

Northern Atomistic Simulations Group Meeting

5 January 2005

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Mr. Emad Noorizadeh	Leicester
Ms. Katie Finch	Manchester
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Abstracts

HyBeacon© fluorogenic probes: investigation of a novel diagnostic tool by molecular dynamics and spectroscopy

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HyBeacons© are innovative fluorescent probes for use in genetic diagnostics and pharmacogenetic profiling. As the probe does not require a quencher or self-complementarity to function, this study investigates the molecular-level mechanism underlying the increase of fluorescence intensity on hybridisation of HyBeacons© with target DNA. To characterise the structure and dynamics of the probe-target system, simulated annealing and constant temperature molecular dynamics simulations were conducted using an implicit solvent model. Both simulated annealing and molecular dynamics indicate the linker, though highly flexible, prefers extended conformations which project the dye away from the DNA. Together with supporting spectroscopic data, a possible explanation of probe mechanism is proposed.

Computational studies of motor neuron disease due to cytotoxicity of human superoxide dismutase.

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Cytosolic Cu,Zn superoxide dismutase (SOD1) is a critical component of the cellular defence against reactive oxygen species and catalyse the superoxide radical anion to hydrogen peroxide and oxygen via the cyclic reduction and reoxidation of copper. Mutations in SOD1 have been associated with the development of amyotrophic lateral sclerosis (ALS), or known as motor neuron disease in UK. The disease often results in death within five years of symptom onset. There is no cure and the disease etiology is still unknown. Some 10% of ALS cases are familial (FALS) and point mutations (more than a hundred has been identified) in SOD1 has been implicate in about 20% of FALS cases. FALS mutants are scattered throughout the SOD1 gene that encodes the protein and a range of the source of toxicity has been suggested: from altered metal ion binding, leading to dysfunctional enzymatic reaction to abnormal interactions of mutant SOD1 with itself or other cellular mechanisms.

Recently, experimental studies show that apo (metal depleted) wild-type SOD1 can become destabilise and undergo self-aggregation into an amyloid-like fibrillar structure. Similar structural aggregates were also formed from some metal-depleted FALS mutant species, although their fully metallated (holo) counterparts were non-toxic. This finding may implicate a possible cause of the sporadic ALS (SALS), which consists of 90% of ALS cases, and occur without the presence of known SOD1 (or other gene) mutations. The apo forms of the enzyme and/or dimer destabilisation can be one of the possible explanations for the large number of distinct SOD1 FALS mutations that possessing a common clinical pathology.

In this work, the crystal structures of holo and apo wild-type SOD1 were used as a basis of molecular dynamics (MD) simulations in order to investigate the underlying molecular mechanisms that implicate the possible toxic nature of SOD1. The results show that structural disruption to the active sites of the protein enzyme causes the beta strand 5 and 6 to become more expose to the solvent and thus prone to unintended protein interactions leading to aggregations, as was found in the experiment. The Zn ions is important to maintain structural integrity of the protein molecule, whereas the Cu ions play no apparent part in this role.

Coarse grained models: Gay-Bern models with a tapered point.

Laurence Ellison

Materials Modelling Group, Materials and Engineering Research Institute, Sheffield Hallam University.

Our group specialises in course-grained molecular simulations of liquid crystalline materials and mesoscale simulations of various complex fluids including liquid crystals and blood using the Lattice-Boltzmann technique. My PhD project is concerned with molecular dynamics simulations of a system of model particles having a uniaxial non-centrosymmetric shape (fig.1), hence we refer to them as 'pears'. This pear shape is incorporated into the intermolecular potential via a contact function $\sigma(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}}_{ij})$. For a pair of particles with arbitrary relative orientations σ gives the separation at which they will just touch (fig.2).

The contact function was developed by my predecessor Fred Barmes [1] who used it in MC simulations of hard pear-shaped particles. Isotropic, nematic and interdigitated smectic phases were observed – unusually rich phase behaviour for a purely hard potential. For MD simulations the contact function is inserted into a shifted version of the Lennard-Jones potential:

$$U(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \mathbf{r}_{ij}) = 4\epsilon \left[\left(\frac{\sigma_0}{\mathbf{r} - \sigma(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}}_{ij}) + \sigma_0} \right)^{12} - \left(\frac{\sigma_0}{\mathbf{r} - \sigma(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}}_{ij}) + \sigma_0} \right)^6 \right]$$

We hope to collaborate with a group based at Bologna University to measure the flexoelectric coefficients from the MD runs. Also we will attempt to develop a well-depth function $\epsilon(\hat{\mathbf{u}}_i, \hat{\mathbf{u}}_j, \hat{\mathbf{r}}_{ij})$ to modulate the strength of the attractive part of the interaction. It should be stressed that the model particle described above is not intended to accurately represent a real molecule. Rather it is designed to investigate the generic effects of changes in the asymmetry of shape and of attractive interactions in a systematic way via well defined model parameters.

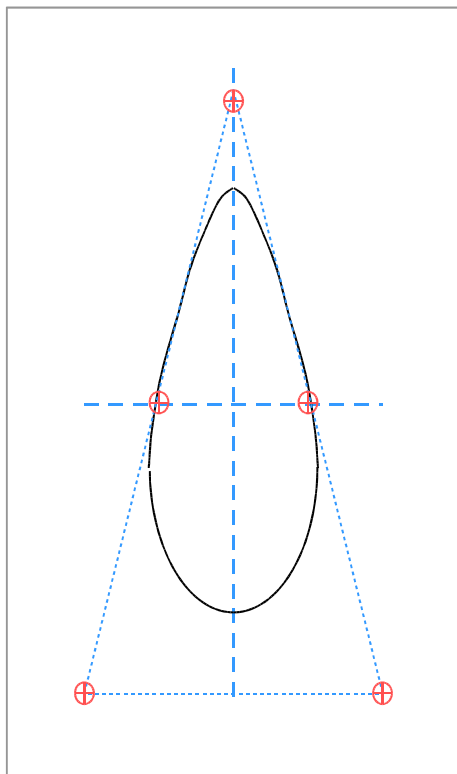


FIG 1

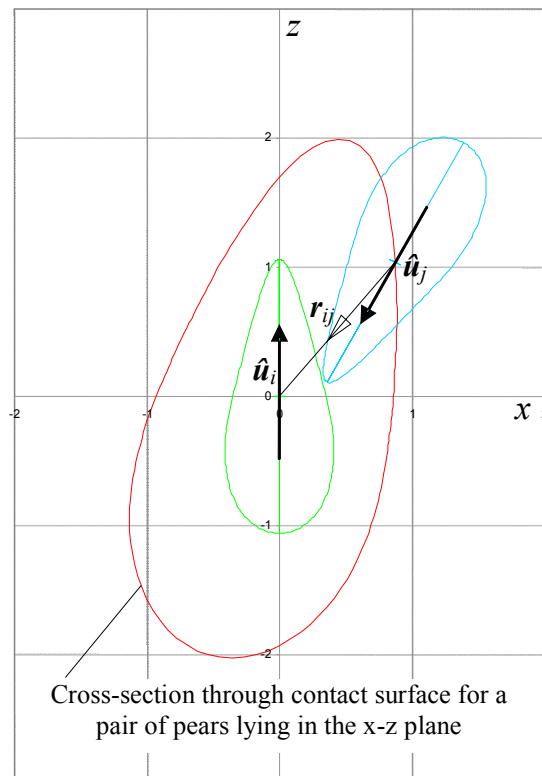


FIG 2

[1] "Computer simulation of hard pear-shaped particles.", F Barmes, M Ricci, C Zannoni and D J Cleaver, Phys. Rev. E **68** (2) 2003.

Simulating mixed gas diffusion in polymer matrices

S. Butler
University of Leeds

Recent efforts to perform accurate molecular dynamics simulations of diffusion processes have struggled to get close to reported experimental values for diffusion co-efficients and solubilities. I will present an overview of two techniques which aim to solve this problem and which form the basis of my doctoral research. I will cover the implementation of Toxvaerd's anisotropic united atom model

and Kikuchi's virtual liquid MD technique in DL_POLY. I will also introduce the dual mode mixed gas diffusion effect and discuss how it can be investigated by simulation.

The coarse-graining of a liquid crystal dendrimer

Z.E. Hughes
University of Durham

Liquid crystal dendrimers are highly interesting molecules but due to the large size are extremely expensive to simulate. Thus the coarse-graining of these dendrimers will allow simulations involving large numbers of these molecules to be done on a reasonable timescale. In this case a 3rd generation (3 branching points) silocarbane LC dendrimer was coarse-grained. Data about the molecule was collected by running a gas phase Monte Carlo simulation on a single molecule. This was then followed up by molecular dynamics simulations of a United Atom model of the dendrimer (H's combined with C's and the mesogens converted to spherocylinders) in a LC solvent (also represented by spherocylinders) in both the nematic and smectic A phases. The information gathered from these simulations was used to construct a coarse-grained model consisting of three parts; a core, flexible linker units and the mesogenic units. Once the coarse-grained model had been constructed simulations of 100 molecules were carried out. These were molecular dynamics NpT simulations starting at a low density and gradually increasing the density. The system did form a smectic A phase at the highest densities thus replicating the phase behaviour of the real molecule.

Investigating the effect of calcium on barite crystal morphology using computer simulations and atomic force microscopy (AFM)

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Barite (BaSO₄) is a major component of inorganic scale that forms in well bores and oilfield pipework. Chemical scale inhibitors (SI's) are used to prevent scales forming, and function by inhibition of nucleation and crystal growth retardation. However, for reasons that are poorly understood, these processes are affected by the presence of cations such as Ca²⁺. We seek to understand why these changes in crystal morphology occur, and thus the mechanism and efficiency of growth inhibition.

In order to understand the structure of barite surfaces at an atomic level and the effect of additives such as Ca²⁺ on these surfaces, a combination of experimental and computer modelling approaches are being used. Atomistic simulation programs (GULP and MARVINS) were used to calculate the bulk and surface properties of BaSO₄ using existing empirical potentials. Crystal morphologies exhibit a variation from classic to complex structures with different concentrations of Ca²⁺, Sr²⁺ and Mg²⁺ modelled on different surfaces of BaSO₄. These models have enabled the prediction of changes in surface properties, and can be used to interpret preliminary observations of the (001) and (210) barite surface morphologies made in air using atomic force microscopy (AFM).

In-situ AFM flow cell experiments are being used to study surface growth and dissolution processes, in the presence of supersaturated solutions of BaSO₄. Recorded images show differences in molecular scale growth on the (001) and (210) surfaces, and also increased rates of growth with increasing ionic strength of solution.

Comparison of experimental investigations with predicted crystal morphologies can help to identify the mechanisms of Ca^{2+} incorporation within the barite crystal structure and the effect on barite growth.

Hamiltonian Techniques for Constant Temperature Molecular Dynamics

Emad Noorizadeh
University of Leicester

Augmenting the energy function with a single additional phase-variable, s , together with its canonical momentum P_s , can generate molecular dynamic trajectories that sample from the canonical ensemble. This key idea was observed by physicist Nose` and has found widespread use in its time re-parameterised Nose`-Hoover form. However it destroys the Hamiltonian structure, therefore it does not have a canonical symplectic structure. Symplecticness is a strong geometric property of the flow of dynamical systems and the importance of it in numerical integrator has become popular. For numerical integrators, the symplectic property has important consequences. One can apply backward error analysis to the symplectic method to approximate the dynamics of Hamiltonian systems. The recent Hamiltonian methods (Nose`-Poincare` chain observed by B. Leimkuhler) of Nose` type schemes are described. Since they keep the symplectic structure, better dynamical sampling can be obtained. Attention then will be paid on analysis of these methods when they are applied to the harmonic oscillator and the nonlinear wave equation.

The DL_POLY Package

Bill Smith
Daresbury Laboratory

The molecular dynamics simulation package DL_POLY is used by several hundred research groups world-wide. The package consists of two complementary molecular dynamic programs: DL_POLY_2 and DL_POLY_3, which differ in their parallel structure and applicability. DL_POLY_2 is more general, but is better suited to smaller parallel simulation (up to 30,000 particles, 100 processors), while DL_POLY_3 is best exploited in large scale simulations (1 million particles, 1000 processors). The package also features a Java GUI which allows construction of DL_POLY input files, execution of the program and analysis of the simulation results. Being written in java it is highly portable. This seminar provides an overview of the DL_POLY package and of its structure and functionality.

http://www.cse.clrc.ac.uk/msi/software/DL_POLY/inde.shtml

Molecular simulation of gas adsorption and transport in nanoporous carbons

Qiong Cai and Nigel Seaton
University of Edinburgh

The objective of our work is to understand the adsorption and transport phenomena in the real carbons by understanding these properties in the virtual carbons, and to provide an appropriate pore-level model for predicting the transport coefficients in real activated carbons. Monte Carlo simulation, combined with percolation theory, is used to extract detailed pore size distribution (PSD) and the coordination number of the pore network for microporous carbons. Database of pore-level diffusion coefficients can be obtained by dual-control-volume grand canonical molecular dynamics (DCV GCMD) simulation. Then the Monte Carlo-Renormalized Effective Medium Approach (MC-REMA)

will be applied to get the effective diffusivity, using the PSD, the coordination number, and the pore-level diffusion coefficients obtained as the input data.

Lattice statics and molecular dynamics calculations using distributed multipole potentials

M. Leslie (Daresbury Laboratory)

Describing the electrostatic interaction between two molecules as an expansion of distributed multipoles, centred on each atom, leads to a far more accurate description of the electrostatics. I will describe the CCP5 programs DMAREL (Lattice statics) and DL_MULTI (molecular dynamics), which have been used for the prediction of new polymorphs of small organic molecules. Many (up to 1000) trial structures are generated using a packing program. DMAREL then relaxes the trial structure using the multipole potential while conserving the space group symmetry. Sometimes the structure will relax to a saddle point in the given space group. In this case the calculation is restarted in the appropriate subgroup to relax to a minimum. DMAREL will produce a plot of internal energy of the unit cell vrs. Cell volume.

Figure 1 shows such a plot for 5-fluorouracil, which is a very common pharmaceutical (anti-cancer properties).

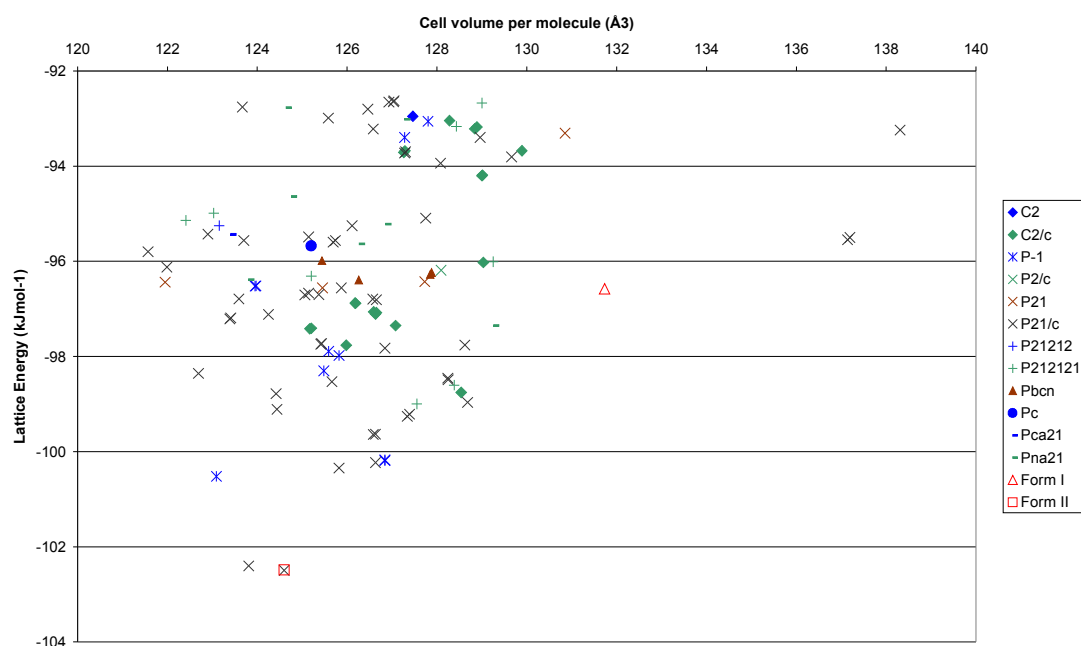


Figure 1. Plot of lattice energy vrs. Cell volume for 5-fluorouracil

Prior to this study, only one polymorph was known (Form I), located at the red triangle in Figure 1. Experimental crystallization found one new polymorph - (Form II). Each molecule in the new polymorph forms two dimer hydrogen bond pairs in a ribbon motif.

Phase II was also found from the theoretical study located at the red square. The crystal structure of 5- fluorouracil as crystallized from water. (Form I) has the fluorines (green) pointing towards each other in the crystal. (Figure 2).

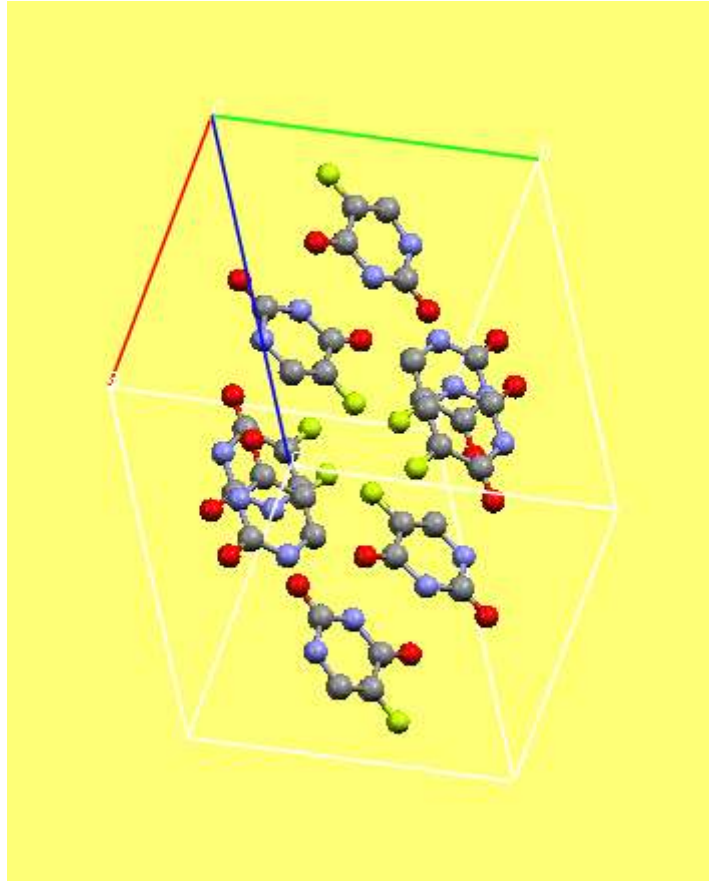


Figure 2. Structure of 5-fluorouracil Form I

DL_MULTI could be used to investigate the dynamics of dissolution. Molecular dynamics studies on HPCx have been done using DL_POLY3 (point charge electrostatics). MD studies of dissolution of form I in water on HPCx using a cluster of 16 fluorouracil molecules with 1938 water molecules. This simulation indicated that the carbonyl oxygens have a tightly hydrogen bonded solvation sphere while the fluorines are less strongly solvated, and suggests that the molecules associate in solution through the hydrophobic F—F contacts while the water inhibits the formation of dimer hydrogen bonds, and this provides nuclei for crystal Form I to grow.

DL_MESO Lattice Boltzmann Component

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DL_MESO is a general purpose mesoscale simulation package developed at Daresbury Laboratory under the auspices of the Engineering and Physical Science Research Council for the EPSRC's Collaborative Computational Project for the Computer Simulation of Condensed Phases. Lattice Boltzmann equation (LBE) is one of the mesoscale methods included in DL_MESO package. DL_MESO_LBE can study fluid flow, phase separation, solute diffusion and thermal conduction of multiphase and multiple component systems under mechanical disturbances. The talk shows the application of the code package to the pure fluid flow under gravity, phase separation of binary system, and the droplet breakdown and coalesces.