Protein-small molecule binding with Martini 3: a practical view

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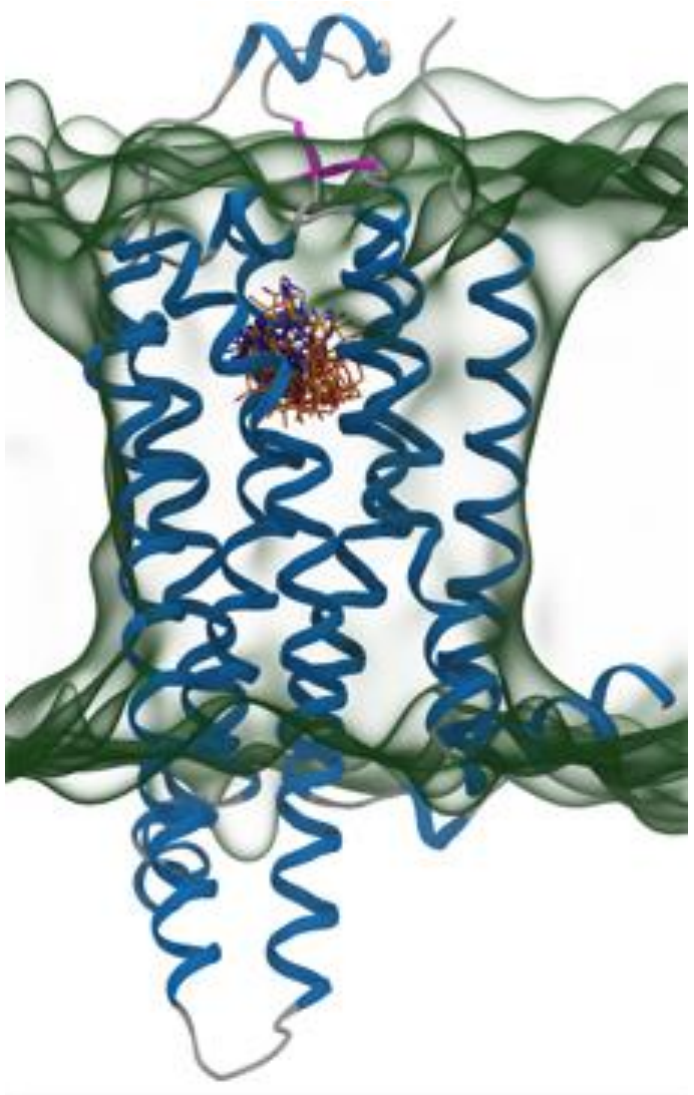
The key requirements to model protein-small molecule binding

- Coverage of chemical space
- Finding/knowing the pocket
- Proper packing
- Hydrophobicity
- Protein and ligand flexibility
- Influence of environment (lipids, water in the pocket, etc).
- Directionality (H-bonds)
- Predict binding affinities
- Predict pathways and Kinetic rates



The key requirements to model protein-small molecule binding

	Molecular docking
• Coverage of chemical space	V
• Finding the pocket	?
• Proper packing	V
• Hydrophobicity	V
• Protein and ligand flexibility	X
• Environment	X
• Directionality (H-bonds)	V
• Binding affinities	?
• Pathways and Kinetic rates	X

Limited by scoring functions

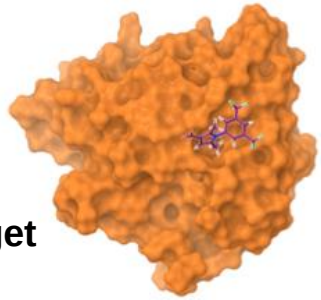
The key requirements to model protein-small molecule binding

	Molecular docking	Atomistic MD	
• Coverage of chemical space	v	v	
• Finding the pocket	?	x	
• Proper packing	v	v	
• Hydrophobicity	v	v	
• Protein and ligand flexibility	x	?	Computational performance and accuracy
• Environment	x	?	
• Directionality (H-bonds)	v	v	
• Binding affinities	?	v	
• Pathways and Kinetic rates	x	?	Computational performance

The key requirements to model protein-small molecule binding

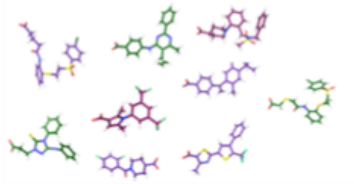
	Molecular docking	Atomistic MD	Martini 2 MD
• Coverage of chemical space	V	V	X
• Finding the pocket	?	X	?
• Proper packing	V	V	X
• Hydrophobicity	V	V	V
• Protein and ligand flexibility	X	?	X
• Environment	X	?	?
• Directionality (H-bonds)	V	V	X
• Binding affinities	?	V	X
• Pathways and Kinetic rates	X	?	X

Pitfalls of Computer-Aided Drug design

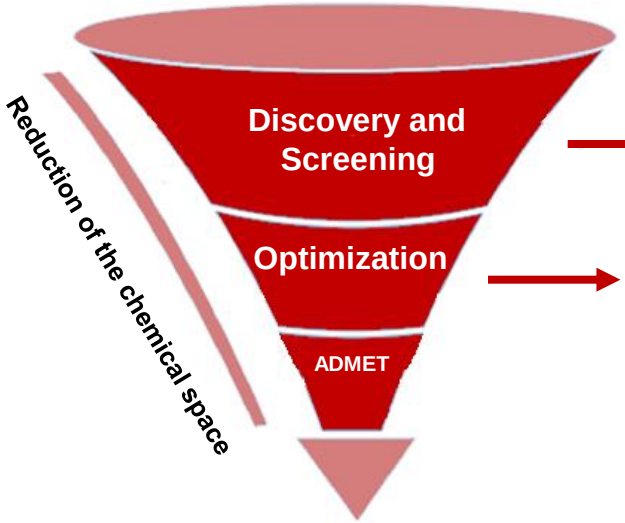


Target

Chemical Space:
millions of compounds



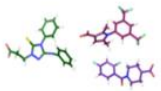
Limitations



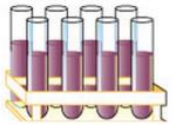
Molecular Docking → Low accuracy

Atomistic MD simulations → Computationally expensive

No kinetics Information

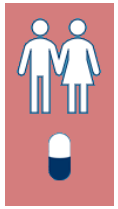


Lead compounds



In-vitro assays

Animal Tests



Clinical Phases

European Medicines Agency

More about limitations: kinetics and hidden pockets

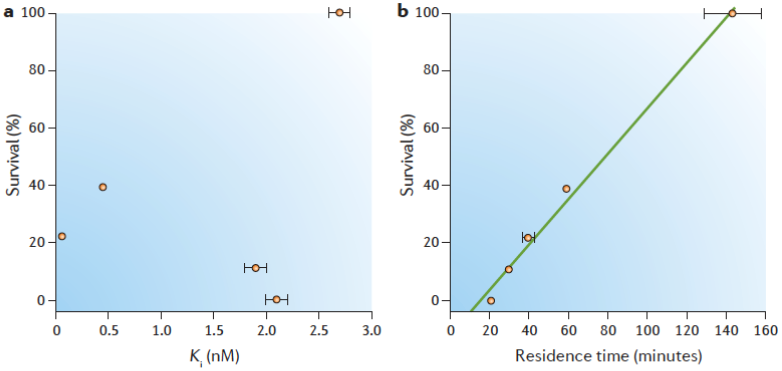
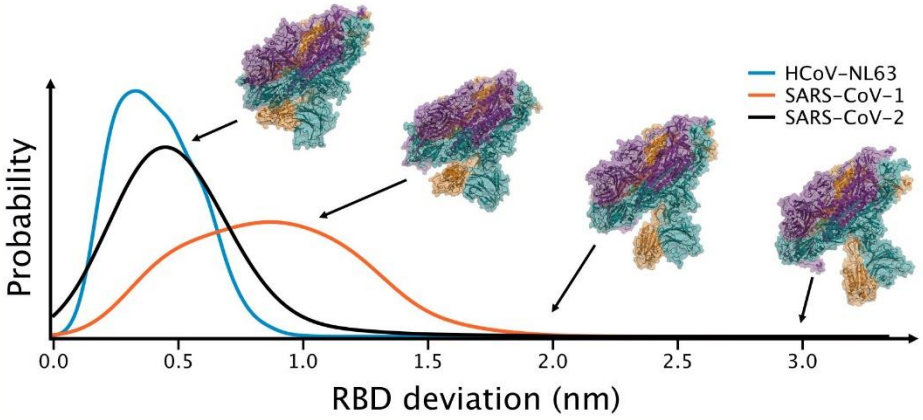


Figure 4 | ***In vivo* efficacy often depends on drug-target residence time.** Lu *et al.*[30] investigated the relationship between the residence time of a series of FabI enoyl-reductase inhibitors and *in vivo* activity. The plots presented here show the percent survival of mice 10 days after they were infected with the bacterium *Francisella tularensis* and then treated with the inhibitors. **a** | Correlation of percent survival with the inhibition constant (K_i). **b** | Correlation of percent survival with inhibitor residence time. Figure is adapted with permission from REF 5, Wiley.

Importance of dissociation rates for the activity

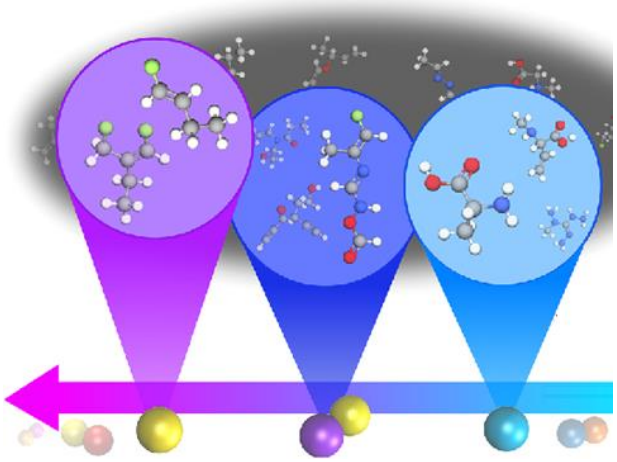
Copeland, R. A. The drug–target residence time model: a 10-year retrospective. Nat. Rev. Drug. Discov. 2016, 15, 87–95.

Hidden (cryptic) and/or multiple pockets



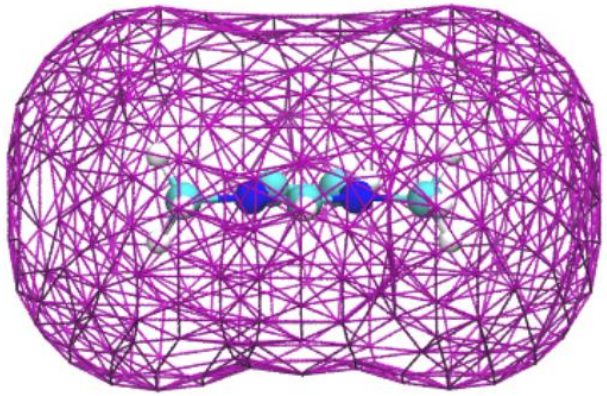
Zimmerman, M. I., et. Al. Citizen Scientists Create an Exascale Computer to Combat COVID-19, Biorxiv, 2020

Can Martini 3 be useful for drug design?



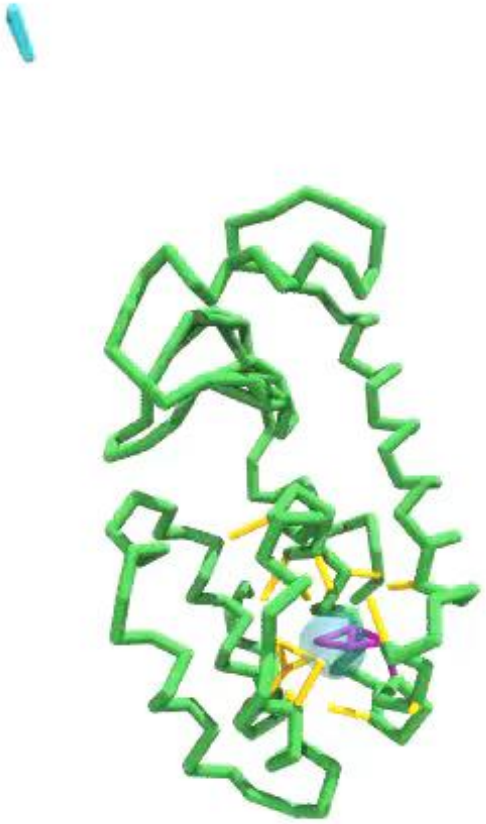
Better Coverage of Chemical Space

Better interactions and packing



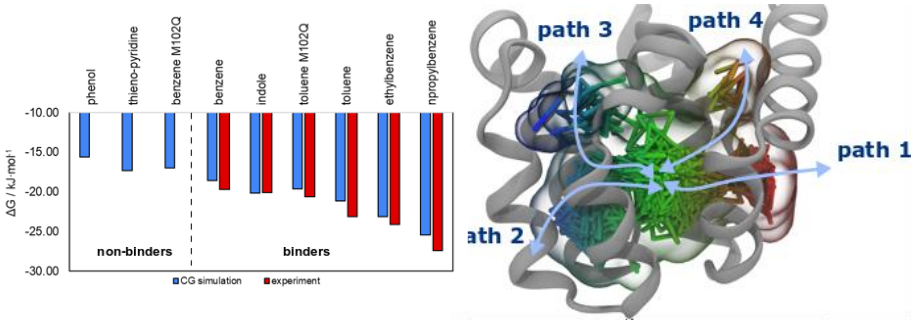
WHAT ABOUT THE PROOF OF CONCEPT?

Protein–ligand binding with the Martini 3?

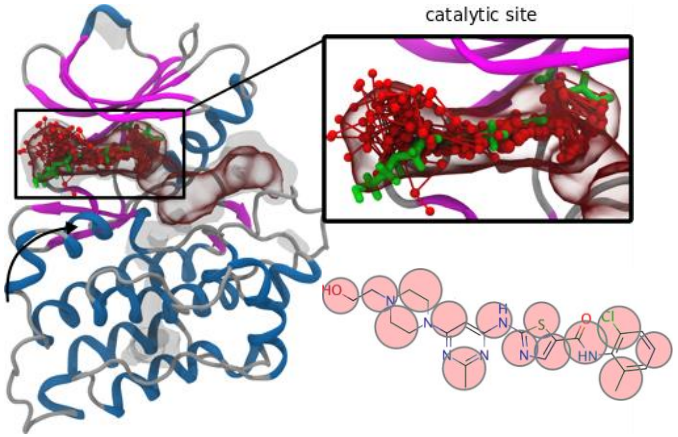


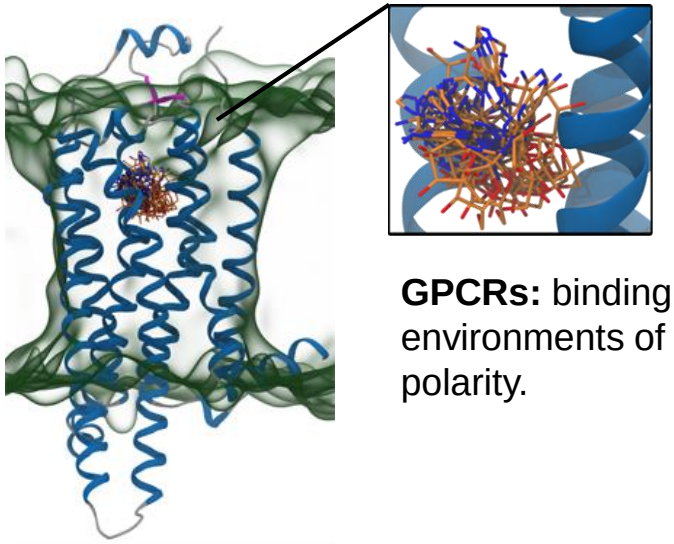
New applications for Martini!
Protein-ligand binding

Proof of concept: quantitative affinities and Trends in kinetics with T4 lysozyme.



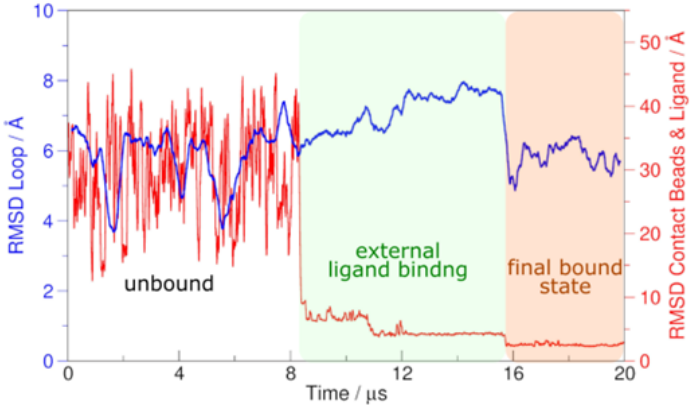
Kinases: higher coverage of chemical space

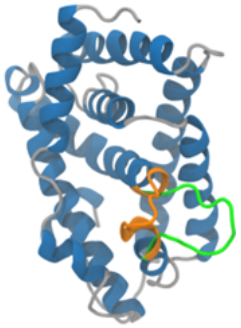




GPCRs: binding in environments of different polarity.

Nuclear Receptors: conformational changes



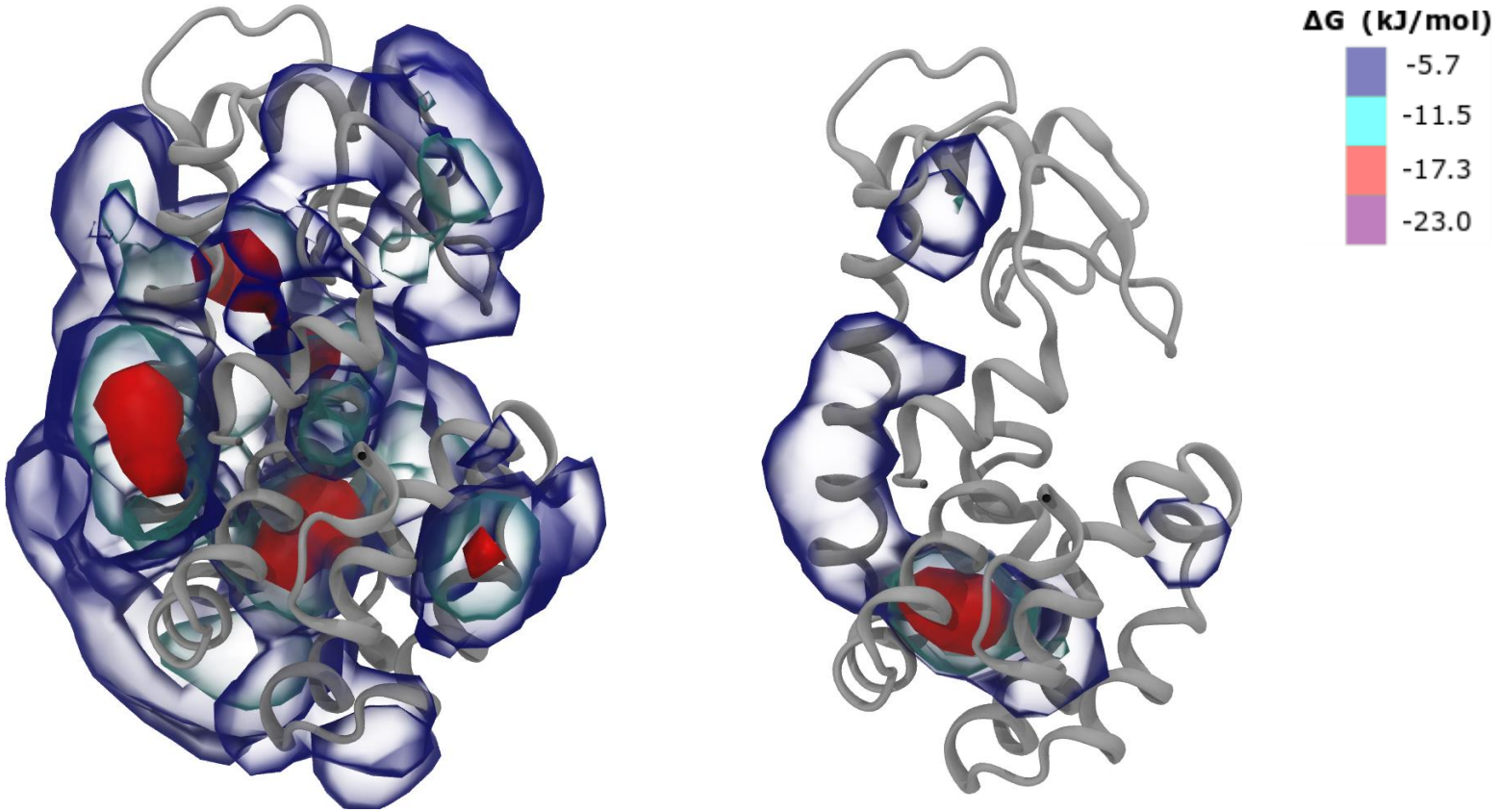


P.C.T. Souza *et. al*, Nature Communications, 2020.

Comparing different Martini versions for protein-ligand binding

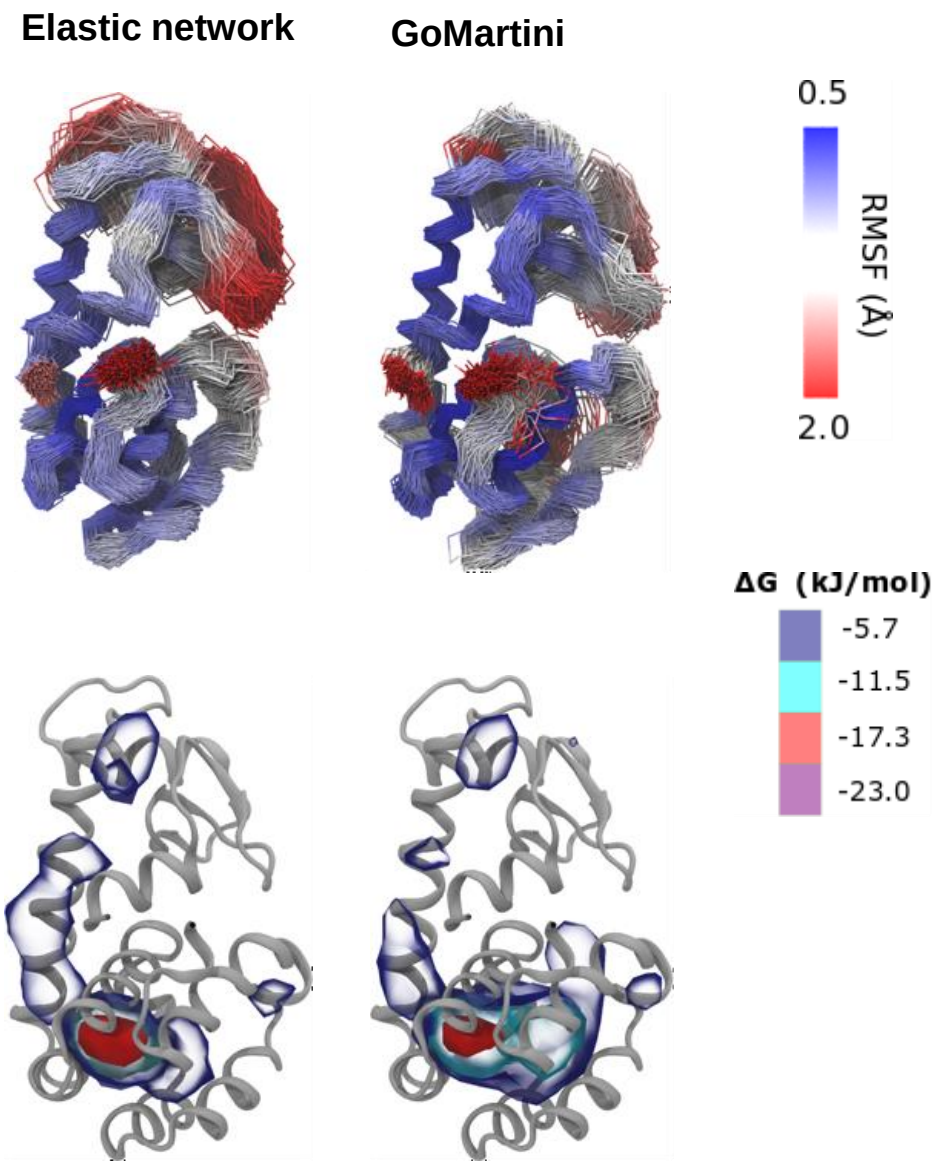
Martini 2

Martini 3



Elastic Network versus GoMartini

- Similar flexibility of elastic network and GoMartini models
- GōMartini show more flexibility in the pocket.
- Both models get quantitative agreement of binding affinity
- GoMartine is possibility more accurate to get intermediate states of binding process.



P.C.T. Souza *et. al*, in preparation, 2021.

A Practical view of protein-ligand binding: Building the system and sampling strategy

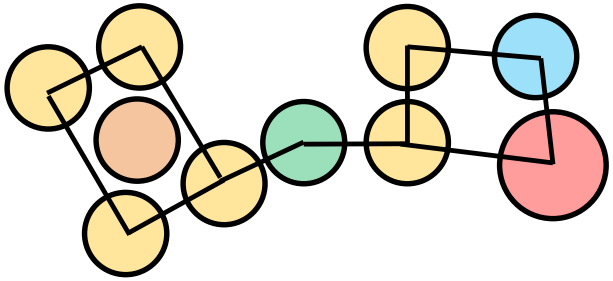
Ligands

- Placed in random initial positions

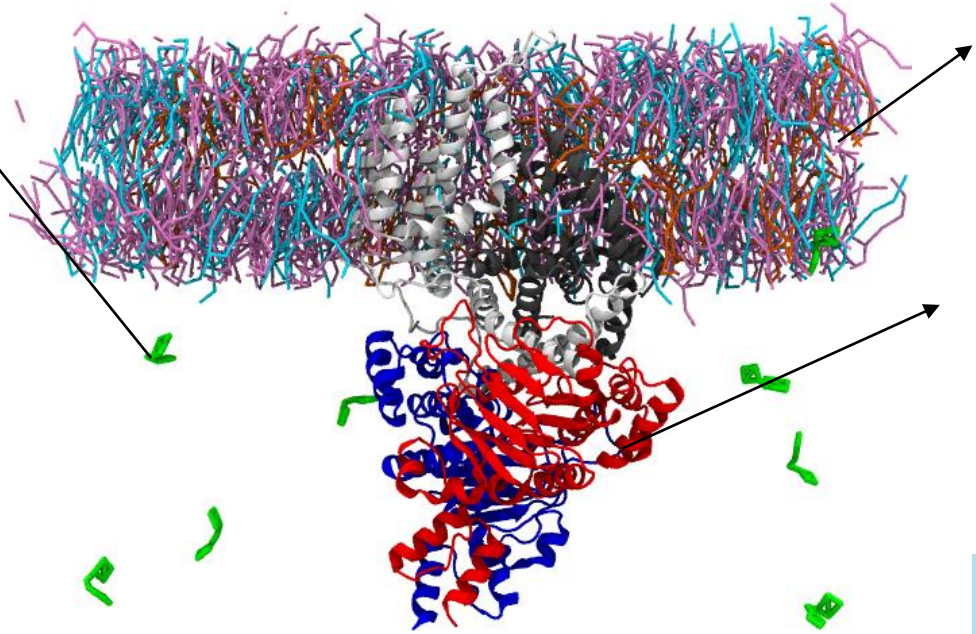
$ gmx insert-molecules

- Concentration vs aggregation

- Model: accuracy versus screening



Lecture and Tutorial: Parametrization new CG models



Environment

- Including complexity

Lecture and Tutorial: Lipids

Protein Model

- Flexible
- Protonation state of residues

Lecture and Tutorial: Proteins

Sampling strategy: tips

- Control simulation: start with ligand in the pocket!
- Additional preliminary simulations to have a idea of minimum time to simulate: you need to get at least 1 association event.
- For brute force: multiple simulations more efficient than long ones.

A Practical view of protein-ligand binding: Preparation of trajetory and analysis

1) Get the ligands at minimal distance from the protein

$ gmx trjconv -pbc cluster -s topol.tpr -f temp.xtc -o trajcluster.xtc -n index.ndx

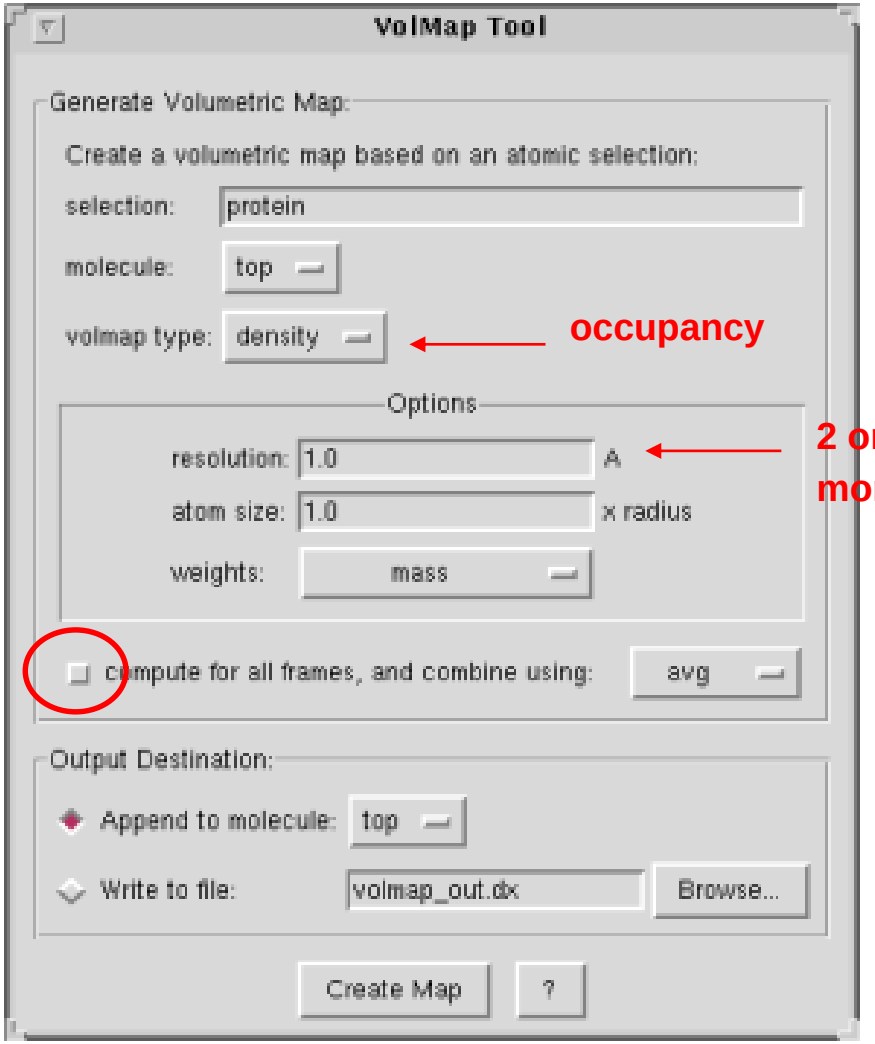
-pbc mole is also an option

2) Center and align the protein

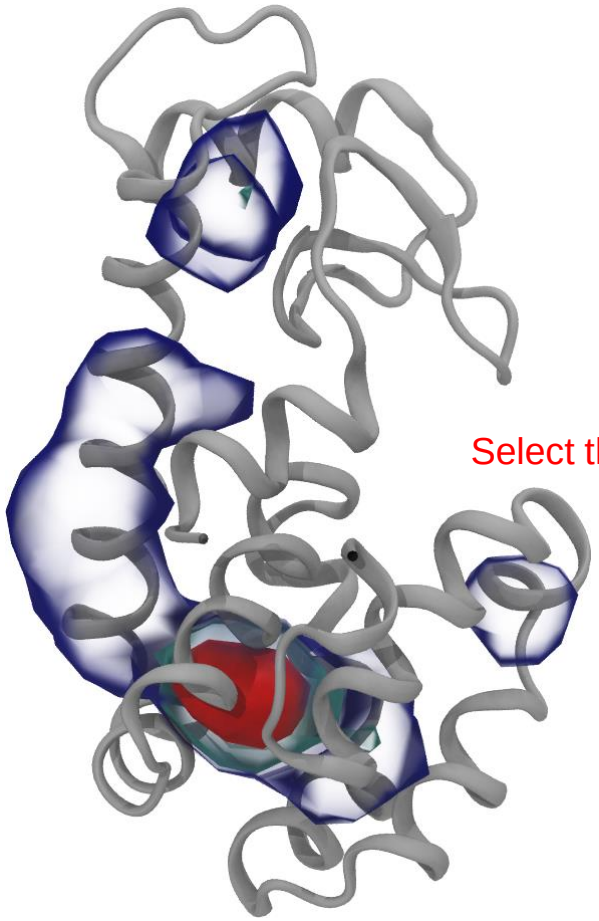
$ gmx trjconv -fit rot+trans -s topol.tpr -f temp.xtc -o trajfitted.xtc -n index.ndx

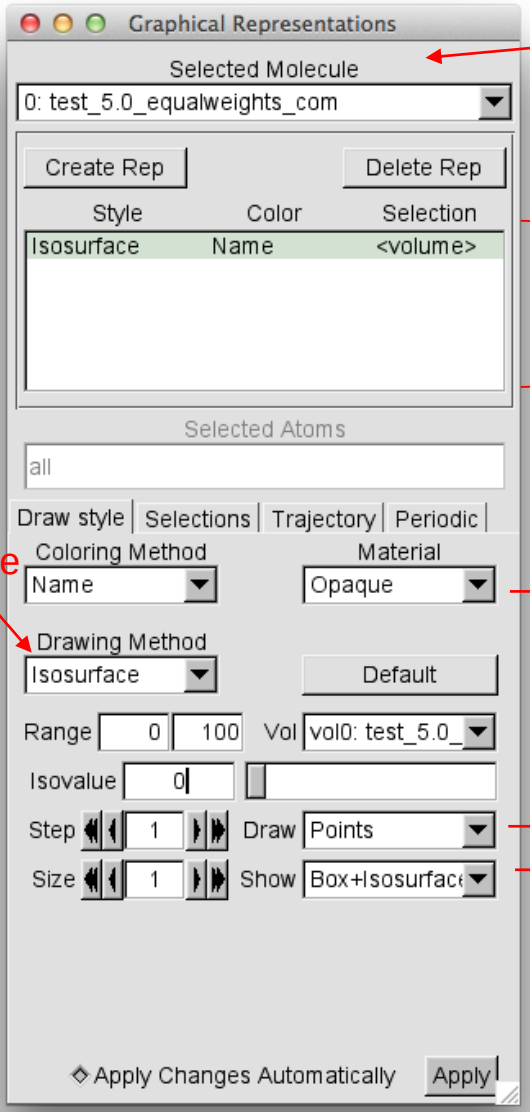
3) Analysis

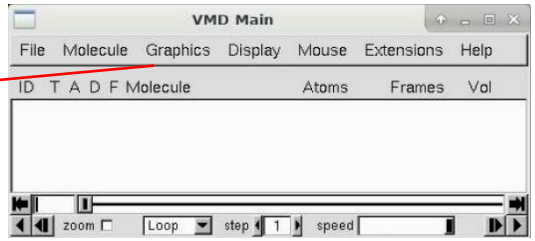
- Clustering and Markov state models
- Ligand density with VMD



A Practical view of protein-ligand binding: Ligand density visualization







multiple representations

VMD Visual Molecular Dynamics

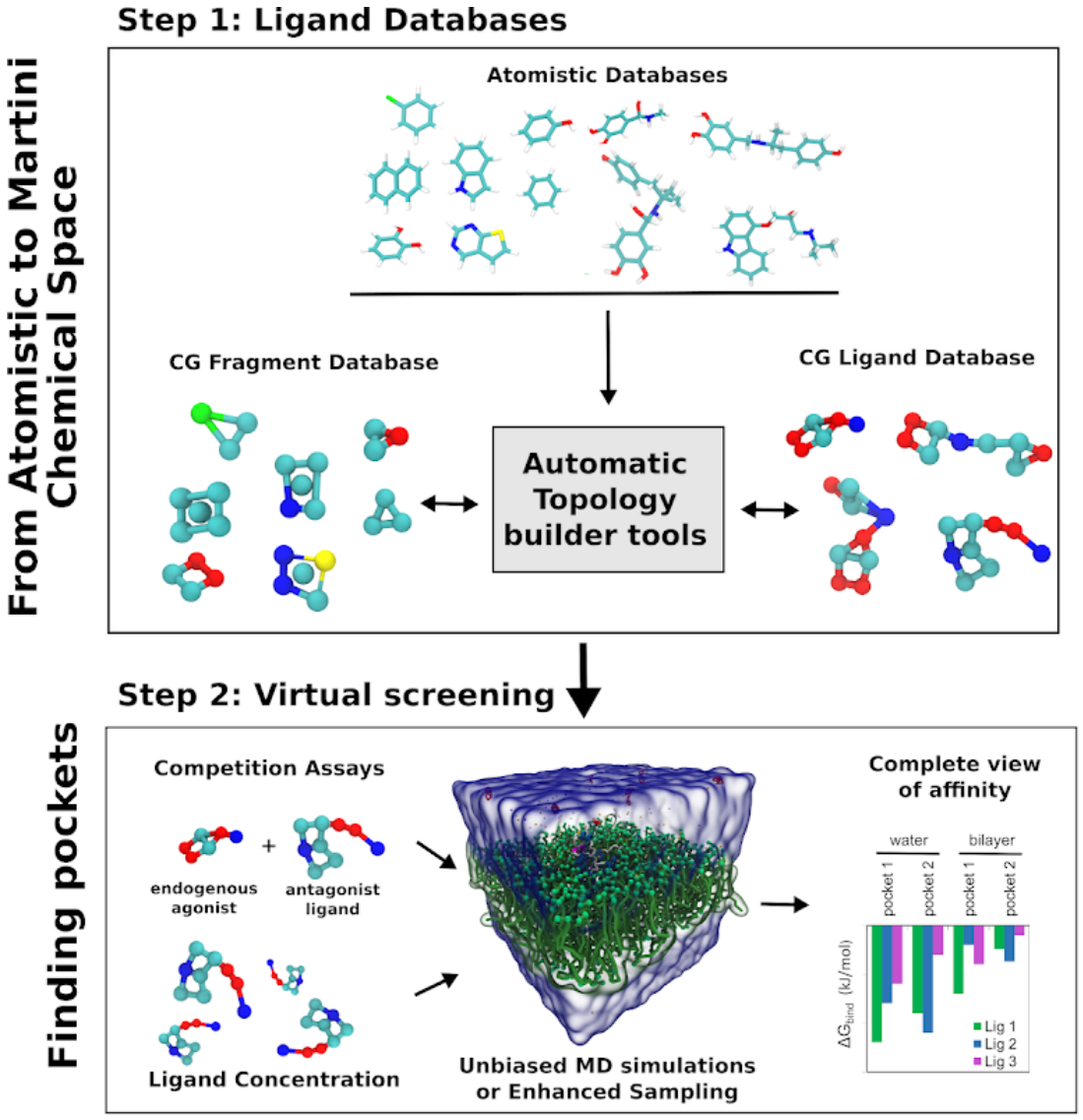
Select this one

Transparency for multiple representations

surface

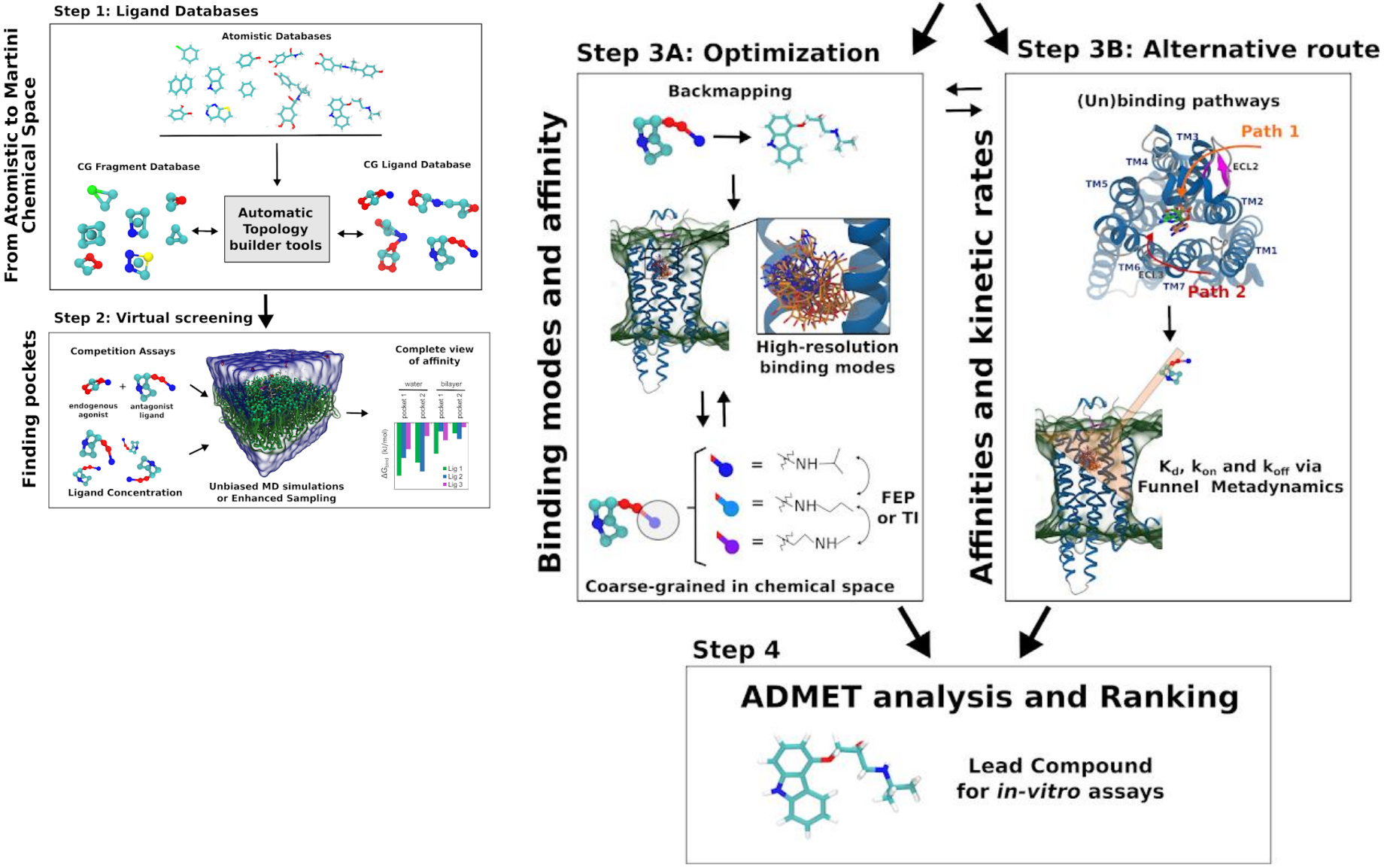
isosurface

Towards virtual screening with Martini 3



P.C.T. Souza *et. al*, Frontiers, 2021.

Towards virtual screening with Martini 3



P.C.T. Souza *et. al*, Frontiers, 2021.

Take-home message

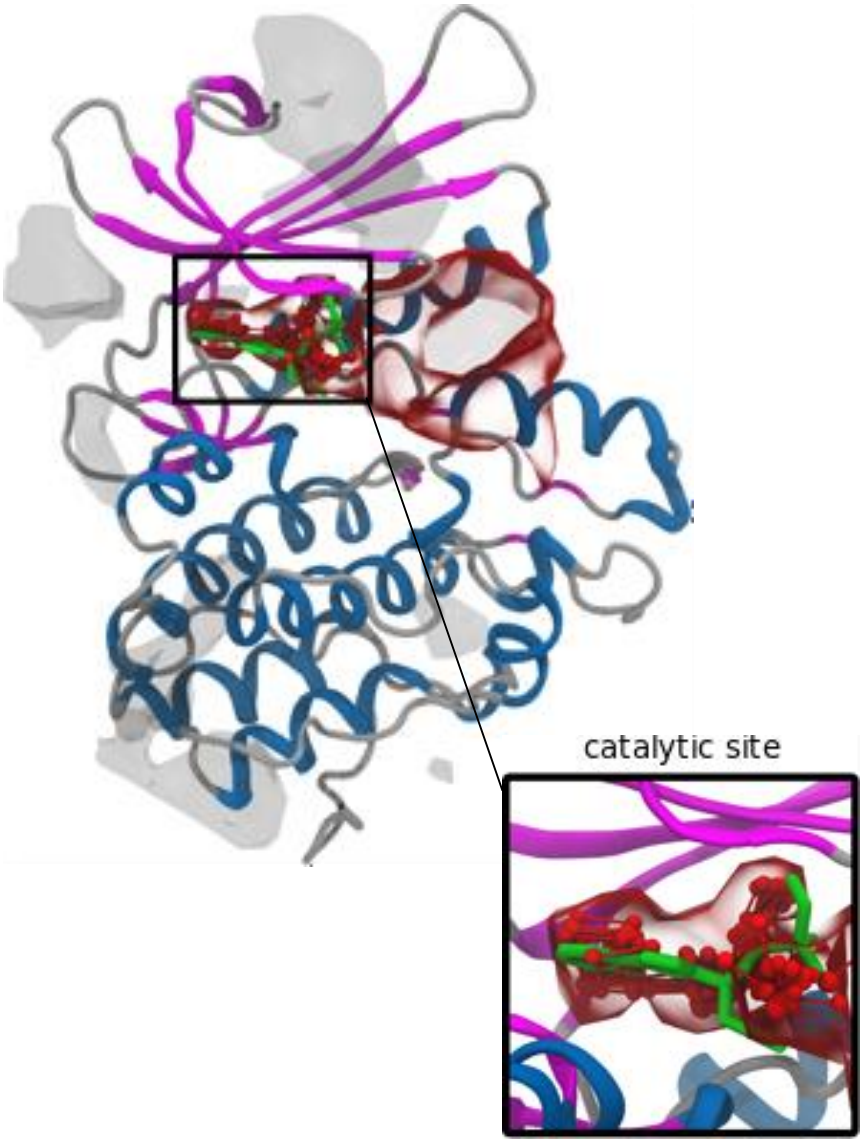
Protein-small molecule binding and computational methods

- No method fulfil all the requirements to be used in all the steps in structural based approaches.

- Martini 3 seems to be new additional option

- GōMartini may help you to better study binding process.

- Still many bottlenecks for screening
  - Database of CG models
  - Automatic parametrization
  - Enhanced sampling



THANKS