The Abdus Salam International Centre for Theoretical Physics

ICTP-SISSA-CECAM Workshop on Molecular Dynamics and its Applications to Biological Systems | (SMR 3627)

13 Sep 2021 - 17 Sep 2021
Virtual, Virtual, Italy

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P01

Diffusion effects in nonlinear dynamics of hepatitis B virus

A dynamic system of viral hepatitis B with healthy, infected cells and free virus is investigated in this work taking into account diffusion effects. The model isshown to be governed by a biological system of equations of prey-predation, competition and commensalism species. The existence of exact traveling waves solutions is established through the (G'/G) expansion method. To further understand the dynamic mechanism of hepatitis B virus infection, we get the Kink, Bright and Dark type profiles and rise out the influence of diffusion parameter on the localization and the amplitude of the solutions which permits us to improve and give more information on the transmission and control of the disease. Numerical simulations are done to give evidence that hepatitis B virus model can be studied by considering the mobility of three species scenarios and also, indicated which dynamic specie cell is more stable than the other.

P02

Yukawa Ratchets in Colloidal System and Complex Plasmas - A Molecular Dynamics Study

Molecular motors work in complex environments which is dominated by fluctuations. Inspite of noisy background, molecular motors are able to move along cytoskeletal filaments within the cell and perform intercelluar transport. Many models have been explored to understand the mechanism of these tiny motors. In this work, we study using Molecular Dynamics simulations, transport properties of a system of driven colloids interacting via Yukawa force. This study explores a generic model with an attempt to understand the mechanism of molecular motors. We find a range of system parameters for which transport is achieved and study its dynamics using diffusive properties.

P03

STRUCTURAL PROPERTIES OF THE AIR/WATER (A/W) INTERFACE

SISSA, Trieste -Italy

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Edward Danquah Donkor

Supervisor: Ali Hassanali

September, 2021

Introduction

The A/W interface is the basic model for hydrophobic interactions and as such has been studied extensively to gain an understand of the hydrophobic interactions that occur in bio-molecules. These hydrophobic interactions are very important when we consider phenomena such as protein folding, micelle aggregation and peptide bond formation, among others. This poster presentation aims to present preliminary studies that is going on to understand the structure of water molecules at the A/W interface. The general aim is to try to characterize the interface adequately and also to probe the structure of the interface and try to make a connection between microscopic structural properties and macroscopic properties such as the surface tension, using standard order parameters which tend to be ill-defined on the interface, and then also use much better tools involving machine learning to gain a better understanding of the interface.

Preliminary results

Average Instantaneous Interface

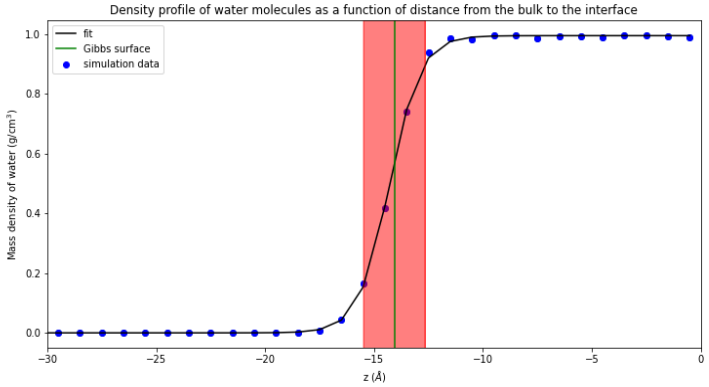

Fig 1: Average density distribution of TIP4P/2005 water molecules.

Average distribution of the orientational tetrahedral order parameter

$$q = 1 - \frac{3}{8}\sum_{i=1}^{3}\sum_{j=i+1}^{4}\left(cos\theta_{ij} + \frac{1}{3}\right)^2 \quad (7)$$

Where θ_{ij} is the angle formed between the bond vectors of a reference oxygen atom and it's four nearest neighbour oxygen atoms [3]. If the structure is perfectly tetrahedral then Eq. 7 returns a value 1, otherwise it is less than one. This quantity is by construction not sensitive to radial order but rather angular order.

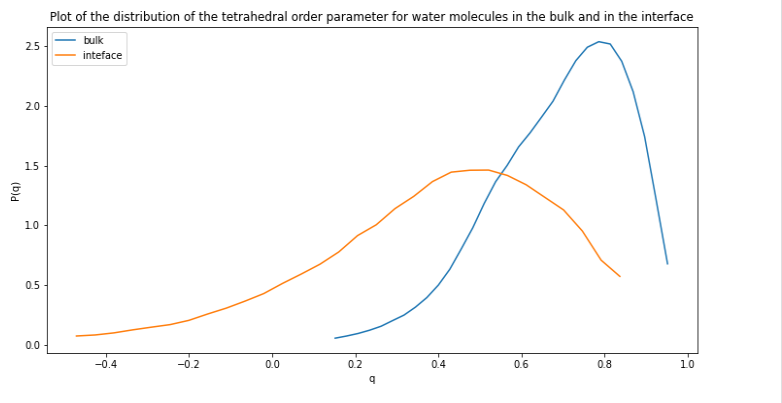

Fig 2: Probability distribution of the orientational tetrahedral order of TIP4P/2005 water molecules

Preliminary conclusions

We have been able to characterize the A/W interface using the average density distribution. We note that the average interface obtained is not a good characterization of the interface since it neglects the fluctuations at the interface.

We also compute the probability distribution of the average orientational tetrahedral order for the TIP4P/2005 water molecules within the Gibbs interface and also for water molecules in the bulk liquid.

We see a shift of the distribution to smaller values of q and also a broadening with a long tail for negative values of q, as compared to the bulk distribution.

The long tail for q < 0 on the interface shows that there are many water molecules on the interface with less than four neighbors, making q an ill-defined quantity on the interface.

These preliminary conclusions point us to the fact that we need more adequate ways to characterize the interface and probe its local order.

Finally, we also compute the surface tension of TIP4P/2005 water and find it to be 68.5 N/m within an error of 0.8 N/m. The next tasks will be to try to understand why the distribution of q has long tails for q < 0 while the surface tension has this high value.

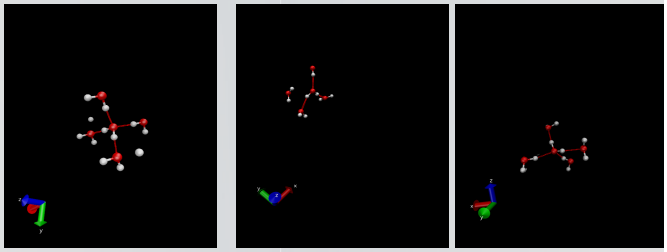

Fig 3: Tetrahedral Structure of Ice 1h (left panel), interfacial water (middle) and bulk water (right)

P04

N-glycan conformers explored by enhanced sampling & machine learning

Glycosylation is one of the bulkiest post-translational modification of proteins but has long been overlooked in molecular dynamics simulations, despite its omnipresence in the cell. However, the structure, function and interaction of many biochemical systems is governed by N-glycans covalently linked to asparagine residues in specific protein sequences. Due to the flexibility of their glycosidic linkages and their sugar units, N-glycans assume many different conformations, unlike the more rigid protein structure to which they are attached. A complete description of their conformational phase space requires thus the consideration of a large number of internal degrees of freedom. We show that an enhanced-sampling molecular dynamics scheme based on enhancing transitions of all relevant barriers with concurrent one-dimensional energy potentials in the framework of metadynamics can in fact capture effectively all biologically relevant global conformers of branched glycans, importantly also including the monomer puckering states. Interestingly, our approach revealed altered N-glycan conformer populations depending on the puckering state of the monosaccharides. These puckering-dependent conformer distributions, so far mostly ignored in glycoprotein simulations, might be crucial in explaining biological phenomena involving N-glycans.

P05

Workshop on Molecular Dynamics and its Application to Biological Systems (from 13-17 September 2021)

Study of the structural, dynamic and thermodynamic properties of Acetaminophen

University of Yaoundé I

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Introduction

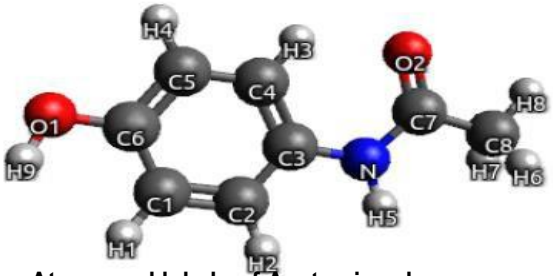
Our work explores the effects of temperature on the properties of a pharmaceutical molecule: acetaminophen (knowing as paracetamol). The structural, dynamic and thermodynamic properties of 90 molecules of Acetaminophen (20 atoms) in the liquid state are calculated at six different temperatures and at a pressure of 1 MPa using classical Molecular Dynamics simulations by DL POLY software from the GAFF force field.

Methods

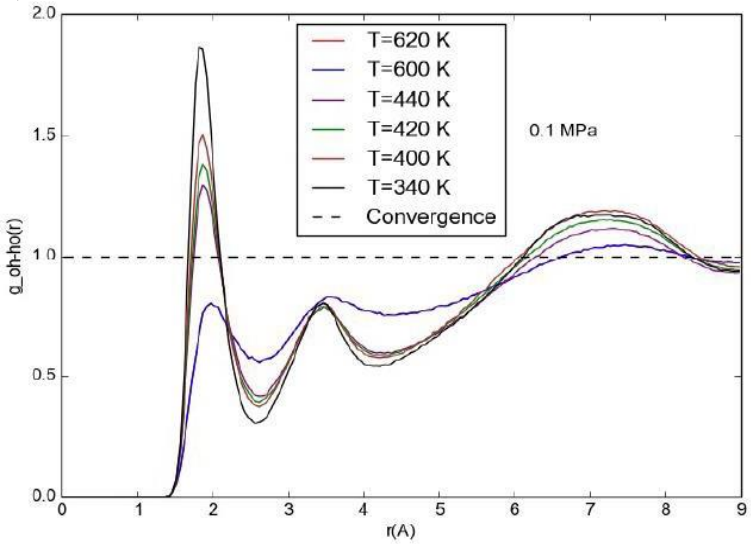
$$V_{GAFF} = \sum_{ij} K_r(b_{ij} - b_{ij}^0)^2 + \sum_{ijk} K_b(\theta_{ijk} - \theta_{ijk}^0)^2 + \sum_{ijkl} \frac{V_n}{2}(1 + \cos(n\phi_{ijkl} - \gamma))$$

$$+ \sum_{i<j} \left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6} + \frac{q_i q_j}{\varepsilon r_{ij}} \right]$$

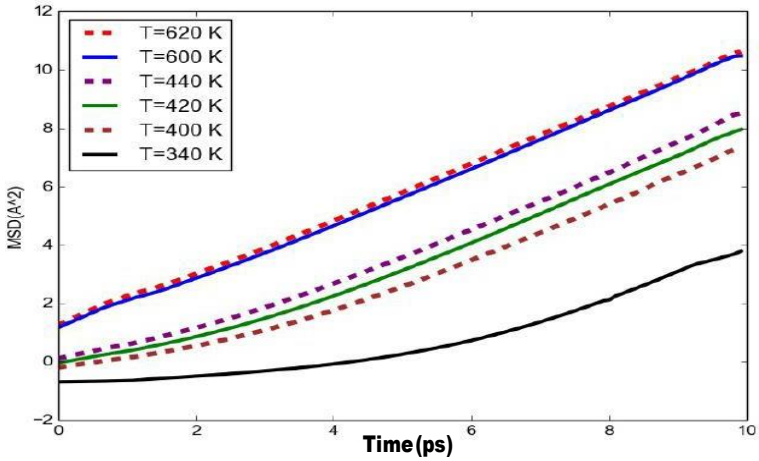
Results



Atoms and labels of Acetaminophen



Radial distribution function of the Oxygen (O1)-Hydrogen (H9) bond



Average square displacement of the centers of mass of acetaminophen molecules

Température (K)	340	400	420	440	600	620
D_T $(10^{-9}m^2/s)$	0.004	0.12	0.24	0.41	3.16	3.46

Translational diffusion coefficients of acetaminophen

Température (K)	620	600	440	420	400	340
ρ $(10^3 g/cm^3)$	0.95	0.95	1.11	1.12	1.14	1.18
ρ_{liq} $(10^3 g/cm^3)$	0.92	0.94	1.09	1.10	1.12	1.17

Densities of acetaminophen at different temperatures

Conclusion

Our results are analyzed in terms of temperatures-induced changes in structural properties by examining the radial distribution functions of differents atoms. The first peak as well the second peak of O1-H9 are found to be well defined even at higher temperatures and a decrease in atomistic disorder during the cooling of the molecules. When cooling Acetaminophen, atoms vibrate less and less because losing energy and this reduces its diffisuve character and its thermal expansion coefficient.

P06

Fitting m6A force field to Denaturation Experiments through Alchemical Free Energy Calculations

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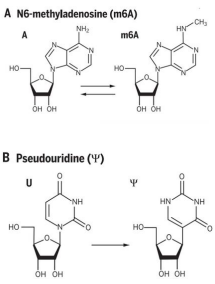
1 - RNA post transcriptional modifications [1]:

Chemical alteration of primary transcript into a mature RNA, through **biochemical** modifications of **nucleobases**



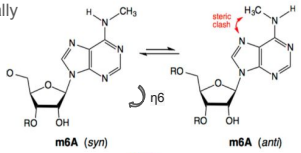
Main questions in the community:
- Which are the **mechanisms** that regulate these modifications?
-What is the **impact** on RNA **structure and dynamics**?
- how are these modifications **functional**?

Motivations:

- Growing interest in the community: more modifications are routinely discovered to be functional in regulatory mechanisms
- Few works in the context of secondary **structure prediction**, almost none at 3D level
- **Molecular Dynamics** may give meaningful insights about the **impact of the modifications on structures and dynamics**
- **m6A** common modifications and widely studied: An upgraded **force field** is needed in order to improve accuracy in MD simulations

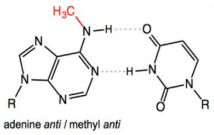
2 - N6-methyladenosine (m6A)

Syn conformation energetically favoured over *anti* (**ΔG = 6.3 kJ/mol**) [2]
Anti is favored when Watson-Crick paired

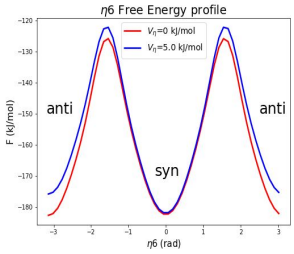


Starting topology: Aduri + tors

- Charges taken from ***Aduri et. al.*** **[3]**
- Reparametrization of N1-C6-N6-C10 (η6) dihedral in order to enforce correct equilibrium between *syn/anti,* using **metadynamics** along η6 plus **reweighting** to enforce **ΔGexp = 6.3 kJ/mol**



$$W(x_i) = e^{\beta B(x_i)} e^{-\beta \frac{V_\eta}{2}[1+\cos(\eta 6(x_i)-\pi)]}$$



$$\Delta G^{anti}_{syn} = -\frac{1}{\beta}\ln\frac{\sum_{syn} W(x_i)}{\sum_{anti} W(x_i)}$$

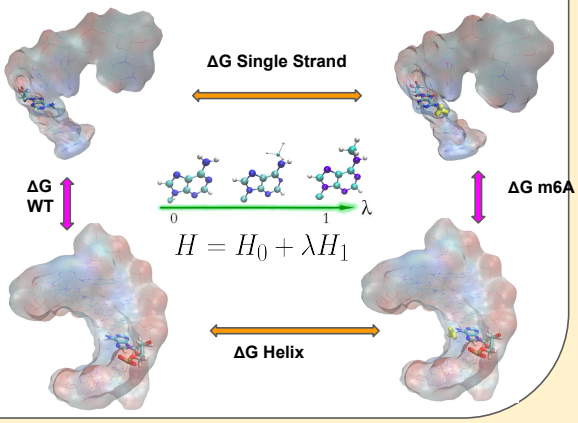
ΔG=1.5 kJ/mol (Aduri)

ΔG=6.4 kJ/mol (Our fitting)

3 - Alchemical Free Energy Calculation (AFEC)

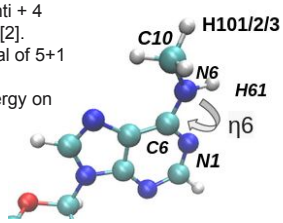
- Path along λ describes the transformation from **A** into **m6A**, by switching *on/off* the non-bonded interactions of certain atoms.
- Optimal sampling is obtained thanks to an **Hamiltonian Replica Exchange**. Set of λ values derived through optimization of **phase space overlap** between replicas -> 16 replica with λ not homogenously distributed in order to enforce as homogenous as possible **acceptance probabilities** between replicas, with values above 20%

- **ΔG** estimators: **BAR** (GROMACS) and binless **WHAM.** Statistical error is computed applying a bootstrap procedure on the WHAM estimation.
- **Thermodynamic Cycle:** Computing **ΔG** through AFEC for the methylation occurring on a duplex or single strand, allows us to directly compare **ΔΔG** to denaturation experiments [2][4] free energies differences (difference in thermal stability for un/methylated duplexes)



4 - Parameters Fitting procedure

- Fit 6 charges + V_η on 5 experimental DDG: syn/anti + 4 denaturation experiments [2].
- Total charge is fixed: a total of 5+1 free parameters
- Recomputing the total energy on the simulate trajectories using 20 sets of, and fitting parameters K1..K20 so that:



$$\Delta U = K_1\Delta Q_1 + K_2\Delta Q_2 + K_3\Delta Q_3 + K_4\Delta Q_4 + K_5\Delta Q_5 + K_6\Delta Q_1\Delta Q_2 + \ldots.. + K_{15}\Delta Q_4\Delta Q_5 + K_{16}\Delta Q_1\Delta Q_1 + \ldots. + K_{20}\Delta Q_5\Delta Q_5$$

- this allows obtaining **ΔU** for arbitrary **ΔQ** without reprocessing
- **ΔQ** found minimizing the cost function through the **L-BFGS-B** Method [**5**].
- α and β are the **hyperparameters** needed to **avoid overfitting**. The are individuated through a cross validation (**Leave one Out)** procedure

$$C = \chi^2 + \alpha\sum_{i=1}^{5}\Delta Q_i^2 + \beta V_\eta^2$$

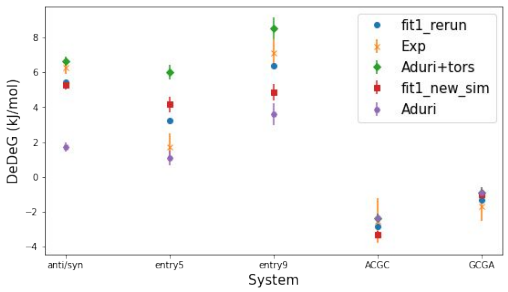
$$\chi^2 = \sum_{i=1}^{N_{exp}} \frac{(\Delta\Delta G_{afec} - \Delta\Delta G_{exp})^2}{\sigma_i^2}$$

5 - Results

- **Training hyper-parameters** using a cross-validation procedure: **α = 125 e^-2 and *β*=0.0001 (kJ/mol)^-2**
- **Training parameters** minimizing the regularized cost function: We identify small charge modifications that lead to a significant improvement of the agreement between Computation and experiments

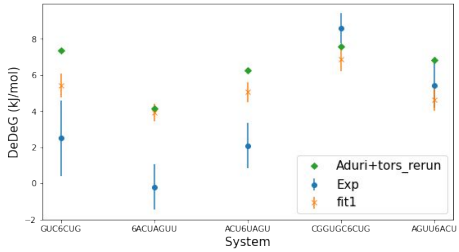
Atom	ΔQ (e)
C6	0.064
N6	0.038
H61	0.070
N1	-0.041
C10	-0.005
H101/2/3	-0.042 x 3
tot	0.000

V_η = 5.0 *kJ/mol*



χ^2	
Aduri:	30.5
Aduri+tors:	6.8
Fit1_rerun:	1.84
Fit1_new_sim:	5.0

- **Testing** the obtained parameters on a new set of 5 denaturation experiments **[4]** not involved in the fitting procedure.



Also for this set, our fitted force field improves the agreement with experiments compared to Aduri+tors

χ^2	
Fit1:	4.6
Aduri+tors_rer:	6.2

[1] *Gilbert, Bell, Schaening.* Science (**2016**)
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[2]*Caroline Roost et al*, JACS (**2015**)
[3] *Aduri et al,* JCTC (**2007**)
[4] *Kierzek et al*, BioArxiv (**2021**)
[5] *Zhu er al,* ACM (**1997**)