Modelling and Reality in Chemistry

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https://liedllab.org/

Emergence of Theoretical Chemistry

3. ***Quantisierung als Eigenwertproblem;***
von E. Schrödinger.

(Erste Mitteilung.)

§ 1. In dieser Mitteilung möchte ich zunächst an dem einfachsten Fall des (nichtrelativistischen und ungestörten) Wasserstoffatoms zeigen, daß die übliche Quantisierungsvorschrift sich durch eine andere Forderung ersetzen läßt, in der kein Wort von „ganzen Zahlen“ mehr vorkommt. Vielmehr ergibt sich die Ganzzahligkeit auf dieselbe natürliche Art, wie etwa die Ganzzahligkeit der *Knotenzahl* einer schwingenden Saite. Die neue Auffassung ist verallgemeinerungsfähig und rührt, wie ich glaube, sehr tief an das wahre Wesen der Quantenvorschriften.

Schrödinger 1926 Ann. Phys. (284) 361-376

Quantum Mechanics of Many-Electron Systems.

By P. A. M. Dirac, St. John's College, Cambridge.

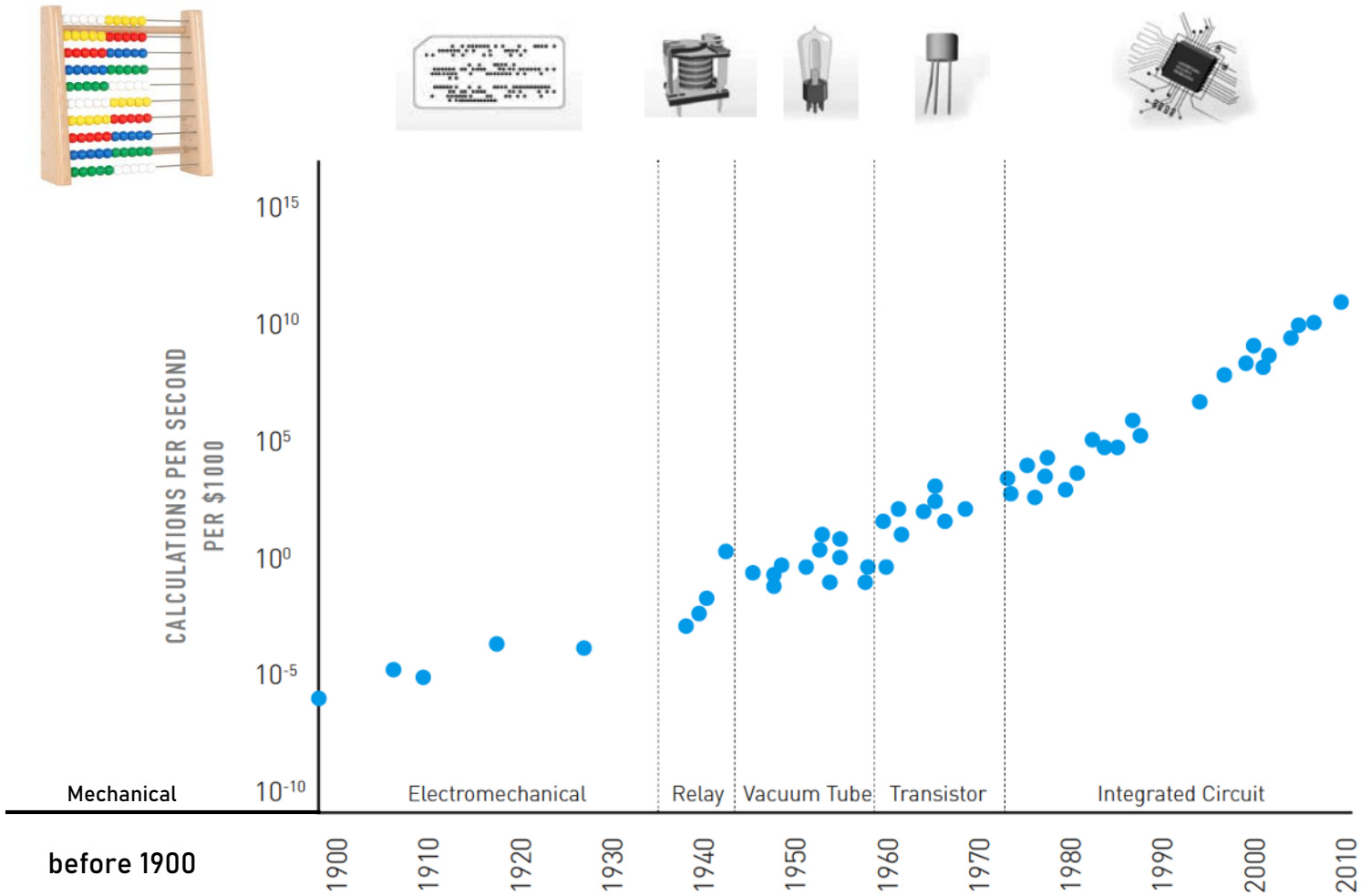
(Communicated by R. H. Fowler, F.R.S.—Received March 12, 1929.)

§ 1. *Introduction.*

The general theory of quantum mechanics is now almost complete, the imperfections that still remain being in connection with the exact fitting in of the theory with relativity ideas. These give rise to difficulties only when high-speed particles are involved, and are therefore of no importance in the consideration of atomic and molecular structure and ordinary chemical reactions, in which it is, indeed, usually sufficiently accurate if one neglects relativity variation of mass with velocity and assumes only Coulomb forces between the various electrons and atomic nuclei. The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.

Dirac 1929 Proc. R. Soc. Lond. A (123) 714-733

Moore‘s Law



https://umaincertaantropologia.org/tag/ciborgue/
https://www.experimentis-shop.de/abakus-rechenrahmen-mit-100-perlen-detail-717.html

Evolution of airplanes

https://www.messynessychic.com/2017/02/22/only-photographs-remained-of-the-first-flying-man-until-now/

https://www.flickr.com/photos/24874528@N04/9268444007/in/photostream/

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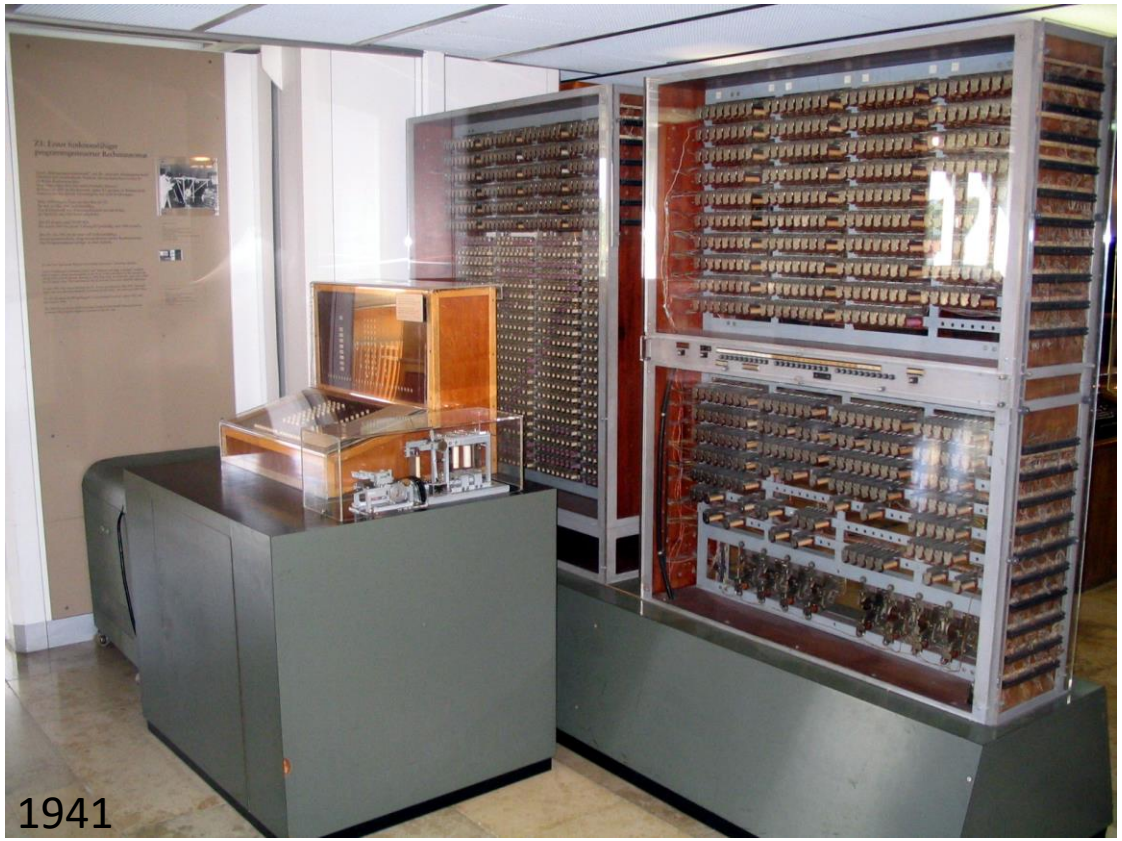
https://www.jetphotos.com/photo/7680662

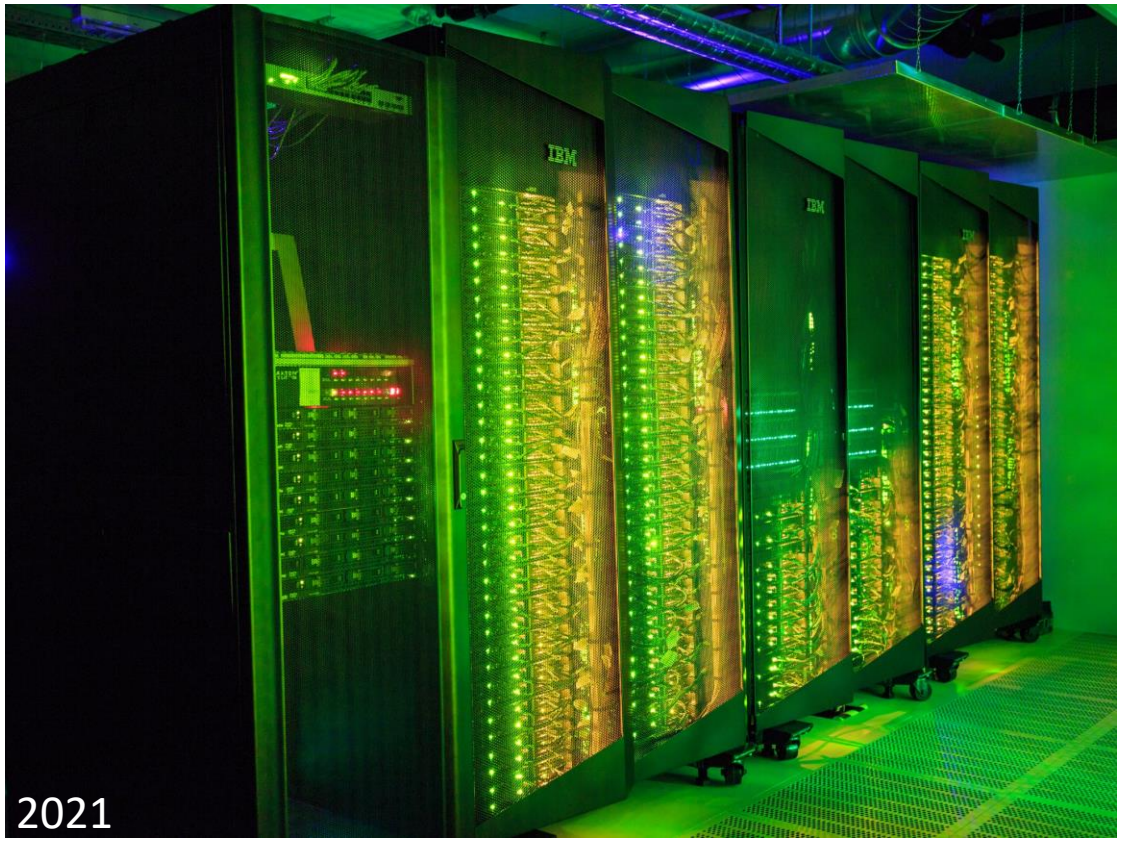
https://vi.wikipedia.org/wiki/Airbus_A350

https://eu.lcsun-news.com/story/news/local/spaceport/2018/12/12/virgin-galactic-space-flight-could-come-thursday/2292279002/

Evolution of computers



https://de.wikipedia.org/wiki/Zuse_Z3



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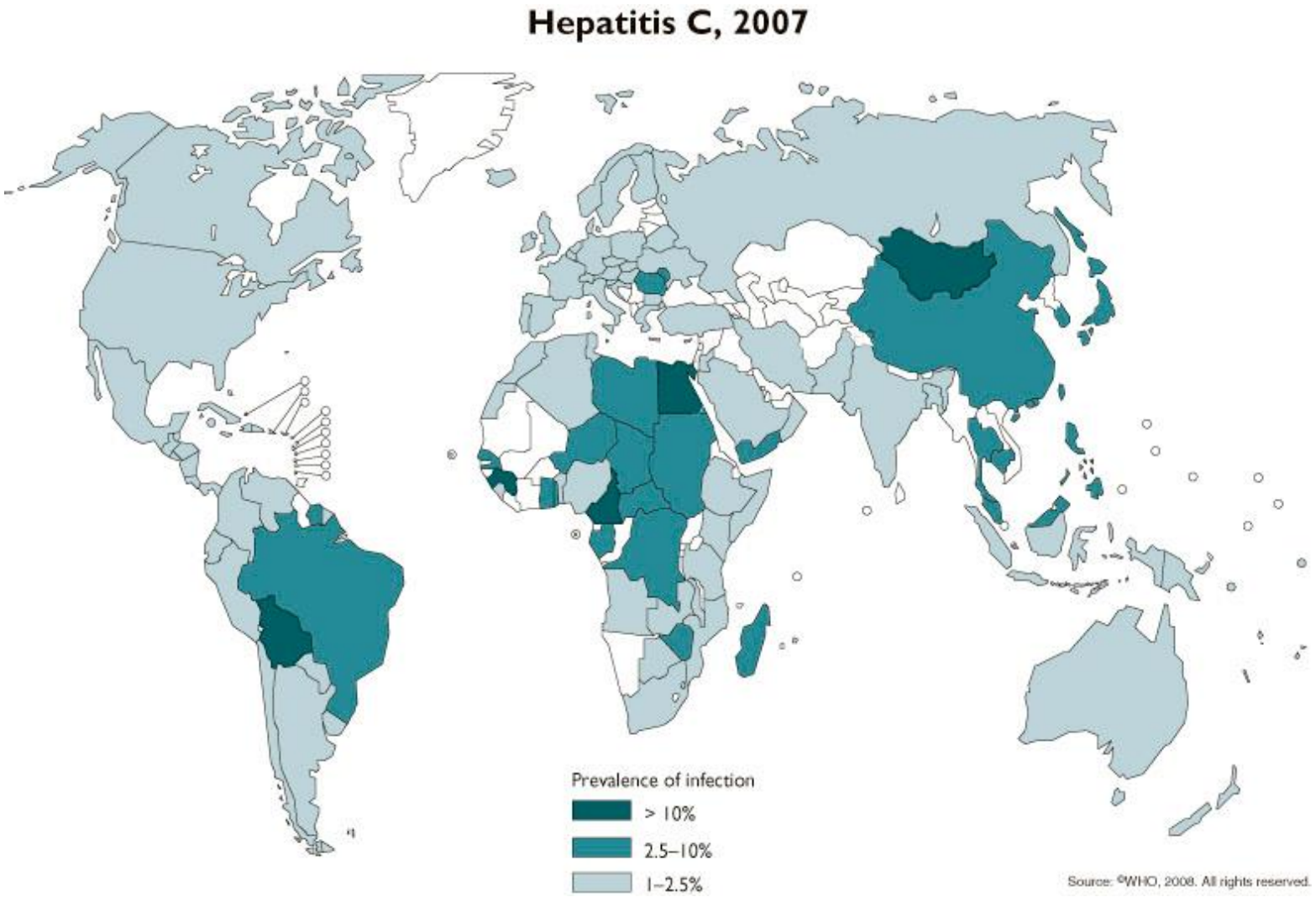
Evolution of computers

https://www.wallpics.net/the-witcher-3-wild-hunt-desktop-wallpapers/
https://www.nvidia.com/de-de/geforce/graphics-cards/30-series/rtx-3090

Hepatitis C



200 million people infected

700 000 deaths per year

Jang & Chung 2011 Gut and liver (5) 117-32

Hepatitis C

https://www.pharmacytimes.com/view/daily-medication-pearl-harvoni-ledipasvir-and-sofosbuvir-

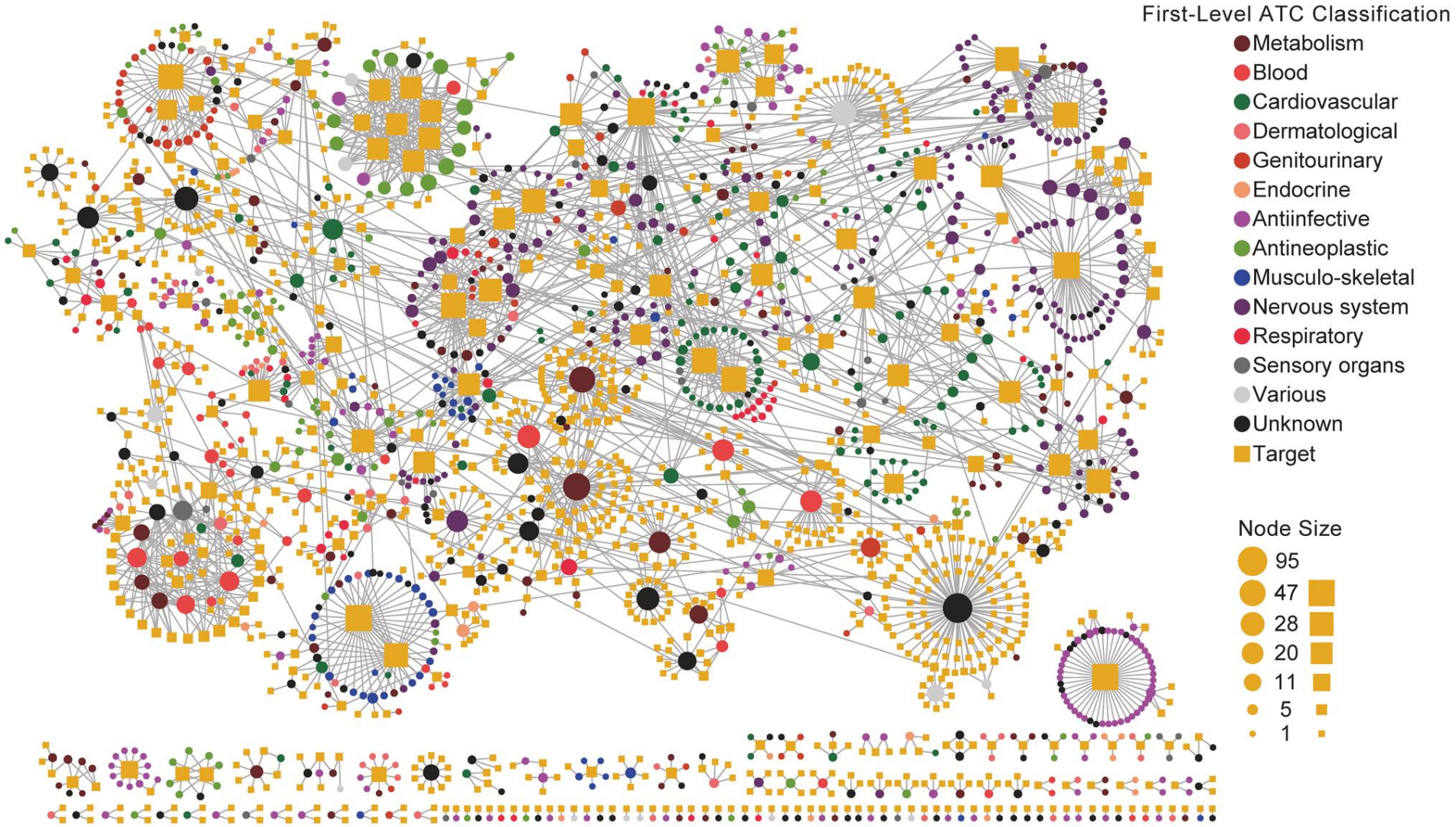
https://www.empr.com/drug/sovaldi/

https://www.empr.com/home/news/epclusa-approved-for-pediatric-patients-with-chronic-hepatitis-c-infection/

Harvoni: 13 864 000 000 USD 2015

Sovaldi: 5 276 000 000 USD 2015

Promiscuity of biomolecular interfaces



Chuang Liu et al. 2020 Physics Reports (846) 1-66 ISSN 0370-1573

Free Energies and Dissociation Constants

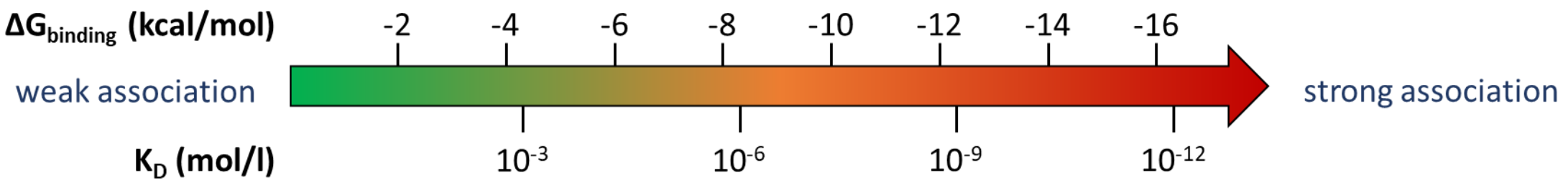
$$\Delta G = \Delta H - T \cdot \Delta S$$

Enthalpic

- Hydrogen bonds
- Polar interactions
- Van der Waals interactions

Entropic

- Loss of degrees of freedom
- Gain of vibrational modes
- Loss of solvent/protein structure



Challenges in modelling in chemistry

1. Degrees of freedom governing chemical processes are electronic, nuclear, atomic, molecular and supra-molecular, and the corresponding particles have different masses and sizes
2. Interactions are governed by quantum mechanics: Dirac or Schrödinger equation, for not too small mass or too low temperature by classical equations of motion
3. At non-zero temperatures, the behavior of particles is governed by statistical mechanics: Fermi-Dirac, Bose-Einstein, or Boltzmann **ensembles of configurations are to be considered, not single structures**
4. The Coulomb interaction is rather long-ranged (distance^{-1}) and induces many-body effects that make accurate modelling rather expensive
5. (Free) energy differences that drive processes can be very small compared to the total energy of the interacting particles
6. Time scales of processes easily span 15 orders of magnitude (fsec => sec)

Challenge: striking an appropriate balance between accuracy and computational cost **while maintaining a physically correct mechanism of the process of interest**

Different levels of resolution of modelling

Table 1: Characteristic sizes of particles at different levels of resolution of modeling, scaling of the computational effort as a function of the number of nucleons (N_n), electrons (N_e), atoms (N_a) or beads (N_b), and the reduction of the number of degrees of freedom N_{df} or interactions and the reduction of computational effort that can be achieved by coarse-graining to the next level of resolution.

Level of resolution	I	II	III	IV	V
Particles	nucleons + electrons	nuclei + electrons	atoms	supra-atomic beads	supra-molecular beads
Mass of bead [amu]	10^{-3}–1	10^{-3}–10^{2}	1–10^{2}	10–10^{2}	10–10^{2}
Size of bead [nm]	10^{-6}	10^{-6}–10^{-5}	0.03–0.3	0.5–1.0	0.5–1.0
Interactions	strong Coulomb Pauli principle	Coulomb Pauli	bonded terms, Coulomb repulsive, van der Waals		Coulomb repulsive, van der Waals
Scaling effort	$N_n^{\geq 3}$	$N_e^{\geq 3}$	N_a^{1-2}	N_b^{1-2}	N_b^{1-2}
Reduction number of degrees of freedom	10–100	10–100	2–5	2–10	
Reduction computational effort	$\geq 10^{3}$	$\geq 10^{3}$	2–25	2–100	

Meier et al. 2013 Angew. Chem. Int. Ed. (52) 2820-2834

Quantum mechanics vs classical mechanics

Table 2: Overview of main differences between quantum and classical mechanics as applied to molecular systems.

Quantum statistical mechanics (QM)	Classical statistical mechanics (CM)
• time-dependent Schrödinger equation: $i\hbar \frac{\partial \Psi(\vec{r}^N,t)}{\partial t} = \hat{H}\Psi(\vec{r}^N,t)$ with wave function Ψ	• Newton's equation: $\vec{f}_i = m_i\vec{a}_i \quad \vec{f}_i = -\frac{\partial V(\vec{r}^N)}{\partial \vec{r}_i}$
• Born-Oppenheimer approximation: nuclei and electrons decoupled	• interaction potential energy function $V(\vec{r}^N)$ is generally pair additive, but polarisation can be included
• probabilistic nature of wave function, $\lvert\Psi(\vec{r}_i,t)\rvert^2$ Uncertainty principle, no trajectory	• phase space trajectory $\vec{r}^N$, $\vec{p}^N$
• Bose-Einstein or Fermi-Dirac statistics (Pauli principle)	• Boltzmann statistics

Meier et al. 2013 Angew. Chem. Int. Ed. (52) 2820-2834

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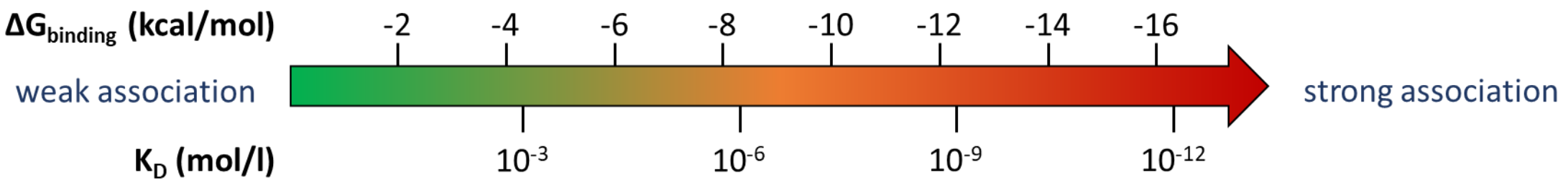
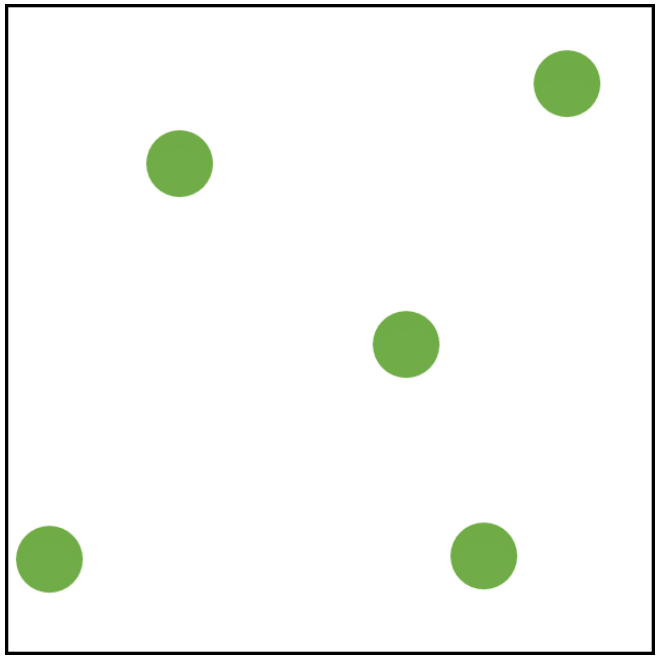


Gases and Crystals

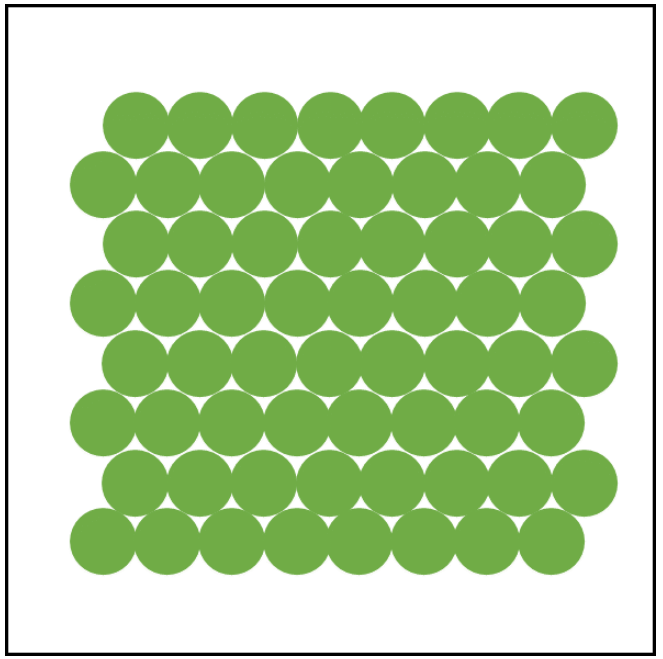
- For gases and crystals, it is possible to calculate probabilities and partition functions directly

gas phase



rare interactions

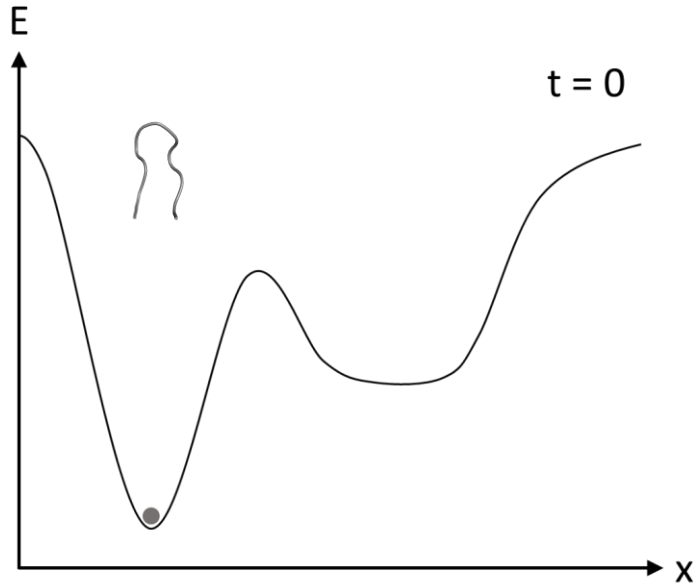
crystal

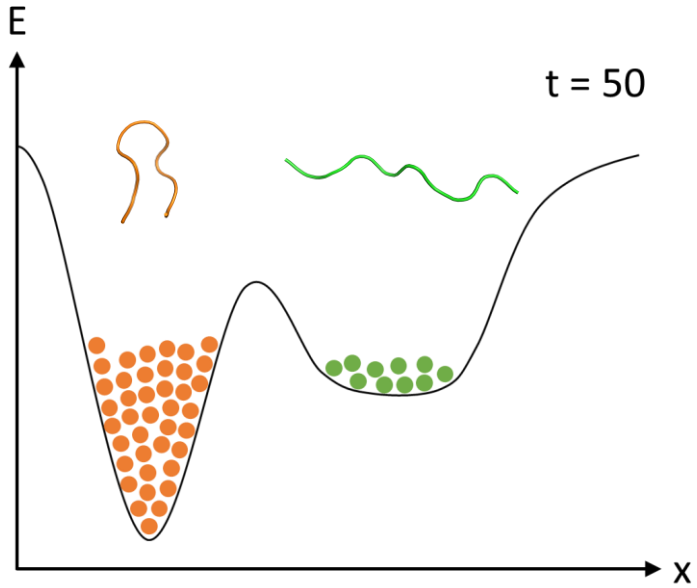


periodic interactions

Liquids

- But: in the liquid phase interactions are persistent, strong and not periodic
- Idea: simulation and observation of the system

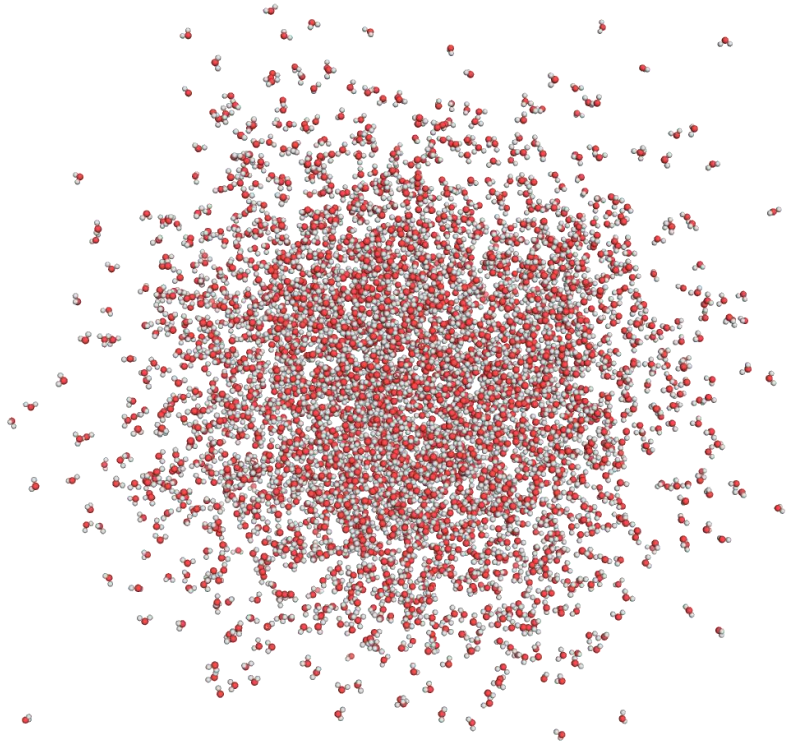




=> important configurations will occur often,
unimportant configurations will occur rarely

Simulation

- But: we cannot simulate 10^{+23} molecules for 1 s

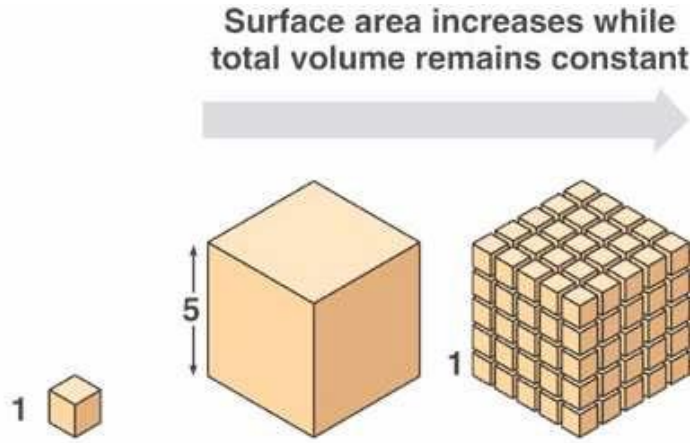


=> so, we hope that we end up with the same result if we simulate fewer particles (10^{+6}) for a „longer“ time (10^{-6} s)
= ergodic hypothesis

- Also, experimental measurements are usually time- and ensemble-averages at the same time

Scaling Problem: Volume ≈ r^3, surface ≈ r^2

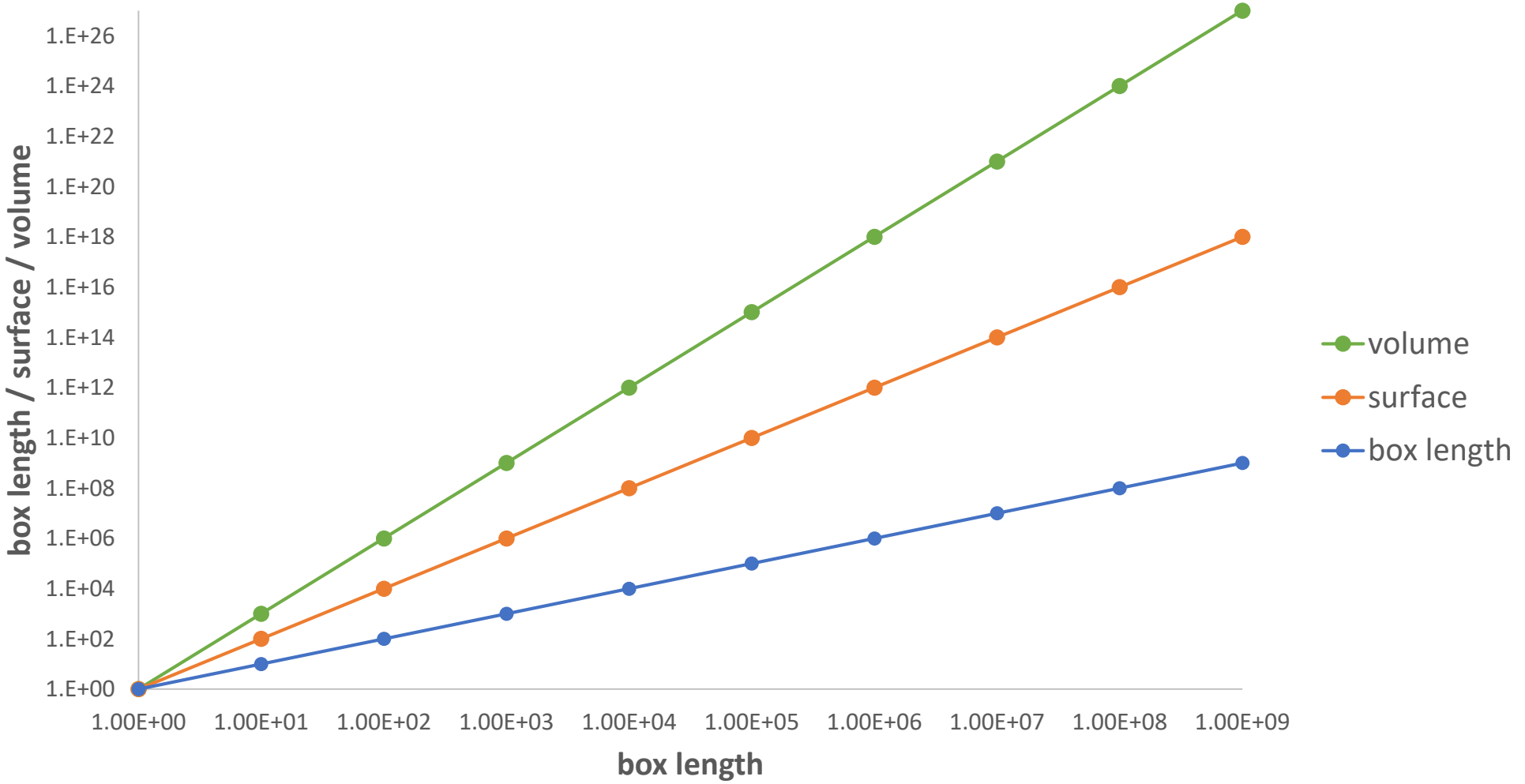
At a box length of r = 1 dm nearly all molecules are in the interior, whereas at r = 100 Å nearly all molecules are at the surface.



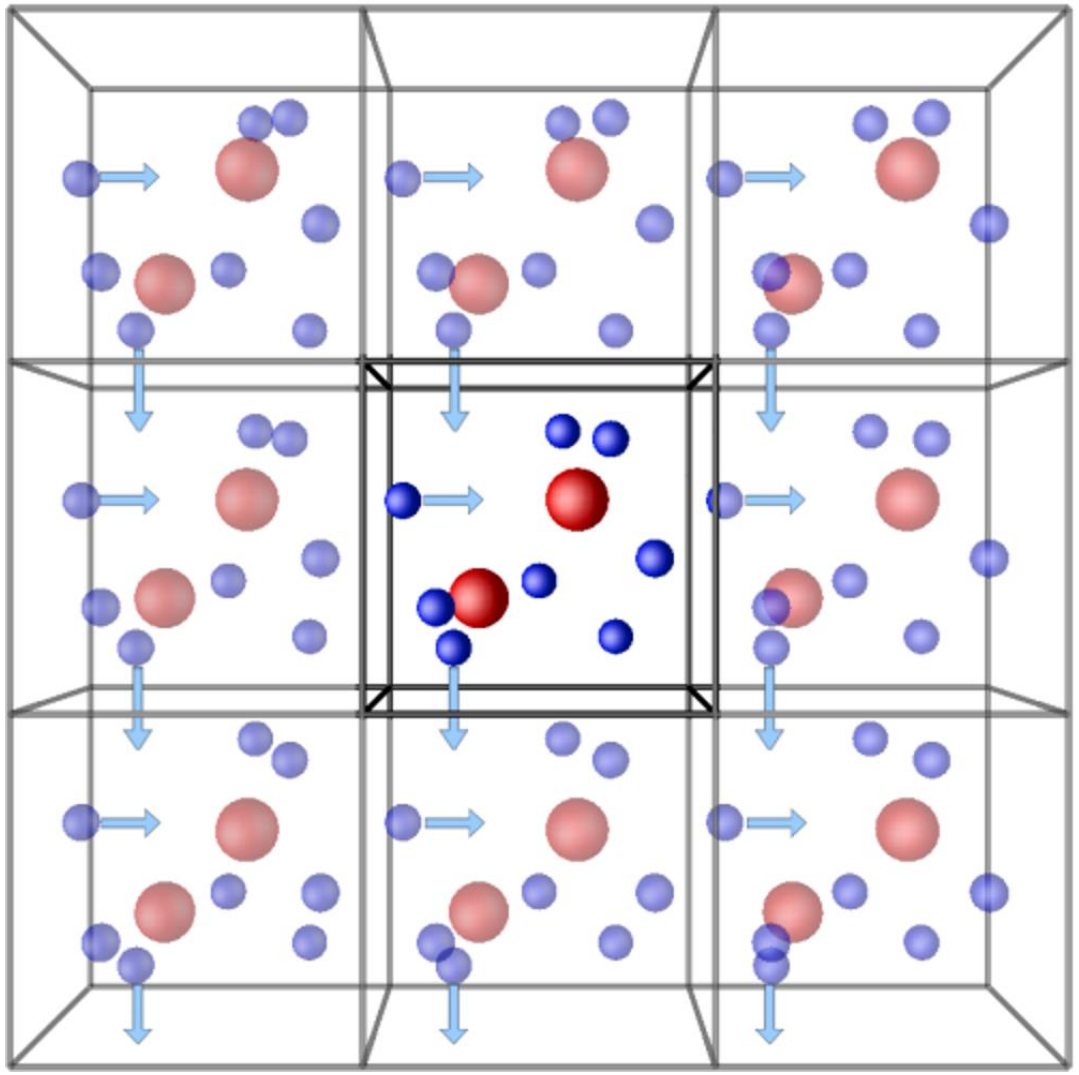
Total surface area (height × width × number of sides × number of boxes)	6	150	750
Total volume (height × width × length × number of boxes)	1	125	125
Surface-to-volume ratio (surface area / volume)	6	1.2	6

https://chemspace.wordpress.com/nano-properties/

Scaling Problem: Volume ≈ r^3, surface ≈ r^2

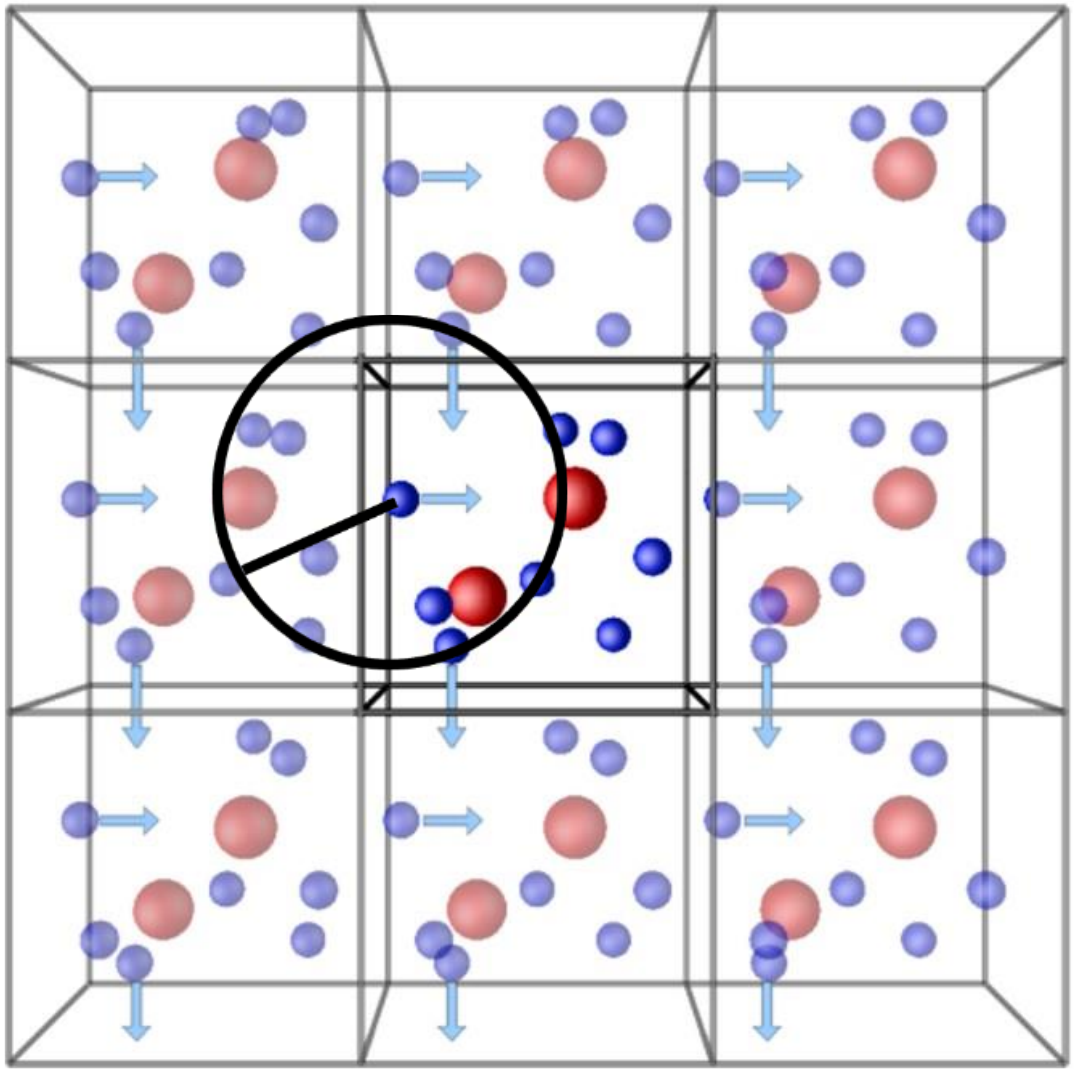


Solution: periodic boundary conditions



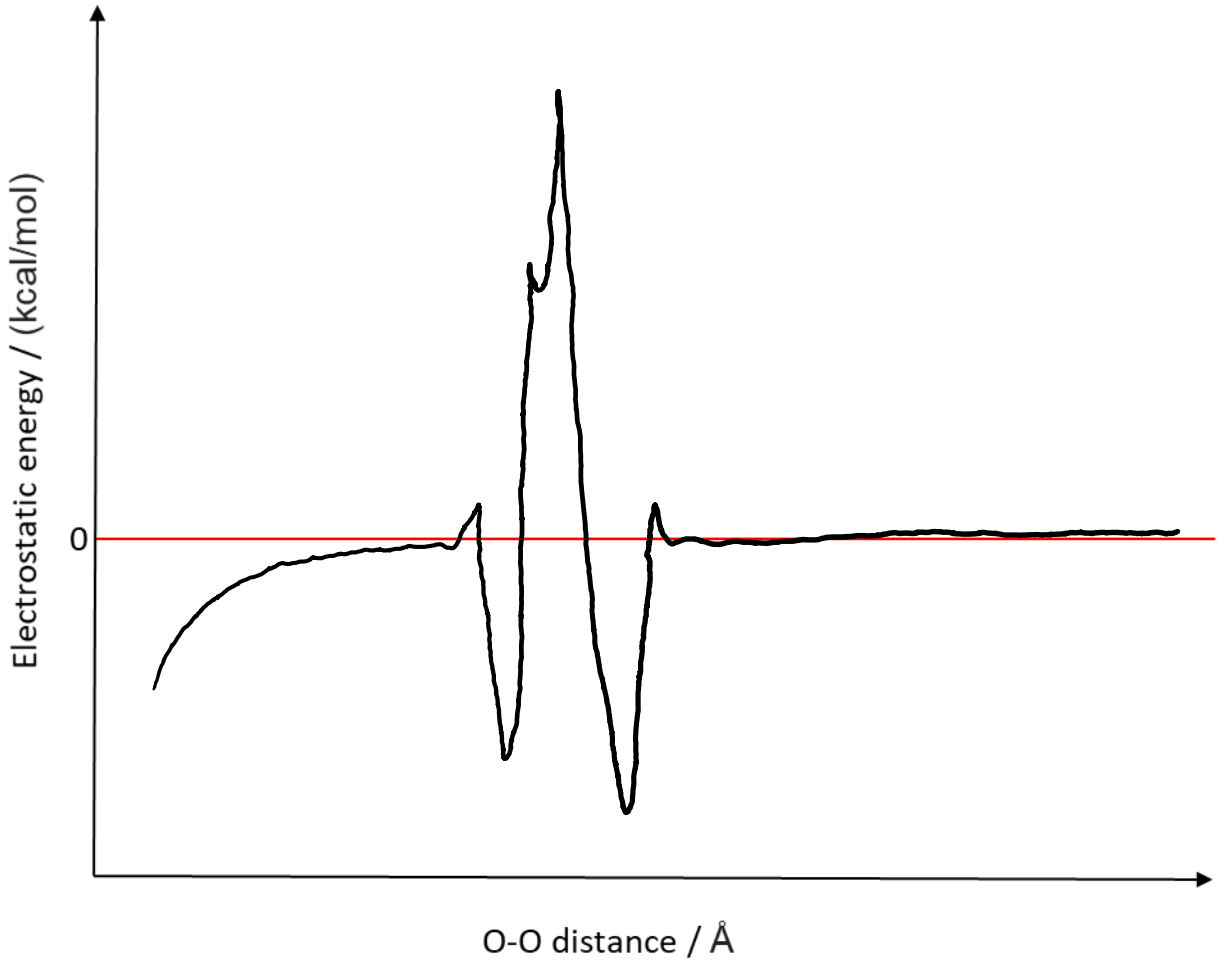
Tesson 2016

Spherical cutoff and minimum image convention

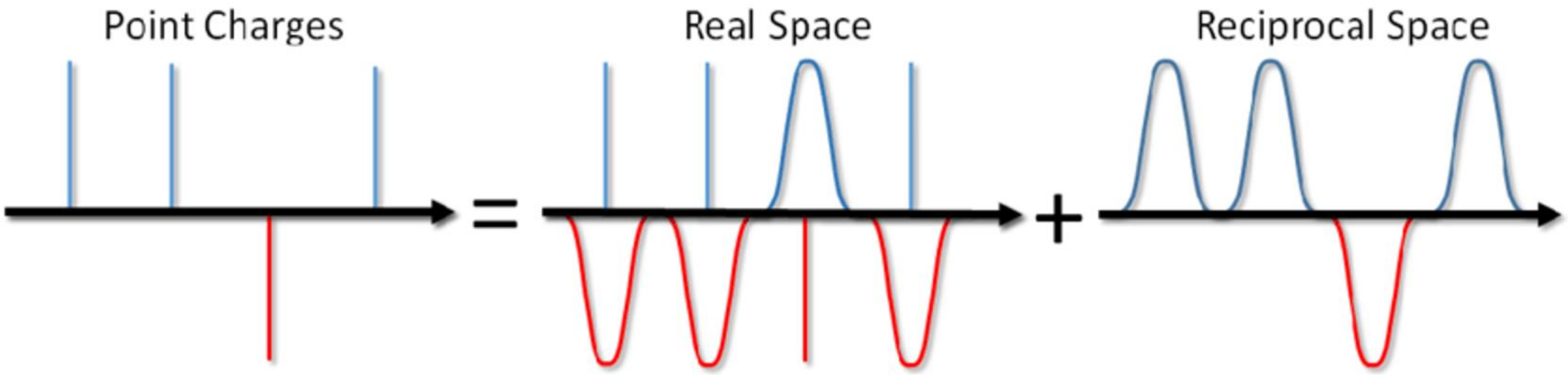


Tesson 2016

Cutoff artefacts



Ewald method



slowly converging sum of periodic charges in real space

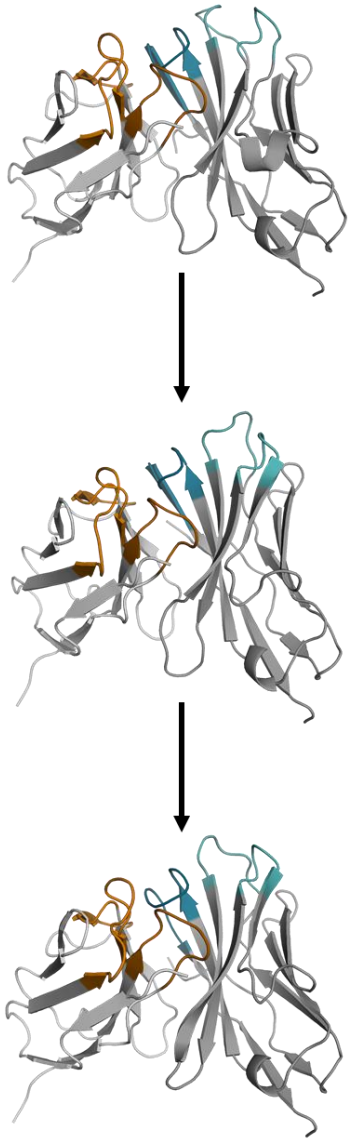
fast converging sum is calculated in real space

rest is Fourier transformed and converges fast in reciprocal space

Chapman 2018

Solution of equation of motion

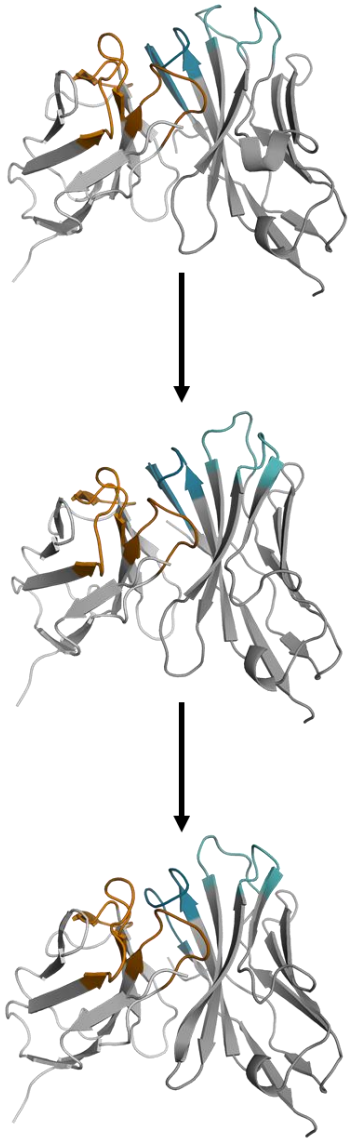
$$F = m\,a$$



Solution of equation of motion

F = m a

$$F(r) = -\frac{\partial E(r)}{\partial r}$$

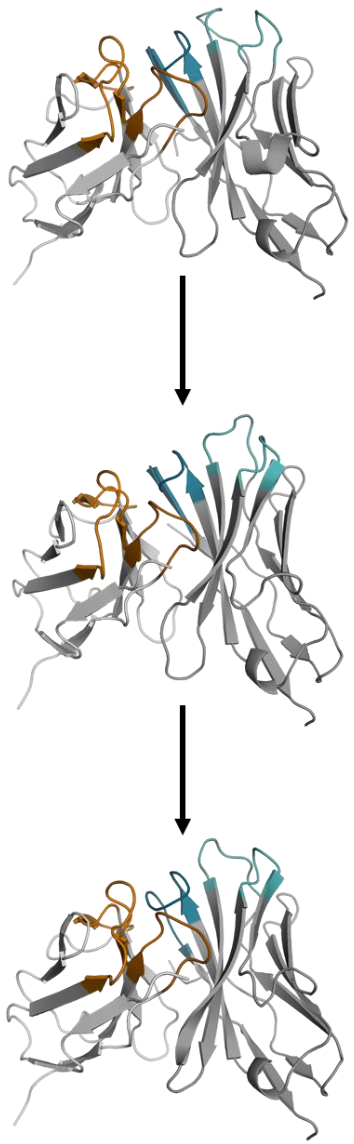


Solution of equation of motion

$$F = m\,a$$

$$F(r) = -\frac{\partial E(r)}{\partial r}$$

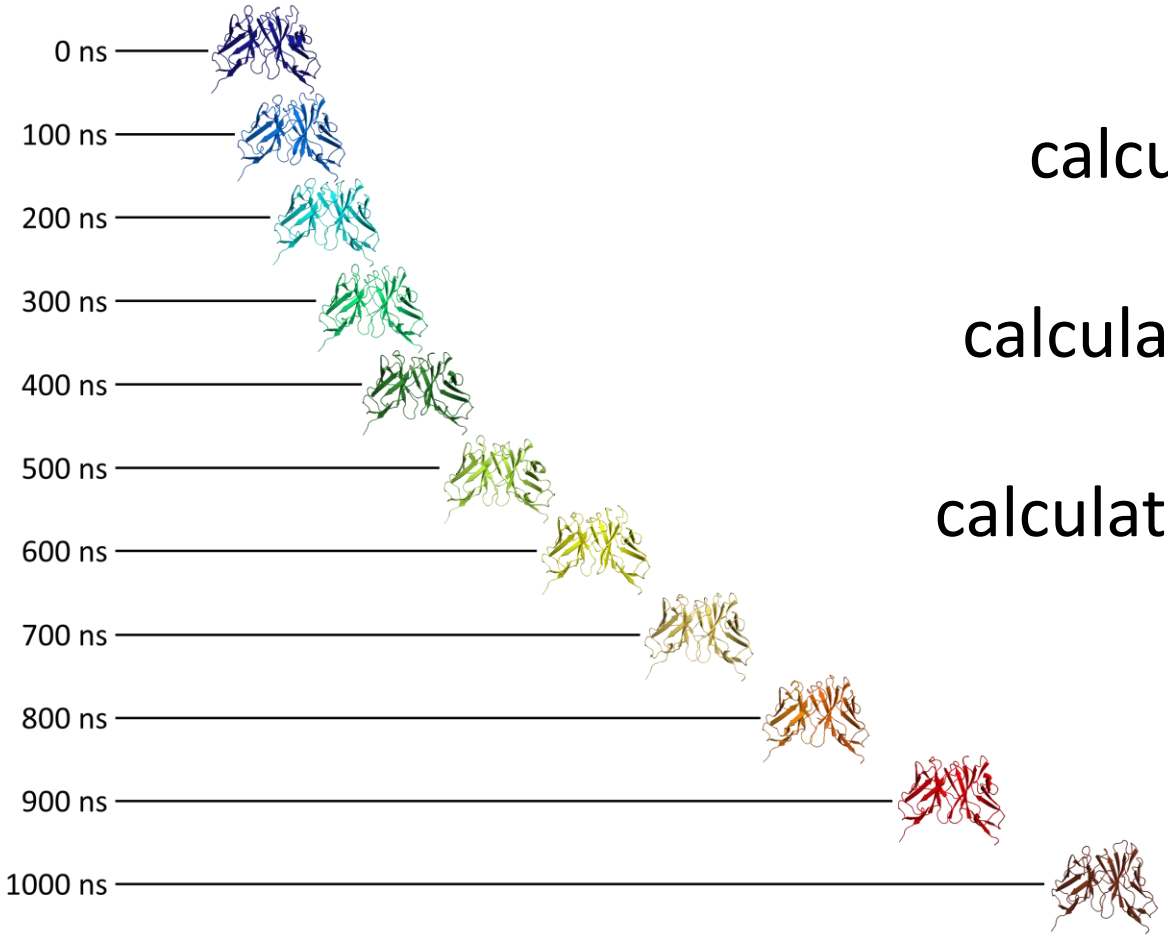
$$\begin{aligned} E_{\text{total}} &= \sum_{\text{bonds}} K_r(r - r_{\text{eq}})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{\text{eq}})^2 + \\ &+ \sum_{\text{dihedrals}} \frac{V_n}{2}\left[1 + \cos(n\varphi - \gamma)\right] + \\ &+ \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}}\right] \end{aligned}$$



Euler method

starting coordinates r_0

starting velocities v_0



calculate forces $f_0 = f(r_0)$

calculate accelerations $a_0 = f_0 / m$

calculate new velocities $v_1 = v_0 + a_0 \Delta t$

calculate new coordinates $r_1 = r_0 + v_0 \Delta t$

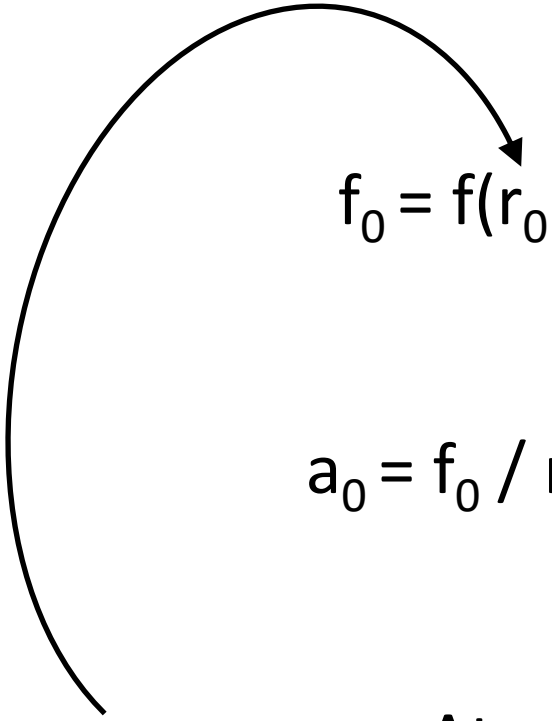
Velocity Verlet Methode

forces

accelerations

new coordinates

new velocities



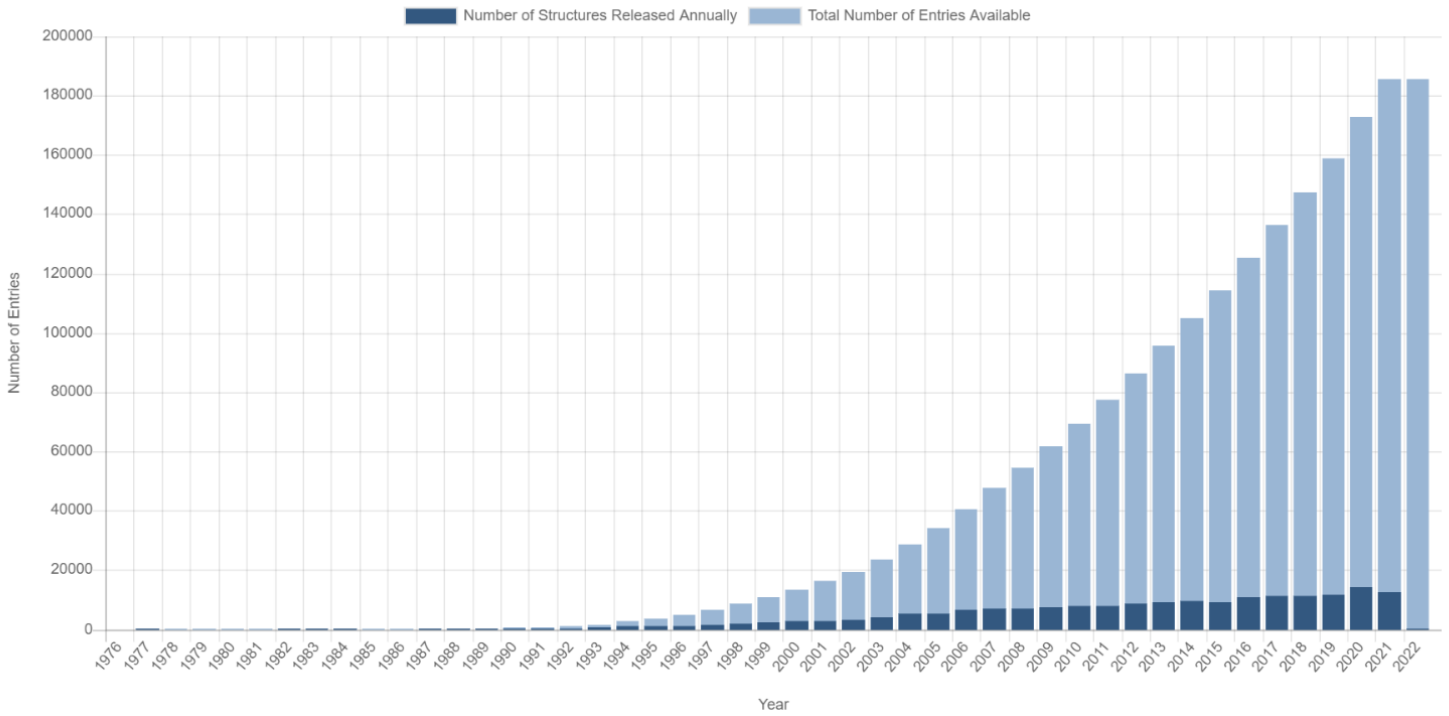
$f_0 = f(r_0)$

$a_0 = f_0 / m$

$r_1 = r_0 + v_0 \Delta t + ½ a_0 \Delta t^2$

$v_1 = v_0 + ½ (a_0 + a_1) \Delta t$

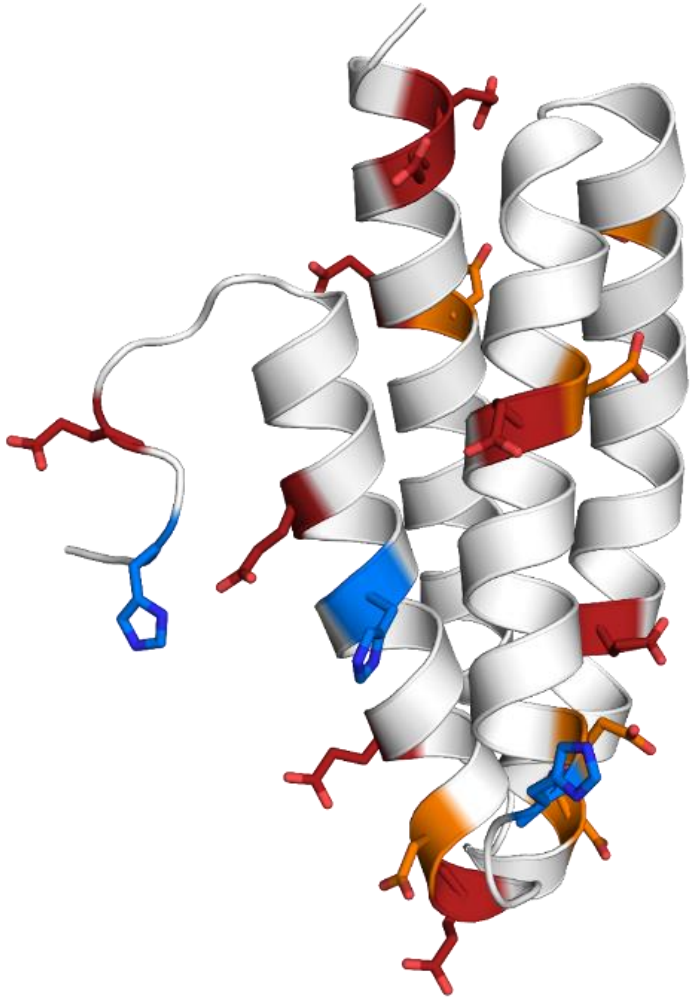
Initial conditions – starting coordinates

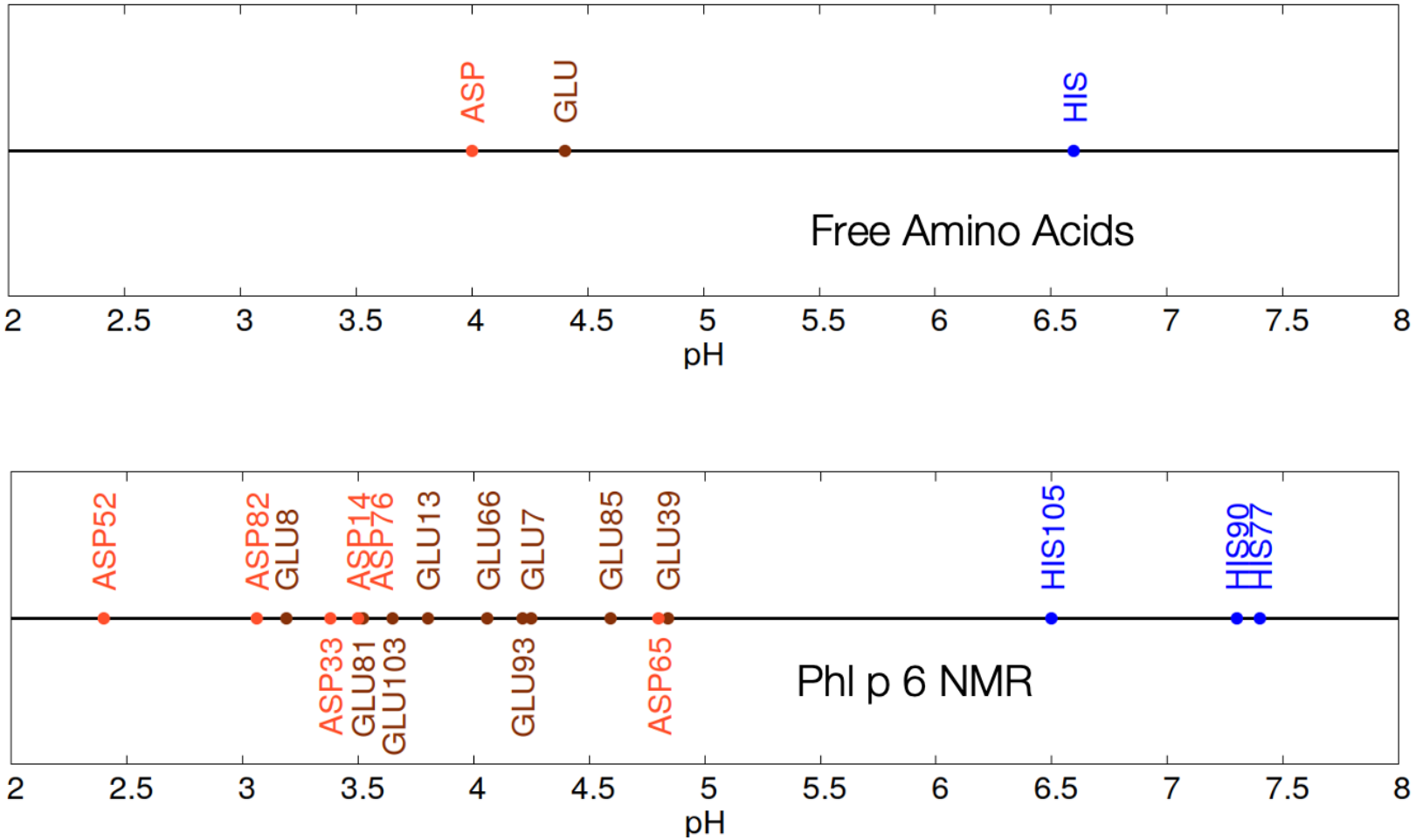


Molecular Type	X-ray	NMR	EM	Multiple methods	Neutron	Other	Total
Protein (only)	143468	11850	6416	178	70	32	162014
Protein/Oligosaccharide	8490	31	1061	5	0	0	9587
Protein/NA	7575	274	2101	3	0	0	9953
Nucleic acid (only)	2387	1391	61	8	2	1	3850
Other	150	31	3	0	0	0	184
Oligosaccharide (only)	11	6	0	1	0	4	22
Total	162081	13583	9642	195	72	37	185610

https://www.rcsb.org/stats/

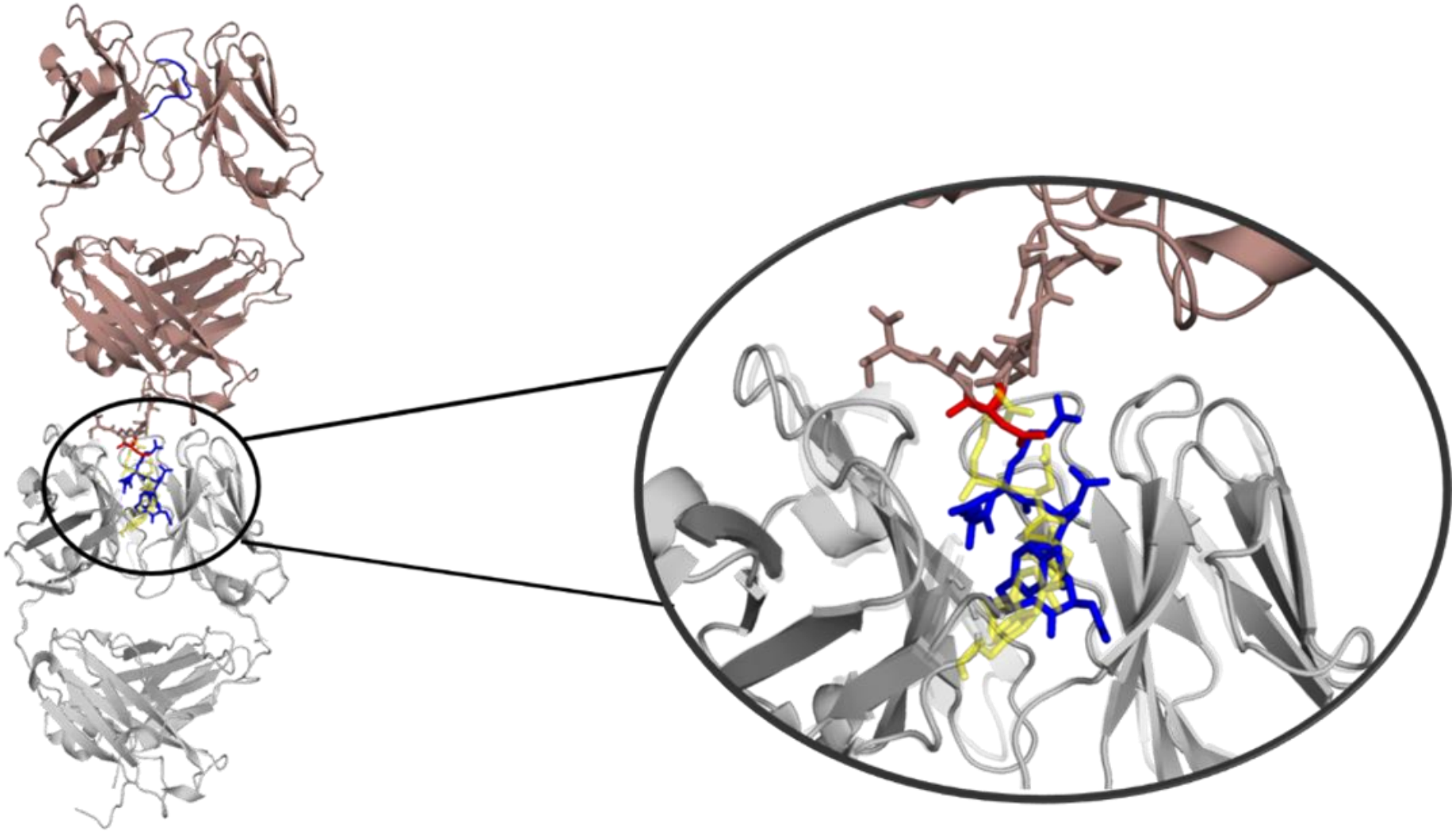
Initial conditions – protonation





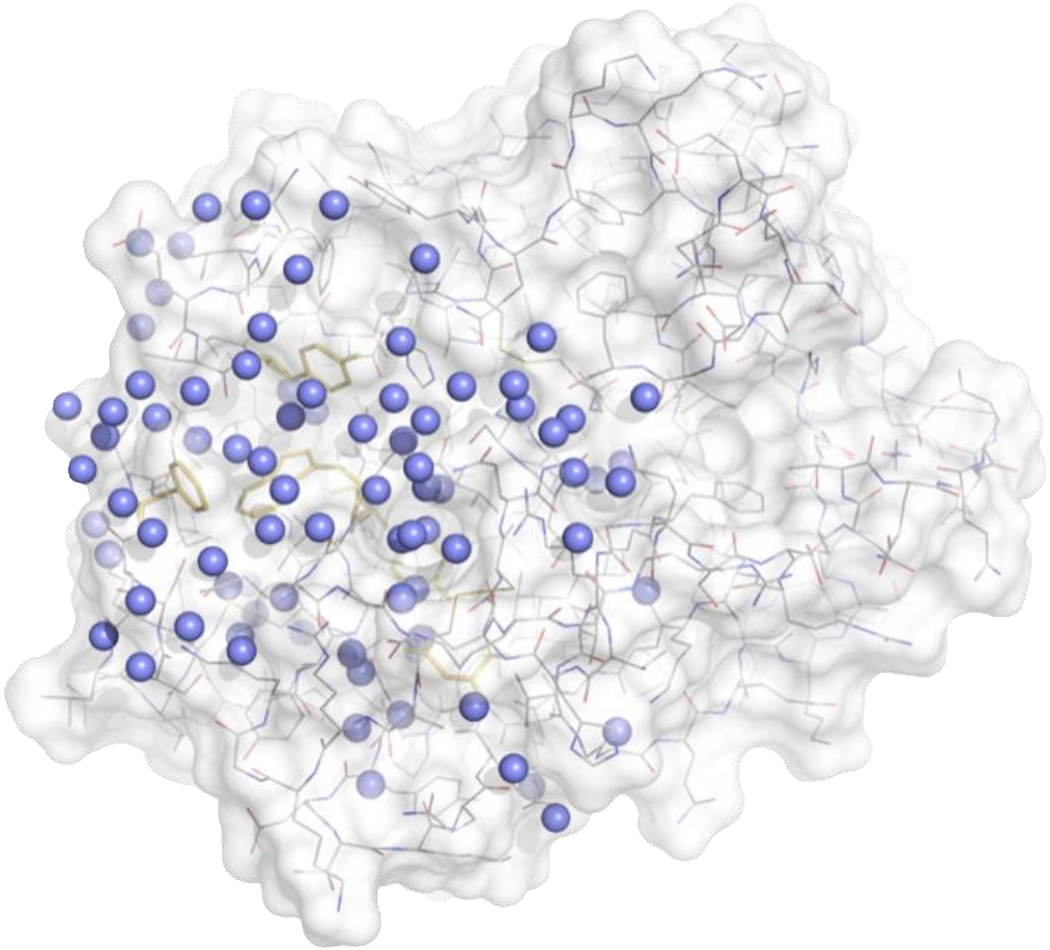
Hofer et al. 2019 J. Chem. Theory Comput. 15:10 5716–5726

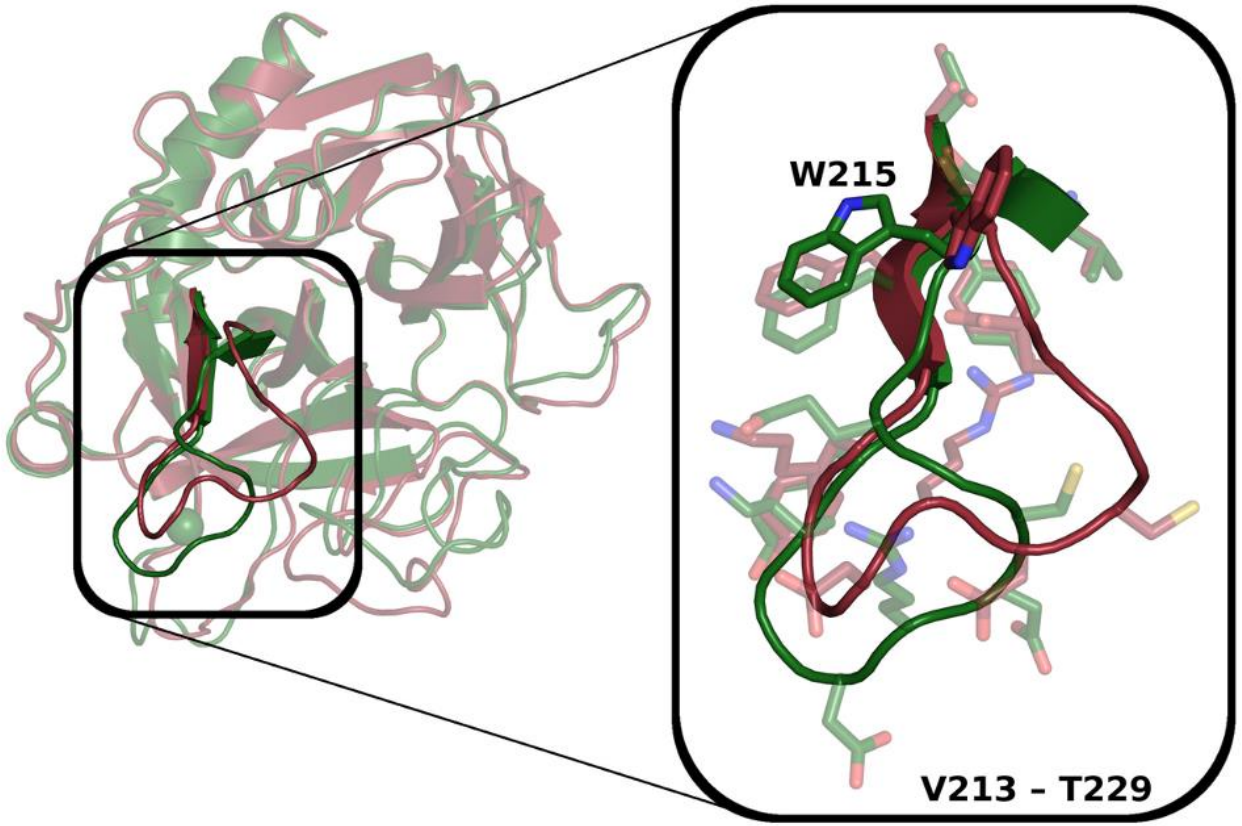
Initial conditions – crystal packing effects



Fernández-Quintero et al. 2019 mAbs 11:6 1077-1088

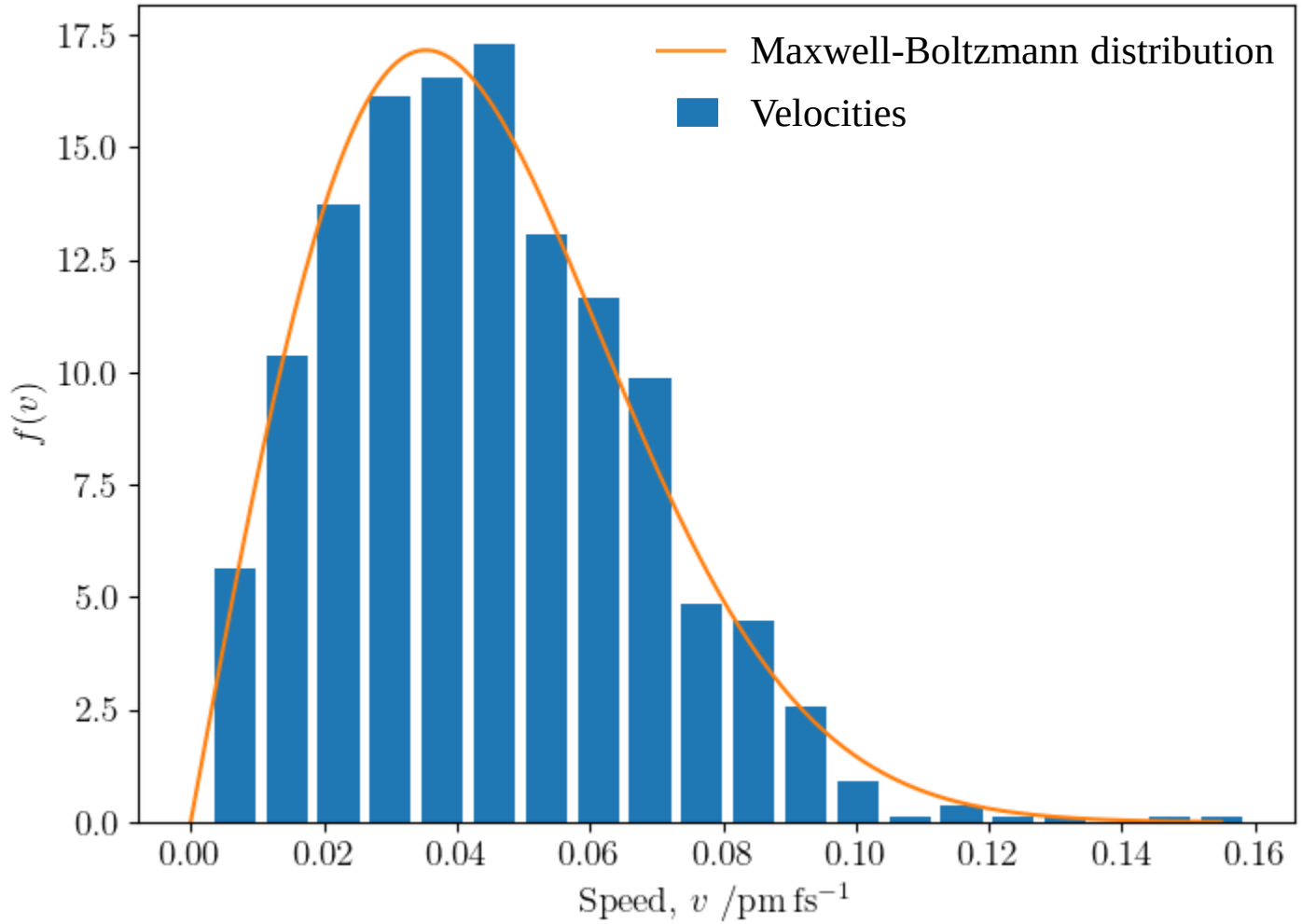
Initial conditions – 10 e^- systems





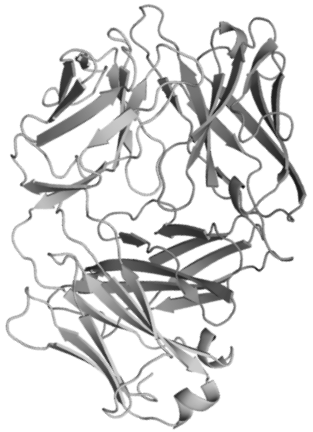
Kahler et al. 2020 Sci. Rep. (10) 1086

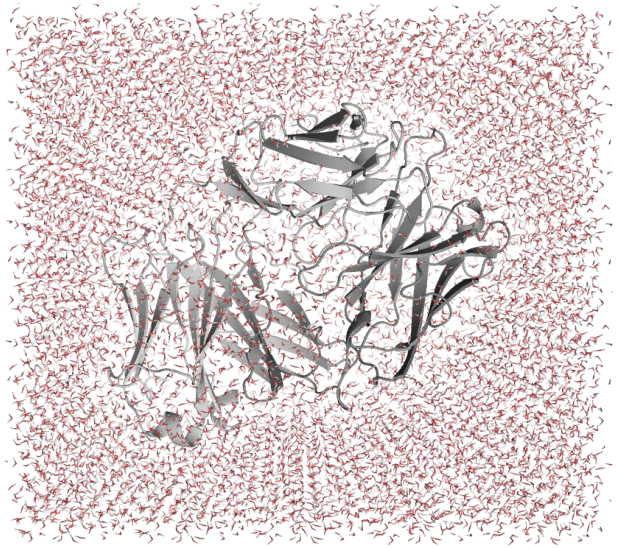
Initial conditions – velocities

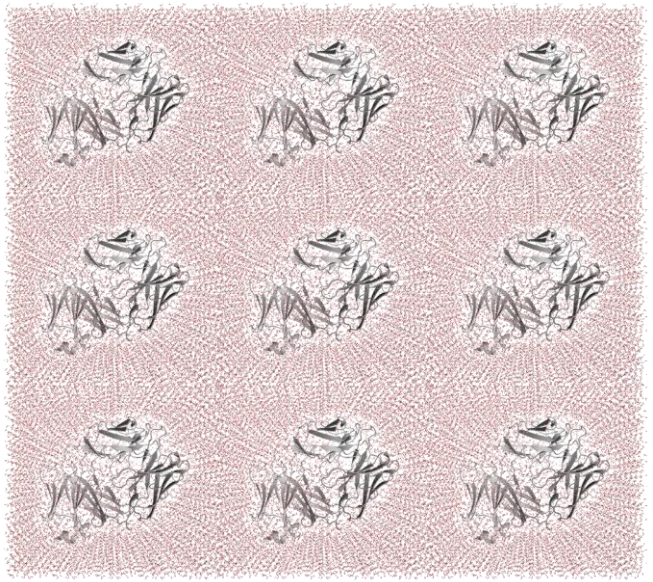


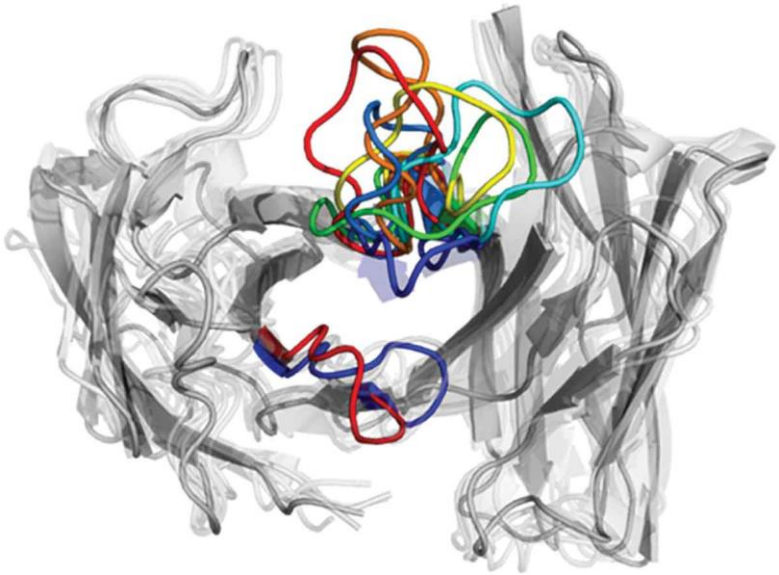
https://scipython.com/book2/chapter-4-the-core-python-language-ii/examples/a-simple-2d-molecular-dynamics-simulation/

Classical MD simulation protocol



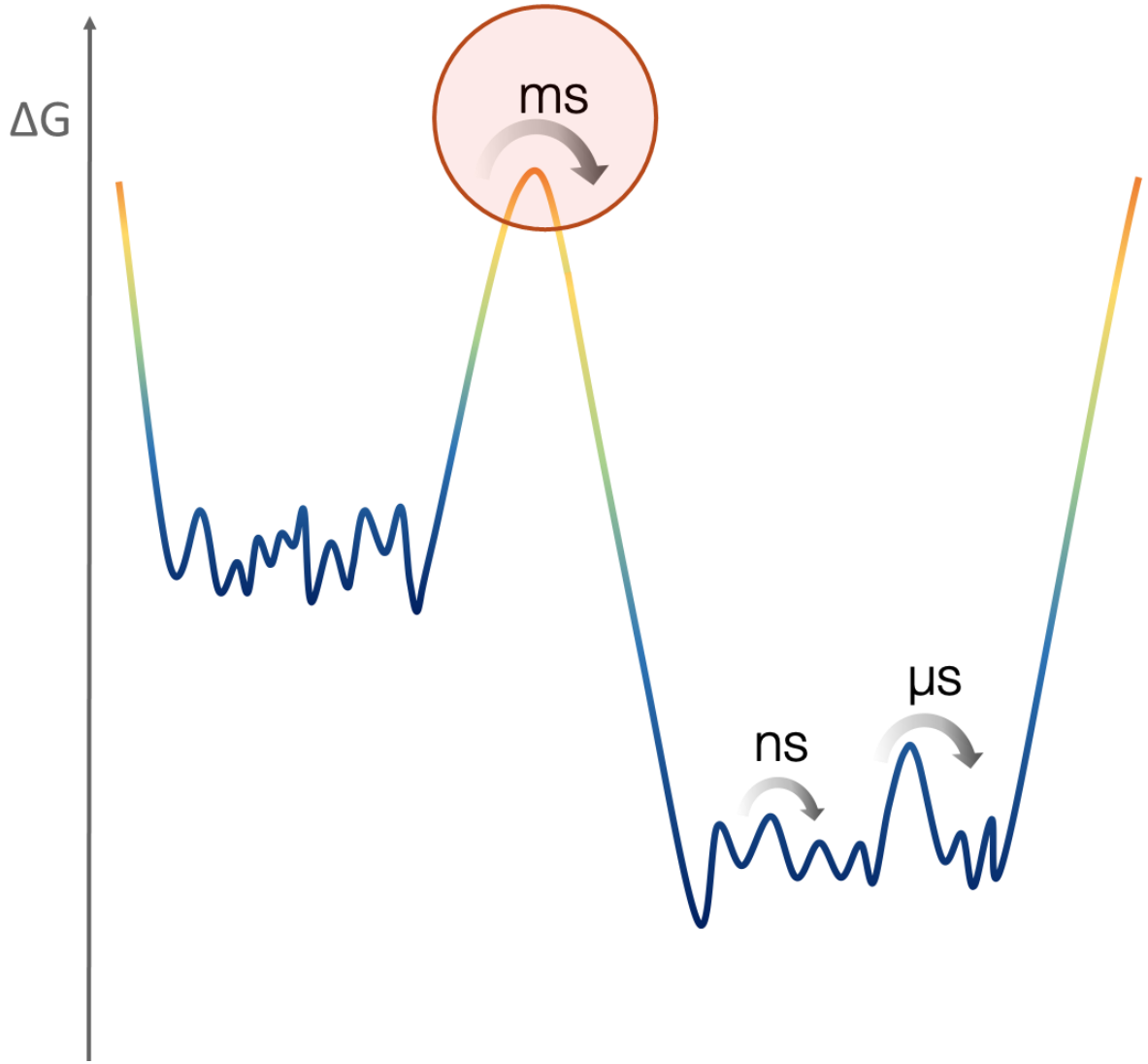


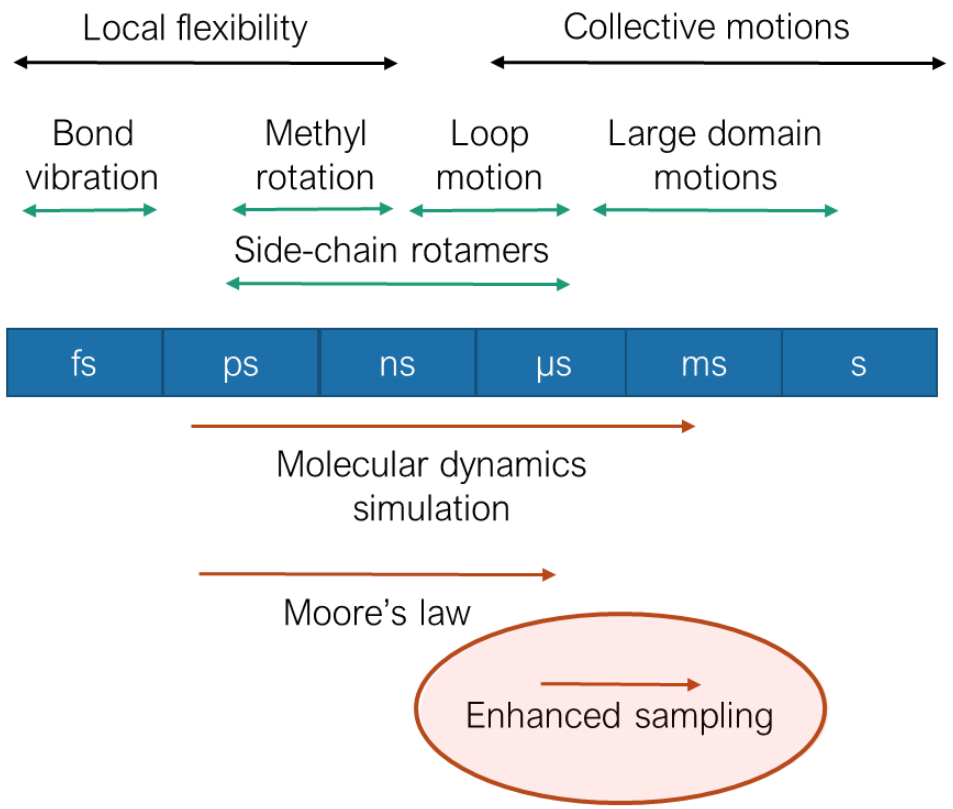




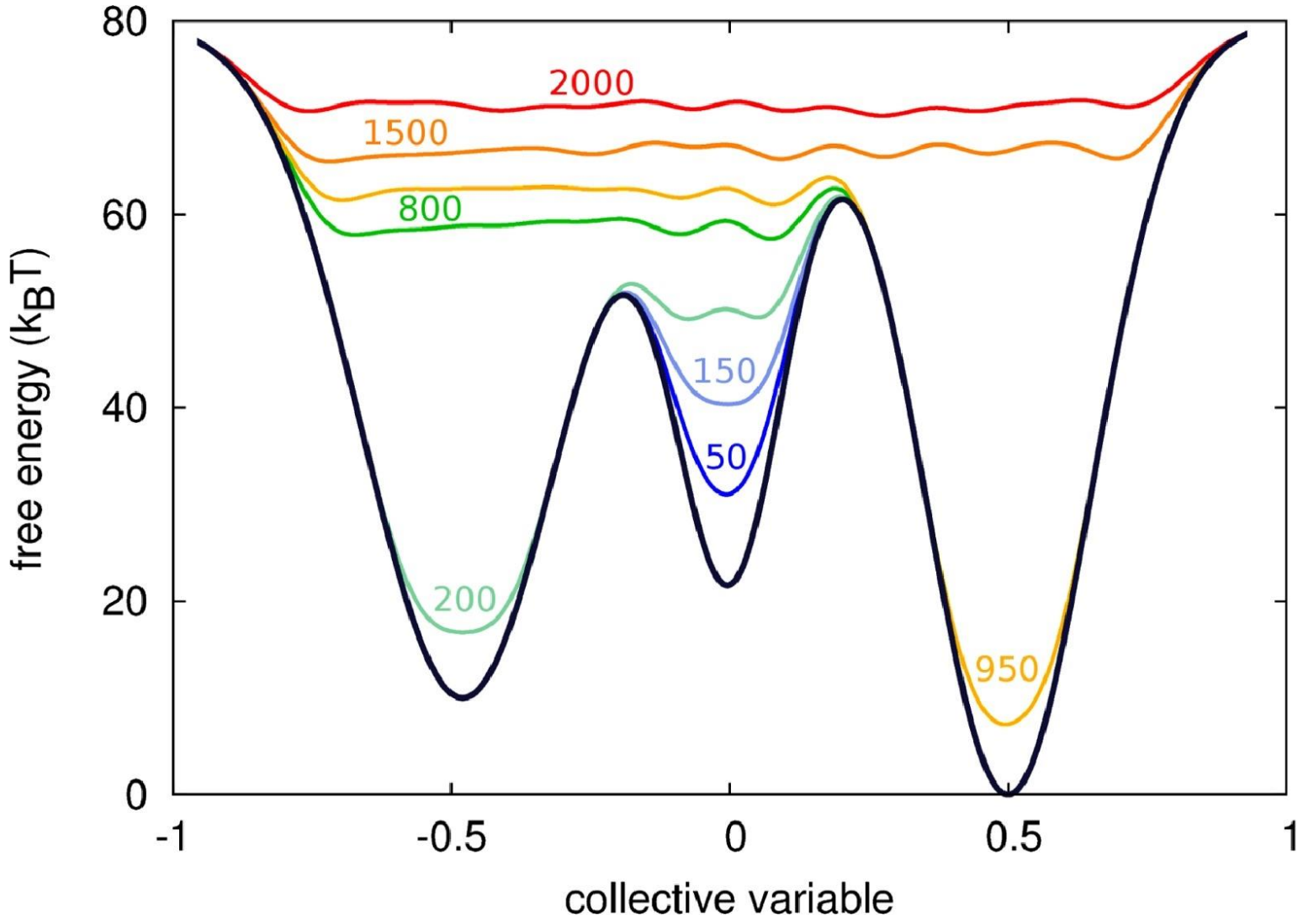
Fernández-Quintero et al. 2019 mAbs 11:6 1077-1088

Enhanced Sampling: from Micro- to Milliseconds



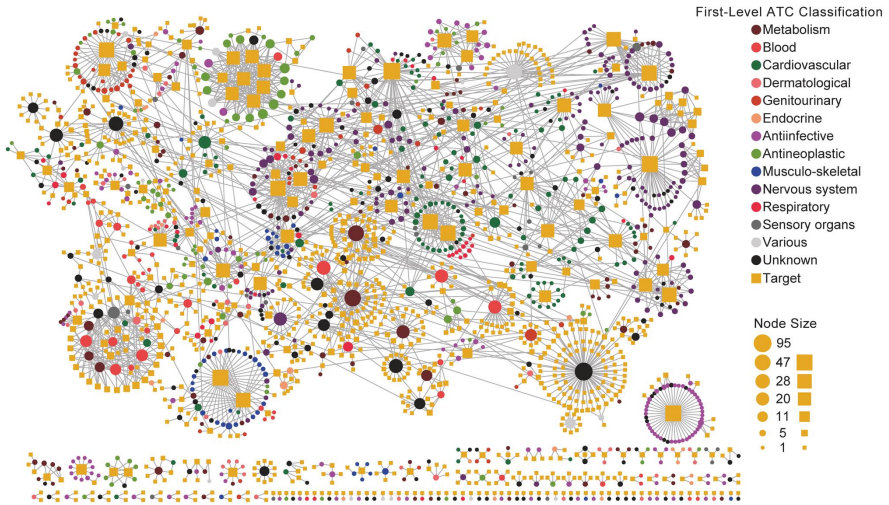


Enhanced Sampling: from Micro- to Milliseconds

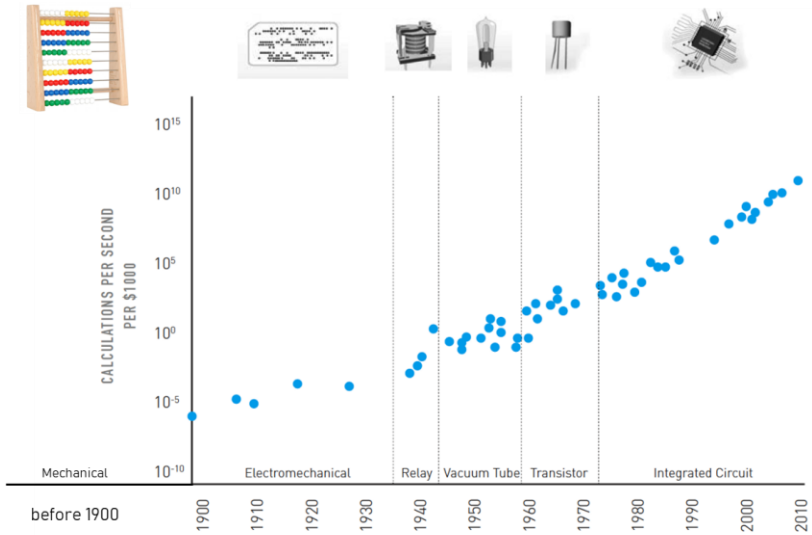


Fabio Pietrucci 2017 Reviews in Physics 2 32-45 2405-4283

Summary



Chuang Liu et al. 2020 Physics Reports 846 1-66 ISSN 0370-1573



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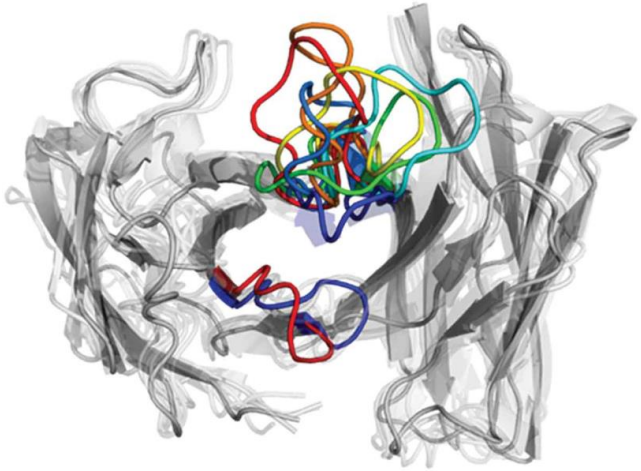


Fernández-Quintero et al. 2019 mAbs 11:6 1077-1088

https://netzfrauen.org/2021/03/27/suez/

Antibody's Next Top Model

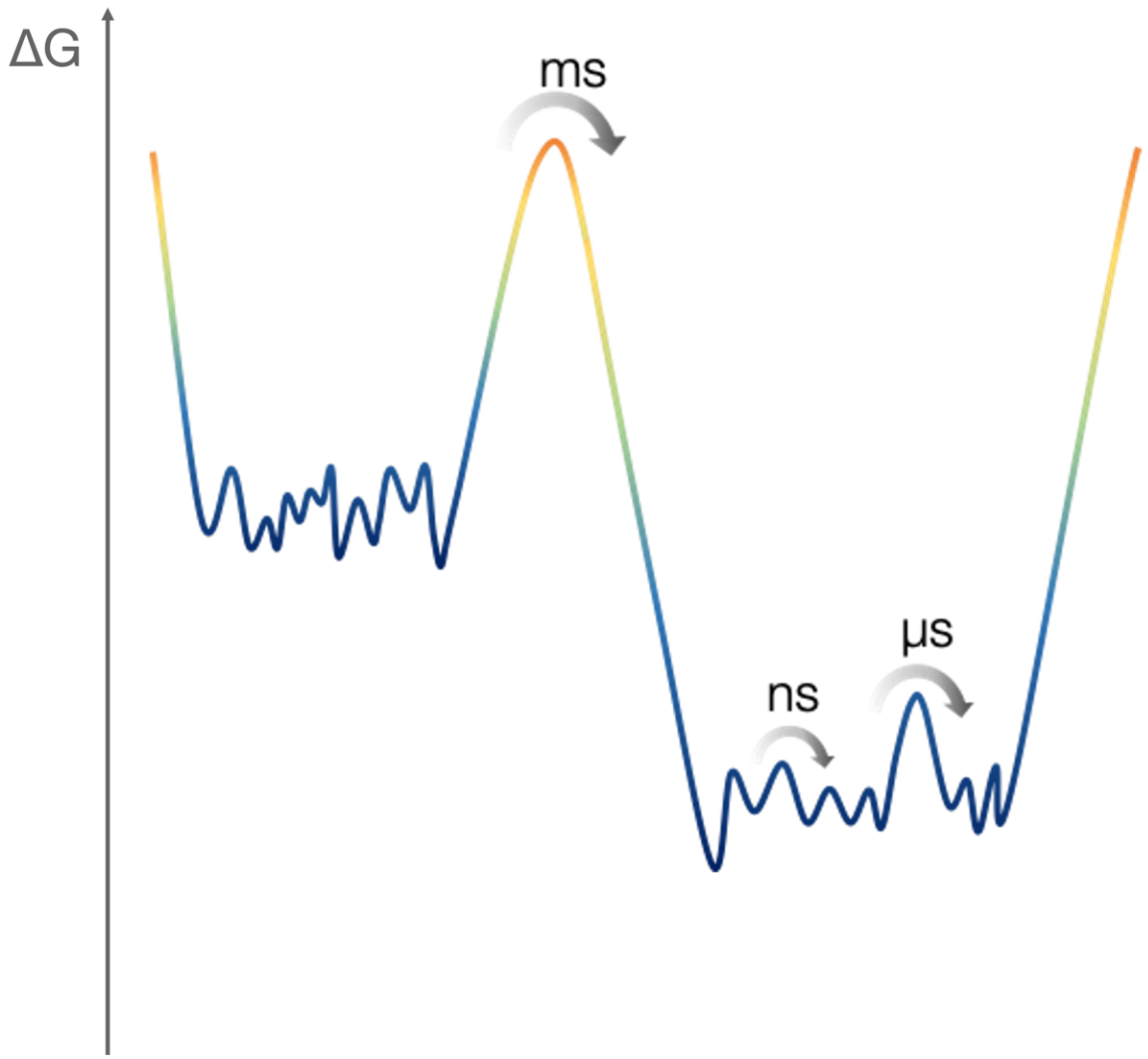
Use of CDR loop ensembles from molecular dynamics simulations guides antibody design and docking

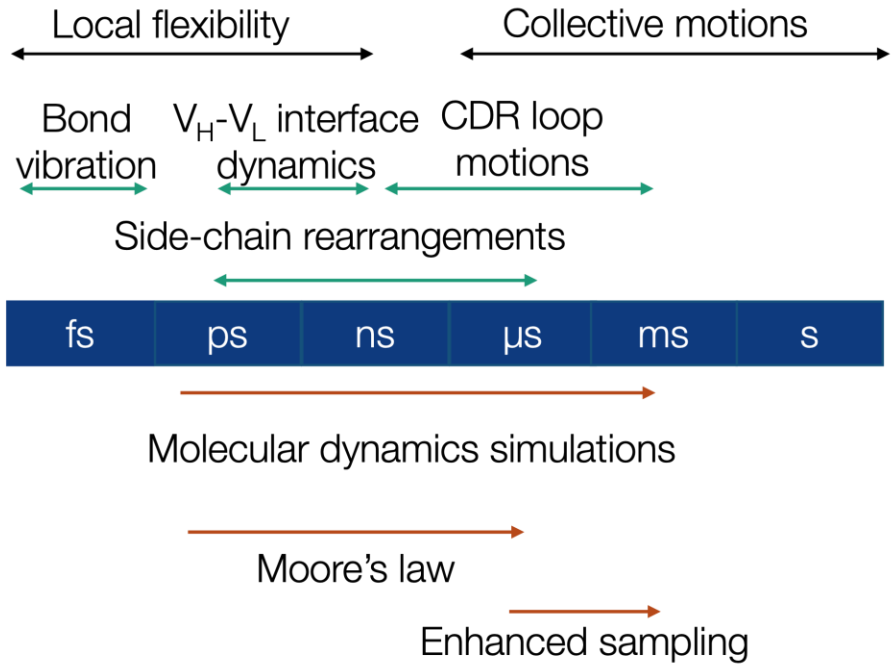
Dr. Monica L. Fernández-Quintero

Monica.Fernandez-Quintero@uibk.ac.at

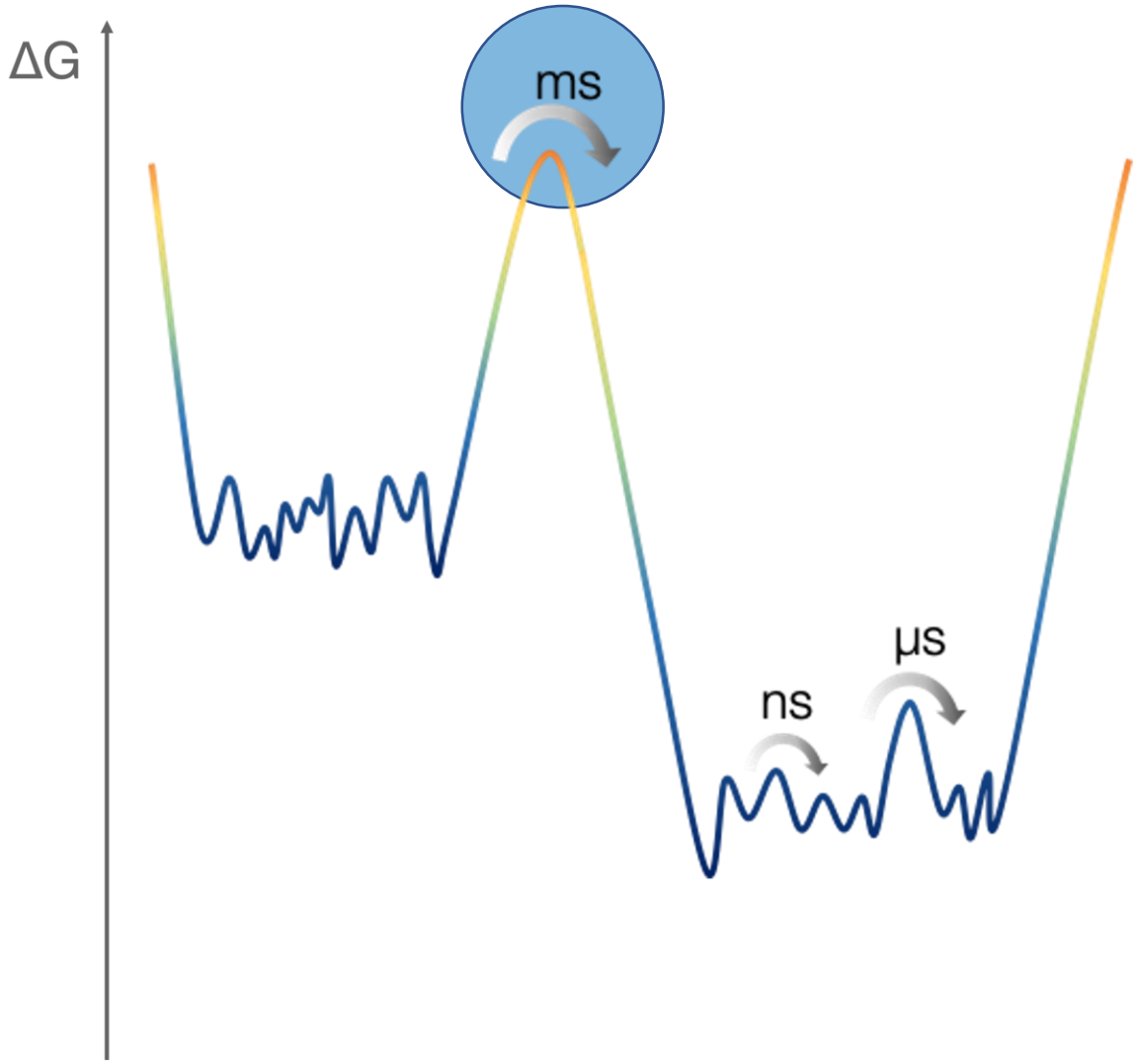
https://liedllab.org/

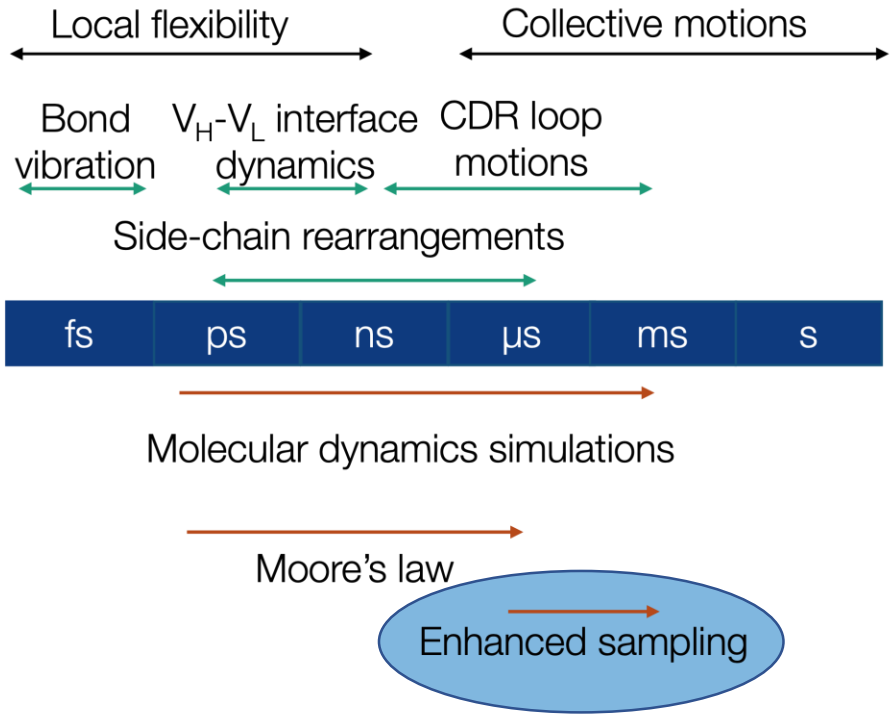
Timescales of Antibody Dynamics



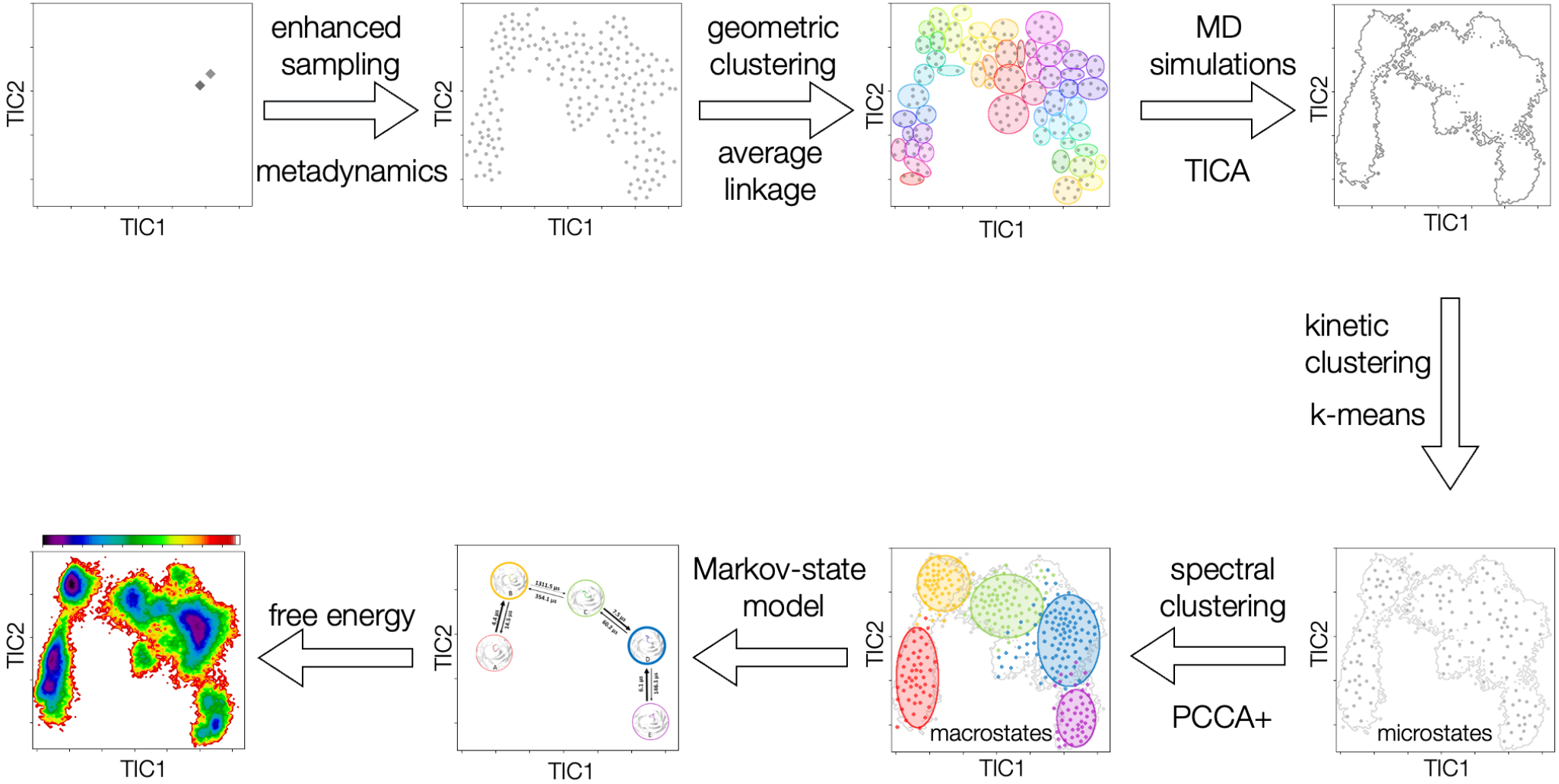


Timescales of Antibody Dynamics

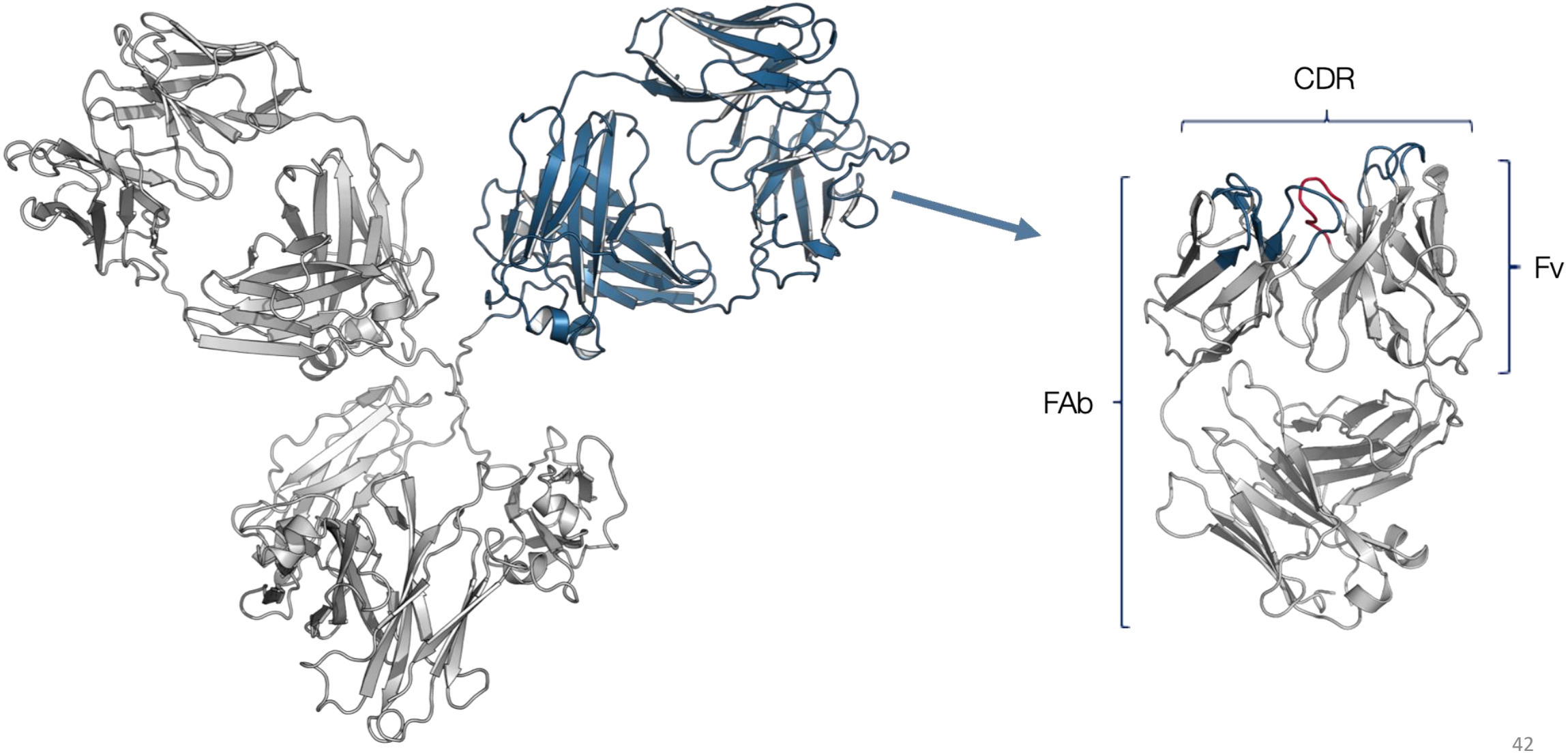




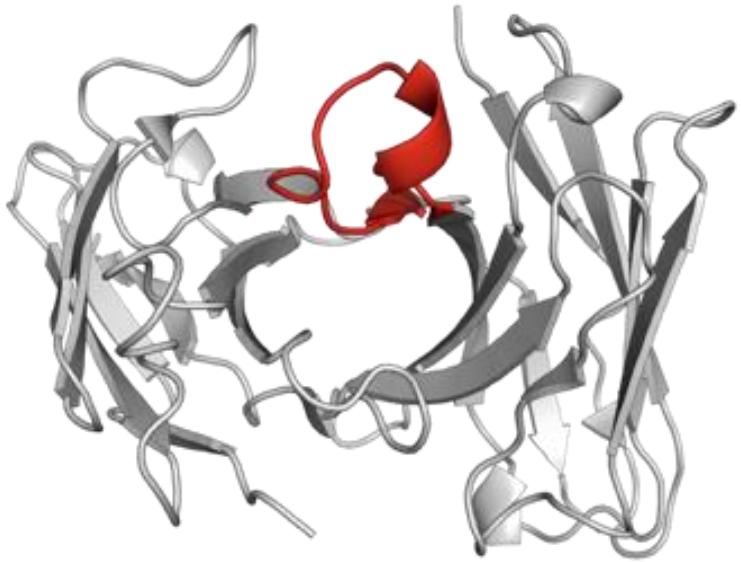
Enhanced Sampling: from Micro- to Milliseconds

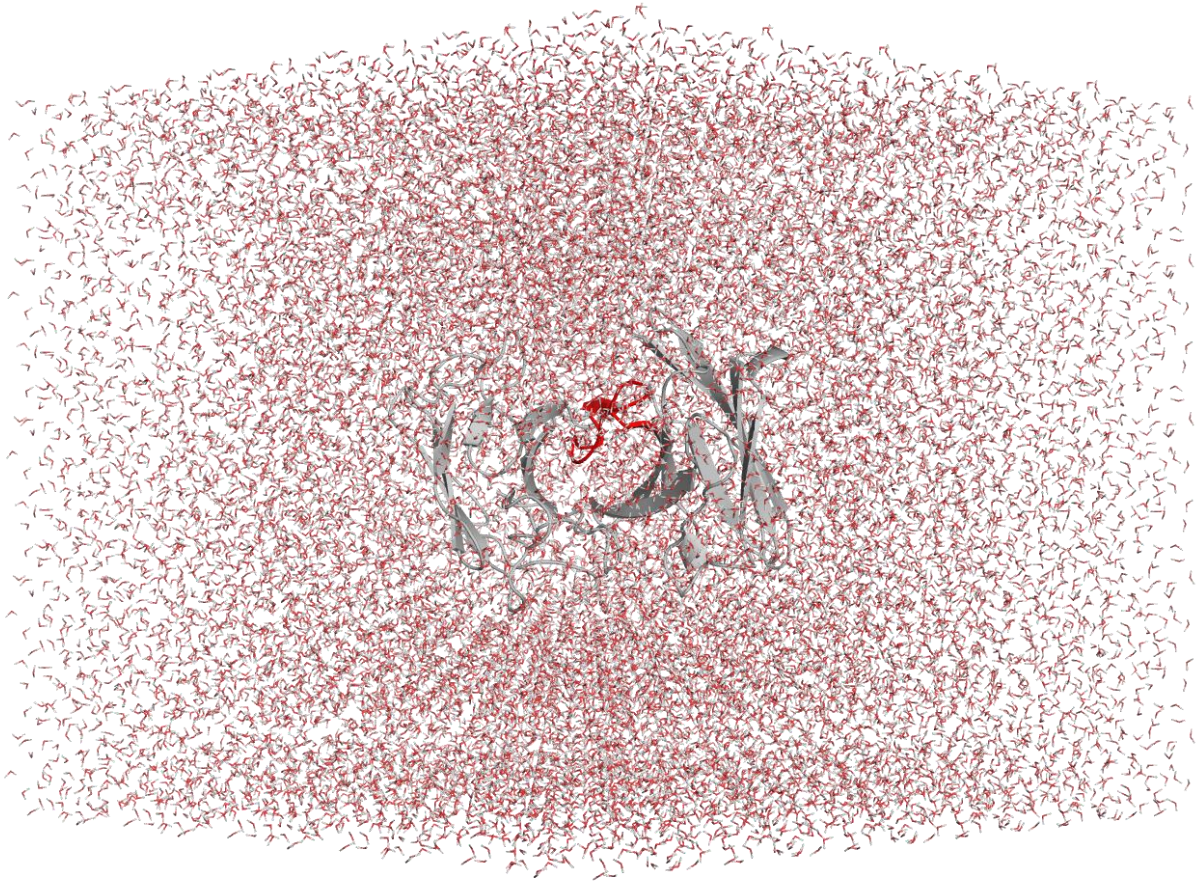


Antibodies: What Are We Looking At?



Ensemble in Solution by Molecular Dynamics Simulations

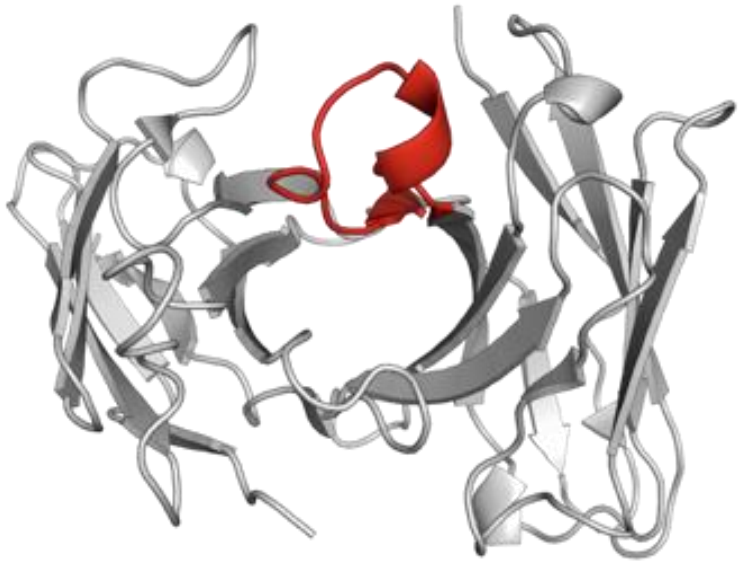


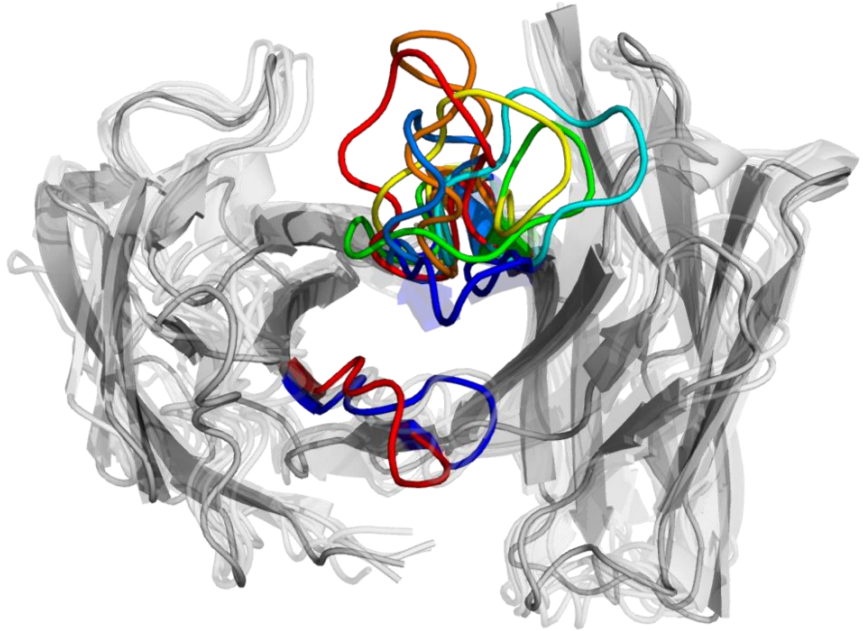


Crystal Structure or Model

MD Simulation

Ensemble in Solution by Molecular Dynamics Simulations

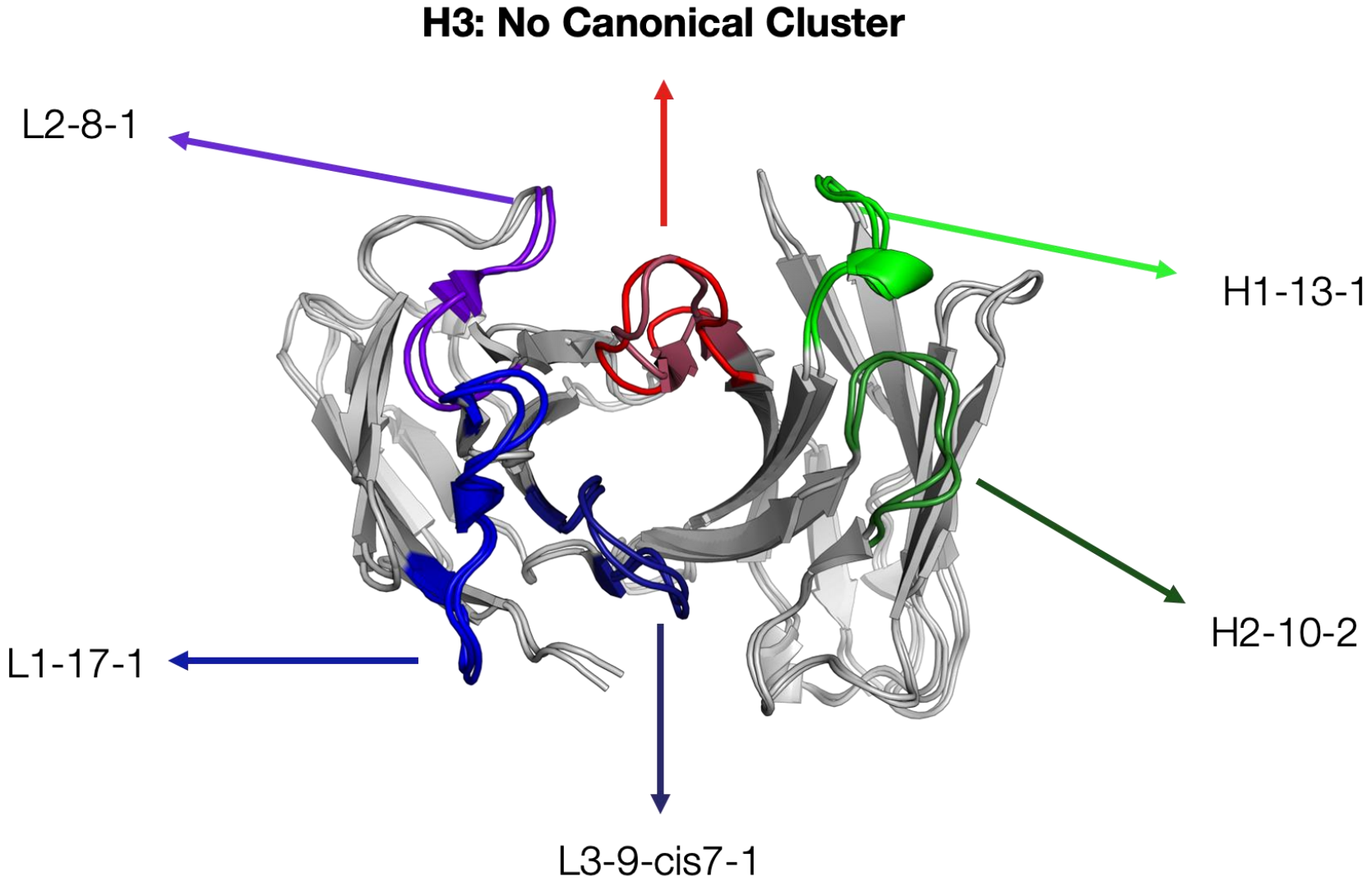




Crystal Structure or Model

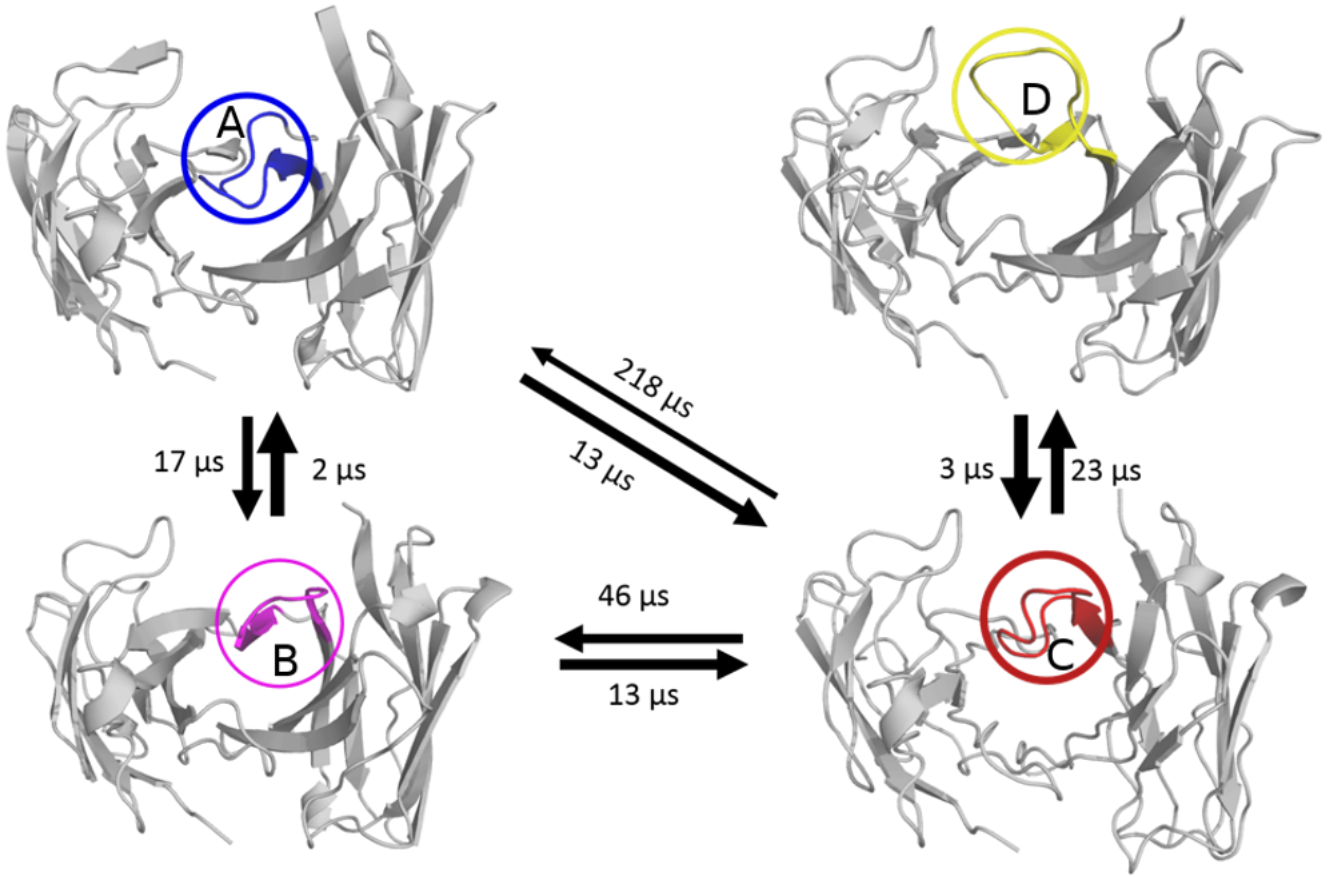
Ensembles in Solution

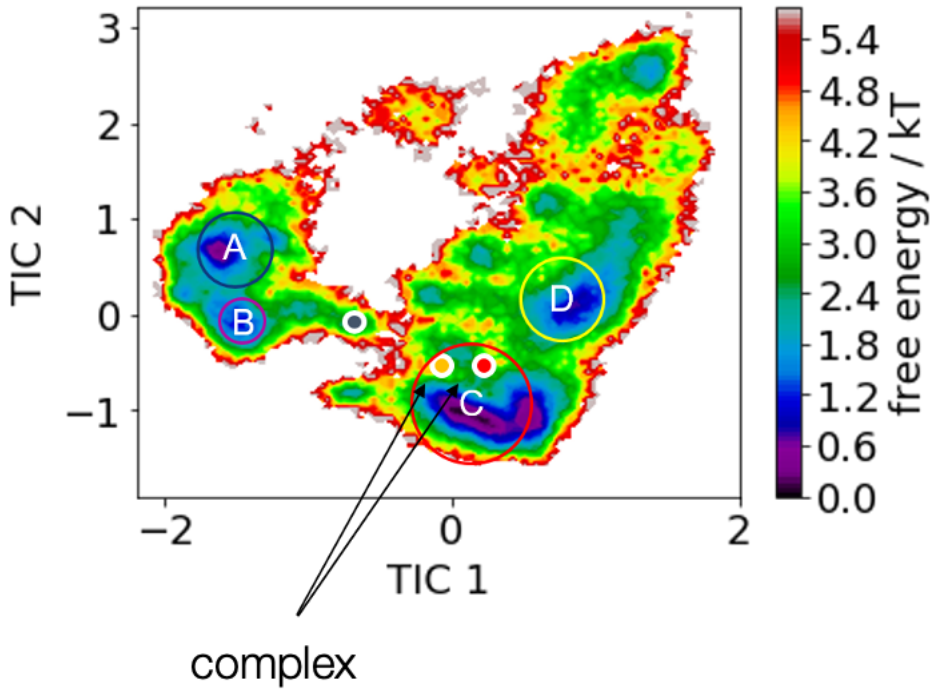
Assigning Canonical Clusters to the CDR Loops



North et al. Journal of Molecular Biology 2011 (406) 228-256

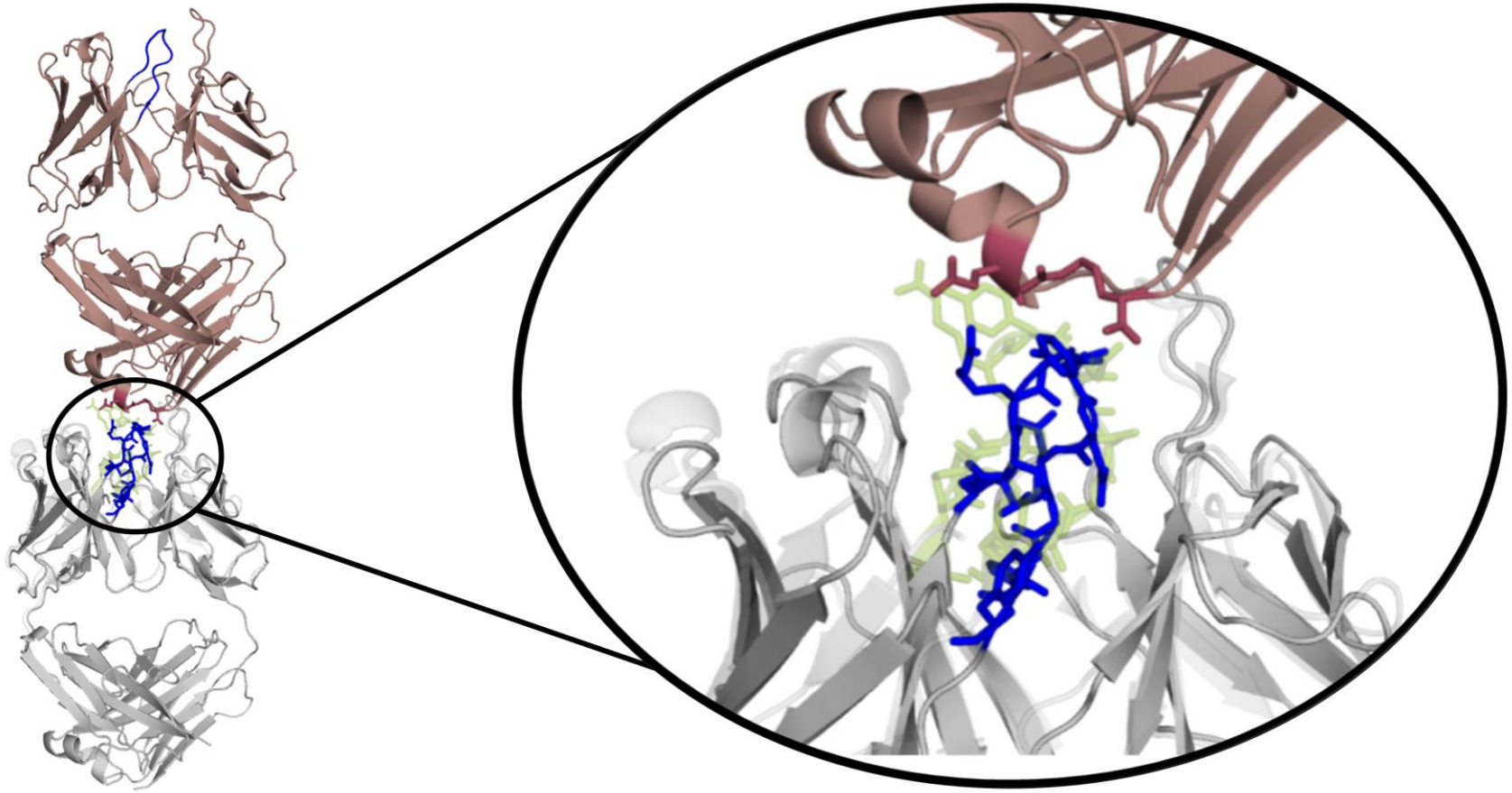
CDR-H3 Loop Ensemble in Solution of anti-Hemagglutinin Antibody Fv 17/9





Fernández-Quintero et al. mAbs 2019 (11) 1077-1088

Crystal Packing Effects of an anti-Hemagglutinin Antibody Fv 17/9



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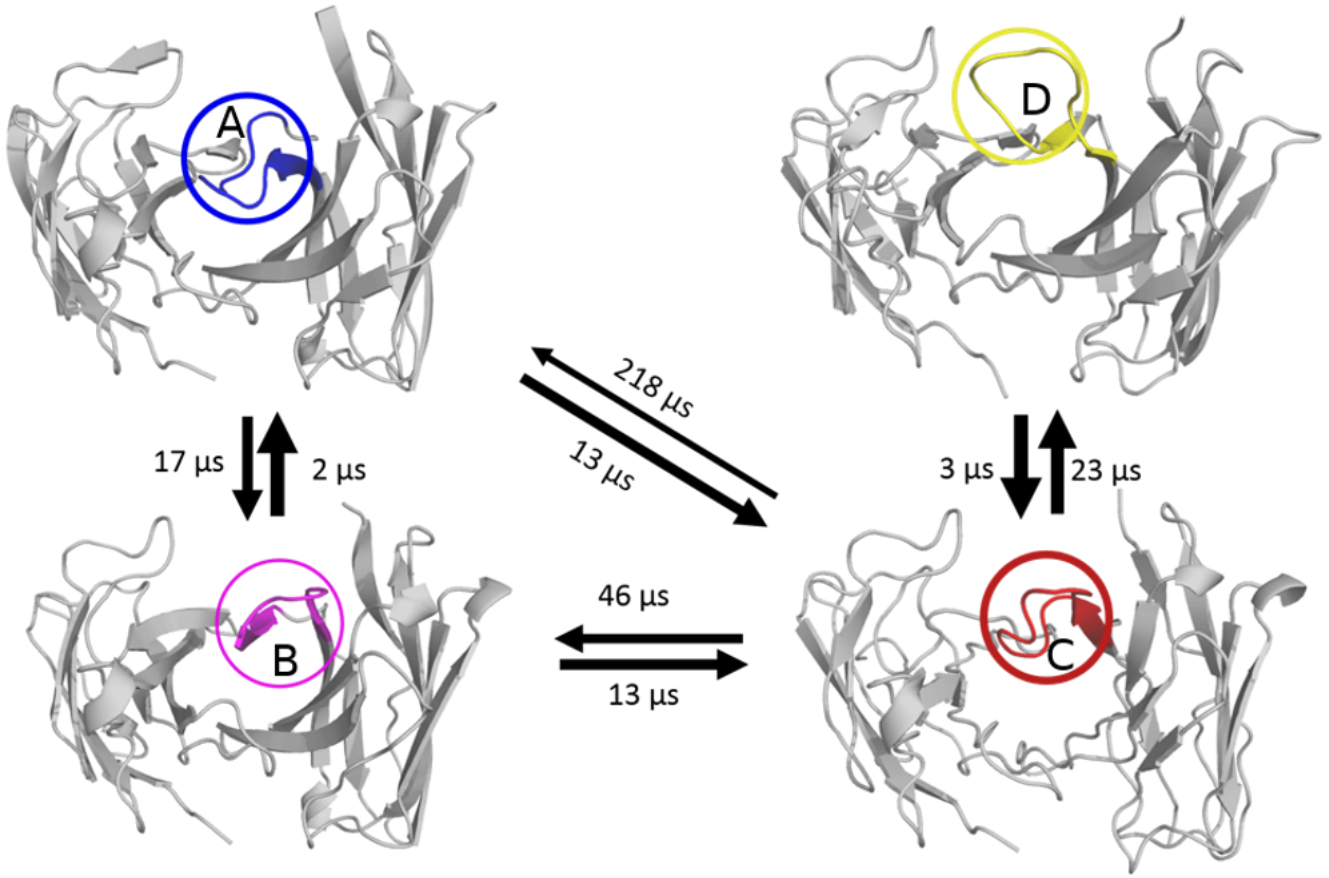
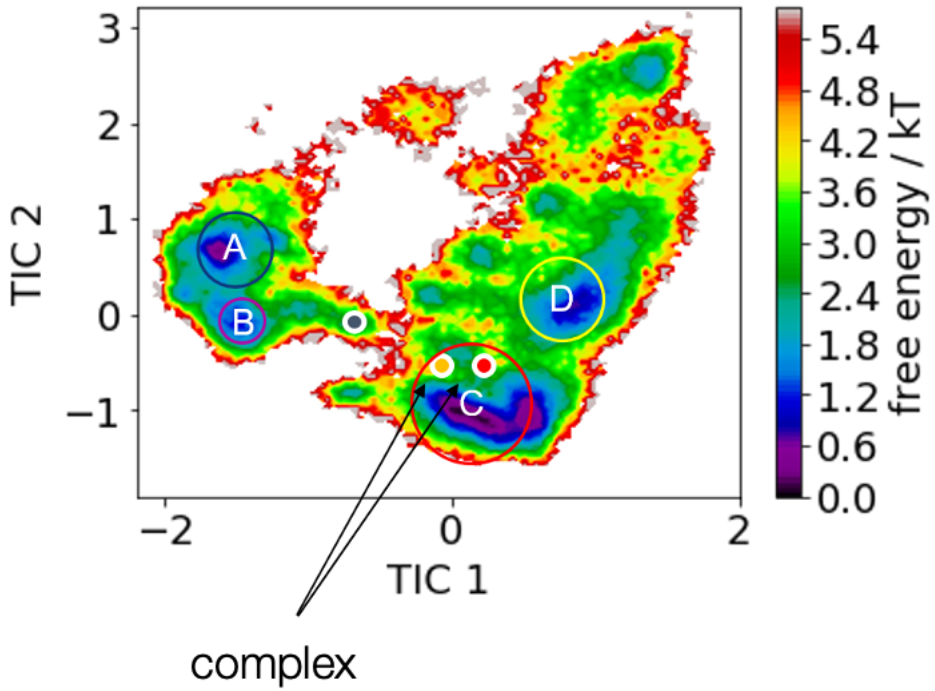
CDR-H3 Loop Ensemble in Solution of anti-Hemagglutinin Antibody Fv 17/9





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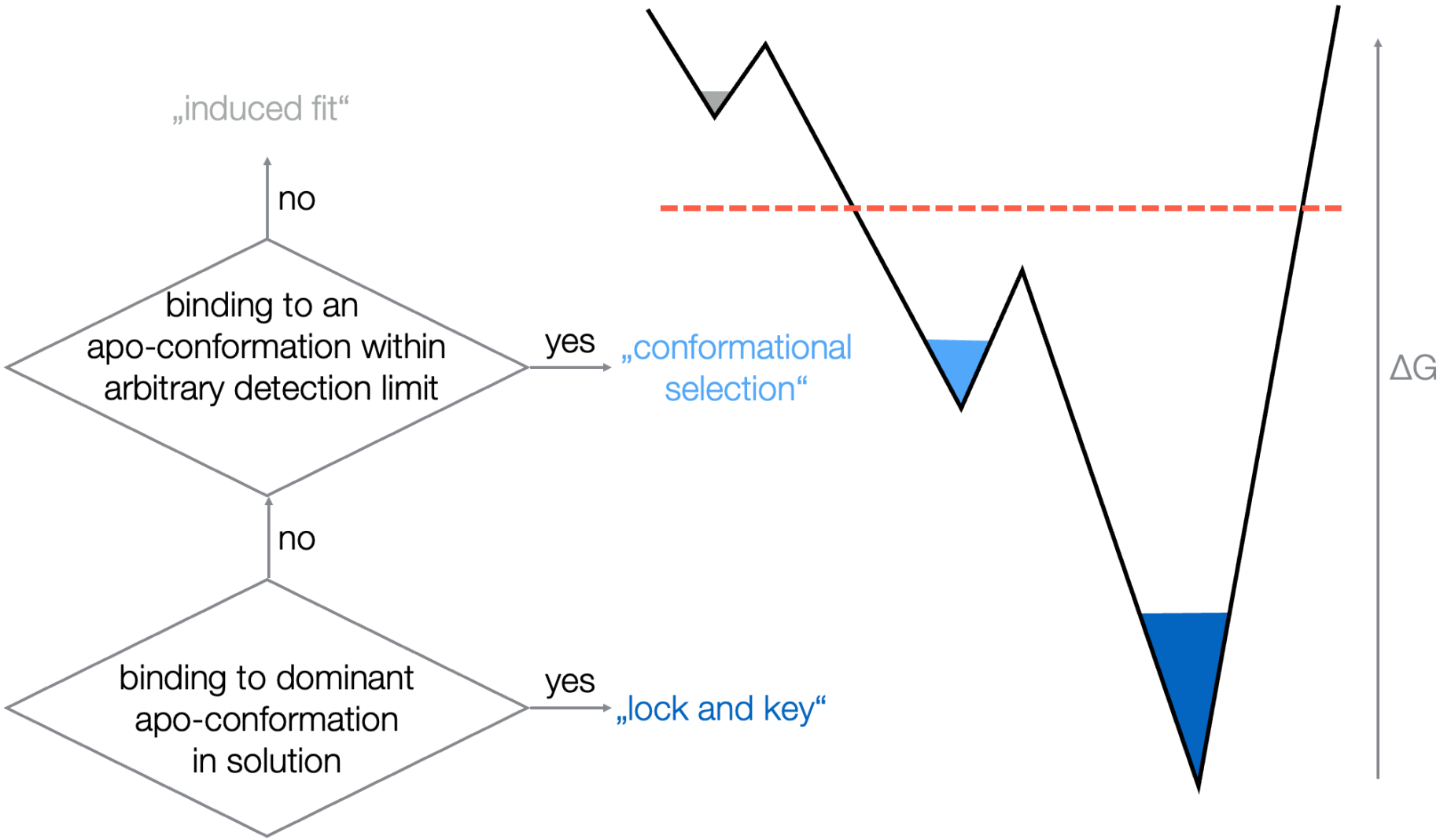
Different Binding Theories



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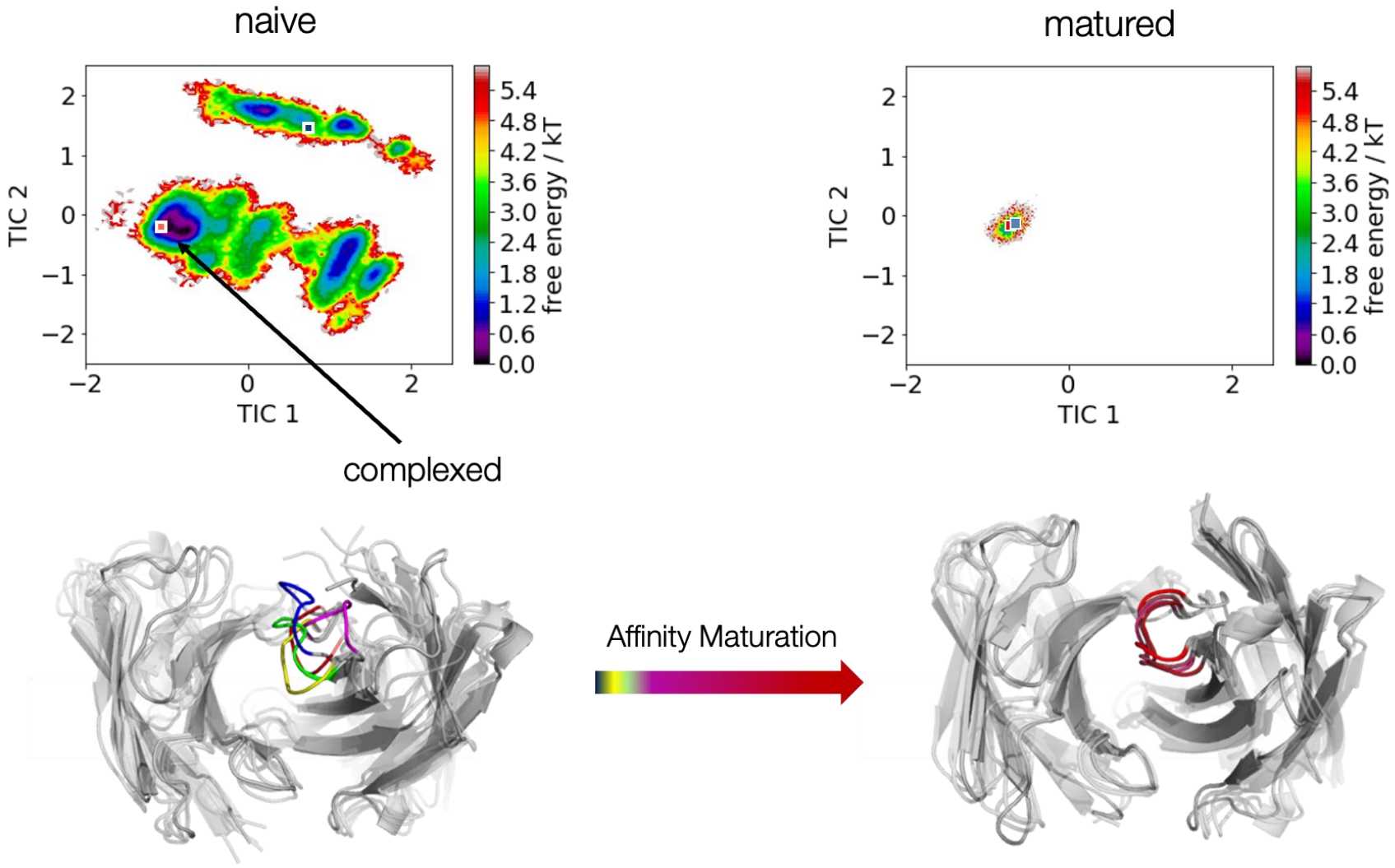
CDR-H3 Loop Affinity Maturation of the Germline Antibody 7G12



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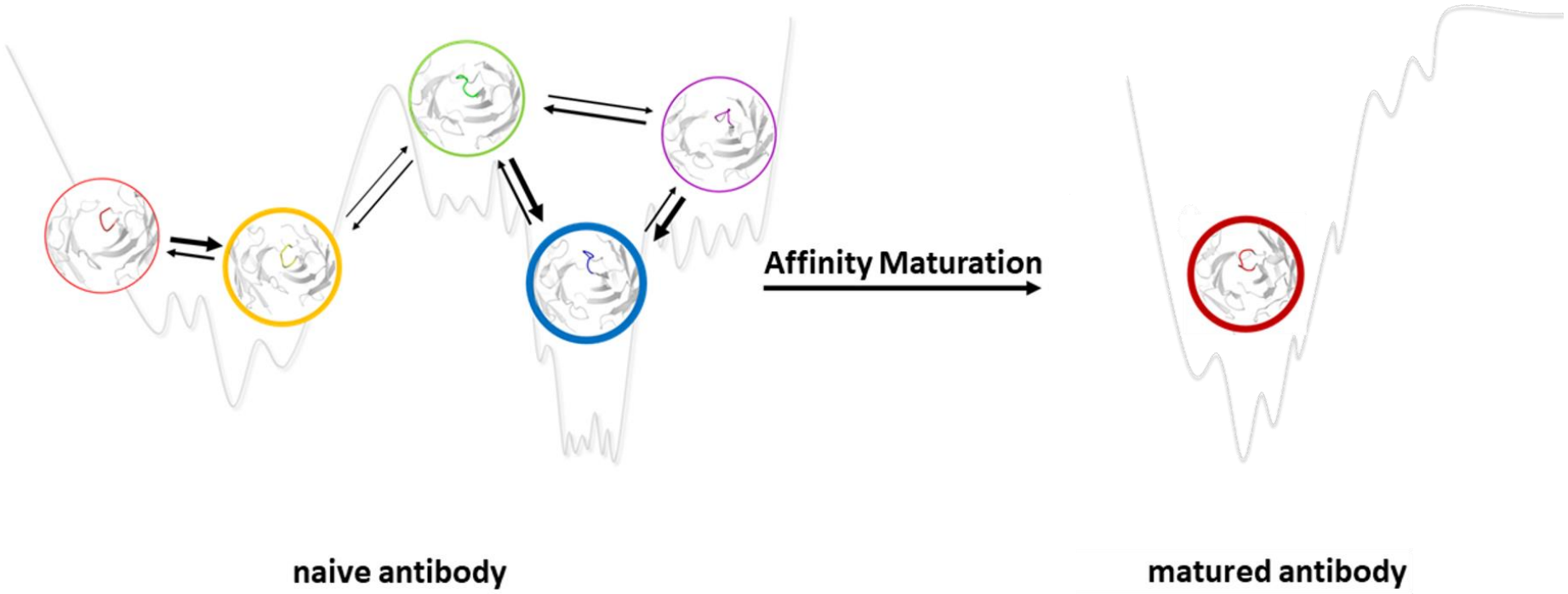
Rigidification upon Affinity Maturation



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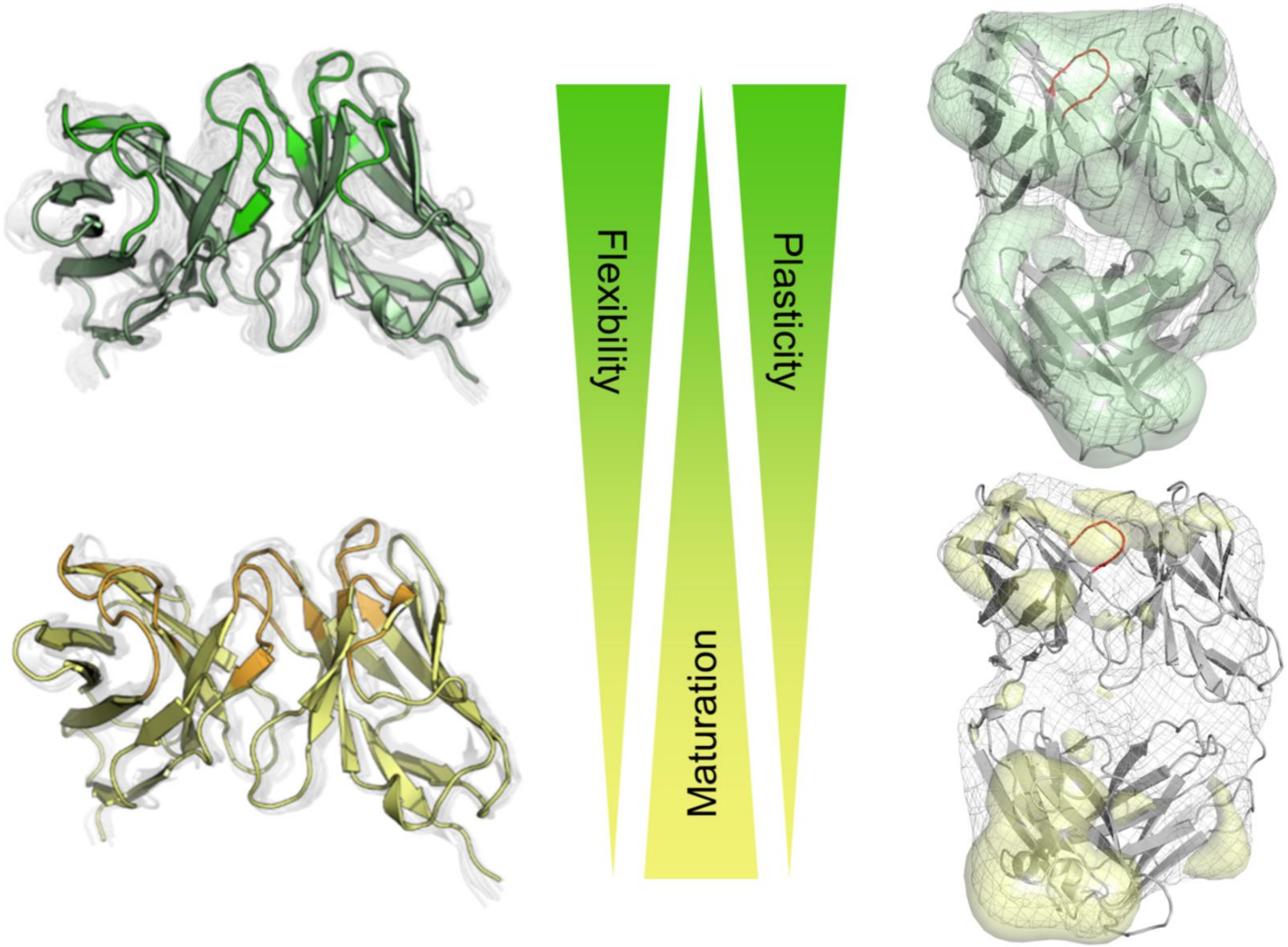
Affinity Maturation Leads to Rigidifcation



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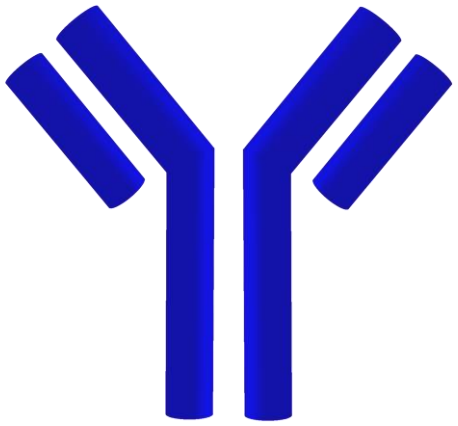
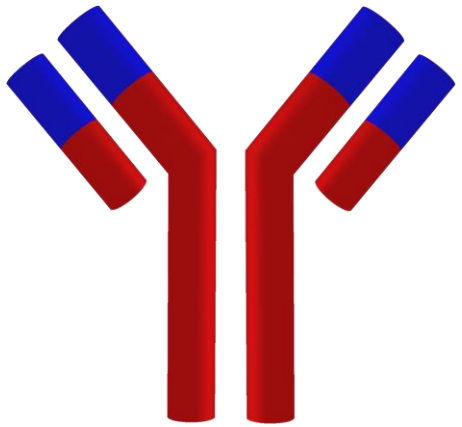
Antibody Humanization

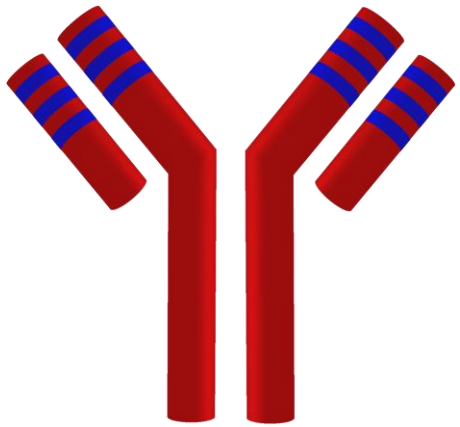
Murine



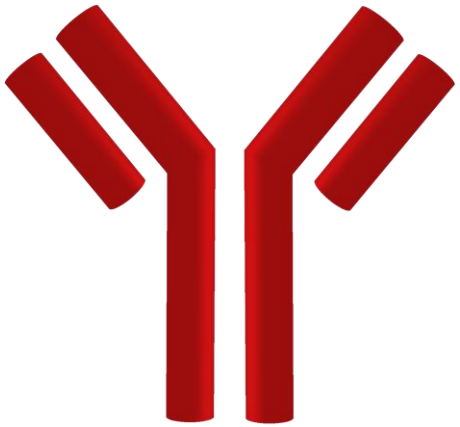
Chimeric



Humanized

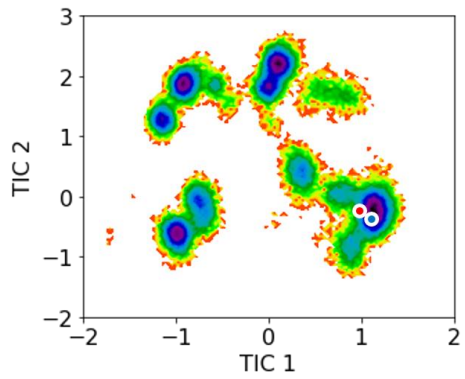


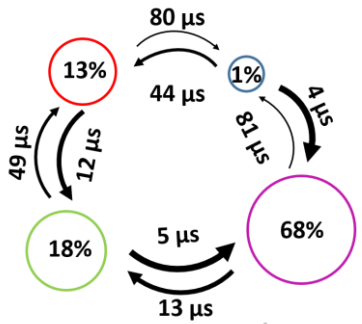
Human

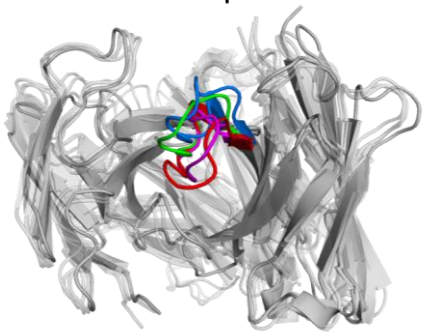


Humanization of Anti IL-13 Antibody

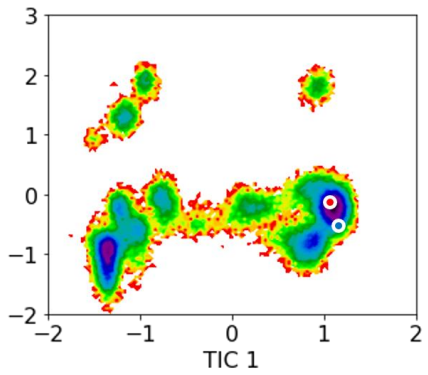
C836 (chimeric)

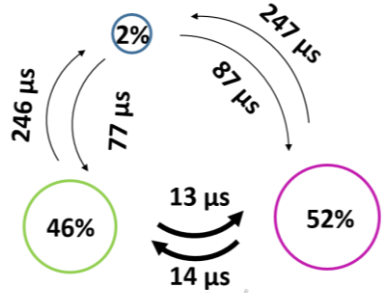


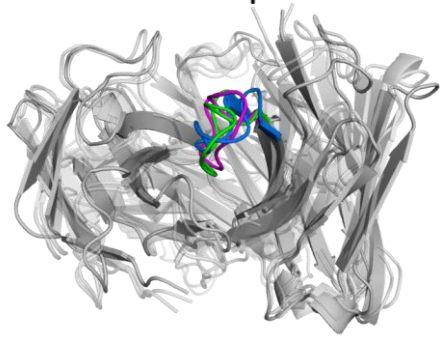




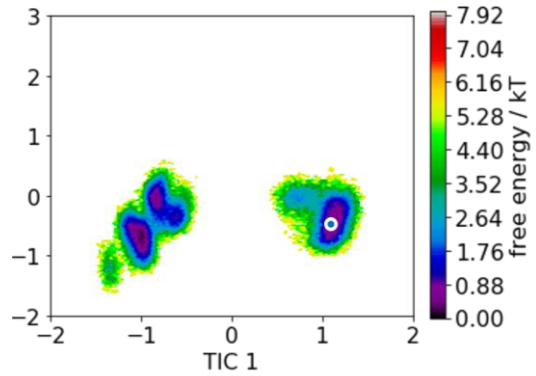
H2L6 (humanized)

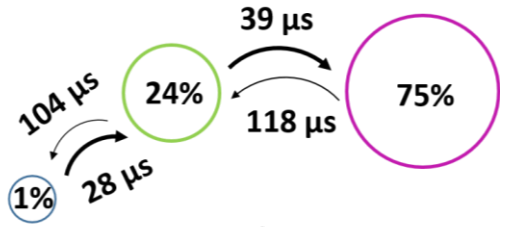


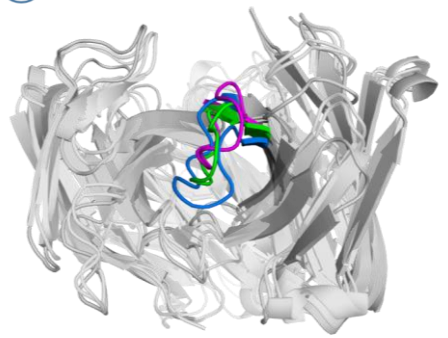




M1295 (optimized)







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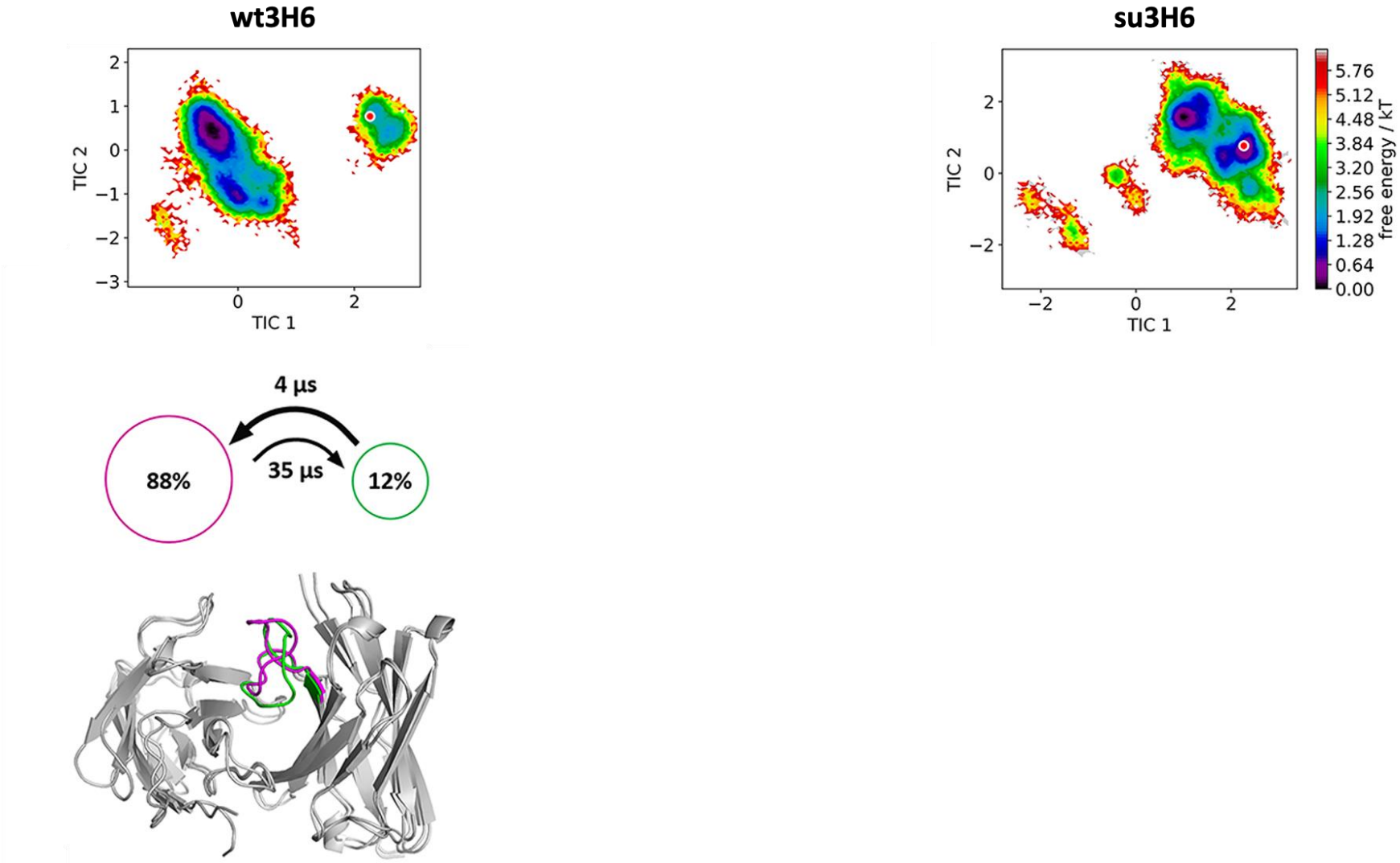
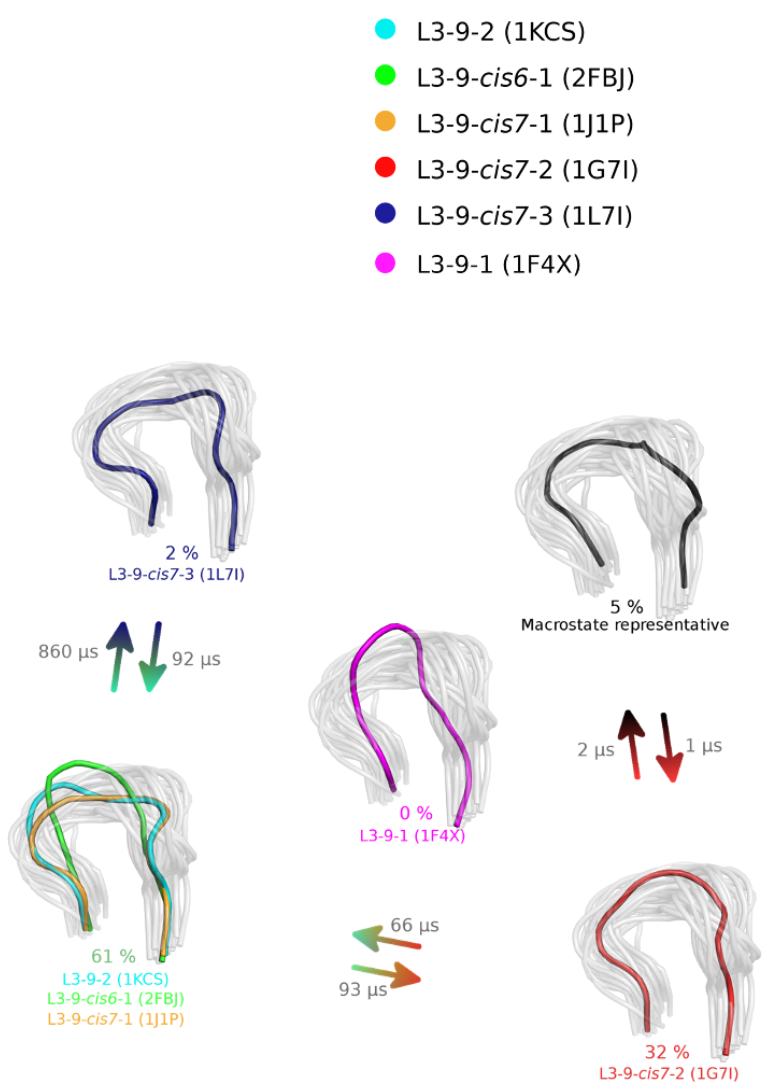
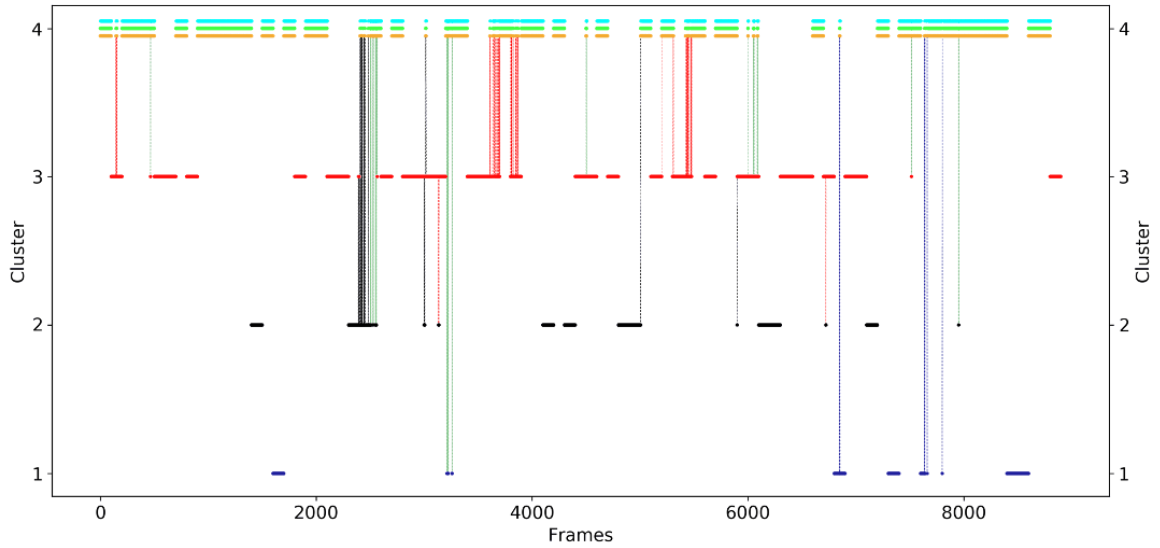
Humanization of Anti-idiotypic Ab2/3H6 against Anti-HIV-1 Antibody 2F5

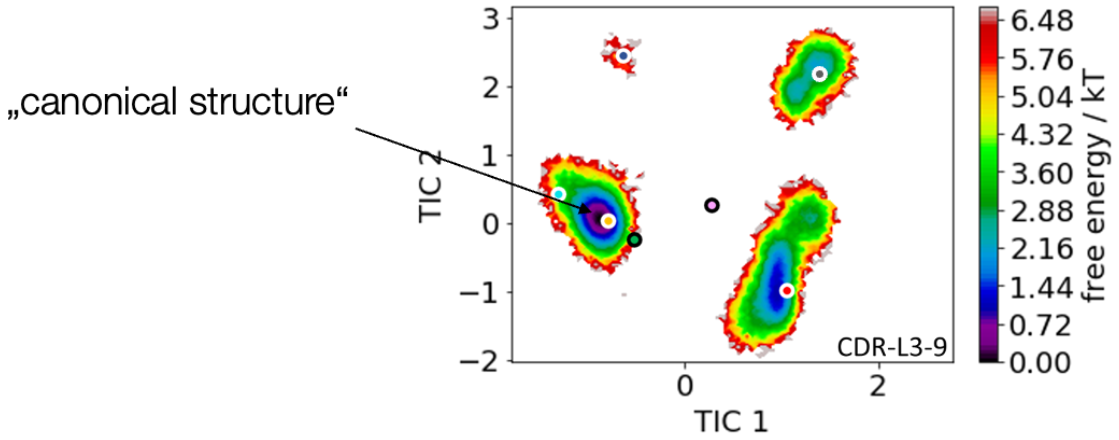


Fernández-Quintero et al. PEDS 2019 (32) 411-422

CDR-L3 Loop Dynamics and Canonical Structures







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CDR-L3 Loop Dynamics and Canonical Structures

CDR-L3 9	L3-9-1 (1F4X)	L3-9-2 (1KCS)	L3-9-cis6-1 (2FBJ)	L3-9-cis7-1 (1J1P)	L3-9-cis7-2 (1G7I)	L3-9-cis7-3 (1L7I)
3EOA	0 %	0 %	0 %	100%	0 %	0 %
3L5W	0 %	0 %	0 %	100%	0 %	0 %
1MLB	0 %	0 %	0 %	100%	0 %	0 %
1FL6	0 %	0 %	0 %	100%	0 %	0 %
1HIM	0 %	0 %	0 %	100%	0 %	0 %
3RVW	0 %	0 %	0 %	100%	0 %	0 %
1NGZ	0 %	0 %	0 %	100%	0 %	0 %
1AJ7	0 %	0 %	0 %	100%	0 %	0 %

non-canonical solution structures
0 %
0 %
0 %
0 %
0 %
0 %
0 %
0 %

Fernández-Quintero et al. Frontiers in Immunology 2019 (10) 2652

CDR-L3 Loop Dynamics and Canonical Structures

CDR-L3 9	L3-9-1 (1F4X)	L3-9-2 (1KCS)	L3-9-cis6-1 (2FBJ)	L3-9-cis7-1 (1J1P)	L3-9-cis7-2 (1G7I)	L3-9-cis7-3 (1L7I)
3EOA	0 %	C1 (89%)	0 %	C1 (89%)	C1 (89%)	C2 (11%)
3L5W	C2 (14%)	C1 (77%)	0 %	C1 (77%)	C2 (14%)	C4 (3%)
1MLB	C3 (14%)	C2 (23%)	C3 (14%)	C2 (23%)	C3 (14%)	C3 (14%)
1FL6	C2 (18%)	C2 (18%)	C2 (18%)	C2 (18%)	C2 (18%)	C1 (76%)
1HIM	C4 (4%)	C3 (7%)	C3 (7%)	C3 (7%)	C4 (4%)	C3 (7%)
3RVW	0 %	C1 (61%)	C1 (61%)	C1 (61%)	C2 (32%)	C4 (2%)
1NGZ	C2 (22%)	C2 (22%)	0 %	C2 (22%)	C2 (22%)	0 %
1AJ7	0 %	C1 (54%)	C2 (18%)	C1 (54%)	C1 (54%)	C1 (54%)

non-canonical solution structures
0 %
C3 (6%)
C1+C4 (55+8%)
C3 (6%)
C1+C2 (51+38%)
C3 (5%)
C1+C3 (77+1%)
C3+C4 (18+10%)

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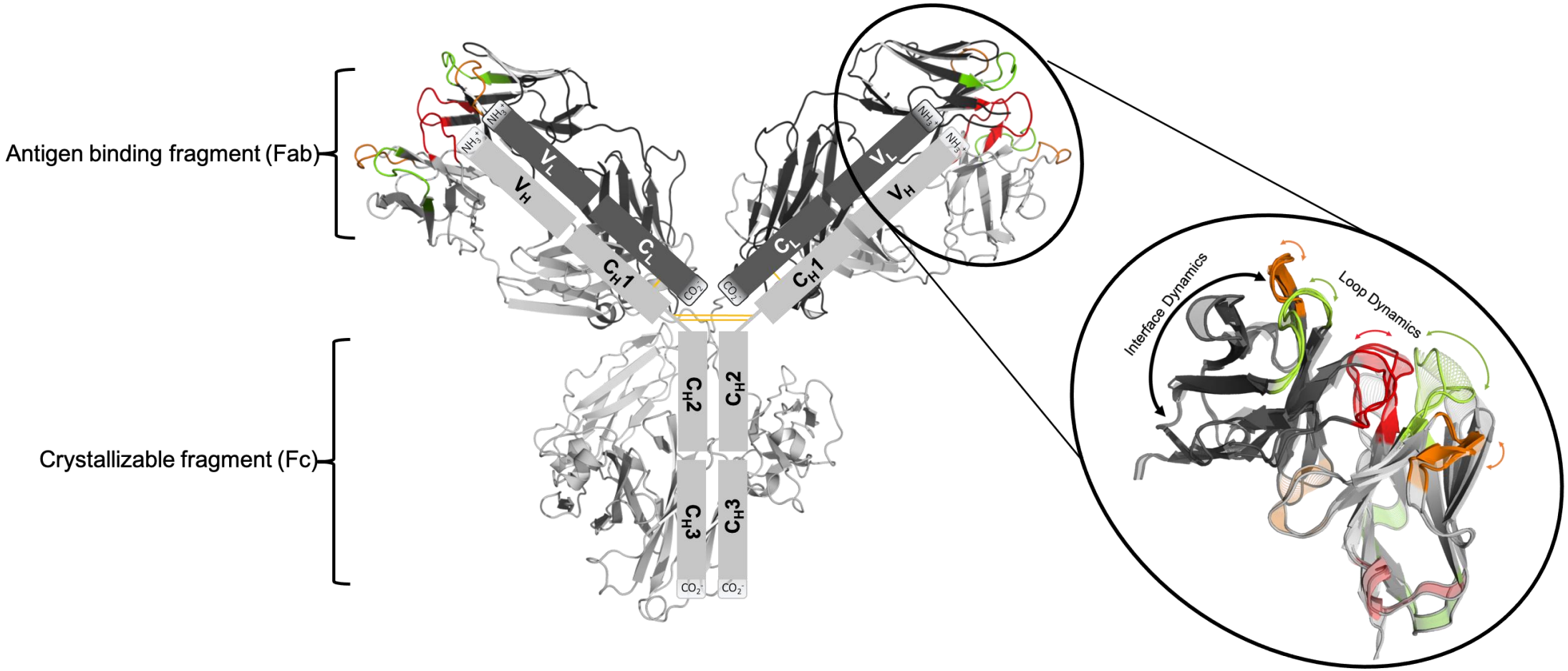
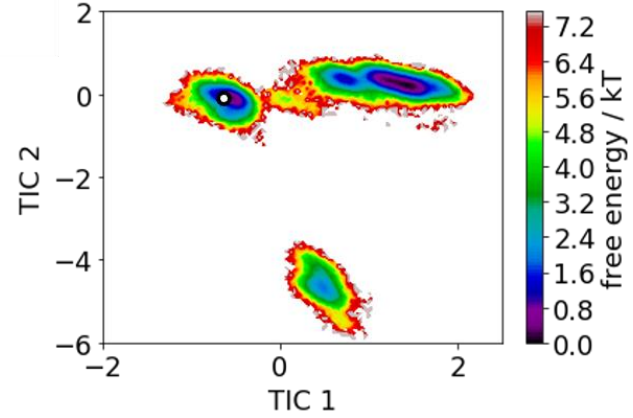
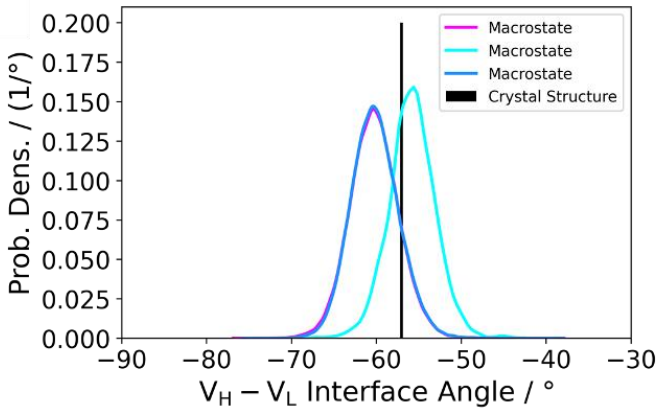
Paratope States in Solution Shift the VH-VL Interdomain Orientations

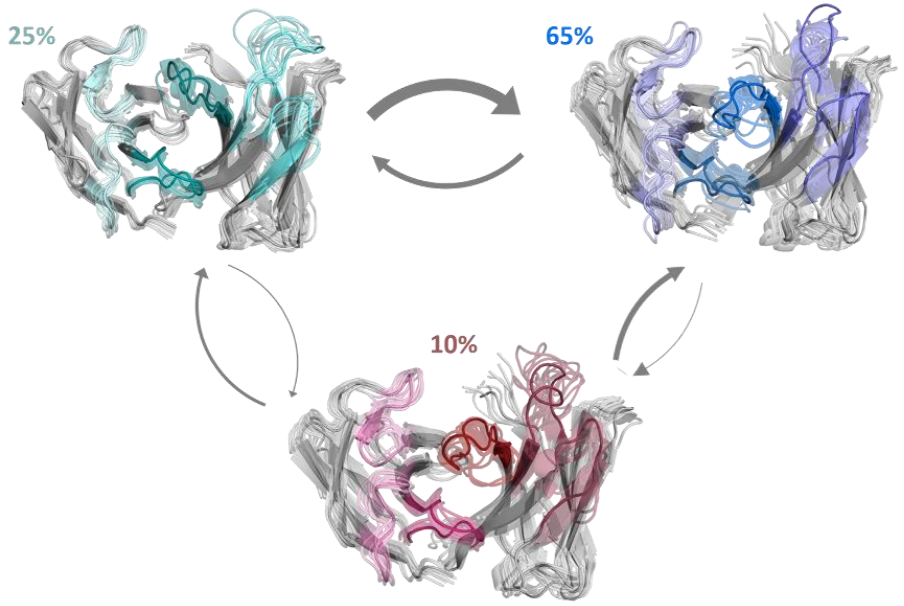


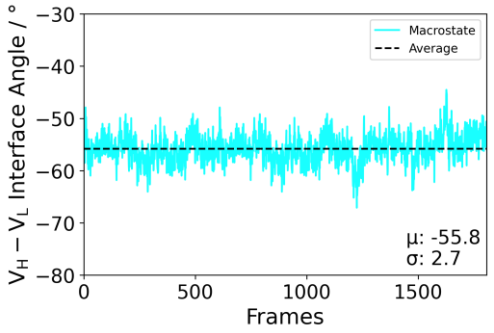
Fernández-Quintero et al. mAbs 2021 (13) 1, e1923122

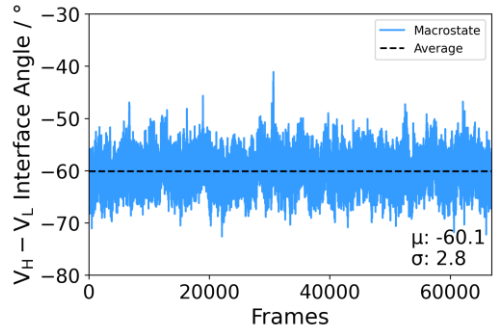
Paratope States in Solution Shift the VH-VL Interdomain Orientations

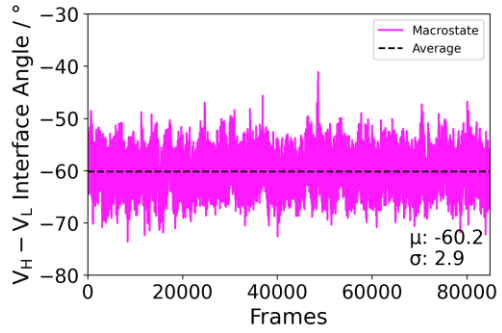












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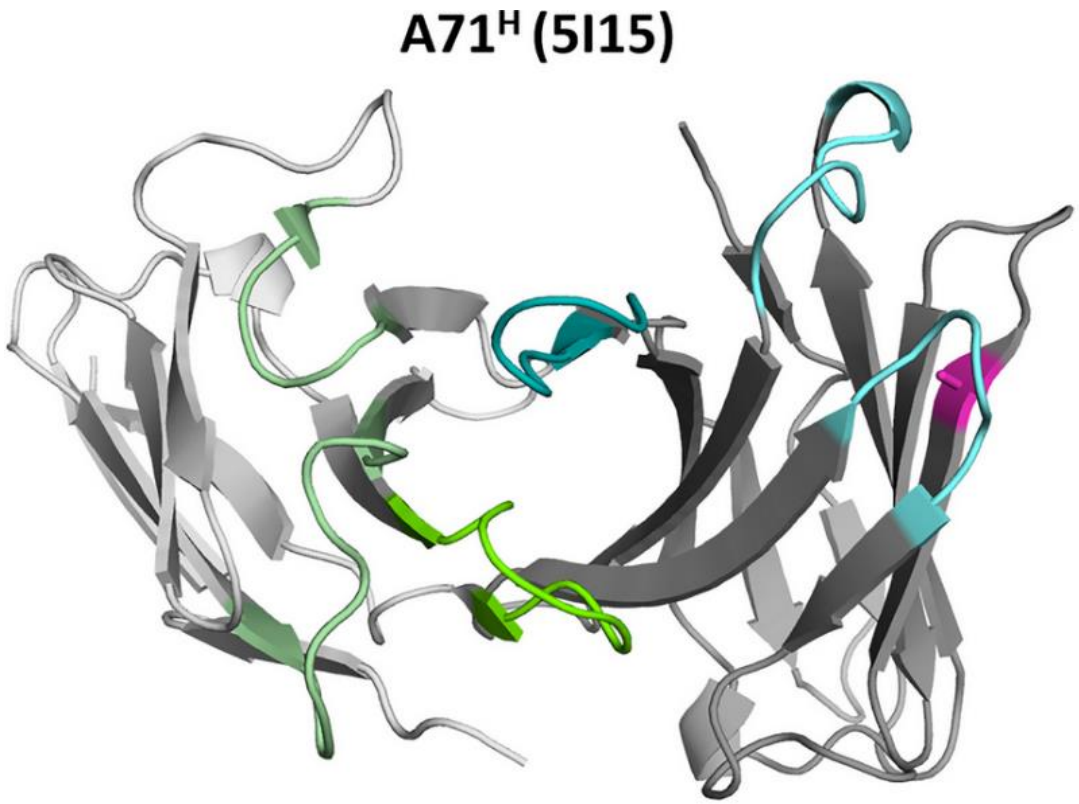
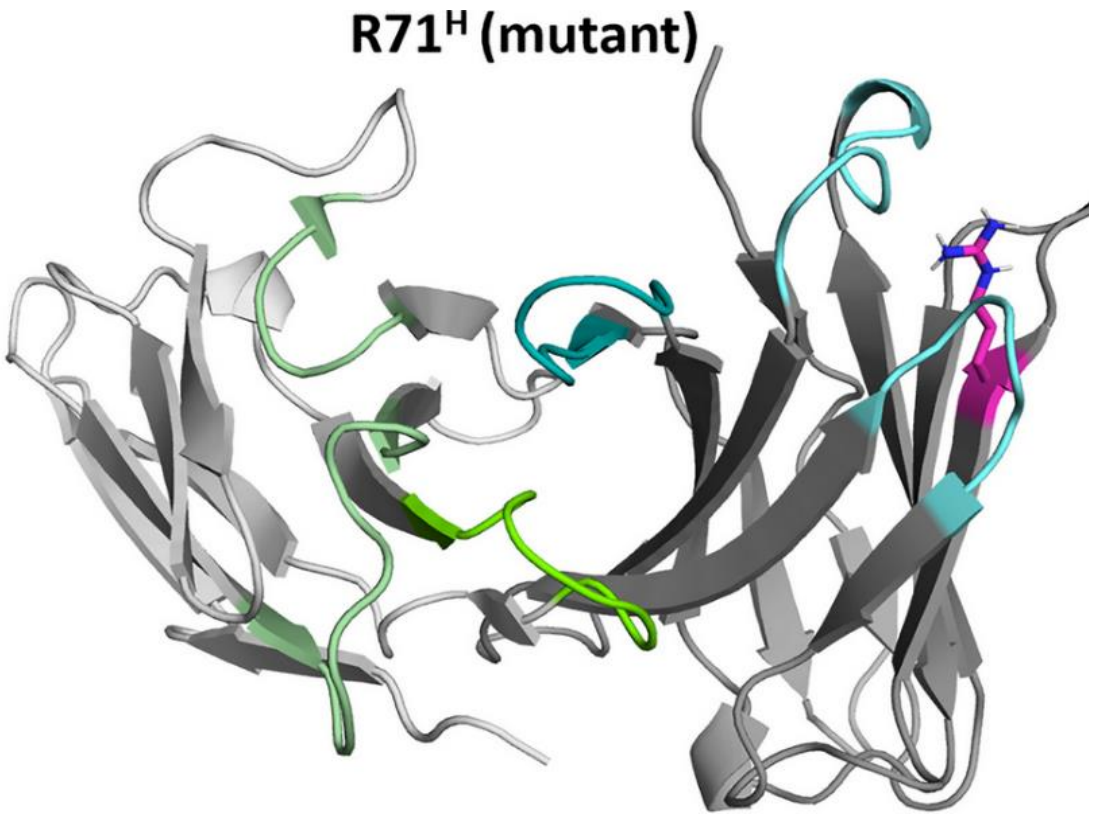
Framework Residue H71 Co-Determines Paratope States





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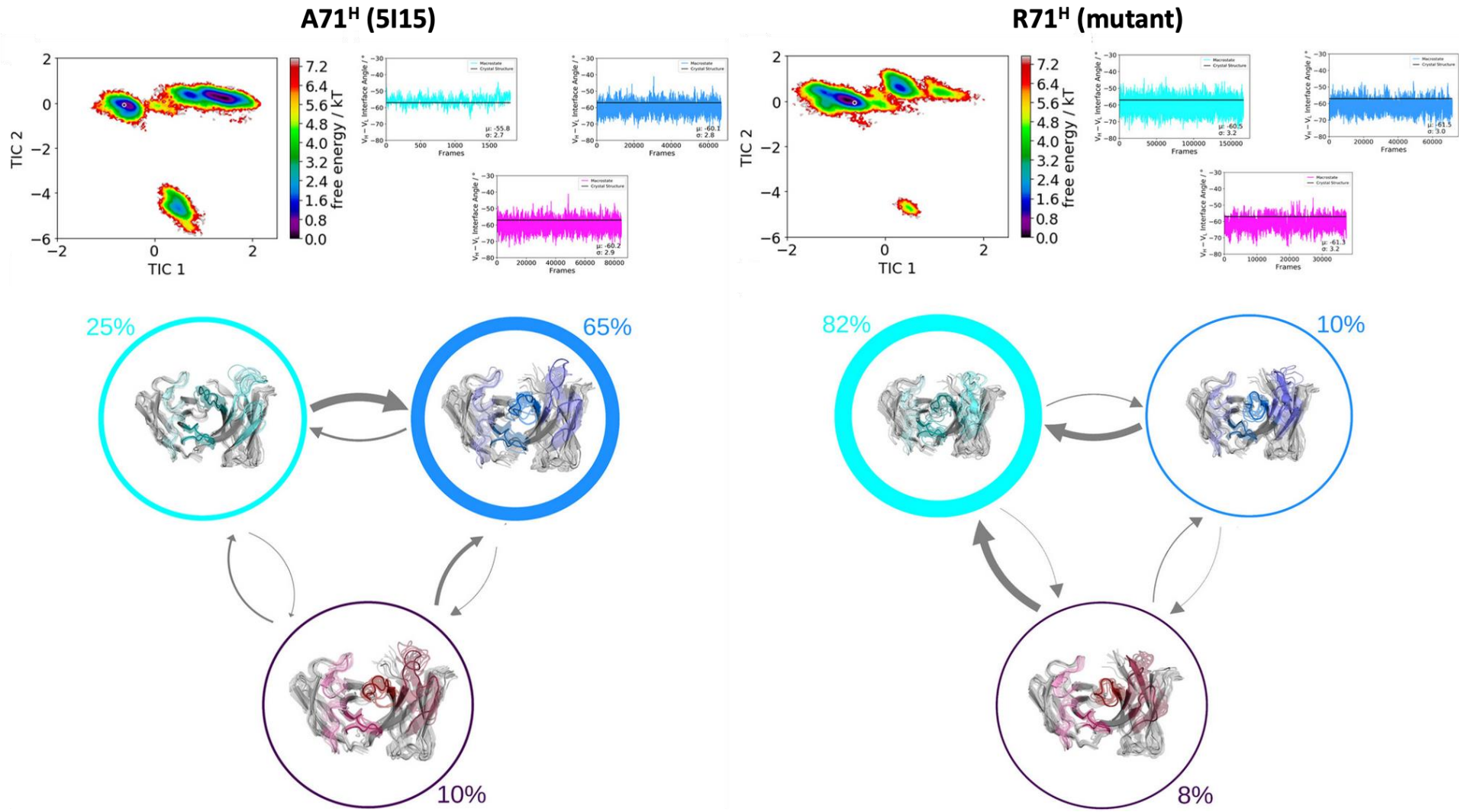
Framework Residue H71 Co-Determines Paratope States



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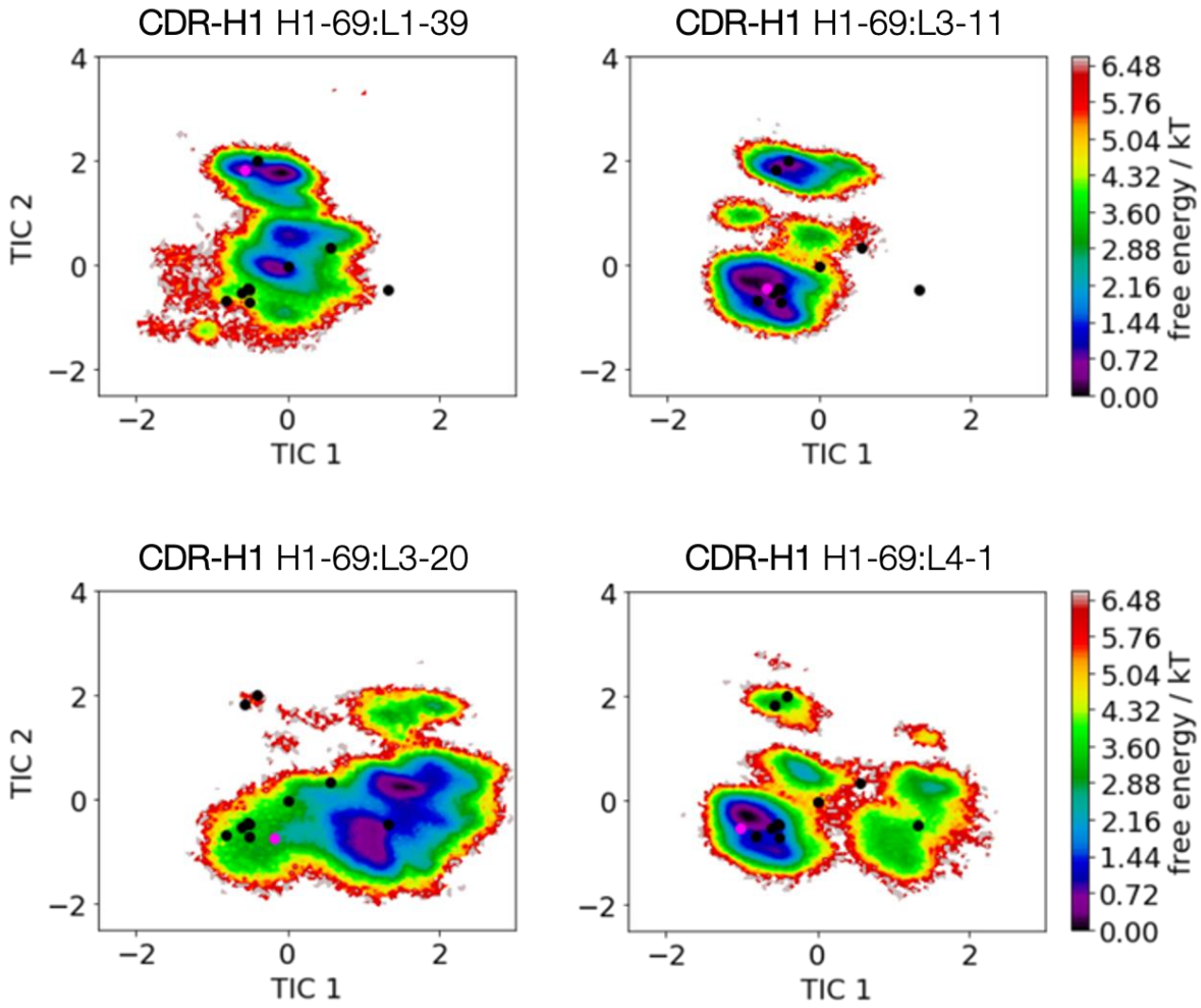
Different Germline Pairings Result in Different Paratope States



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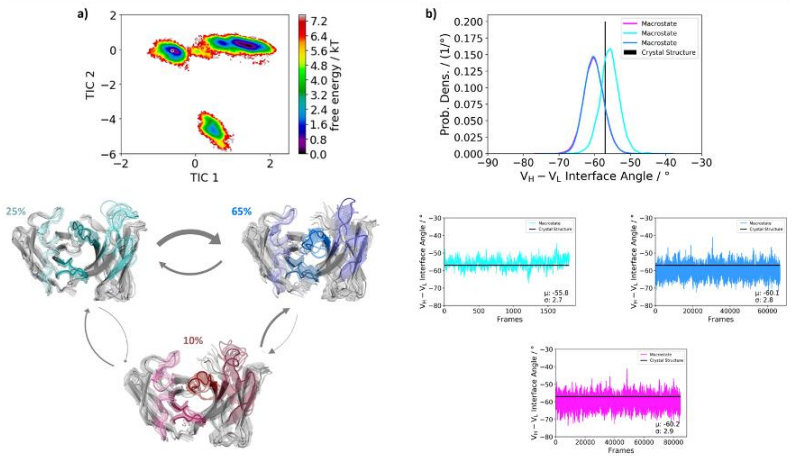
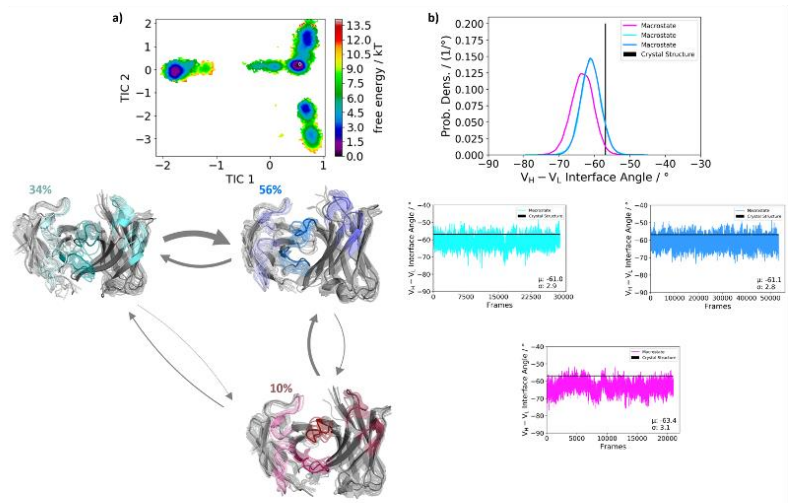
Different Germline Pairings Result in Different Paratope States

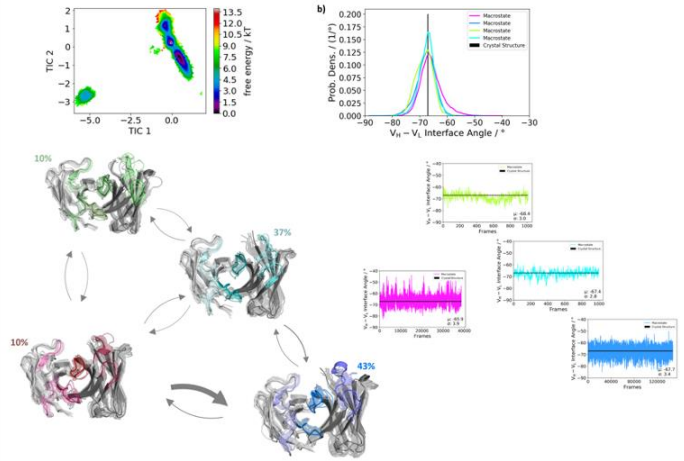
H1-69:L1-39



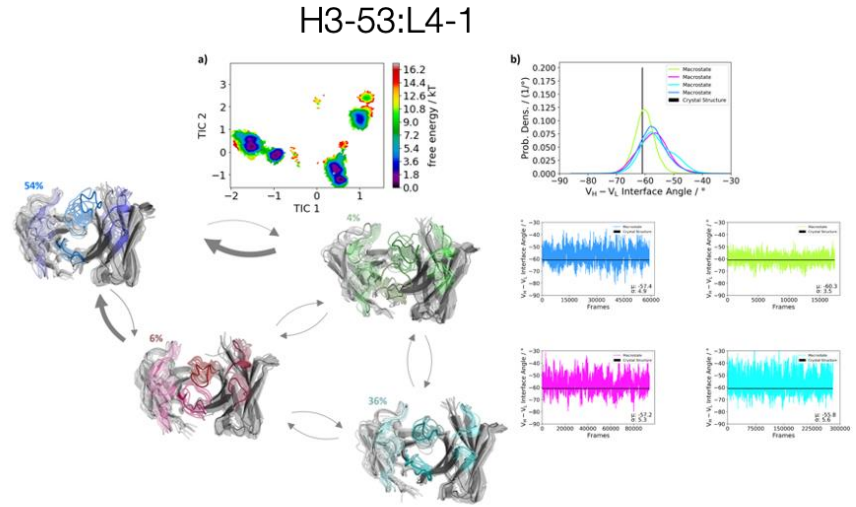
H5-51:L1-39



H3-23:L3-20



H3-53:L4-1



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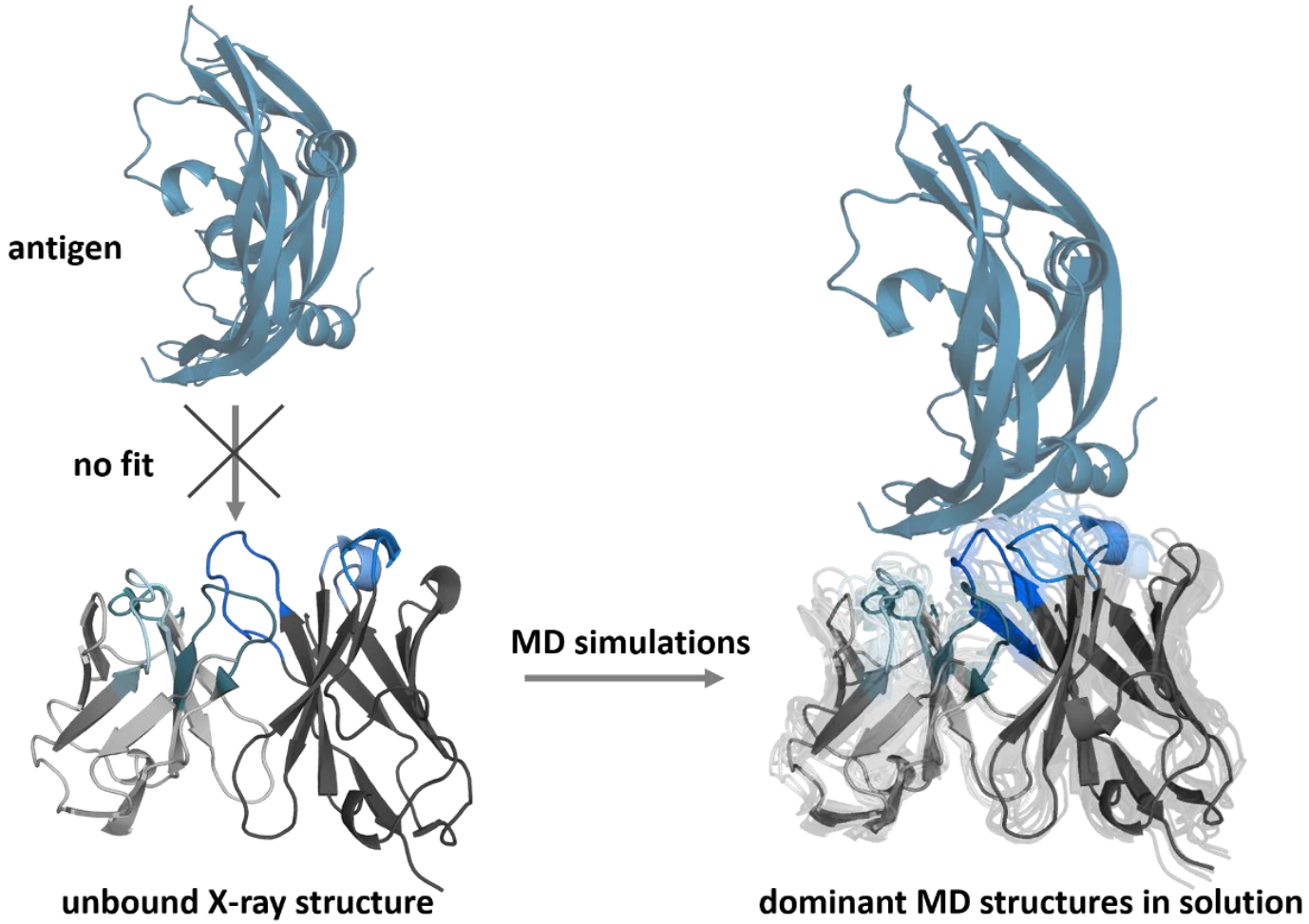
Paratope States in Solution Improve Structure Prediction and Docking



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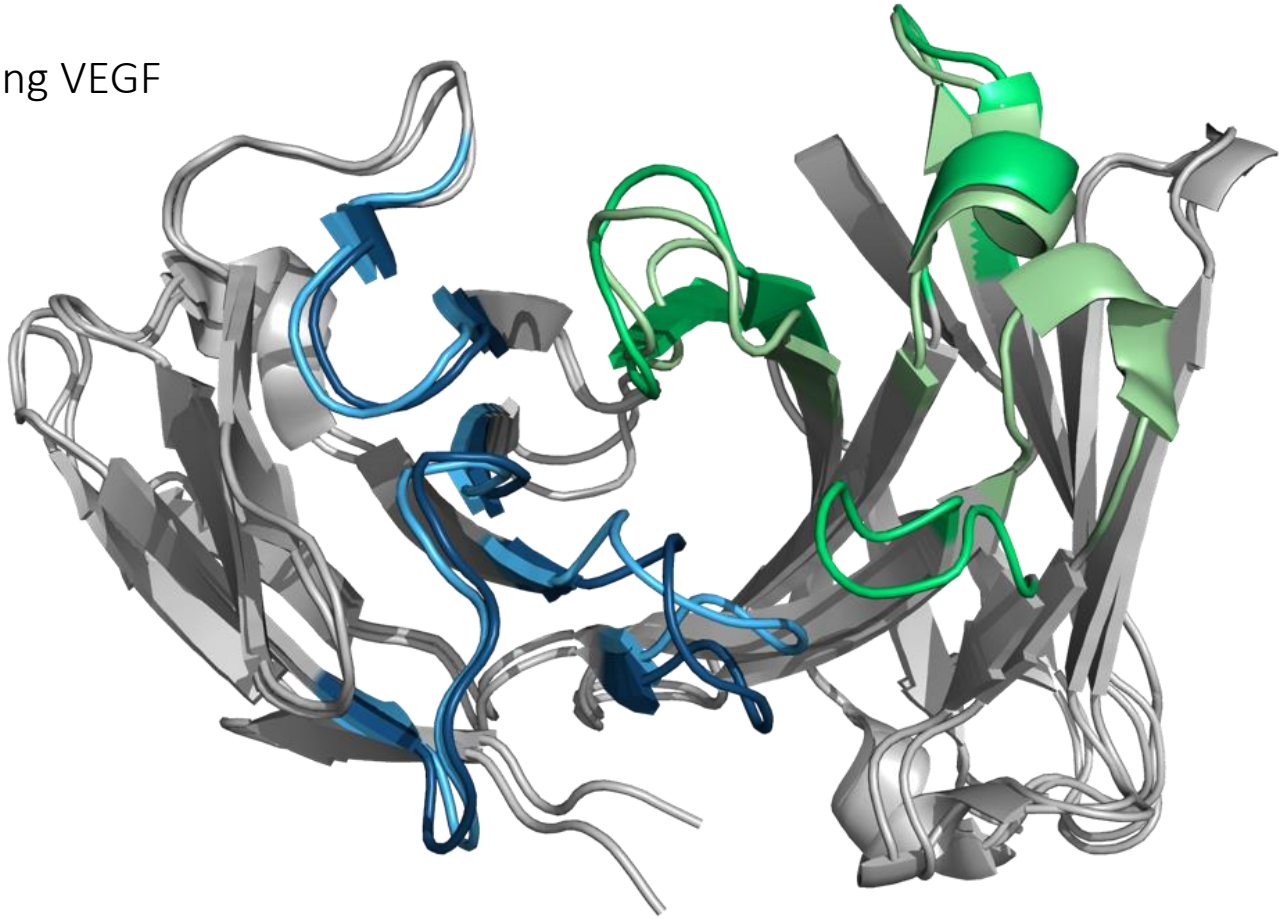
Paratope States in Solution Improve Structure Prediction and Docking

G6 Fab binding VEGF



Fernández-Quintero et al. Structure 2022 (30) 1-11

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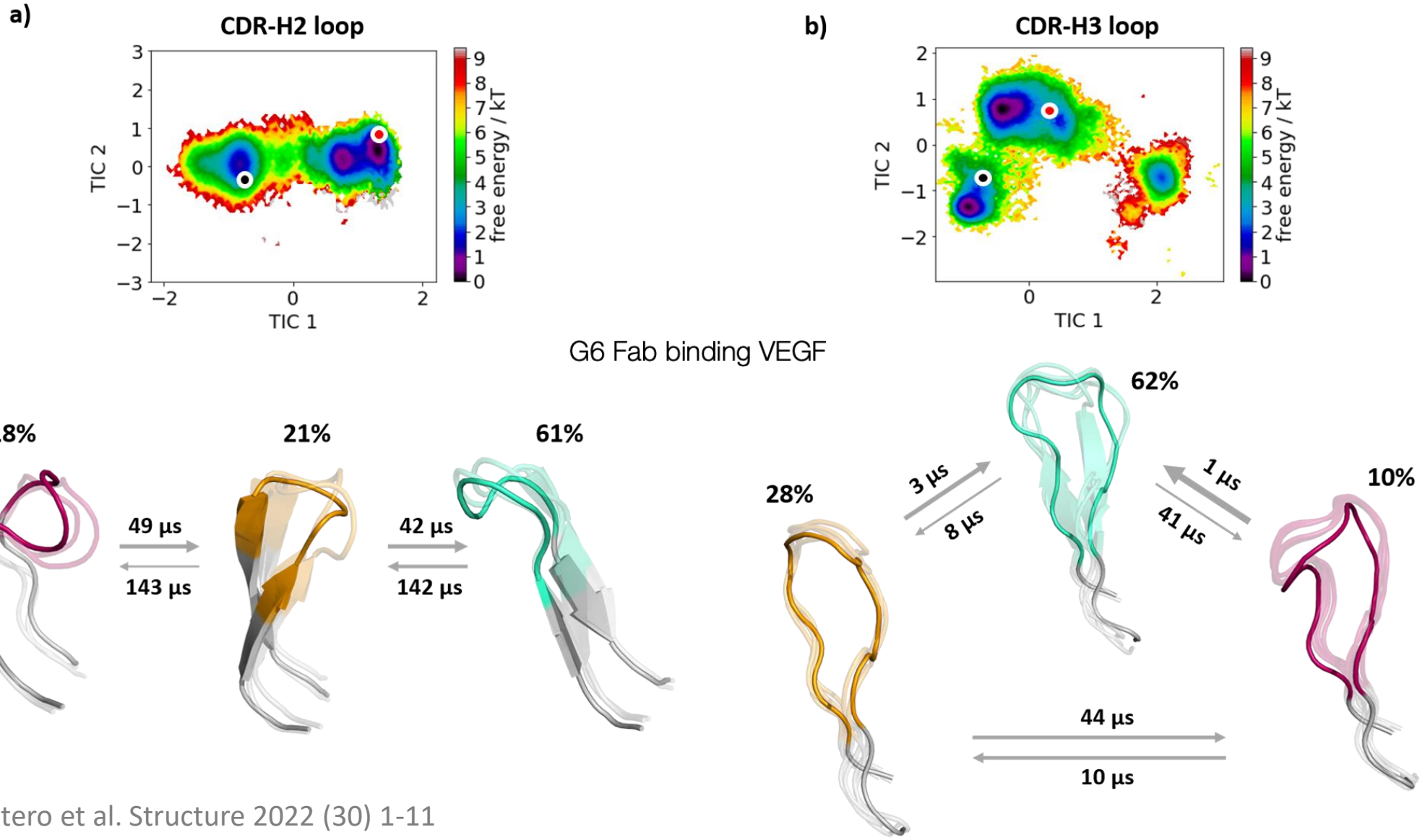

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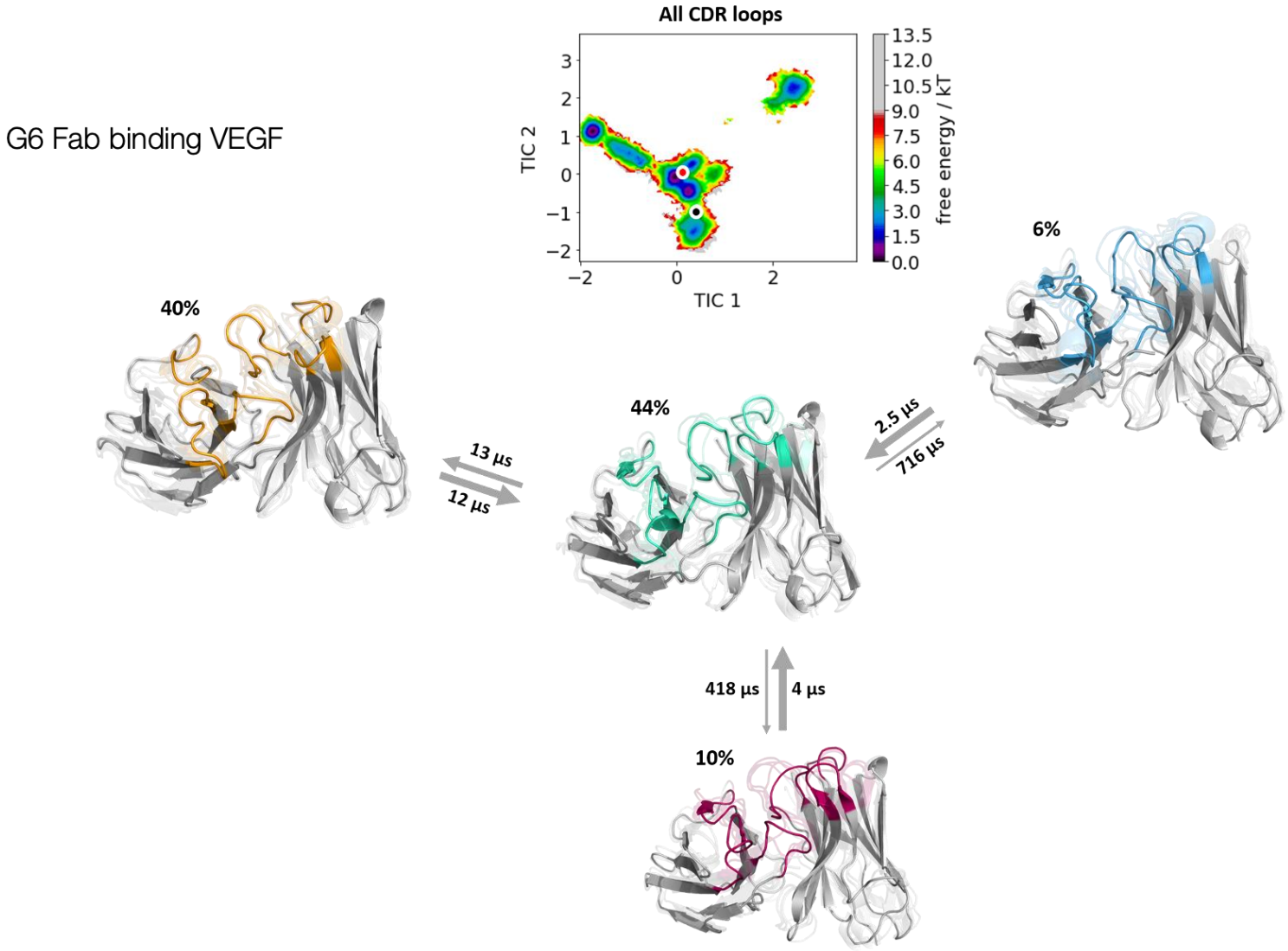

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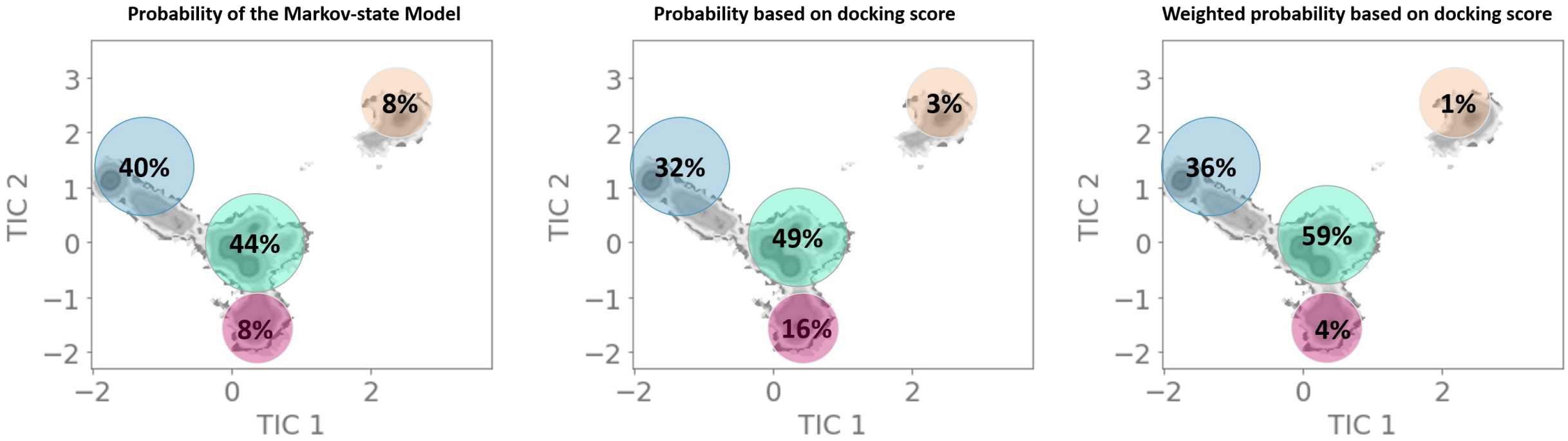

Fernández-Quintero et al. Structure 2022 (30) 1-11

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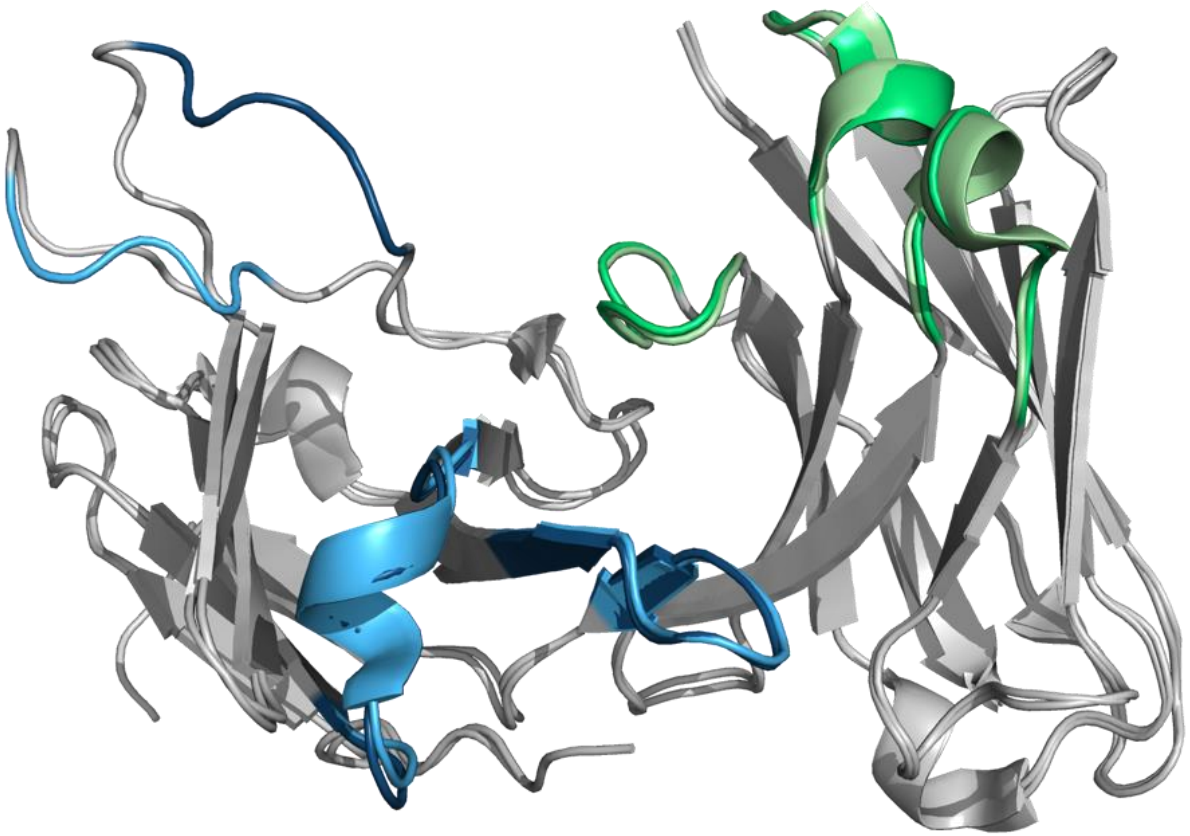
MOR04357



Fernández-Quintero et al. Structure 2022 (30) 1-11

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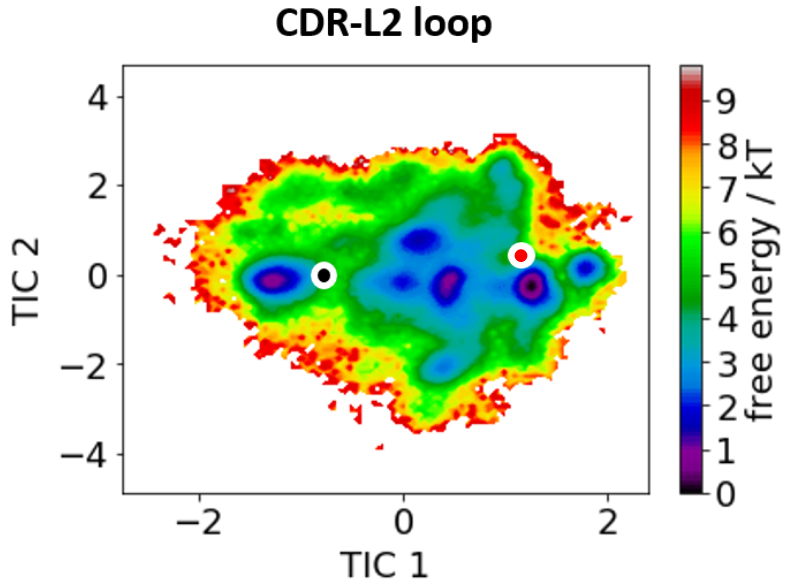

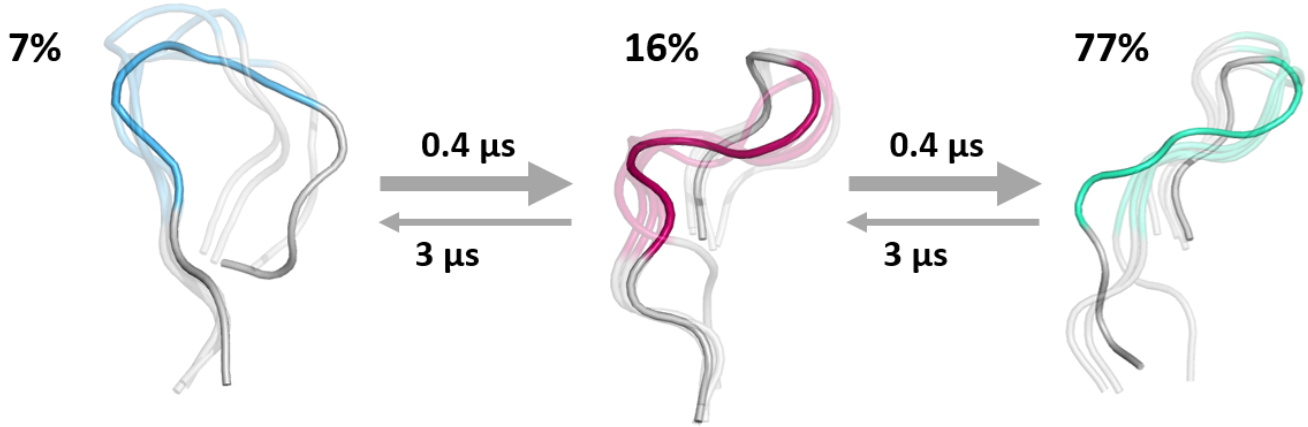

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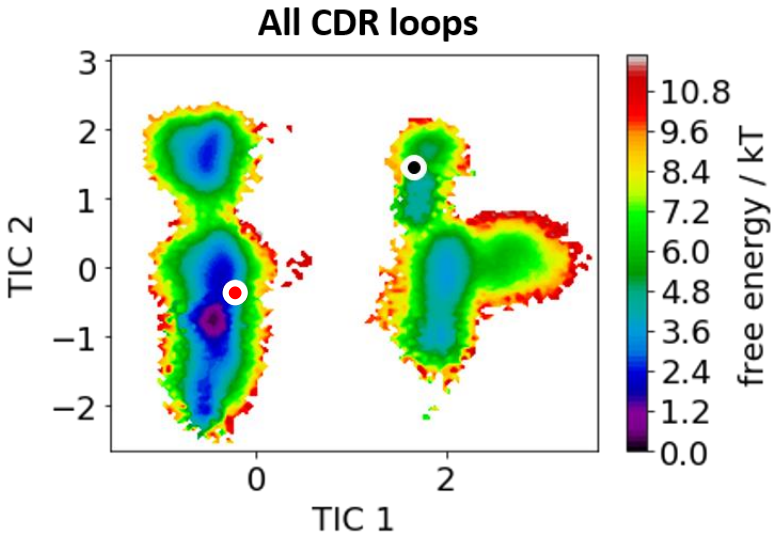

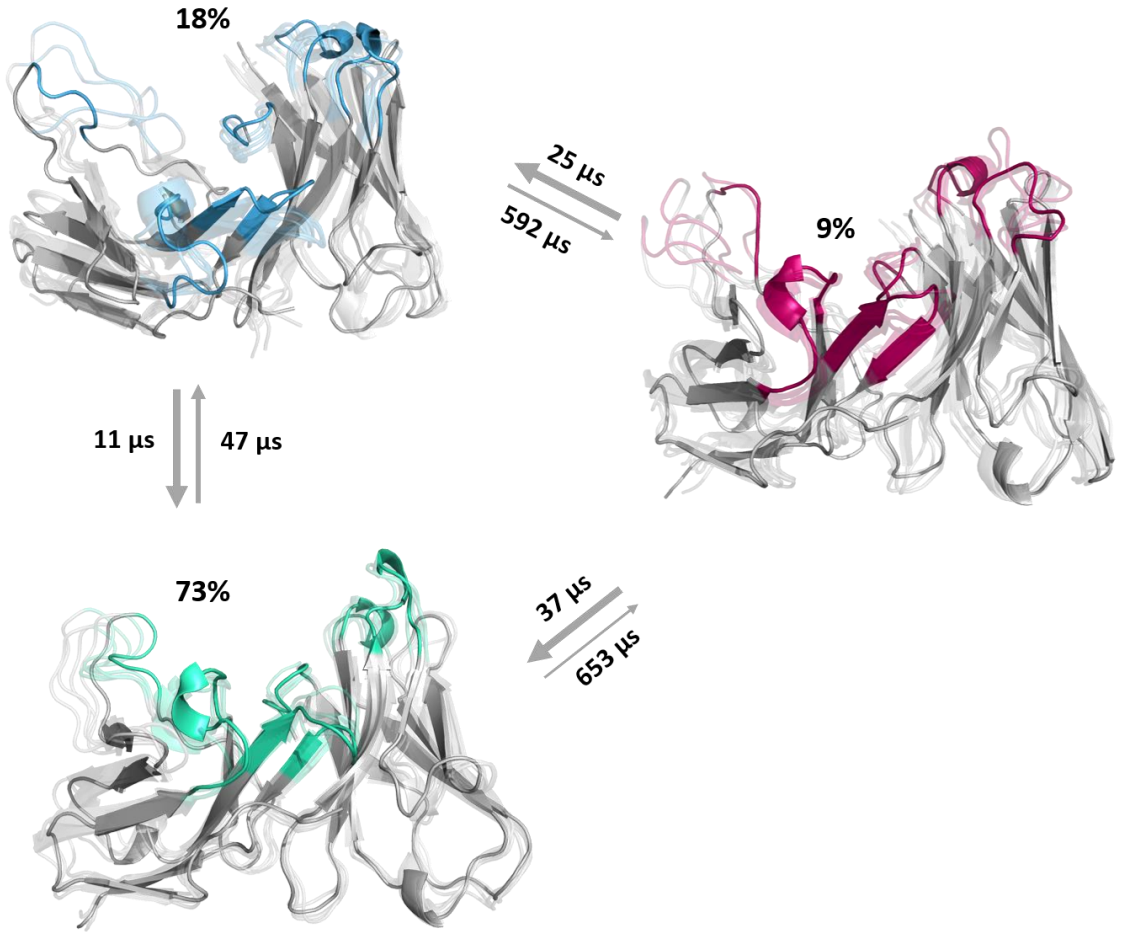

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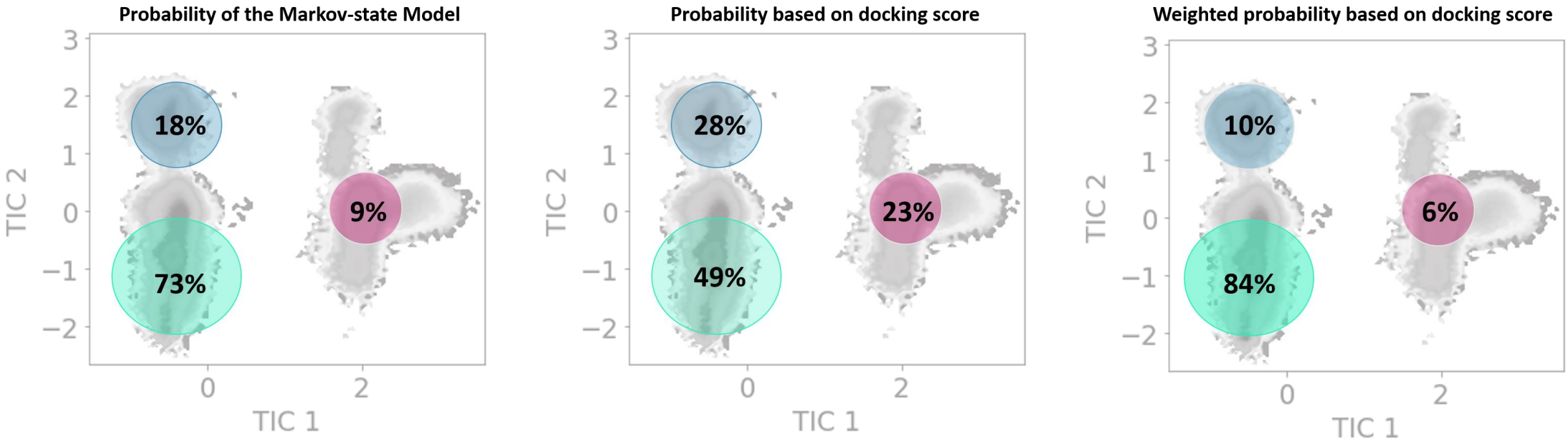

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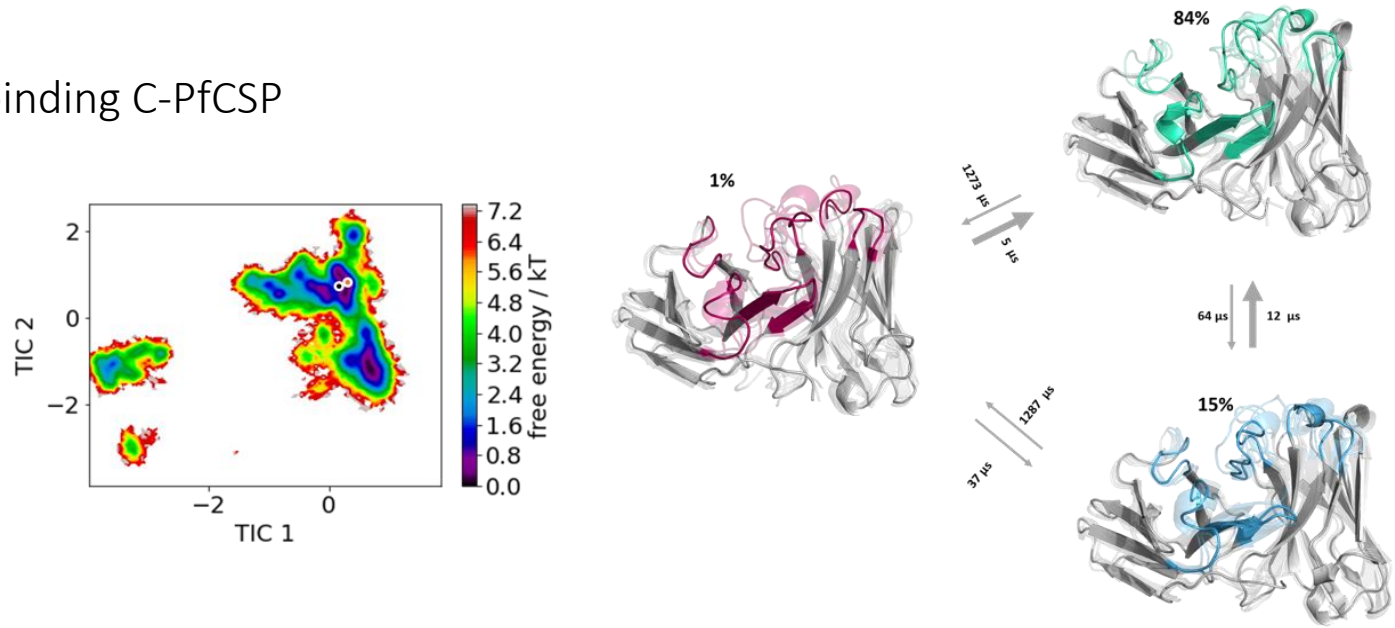
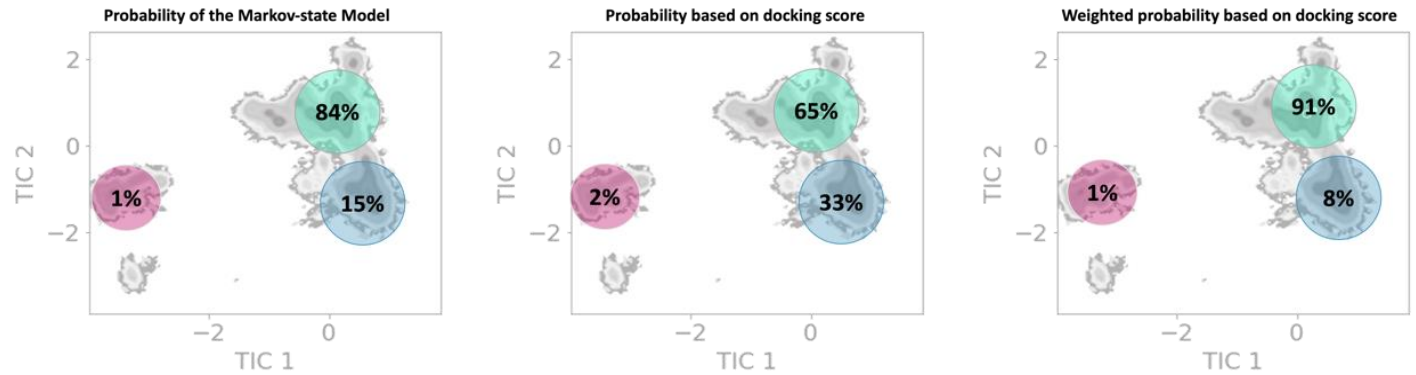
Paratope States in Solution Improve Structure Prediction and Docking

1710 antibody binding C-PfCSP





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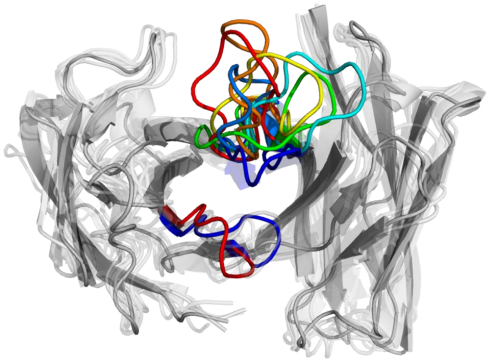
Paratope States in Solution Improve Structure Prediction and Docking

Antibody PDB	Classification	Probability of the Markov-state Model	Probability based on docking score	weighted probability based on docking score
2FJF	difficult	44%	49%	59%
5D7S	difficult	73%	48%	84%
4DVB	difficult	75%	39%	83%
6B0W	rigid	84%	65%	91%
1MLB	rigid	58%	37%	71%
3EO9	medium	69%	52%	78%

Fernández-Quintero et al. Structure 2022 (30) 1-11

Conclusions

- CDR loops are highly flexible and need to be characterized as conformational ensembles in solution.



- The relative V_H-V_L dynamics occurs in the low nanosecond.

- Affinity maturation leads to a local and global rigidification of both antibody and T-cell receptors.

- Antibodies exist as several interconverting paratope states.

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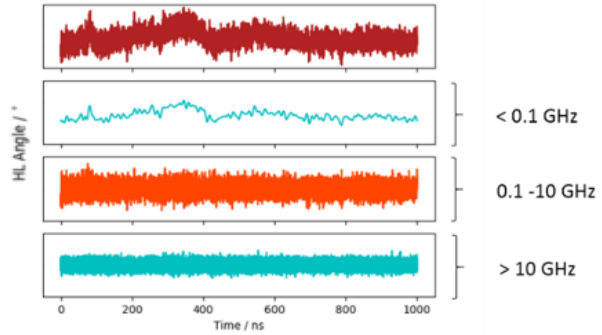

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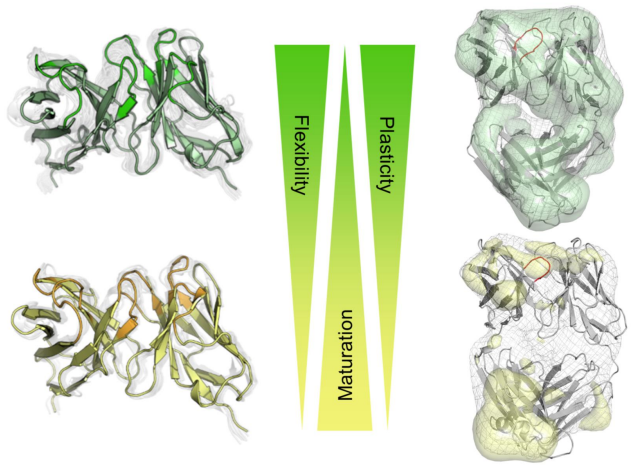

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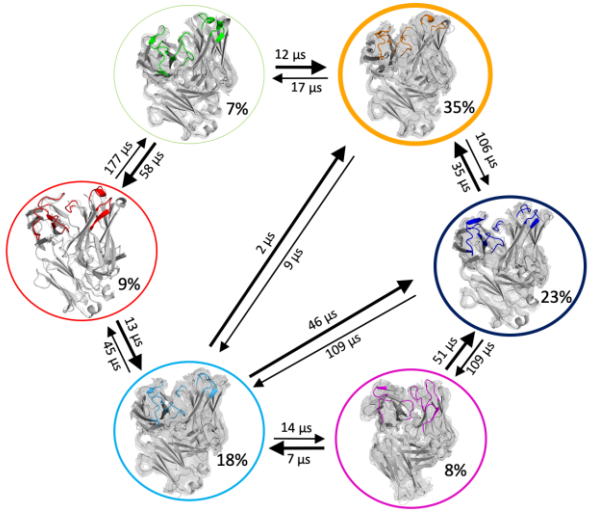

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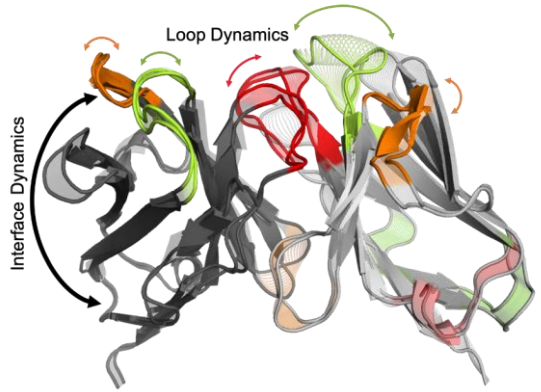
- Specific framework residues and different germline pairings result in different paratope states in solution.
- Antibody-antigen docking profits from reasonable ensembles in solution.



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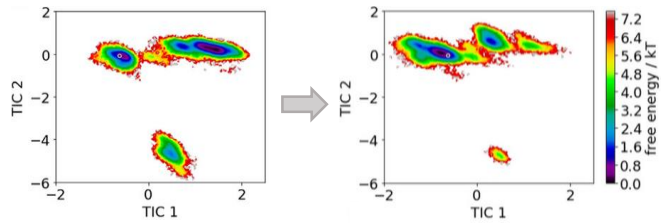

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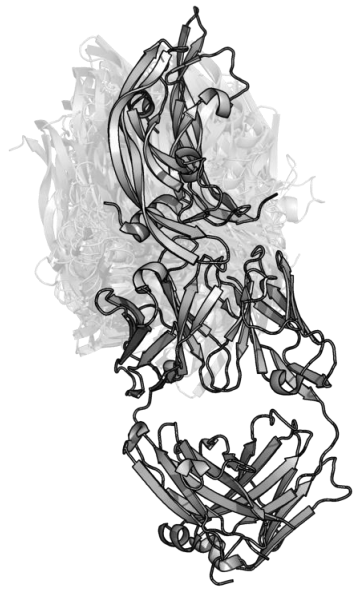

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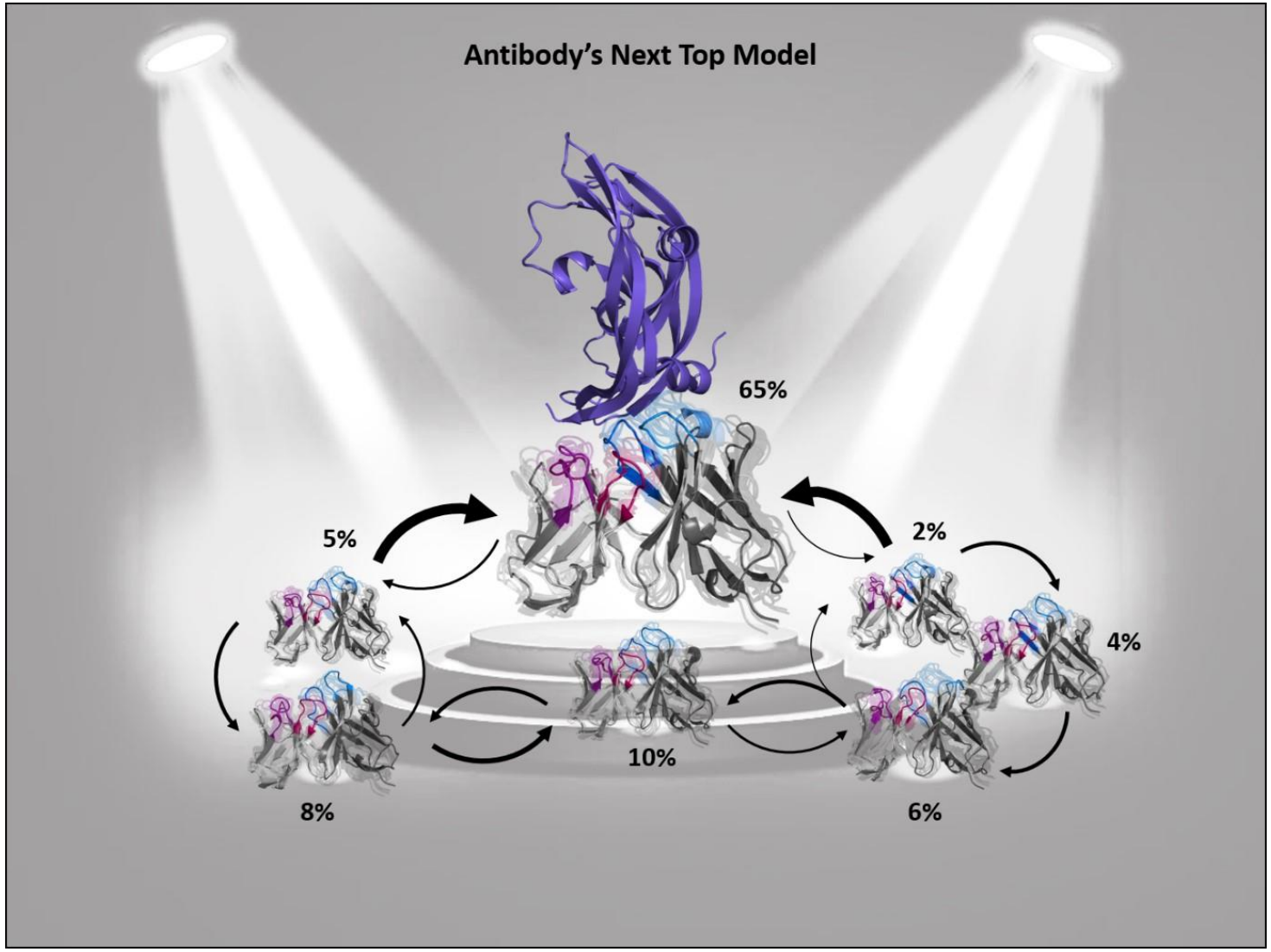

Acknowledgments

FWF Der Wissenschaftsfonds.

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