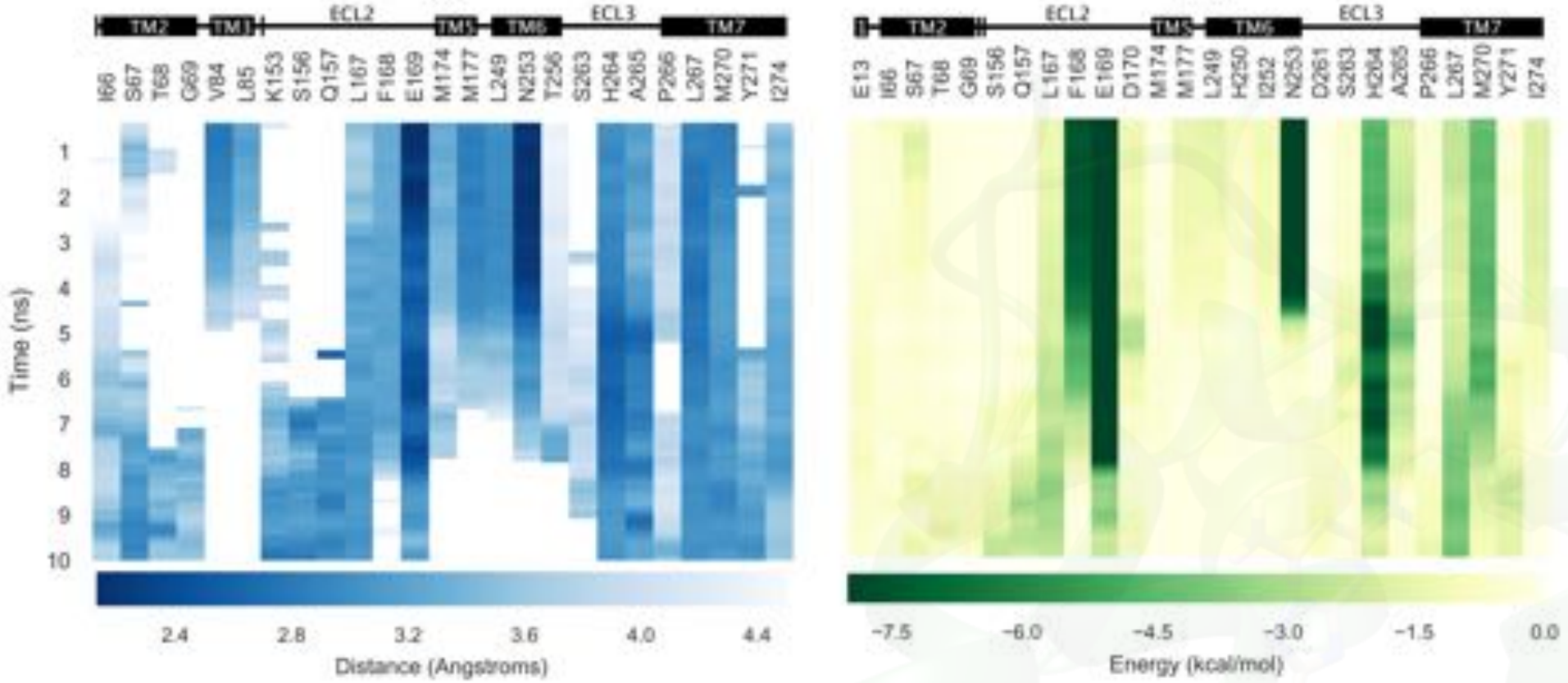
Computed change in ligand solvation energy correlates with experimental residence time

- There is a strong correlation ($R^2 = 0.79$) between the solvation energy (ΔE_{LW}) and residence time

- Ring groups reduce bound solvation, increasing ΔE_{LW} and residence time



Intermediate protein-residue contacts confer residence time



- When initial contacts are mutated experimentally, equilibrium binding affinity is affected
- Intermediate contacts, when mutated, have a greater effect on residence time

Summary

- Drug-target residence time is emerging as a key optimising parameter for drug discovery

- We have developed and tested an ensemble-based steered MD protocol that can predict and rationalise residence time
  - The change in solvation energy (ΔE_{LW}) is a predicator of residence time
  - Protein-residue interactions, identified from the simulation ensembles, are known to affect residence time and/or binding affinity

Acknowledgments

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Read the paper:

Potterton *et al*. Ensemble-Based Steered Molecular Dynamics Predicts Relative Residence Time of A2A Receptor Binders. **2019** *Journal of Chemical Theory and Computation*

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