Simulating transition metal trafficking: the activation of urease

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Trieste, 26/05/2017

IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI

Nutrients and poisons

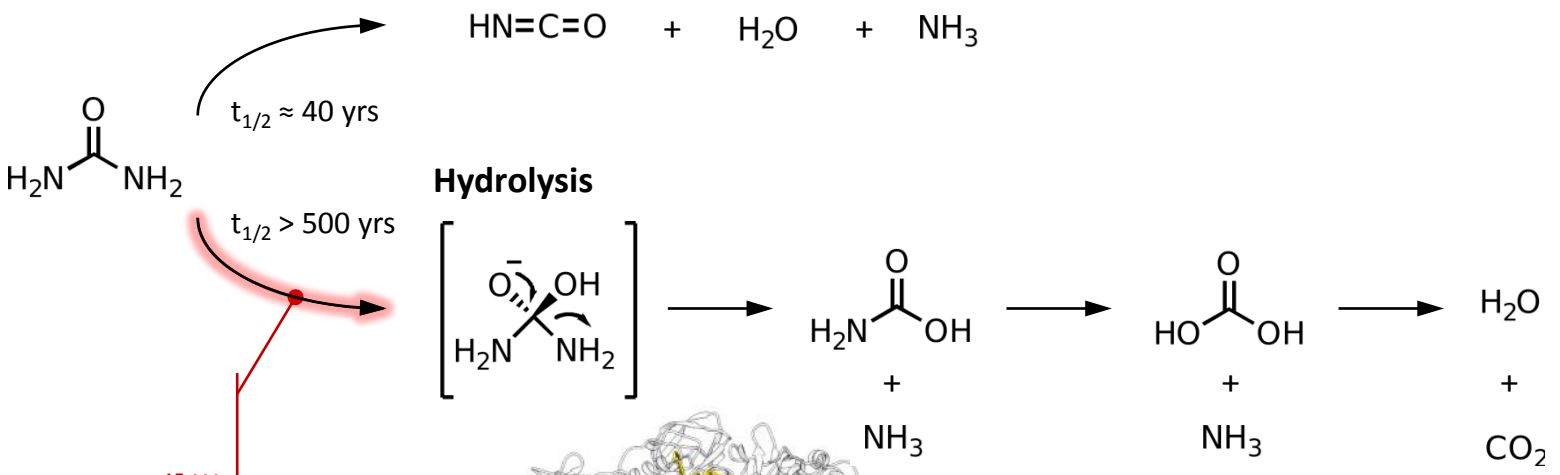
- Electric signalling
- DNA/RNA stabilization
- Catalysis

	1												13	14	15	16	17	18
1	H	2																He
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg	3	4	5	6	7	8	9	10	11	12	Al	Si	P	S	Cl	Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
6	Cs	Ba	*	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	**	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub	Uut	Uuq	Uup	-	-	-

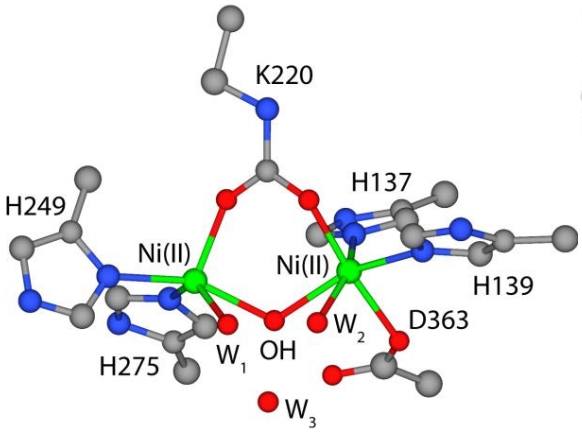
*	La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu
**	Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr

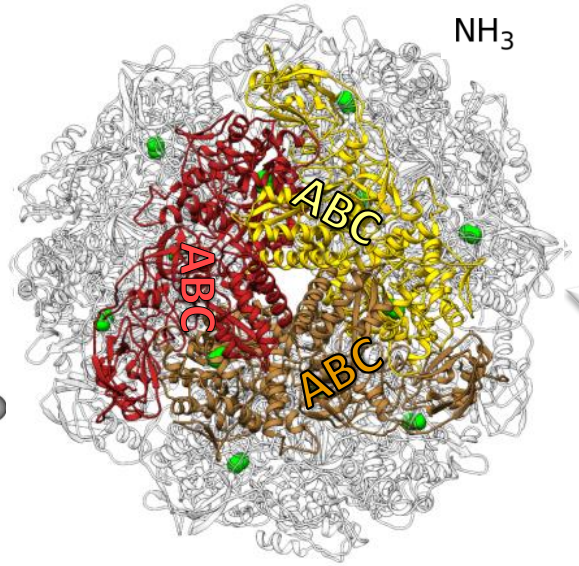
The fate of urea

Decomposition



Urease:
$t_{1/2} \approx 20$ μs
Rate enhancement > 10^{15} !!!



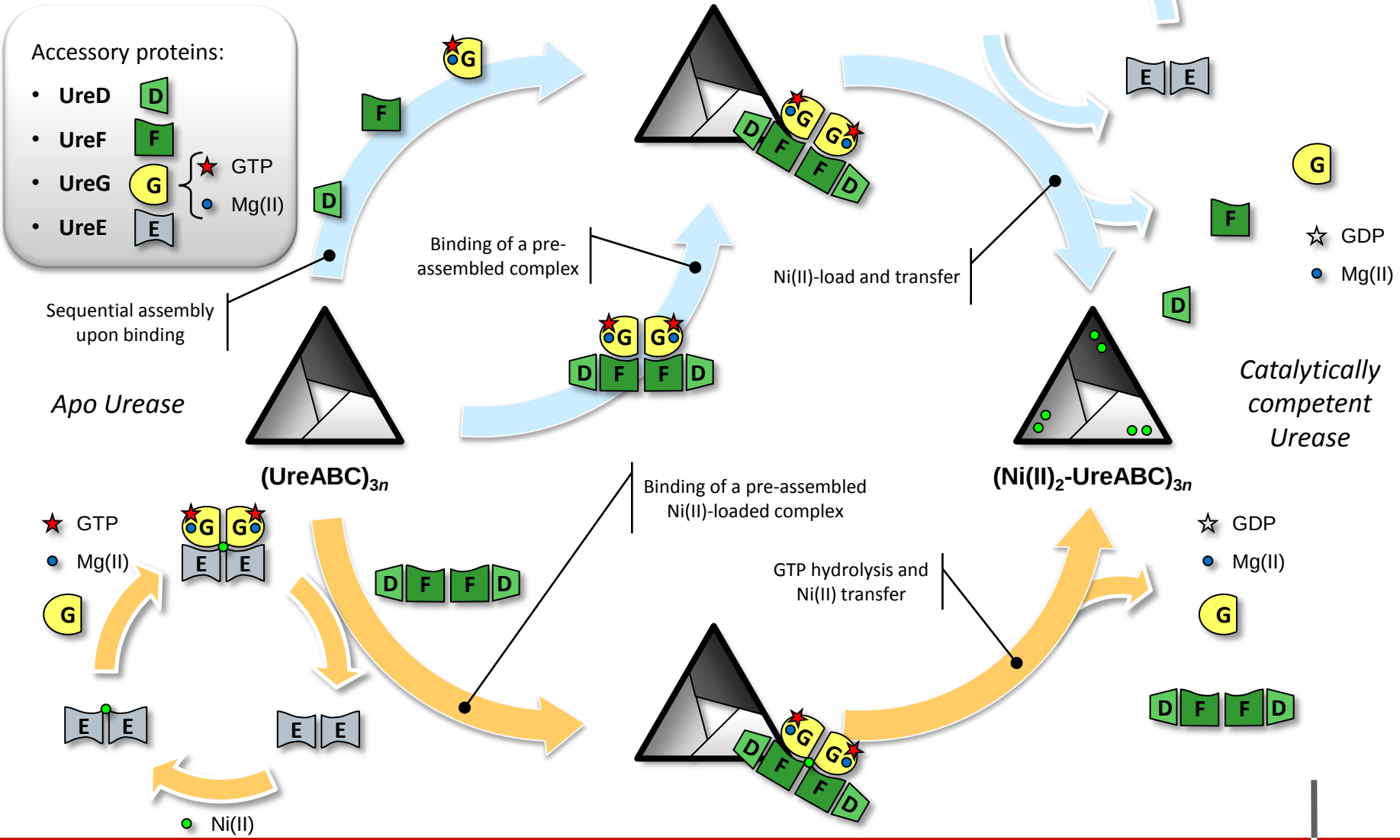


$(UreABC)_{3n}$

Where?

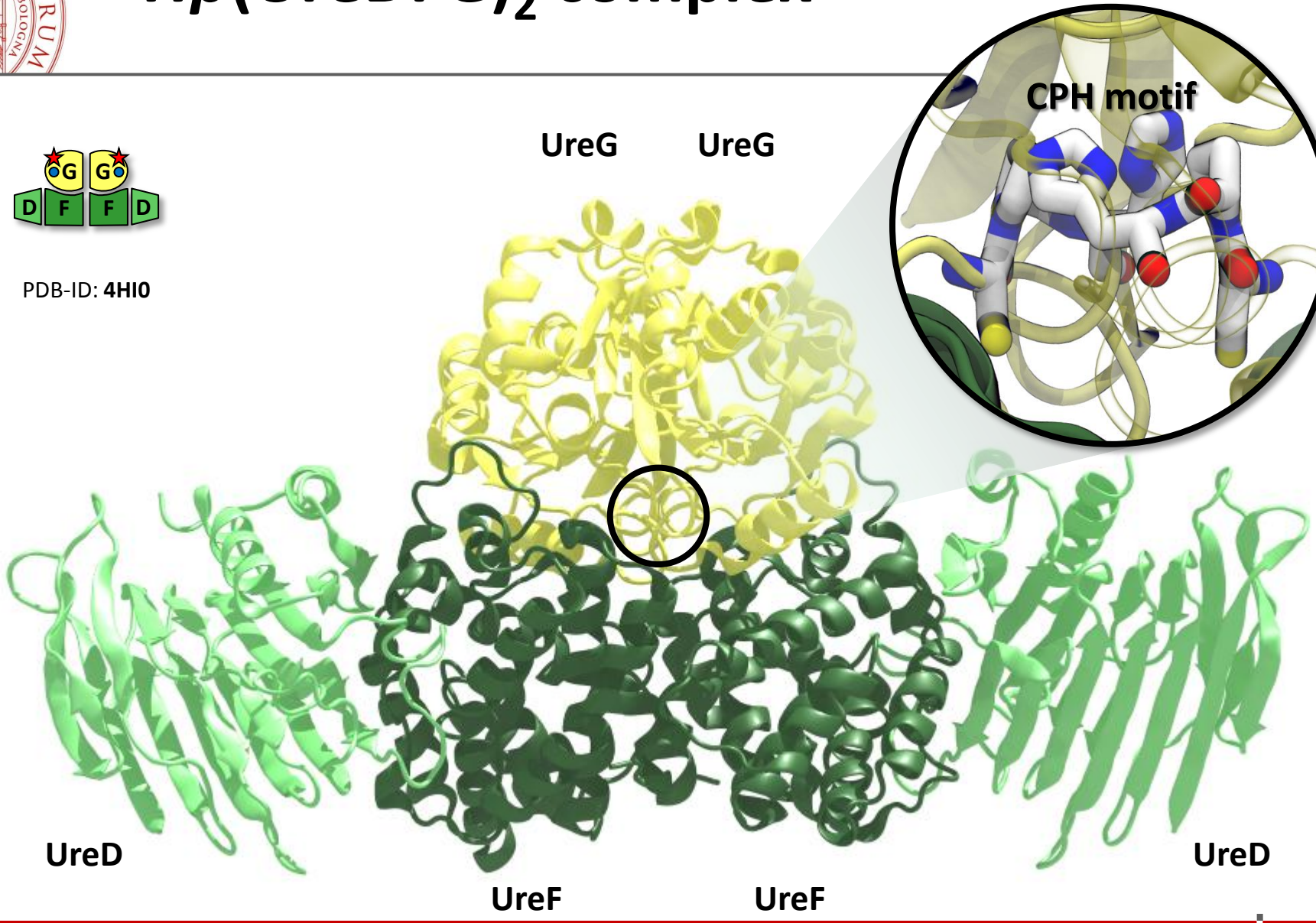
- **Plants, fungi, algae**
- **Ureolytic bacteria** (*H. pilori*, …)
- **Soil… everywhere!**

Activation of urease



Hp(UreDFG)$_2$ complex

PDB-ID: **4HI0**



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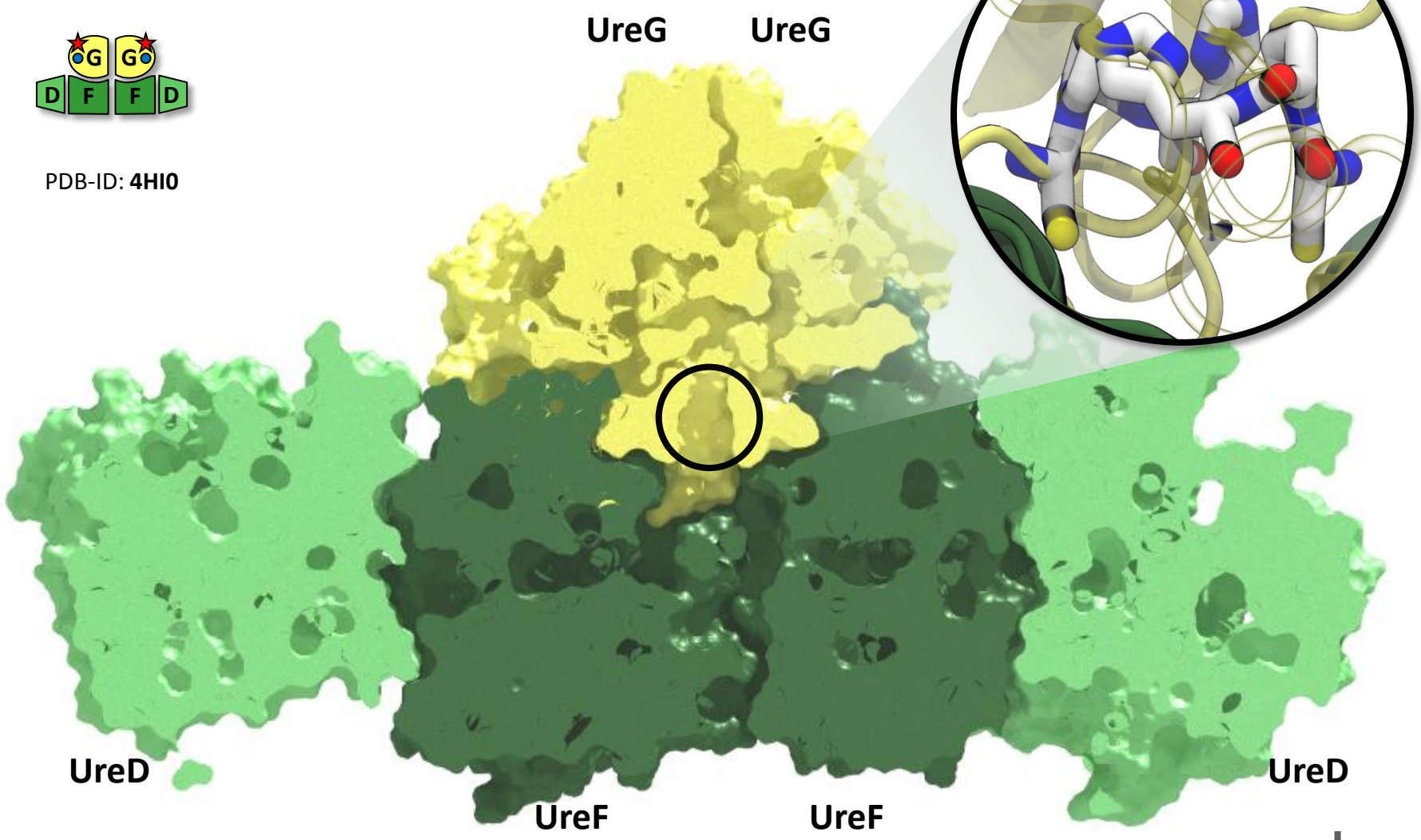
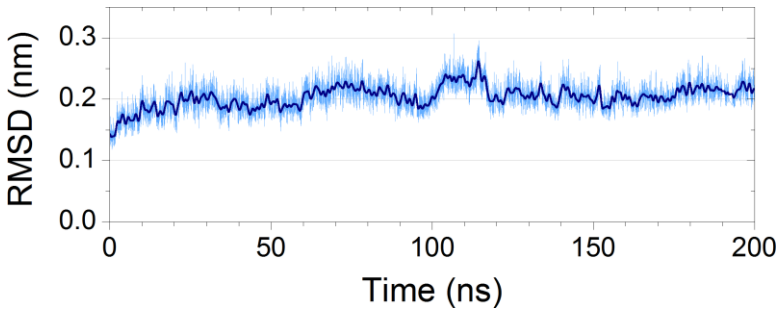


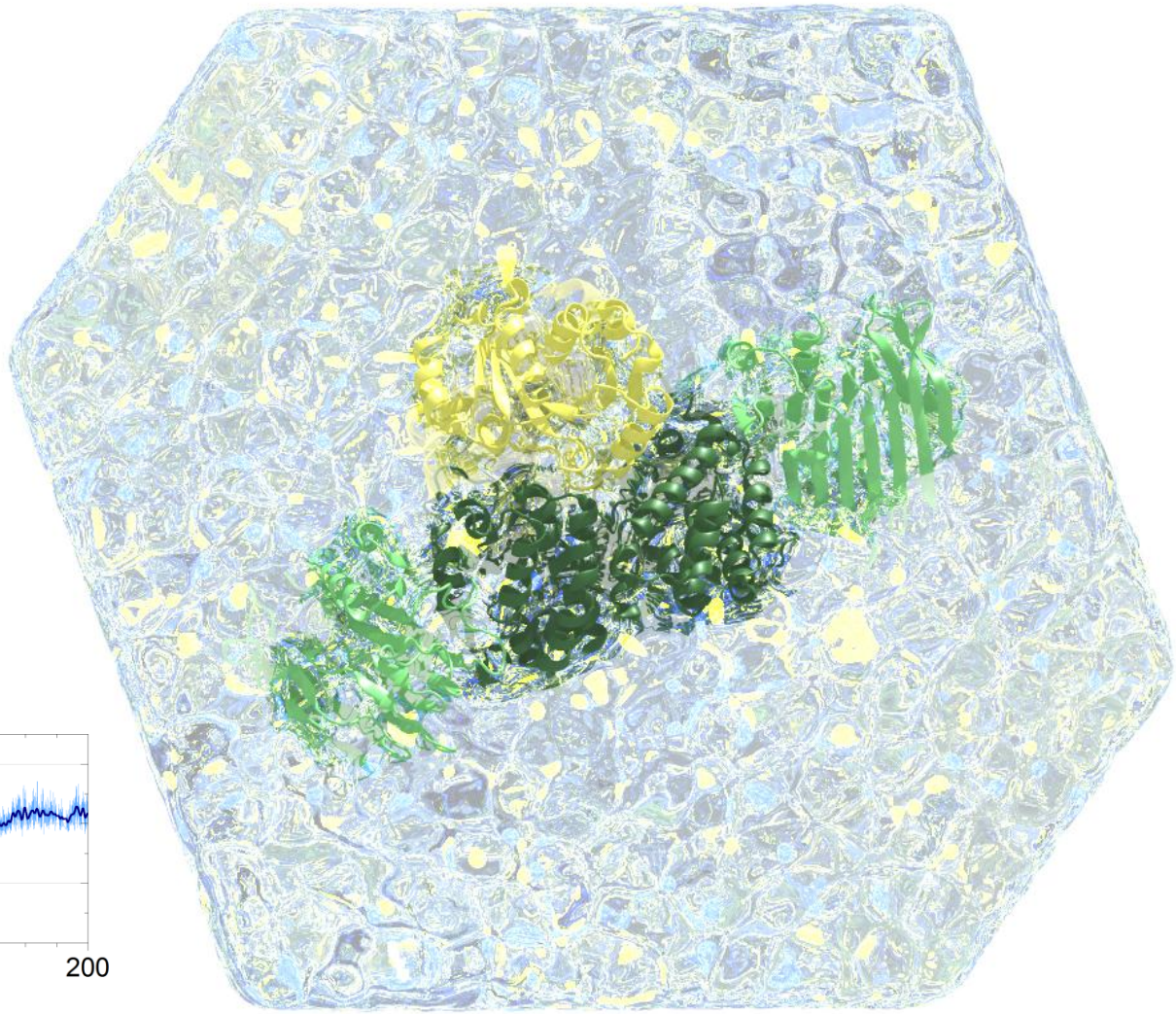
Zambelli B., Berardi A., Martin-Diaconescu V., Mazzei L., Musiani F., Maroney M., Ciurli S. *J. Biol. Inorg. Chem.* **2014,** 19, 319

Hp(UreDFG)$_2$ complex: dynamics

Computational setup:

- Total atoms: ca. 340,000
- AMBER99sb force field
- Explicit water (TIP3P)
- Ionic strength: 0.150 M
- NPT ensemble
- MD engine: Gromacs 4.6
- δt = 1.0 fs

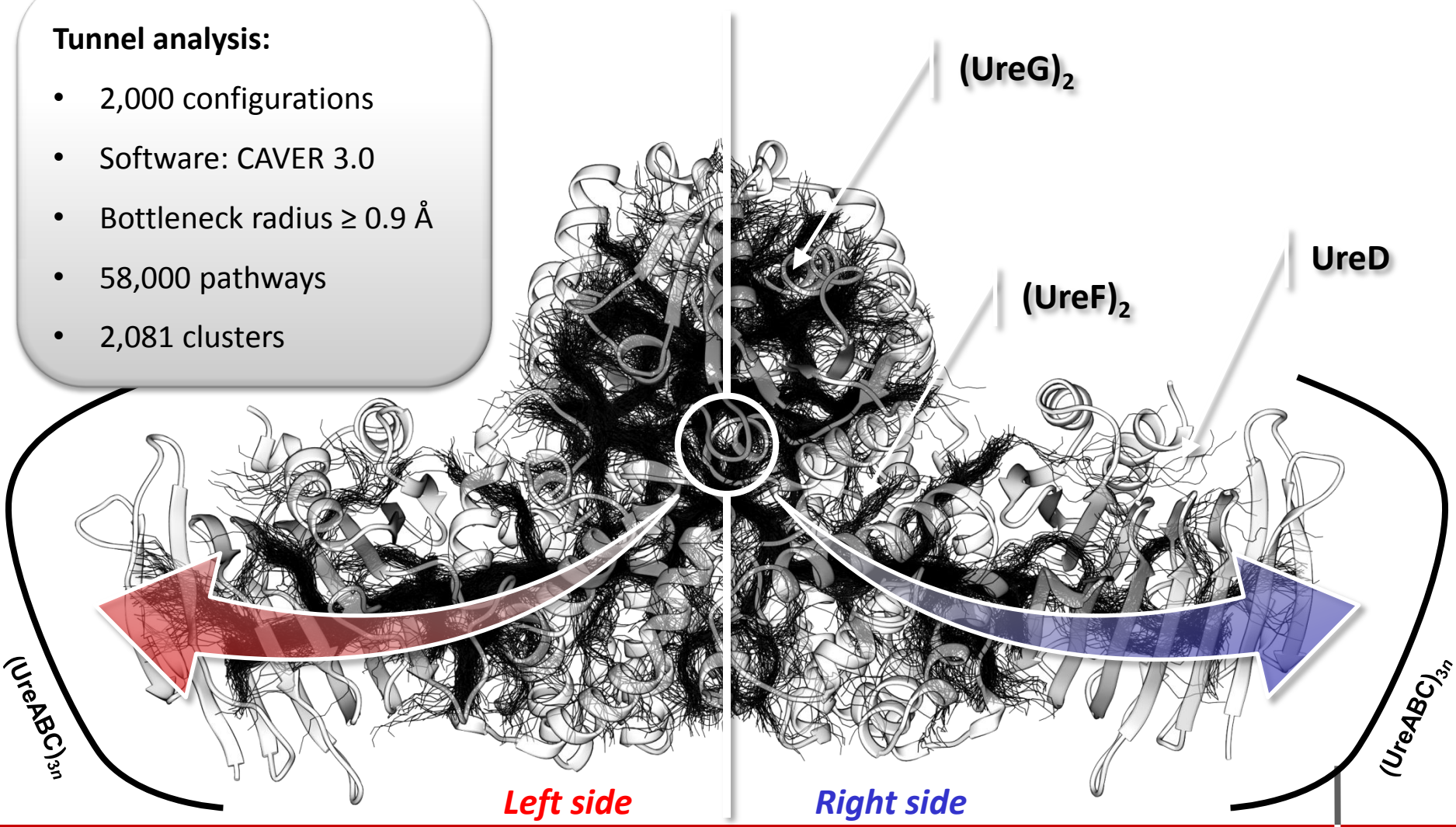




Hp(UreDFG)$_2$ complex: dynamics

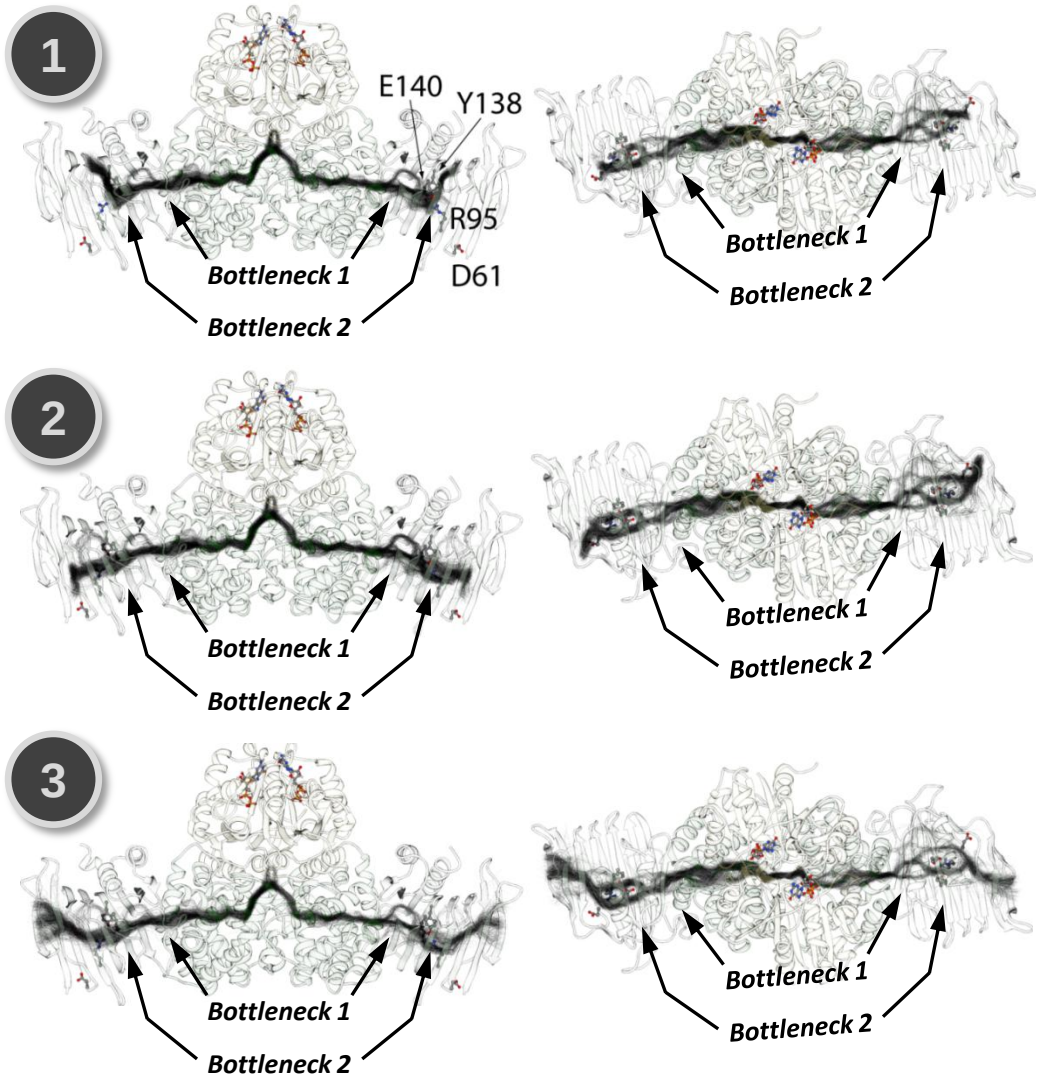
Tunnel analysis:

- 2,000 configurations
- Software: CAVER 3.0
- Bottleneck radius ≥ 0.9 Å
- 58,000 pathways
- 2,081 clusters

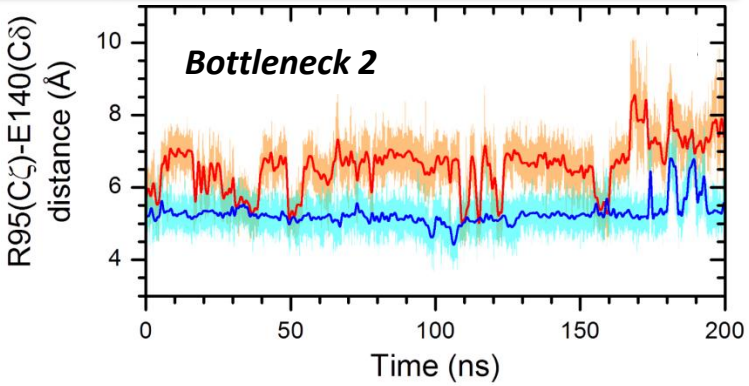


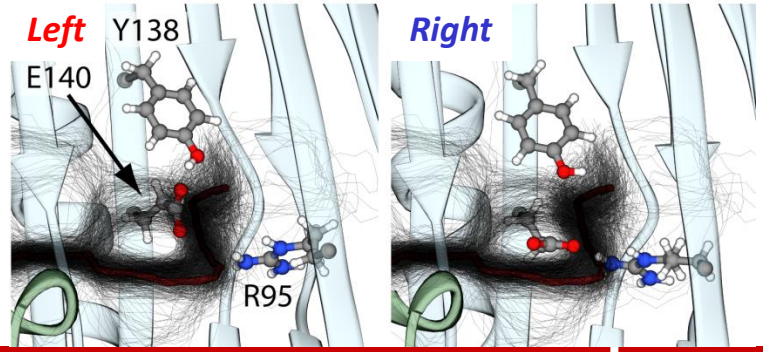
Musiani F., Gioia D., Masetti M., Falchi F., Cavalli A., Recanatini M., Ciurli S. *J. Chem. Theory Comput.* **2017,** 13, 2322

Routes and gateways



Tunnel no.	no. frames (left/right)	Persistence	Av. length (Å) (left/right)
1	1745/534	57%	78/80
2	1457/678	53%	86/89
3	831/331	29%	95/98
4	228/103	8%	77/69
5	269/20	7%	97/115





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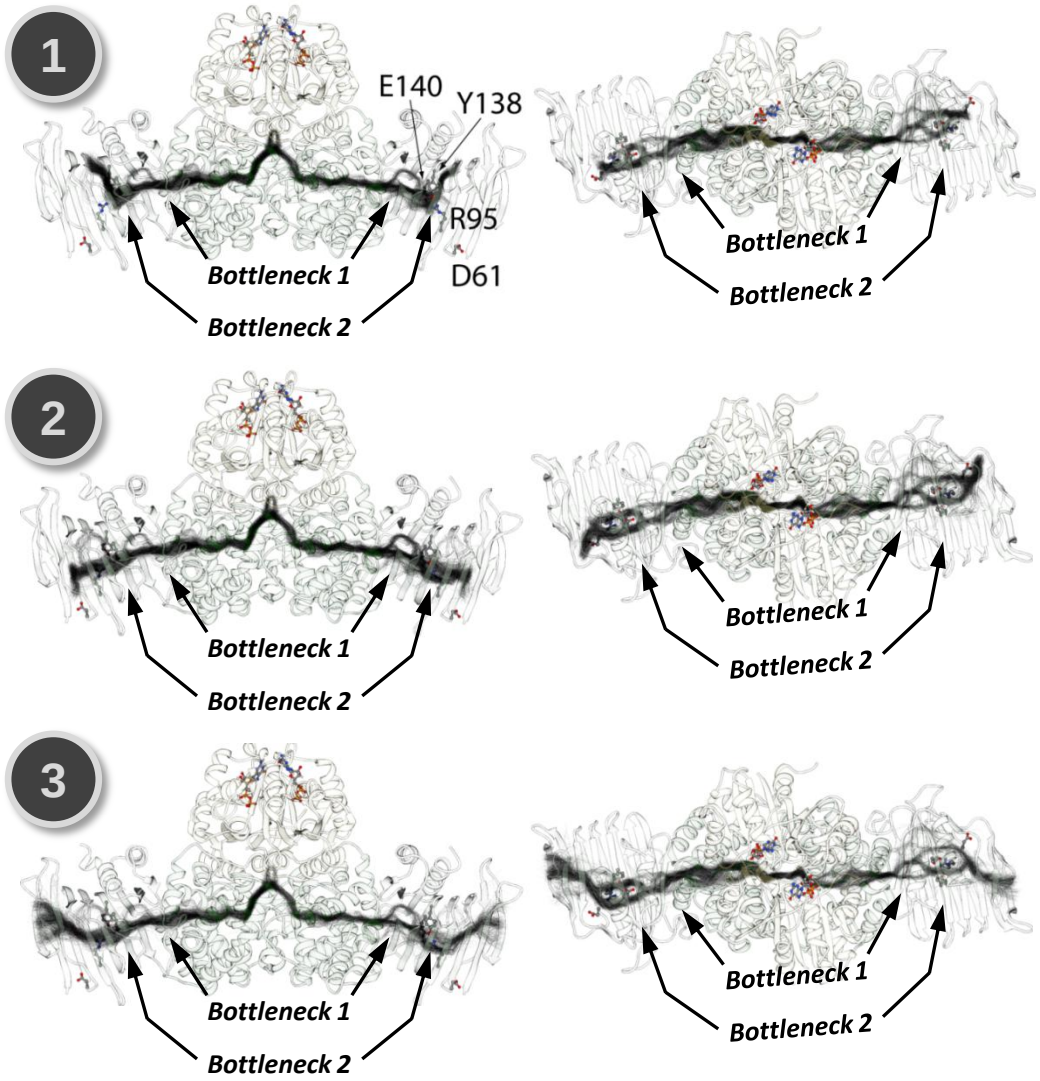

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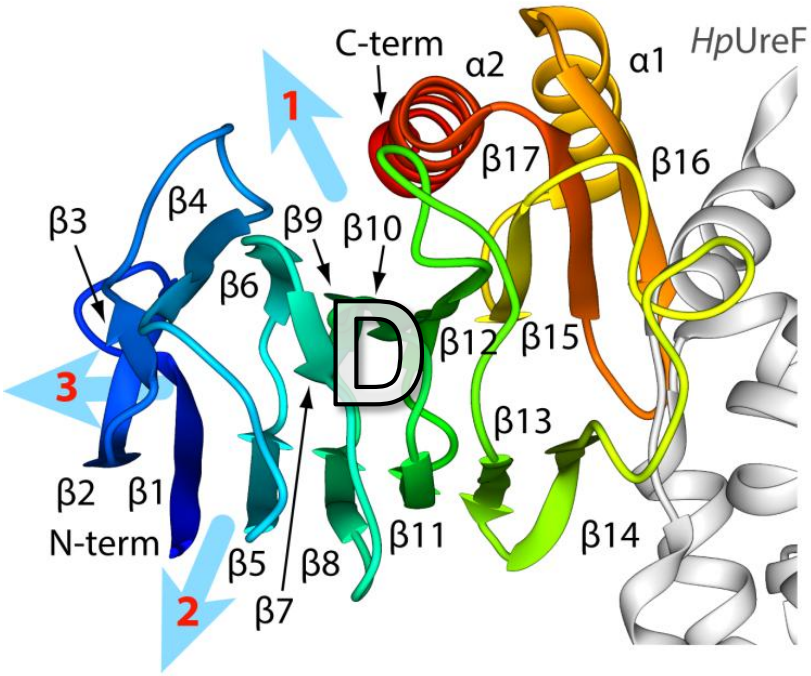
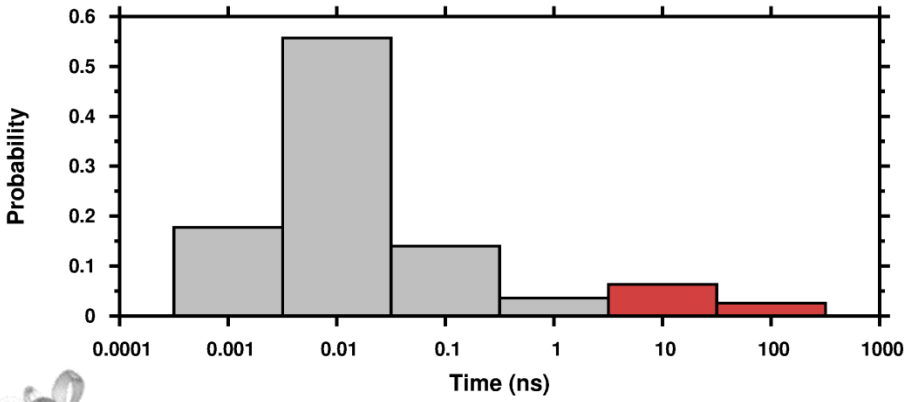
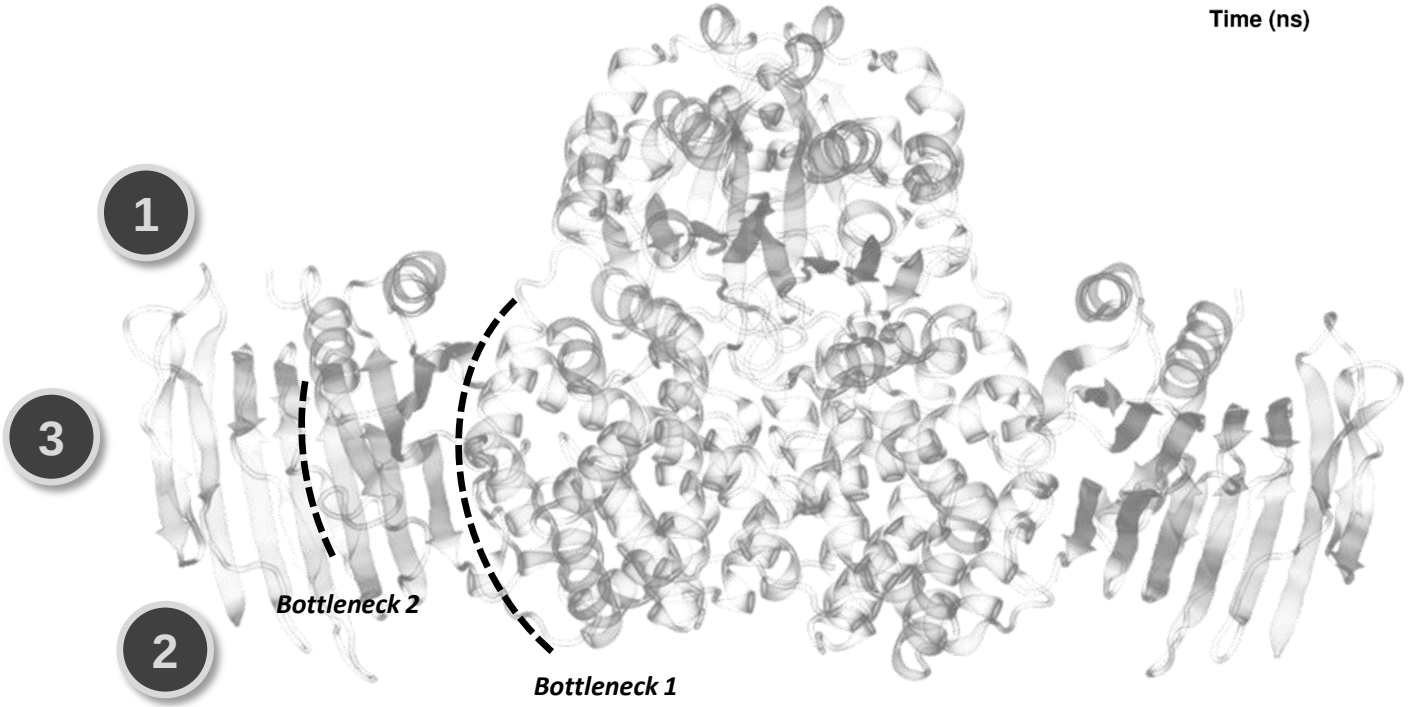


Water transport

Water molecules:

- Total: 108,896
- Passing through bottleneck 2: 511





Water transport

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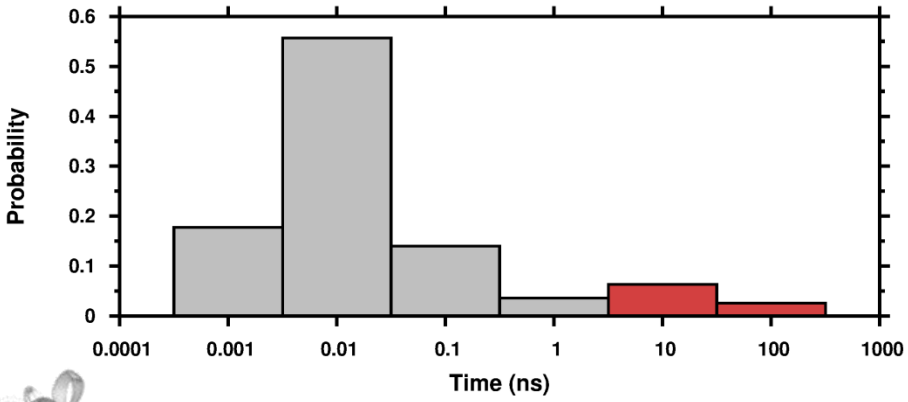
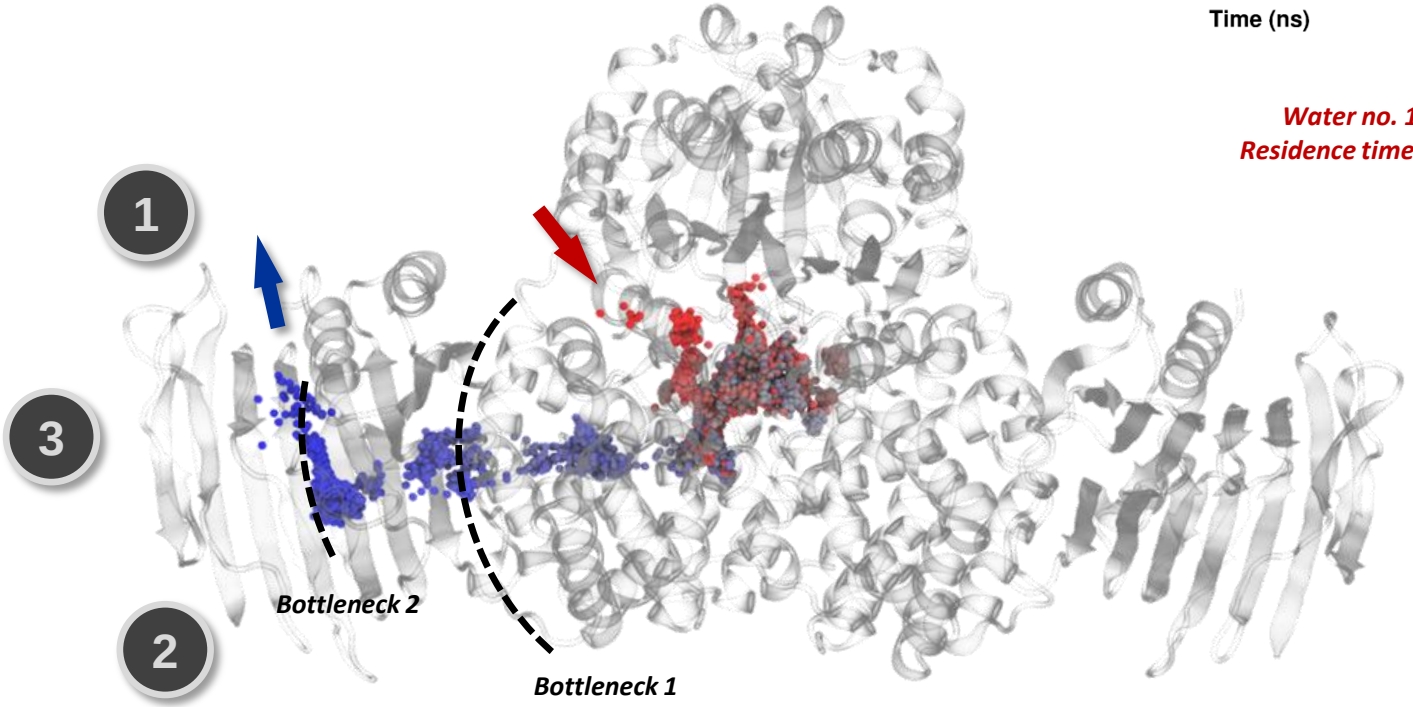


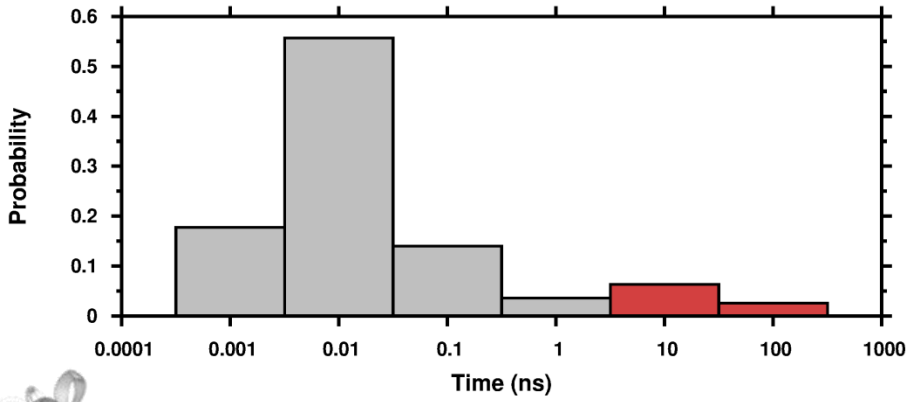


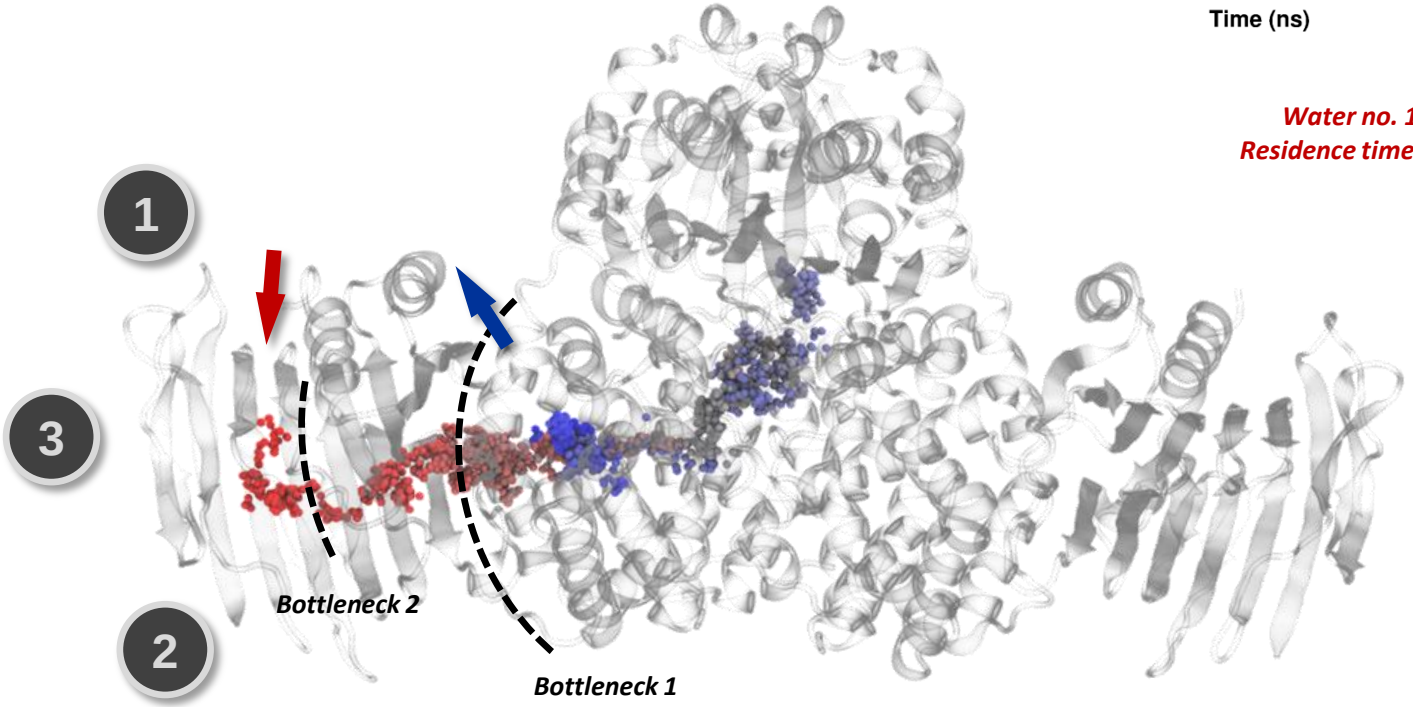
Water no. 131
Residence time: 55 ns

Water transport

Water molecules:

- Total: 108,896
- Passing through bottleneck 2: 511



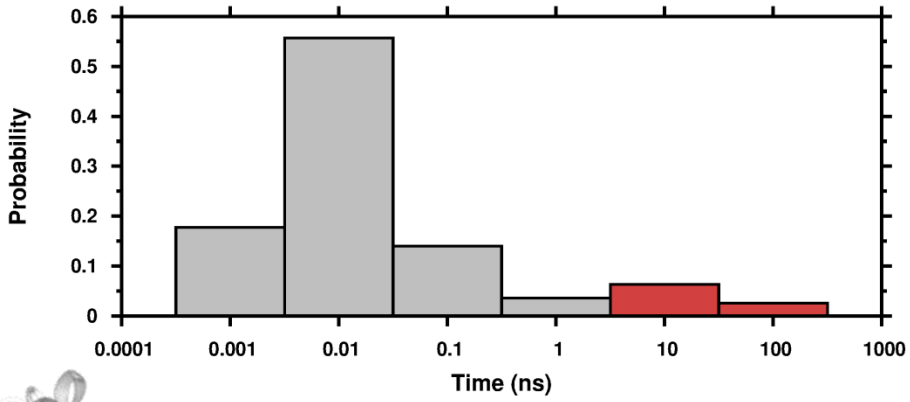


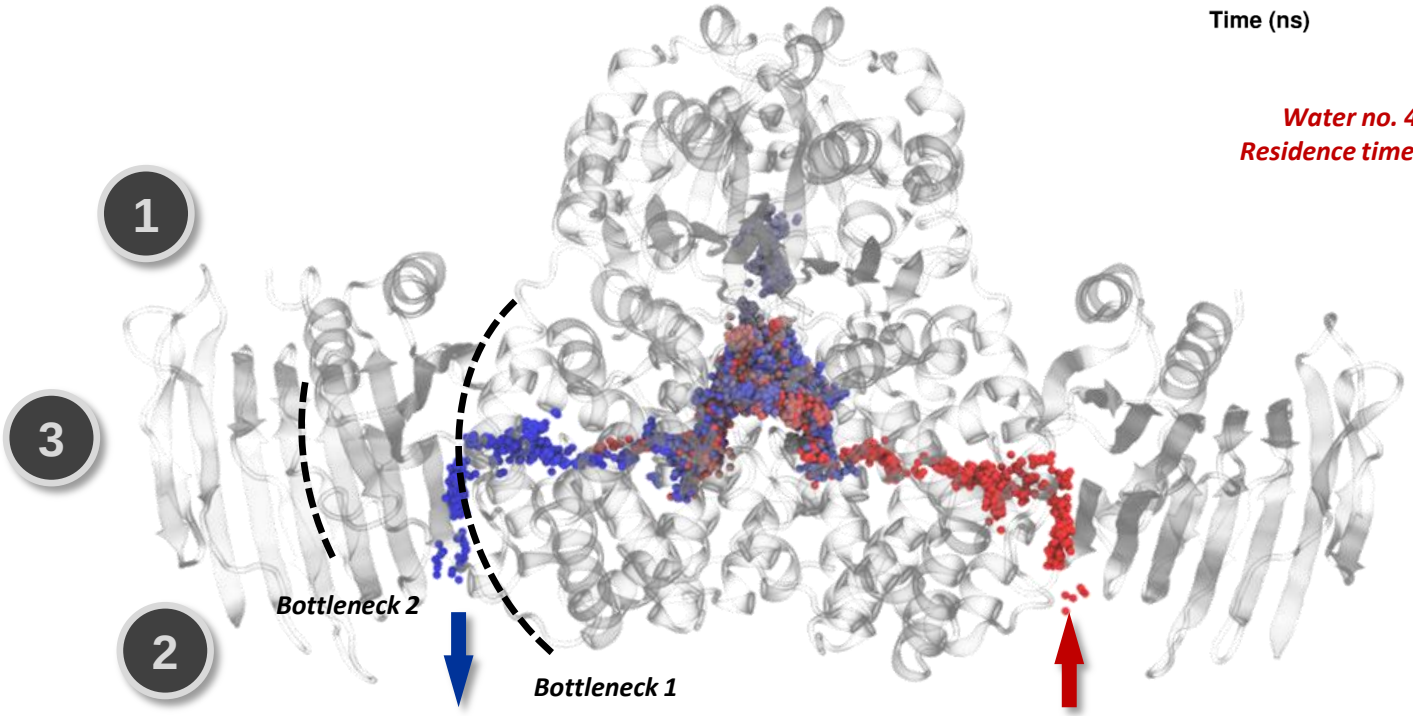
Water no. 136
Residence time: 85 ns

Water transport

Water molecules:

- Total: 108,896
- Passing through bottleneck 2: 511

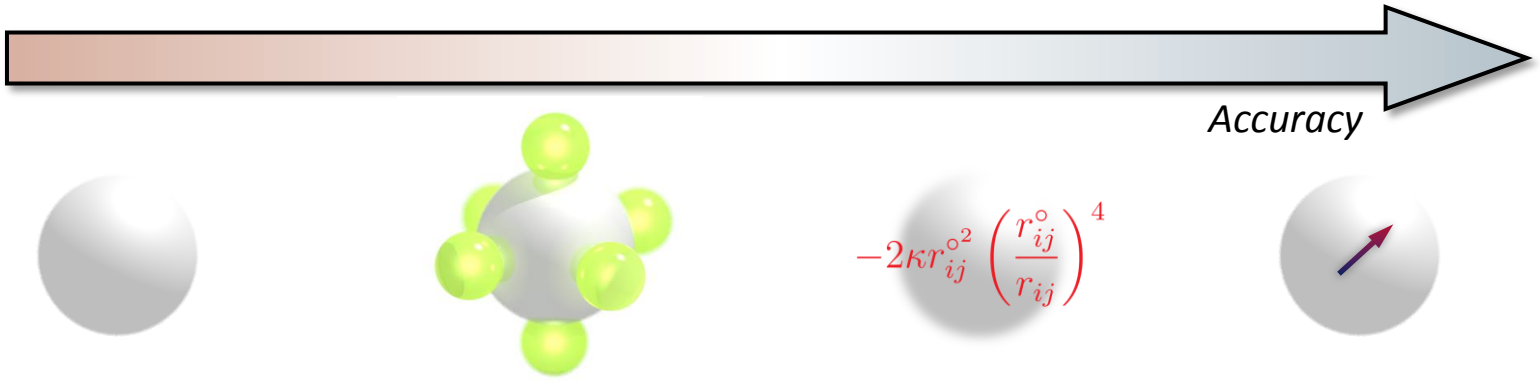




Water no. 477
Residence time: 24 ns

Models and observables

- **Classical mechanics ion models and available Ni(II) parameterizations**



12-6 LJ models

Multisite ("dummy") models

12-6-4 LJ model

Polarizable models

- Won Y. *J. Phys. Chem. A* **2012**, 116, 11763
- Li P., et al. *J. Chem. Theory Comput.* **2013**, 9, 2733

- Li P. and Merz K.M. Jr. *J. Chem. Theory Comput.* **2014**, 10, 289

- Duarte F. et al. *J. Phys. Chem. B* **2014**, 118, 4351
- Jiang Y., et al. *J. Chem. Theory Comput.* **2016**, 12, 3250

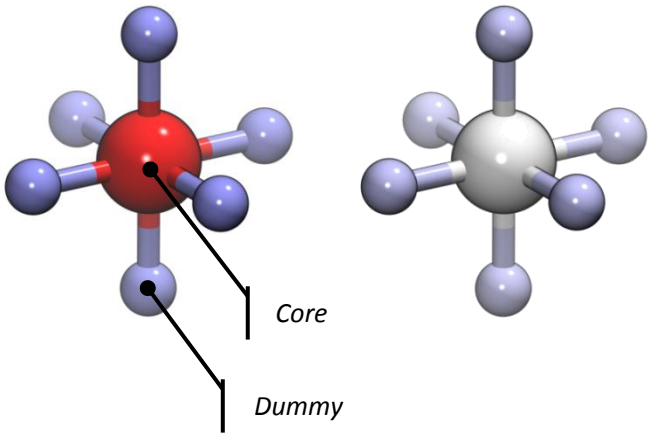
- **Commonly targeted observables**

Metal-oxygen distance	2.06 ± 0.01 Å
Coordination number	6
(Intrinsic) free energy of solvation	–473.2 kcal mol^{-1}

- Marcus Y. *Chem. Rev.* **1988**, 88, 1475
- Marcus Y. *J. Chem. Soc. Faraday Trans.* **1991**, 87, 2995

How many degrees of freedom?

- **Divalent octahedral ion**



$$V_{LJ} = \epsilon_{ij}\left[\left(\frac{r^{\circ}_{ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r^{\circ}_{ij}}{r_{ij}}\right)^{6}\right]$$

$$V_{LJ} = \frac{A_i A_j}{r_{ij}^{12}} - \frac{B_i B_j}{r_{ij}^{6}}$$

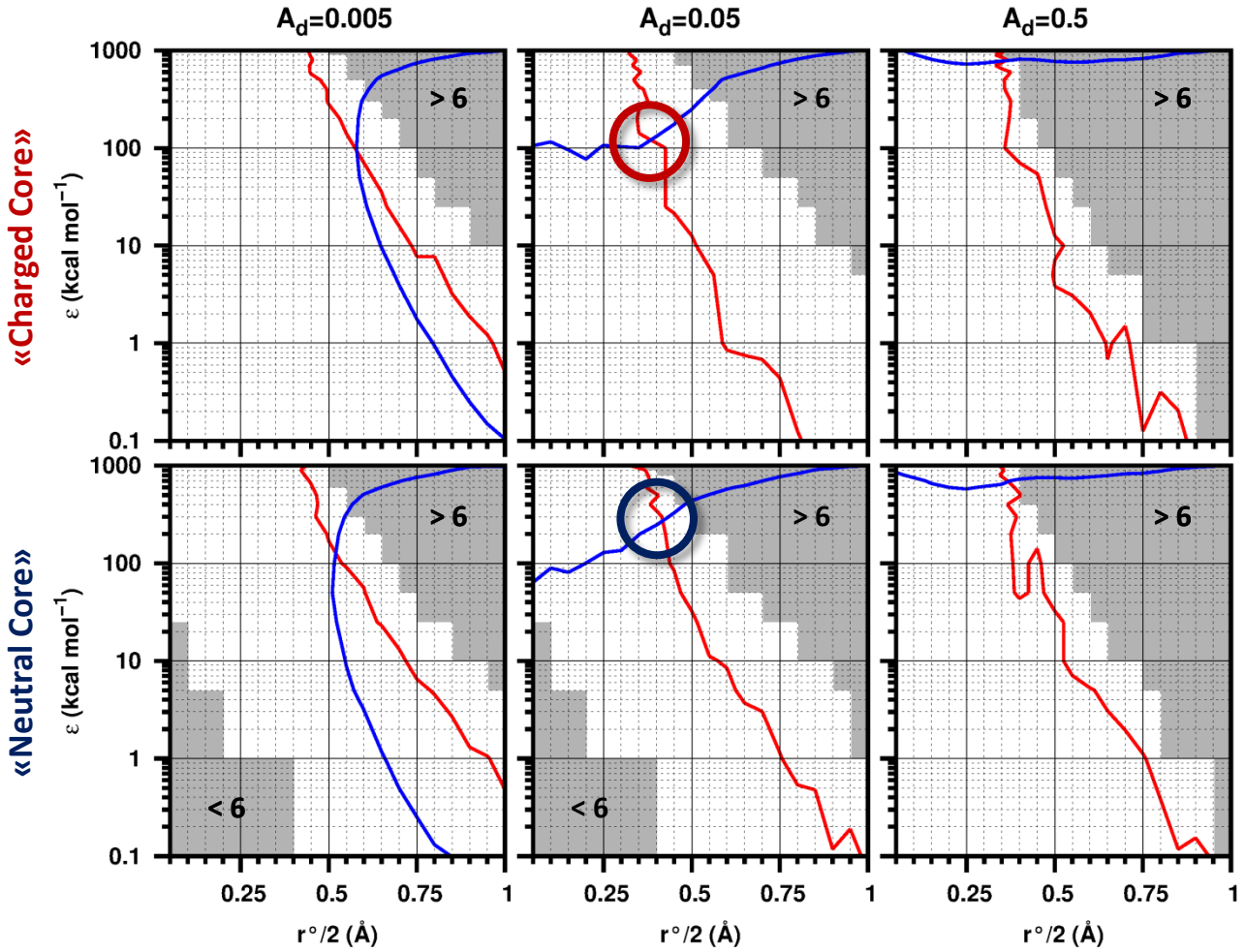
$$A_i = \sqrt{\epsilon_{ii}\left(r^{\circ}_{ii}\right)^{12}}$$

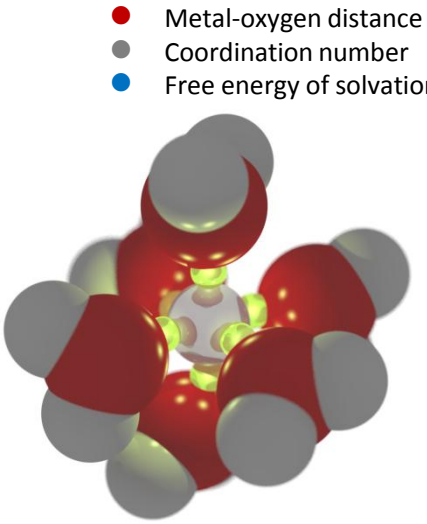
$$B_i = \sqrt{2\epsilon_{ii}\left(r^{\circ}_{ii}\right)^{6}}$$

d.o.f.	Customary choices
Mass	$m_c = A - 6m_d$ $m_d = 3.0$ u
Bonded parameters	• Oelschlaeger P. et al. *J. Mol. Biol.* **2007**, 366, 687
Partial charges	$q_c = Z - 6q_d$ $\quad q_d = 0.5$, $q_c = -1.0$ «Charged Core» $\quad q_d = 0.33333$, $q_c = 0.0$ «Neutral Core»
L-J parameters	$A_d = 0.05$ kcal$^{1/2}$ mol$^{1/2}$ Å^6 $\quad$ { $A_{0.5}$, $A_{0.05}$, $A_{0.005}$ } $B_d = 0.00$ kcal$^{1/2}$ mol$^{1/2}$ Å^3 ε_c / $r^{\circ}_c/2$ $\quad$ A_c / B_c $\quad$ *optimized*

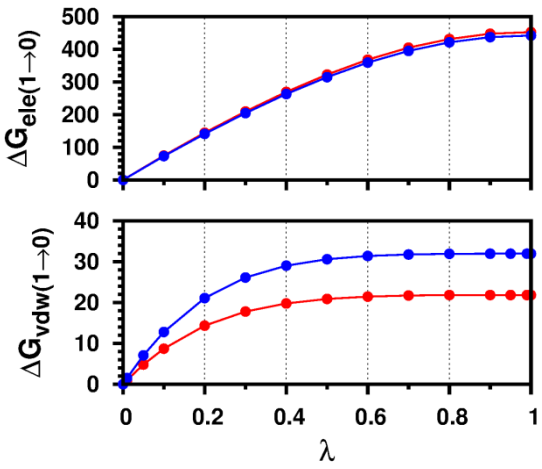
Parameter space scanning

- **Finding intersection points**



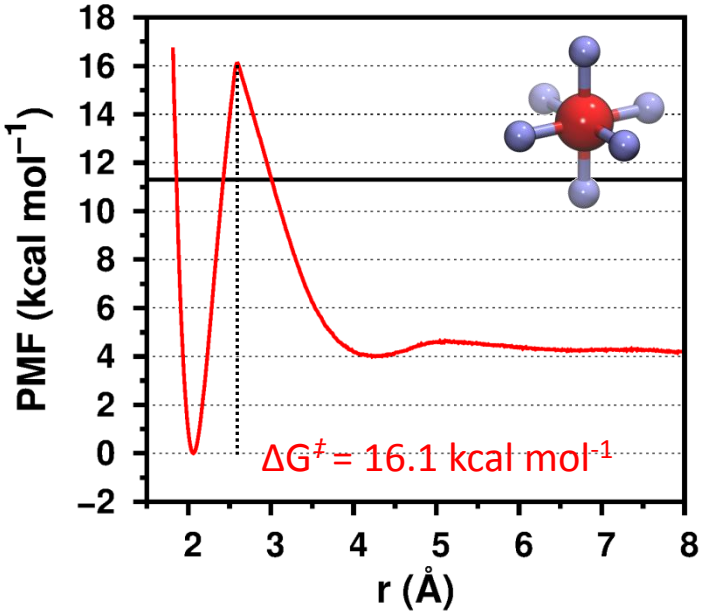


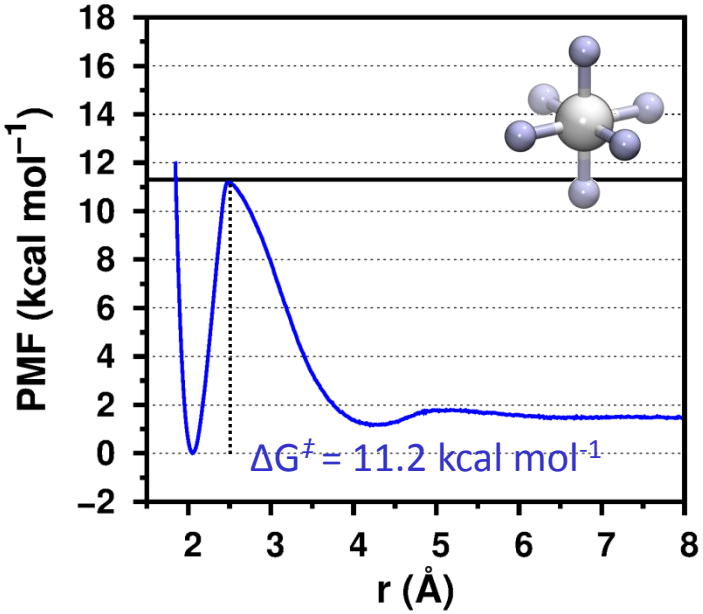
- **Focusing procedure**



Validation of the models

- **Can we reproduce the nickel-water exchange rate?**





$$k_{ex} = \frac{1}{2\pi}\sqrt{\frac{W_0''}{\mu}}\, e^{-\frac{\Delta G^{\ddagger}}{k_B T}}$$

$k_{ex} = 2.0 \cdot 10^{1}$ s^{-1}

$k_{ex} = 7.7 \cdot 10^{4}$ s^{-1}

Expl. $k_{ex} = 1.6 \cdot 10^{4}$ s^{-1}

- Frey C. M. and Stuehr J. E. *J. Am. Chem. Soc.* **1972**, 94, 9989

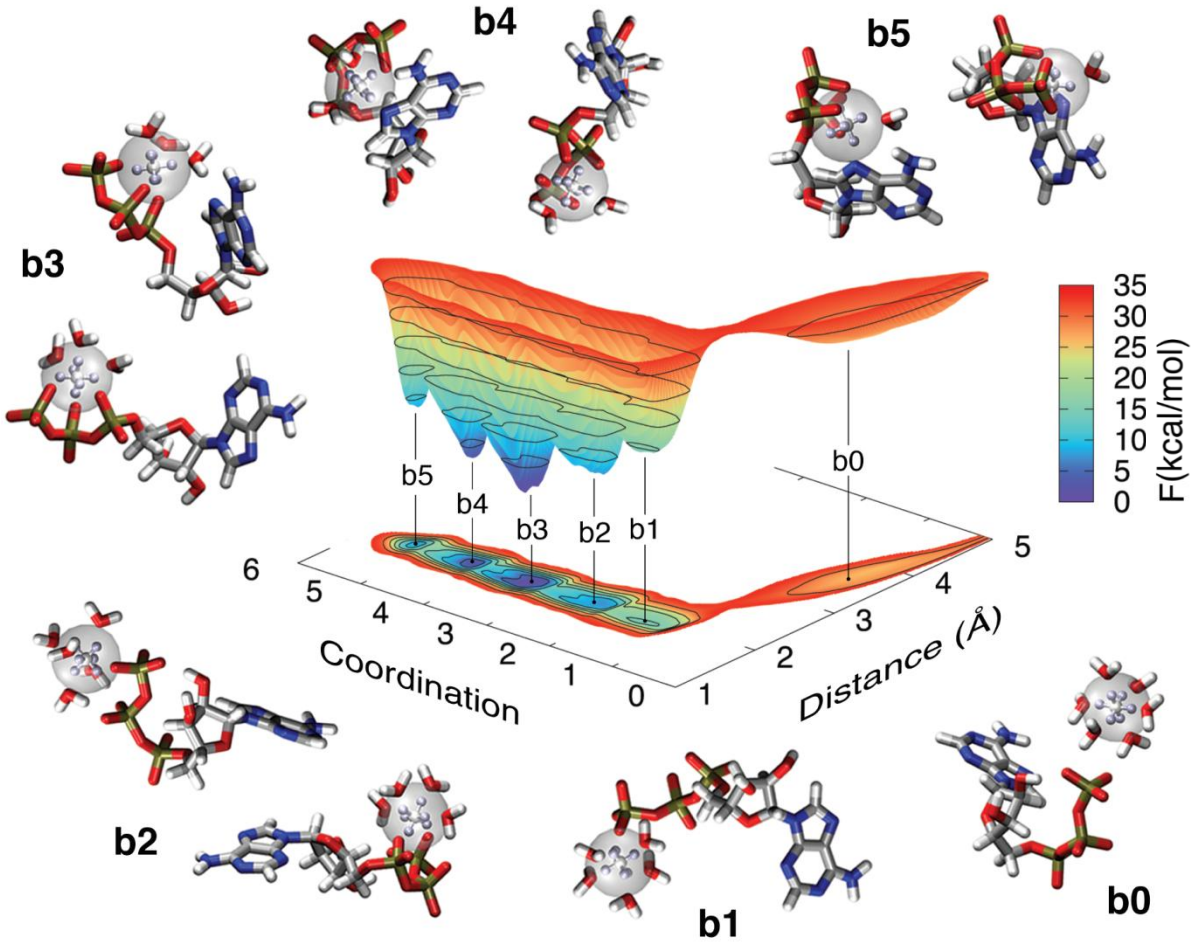
Validation of the models

- **A real life complexation study (ATP-Ni(II))**

- **Metadynamics at last!**

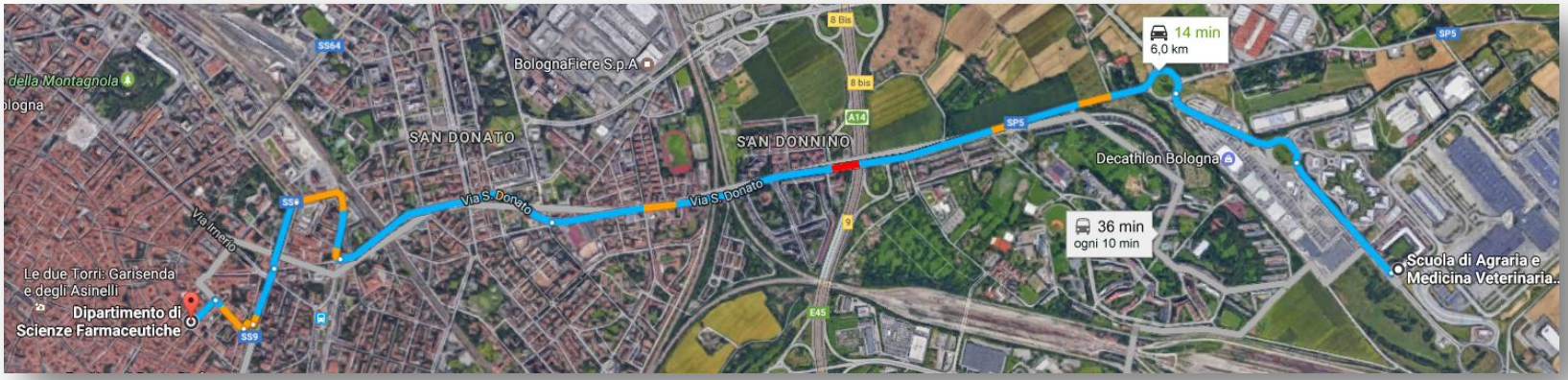
$$\begin{cases} s_1 = \dfrac{\beta}{\log \sum_{ij} \mathrm{e}^{\frac{\beta}{r_{ij}}}} \\ s_2 = \sum_i \sum_j \dfrac{1-\left(\frac{r_{ij}}{r_0}\right)^n}{1-\left(\frac{r_{ij}}{r_0}\right)^m} \end{cases}$$

- **Adaptive Gaussians**



Acknowledgments

Department of Pharmacy and Biotechnology



Laboratory of Computational Medicinal Chemistry

- Prof. Maurizio Recanatini

- Dario Gioia — Tunnel and water analysis
- Mattia Bernetti — Ni models validation
- Martina Bertazzo — Tunnel clustering

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- Riccardo Ocello
- Dott. Maria Ferraro
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- Dott. Francesco Musiani

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