A pH replica exchange scheme coupled to the stochastic titration constant pH MD method

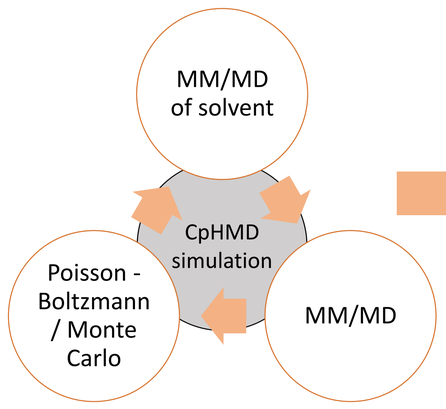
Diogo Vila-Viçosa[1], Chris Oostenbrink[2] and Miguel Machuqueiro[1]

[1]*Centro de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, 1749-016 Lisboa, Portugal;*
[2]*Institute of Molecular Modeling and Simulation; University of Natural Resources and Life Sciences*

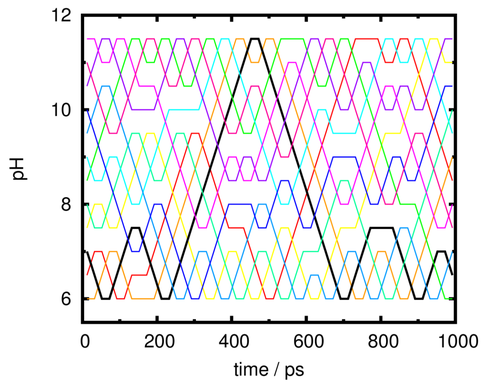
email: diogo.vicosa@fc.ul.pt *www: http://intheochem.fc.ul.pt/Members/diogovv.html*

Goal

- Implement a pH replica exchange (**pHRE**) scheme within the stochastic titration constant-pH molecular dynamics (**CpHMD**) framework



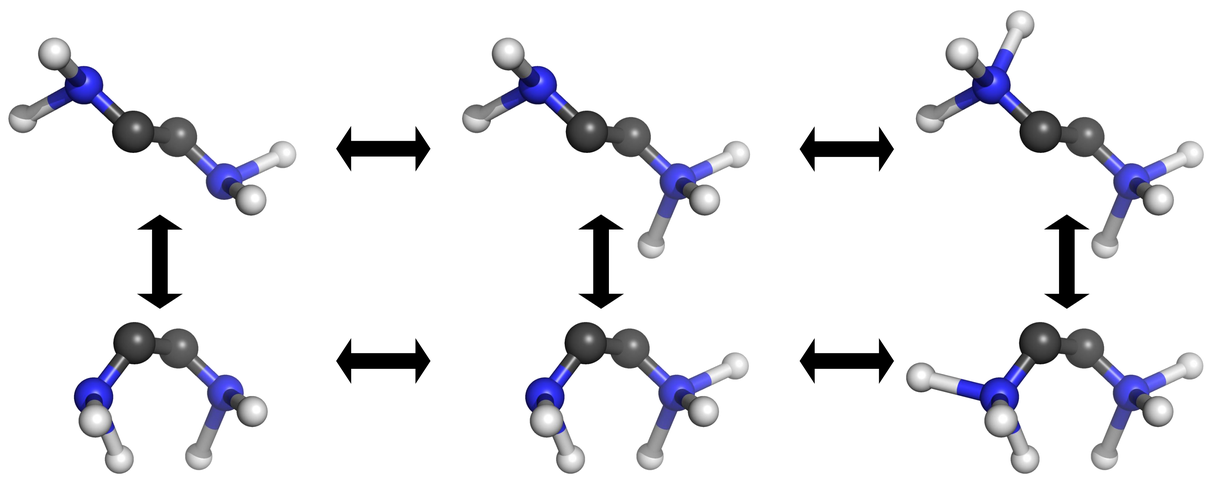
Methods

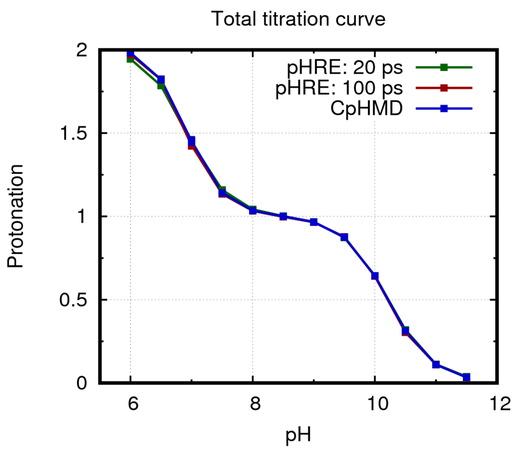


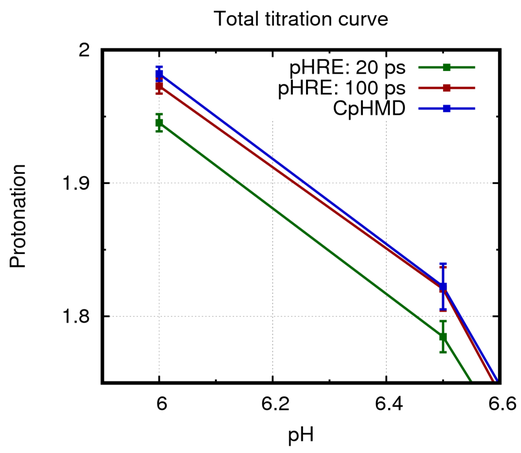
- GROMACS 4.0.7 (MM/MD)
- GROMOS 54a7 force field
- DelPhi (Poisson - Boltzmann)
- PETIT (Monte Carlo)
- 2 pHRE freq. (20 and 100 ps)

$$p = min(1, e^{-\ln 10(\mathrm{pH}_2 - \mathrm{pH}_1)(N_1 - N_2)})$$

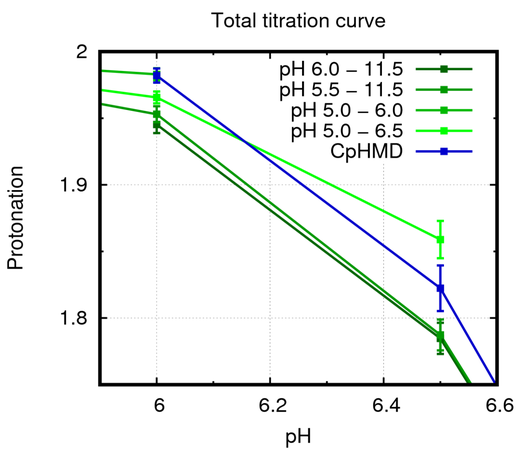
Ethylenediamine

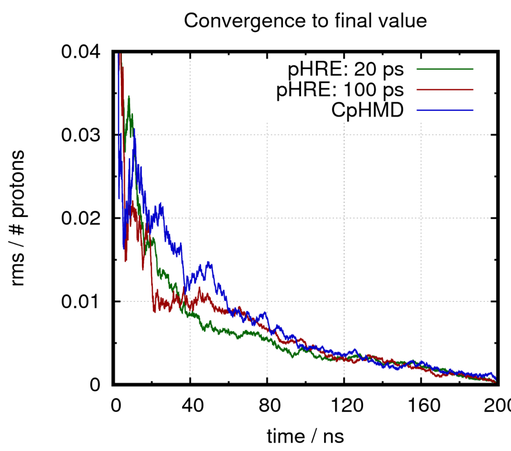






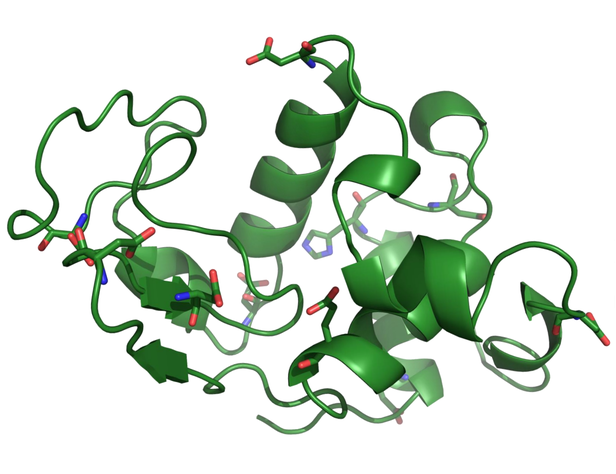
- The titration curves are almost identical
- pHRE frequency has a small influence

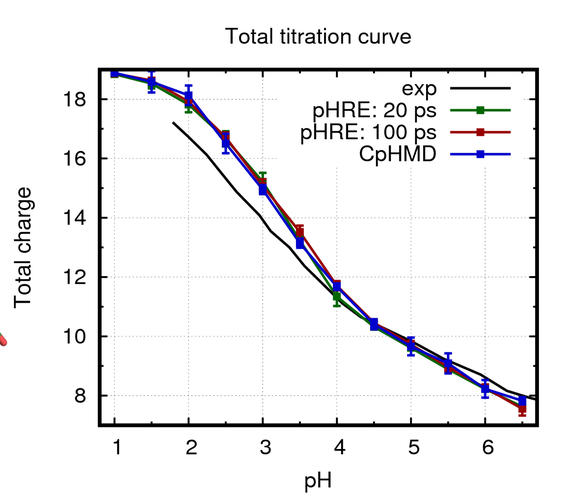




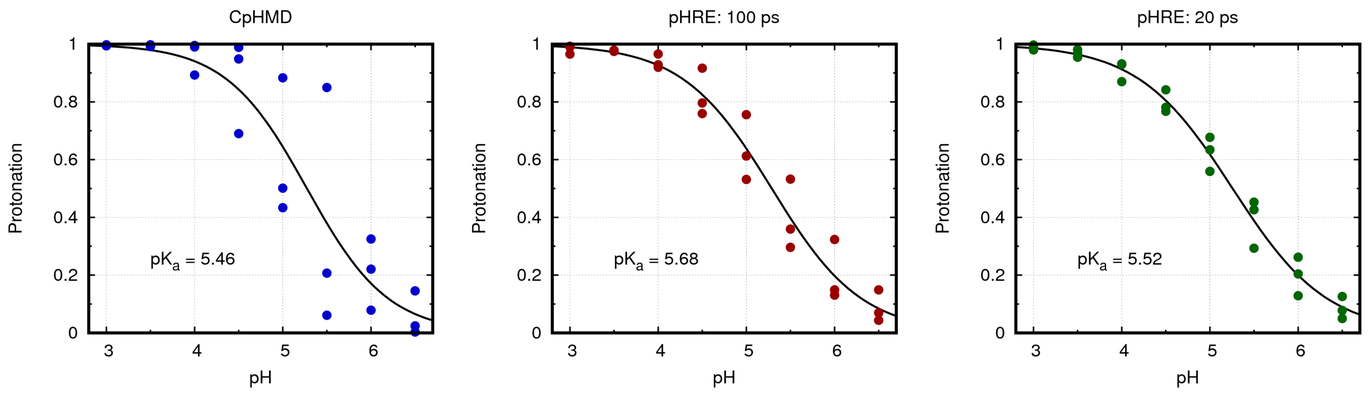
- The effective number of exchanges must be carefully chosen
- In this small system, convergence speed is similar

Hen egg-white Lysozyme

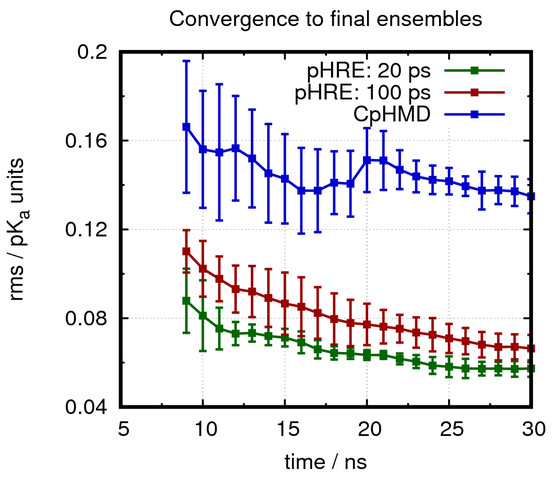




- Titration curves and individual pK_a values are very similar
- In a complex system, pHRE frequency do not show a significant effect



Residue	Experimental	CpHMD	pHRE: 100 ps	pHRE: 20 ps
Glu 7	2.85	3.38	3.36	3.34
His 15	5.36	5.49	5.43	5.43
Asp 18	2.66	3.64	3.65	3.57
Glu 35	6.20	5.46	5.68	5.52
Asp 48	1.60	2.09	2.11	1.95
Asp 52	3.68	3.92	4.01	3.85
Asp 66	0.90	3.12	3.20	3.15
Asp 87	2.07	2.30	2.26	2.31
Asp 101	4.09	3.90	3.98	3.77
Asp 119	3.20	2.72	2.73	2.80
C-Ter	2.75	3.20	3.22	3.24
RMSE	-	**0.83**	**0.83**	**0.82**



pHRE simulations convergence is significantly faster

Conclusions / Future Perspectives

☑ pH dependent conformational spaces are equivalent in both approaches

☑ The choice of pHRE frequency is determinant for the success of this approach

☑ The convergence of the titration curves is faster in pHRE schemes

☑ Can be applied to more challenging systems (water / membrane interface, for example)

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