CompBioMed

Newsletter Issue No. 2
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Welcome

Prof. Peter V Coveney
Principal Investigator & CompBioMed Coordinator

In the three months that have elapsed since the publication of our first issue, many things have occurred while others are shortly to take place. We held a tutorial workshop on 30 May followed on 31 May by a meeting on the calculation of free energies using molecular simulation; these were joint meetings with the BioExcel Centre of Excellence. Both are reported on pages 1 and 3, and together they attracted over one hundred people. On 5 July, CompBioMed had its nine month review at the European Commission in Brussels; a short report is provided below (page 2).

Our research, education and training, and outreach activities have all proceeded apace over the period. In the research area, a new award has recenty been announced on the Tier-0 supercomputer SuperMUC at the Leibniz Rechenzentrum in Garchug to Prof D Kranzlmüller (LRZ), Prof P V Coveney (UCL) and Dr H van Vlijmen (Janssen). EPCC at the University of Edinburgh, SURFsara in the Netherlands and PRACE (Partnership for Advanced Computing in Europe) have started a massive open online course (MOOC) in Supercomputing that will be useful for amateurs and experts alike. We have welcomed a further 5 Associate Partners (see pages 2 & 3).

In terms of outreach, we are now preparing for the biggest public event we have staged so far — "The Virtual Human" at the IMAX theatre within the London Science Museum, on the evening of 27 September 2017. All are most welcome to attend. You can reserve your place by going online at http://my.sciencemuseum.org.uk/single/SYOS.aspx?p=121972

CompBioMed & BioExcel Free Energy Workshop

The **Free-Energy Workshop in London (31st May 2017)** saw more than a hundred researchers from across Europe, representing both academia and industry, brought together for a joint meeting organised by the CompBioMed and BioExcel Centres of Excellence (CoEs). The event, held at University College London, focused on the use of cutting edge computational techniques to calculate free energies relevant for applications in the life and medical sciences (such as drug design and treatment selection). The main meeting was preceeded by a one day meeting in attendees discussed common issues in method and software development. This tutorial workshop (with 25 attendees) was structured as an unconference with the agenda determined by the participants as it progressed. This resulted in highly constructive discussions of both detailed techical issues and high level issues, such as the desire for better open data practices in the field.

Poster session and lunch at the Free Energy Workshop

The speakers in the main programme had a diverse set of backgrounds, coming from both CoEs, a broad range of research groups in academia and industry as well as commercial software vendors. The meeting was opened by Professor **Peter Coveney**, leader of the CompBioMed project, who introduced the aim of the meeting to discuss state of the art free energy calculation techniques in the context of life and medical science. Coveney also discussed the need for access to powerful computing resources in order to perform these calculations. A brief introduction to BIoExcel by **Bert De Groot** then led into the main programme.

Chris Oostenbrink started proceedings by describing how insights from approximate methods can be used to get more precise results from fewer simulations in alchemical free energy calculations and gain better understanding where to focus additional simulation efforts. He was followed by **Berk Hess** who presented the use of a novel metric that facilitates more effective sampling along reaction coordinates and consequently the observation of rare events. A lively debate was sparked by **Peter Coveney**'s talk describing how ensembles of short simulations generally provide more reliable free energy estimates than single long duration runs, which are seldom reproducible. After exchanges with Berk Hess and Erik Lindahl it was generally accepted that whilst ensembles offer improved statistical performance and uncertainty quantification, the short duration necessarily places some limitations on binding events in which large conformational changes occur.

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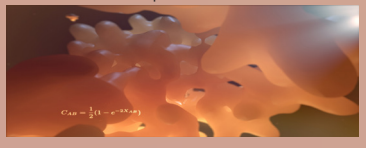
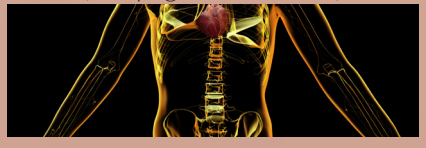
Upcoming Events

CompBioMed & OpenMulitMed Workshop at EPMA 2017, Valletta, Malta
14-17 September 2017



"The Virtual Human" IMAX event at the Science Museum Lates, London, 27 September 2017
(see page 4 for details)



CompBioMed Session at WFITN 2017, Budapest, Hungary
16 October 2017

9-Month Interim Review Meeting

The CompBioMed 9-month review took place at the European Commission's offices in Beaulieu, Brussels, on 5 August 2017. Our Centre of Excellence was well represented by at least one participant from every core partner. Along with two Project Officers from the Commission and four Reviewers, this made for a crowded but lively venue. The meeting kicked off at 9:15 a.m. and ended on the dot at 4 p.m. We managed to convey the sense of excitement and purpose very effectively, while leaving ample time for questions and answers, thanks to some well organised preparations including discussions before a delightful dinner on the preceding night within Brussels. At the time of writing, we await formal feedback from the Commission, which will serve to help focus some of activities in the coming years.

A full room for our 9-month review meeting - good to see so many people in attendance.

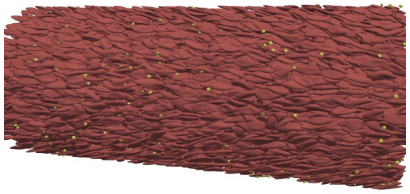
Reviewers and CompBioMed Core Partners discuss the merits of the project in Brussels

Cellular level *in silico* modelling of blood rheology

Dr Gábor Závodszky and Prof. Alfons Hoekstra

University of Amsterdam.

Blood is a complex fluid constituted of various components suspended in plasma. Many of its intriguing properties originate from this cellular nature. Red blood cells are the major component; they transport oxygen and determine the bulk behaviour of blood. Platelets, the second most numerous cells, form the link between transport dynamics and several vital biochemical processes such as clot formation. With the recent advancement of micro-medical devices modelling the small-scale behaviour is gaining more importance. Accurate modelling of blood flow related phenomena, such as the formation of a thrombus, the appearance of non-Newtonian viscosity, the margination of platelets, the Fåhræus effect, or the appearance of a cell-free layer, on this scale requires a description of the dynamics at the level of individual cells. This, however, presents several computational challenges that can only be addressed by high performance computing. We tackle these complexities using HemoCell (www.hemocell.eu), a parallel computing framework for dense cellular suspensions which implements validated mechanical models for red blood cells [1] and is capable of reproducing the emergent transport characteristics of such a complex cellular system.



[1] Závodszky, G., van Rooij, B., Azizi, V., Hoekstra, A. (2017). Cellular level in-silico modelling of blood rheology with an improved material model for red blood cells. Frontiers in Physiology, doi: 10.3389/fphys.2017.00563

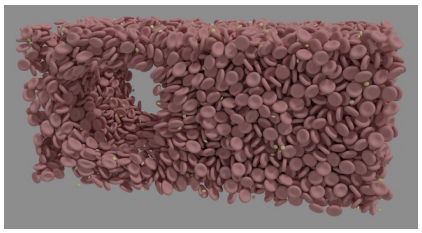
[2] Mountrakis, L., Lorenz, E., & Hoekstra, A. G. (2014). Validation of an efficient two-dimensional model for dense suspensions of red blood cells. International Journal of Modern Physics C, 25(12), 1441005.

[3] Mountrakis, L., Lorenz, E., Malaspinas, O., Alowayyed, S., Chopard, B., & Hoekstra, A. G. (2015). Parallel performance of an IB-LBM suspension simulation framework. Journal of Computational Science, 9, 45-50.

Within this framework, the plasma is modelled as a continuous Newtonian fluid simulated using the lattice Boltzmann method (based on Palabos, an open-source LBM solver). The cells are represented as triangulated discrete element membranes coupled to the plasma flow through a tested in-house immersed-boundary implementation [2]. The material models of the different cell types (e.g. RBCs, platelets, white blood cells) are realised as sets of forces acting on the triangulated surfaces.

We put strong emphasis on optimisation and efficiency, both from the side of the source code implementation and the methodology. As a result, HemoCell is computationally capable of handling a large domain size with high number of cells (> 104-106 cells), therefore it is able to bridge the cell-based micro-scale and the continuous macroscopic domains.

The simulations can be scaled up to the order of 106 cells executing on 8192 cores without significant loss of parallel efficiency [3]. The code structure is designed to be very flexible to accommodate various scenarios. It is also easy to extend it with additional modules, such as material models or cell types, or even chemical constituents. This modular structure allows our partners to add new functionality (e.g. a module for platelet bonds and a module for a white blood cell material model and trafficking is currently under external development). Thus, HemoCell can provide a common ground for cooperation to build insight into the properties of cellular flows.



PozLab

PozLab is an independent research and development laboratory situated in Poznan, Poland. Their core business activity includes both early and late stage development of drug products on laboratory and pilot plant scale. Contact point for this Associate Partner is Anna Krause (anna.krause@pozlab.pl)

Electric Ant Lab BV

Electric Ant Lab (EAL) is an independent private research laboratory providing contract-researach consulting and simulation services in the field of rheology and transport of complex fluids. One specific focus of EAL's work lies in the detailed modelling of flow and transport of blood cells in microfluidic and biomedical devices. Founder and CSO of EAL Dr Eric Lorenz is the main contact (e.lorenz@electricant.com)

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Dr David Wright
University College London

Davide Branduardi was the first industry speaker and summarized some of the efforts of Schrödinger to create a robust combination of simulation technologies and free energy estimator. He also described the idea of error analysis based on cycle-closure corrections across multiple simulations to measure calculation reliability.

The second session saw **Antonia Mey** describing her group's experiences taking part in SAMPL5 competitions. Her post-mortem analyses of their attempt suggested that uncertainties in binding site water placement and ligand binding modes, amongst other factors, can critically cloud the validity of computed binding free energies. A potential solution to the issue of water placement was detailed by **Hannah Bruce McDonald** whose work concerns the use of grand canonical Monte Carlo simulation to predict water networks during relative ligand binding free energy computations. She presented results that suggest that this approach has great potential to boost the predictive capabilities of free energy calculations. Returning to the topic of the factors limiting the current ability of free energy simulations to reproduce experimental values, **Phil Biggin** gave examples of how the preferred binding orientation of a ligand for different proteins can be determined. He also showed how difficulties in predicting this influenced his calculations for a range of bromodomains. Next, **Alexander Heifetz** shifted to a higher level of theory describing the Fragment Molecular Orbital method which aims to make quantum mechanical approaches feasible for large biological systems by reducing the high computational cost.

Erik Lindhal and **Bert De Groot** talked about automation and analysis tools provided in the GROMACS ecosystem, the former highlighting the STaGE tool for generating small molecule topologies and Copernicus for distributing calculations over a network, and also making firm recommendations on analysis strategies for alchemical calculations. De Groot showcased how the pmx tool can fully automate the setup of free energy calculations using a variety of forcefields, going on to discuss how a consensus approach outperforms the accuracy of individual force fields. **Gianni De Fabritiis** bridged the two topics, talking both about the HTMD platform for system building and simulation coordination and the use of machine learning to estimate binding strength. He highlighted the requirement that simulation based methods need to at least outperform less computationally expensive machine learning approaches.

On the applications side, contributions showed that computational approaches are now starting to make an impact both in drug discovery and clinical settings. Two contributions from researchers at pharmaceutical companies, **Gary Tresadern** (Janssen) and **Daniel Seeliger** (Boehringer), highlighted how reduced cost and increasing computational power are making simulation an attractive option for industry. Both also provided examples of the difficulties still facing the field, including accounting for long timescale conformational changes and the need to achieve reproducibility of both computational and experimental data. **Phil Fowler** (Oxford) talked about how he is leveraging simulation to assess antibiotic resistance. His work is paving the way for the use of molecular simulation within the UK's NHS to detect resistance and tailor treatment choices accordingly. In the final talk of the day, **Miguel Machuqueiro** demonstrated how simulations can be used to probe changes in protonation state that influence the interactions of ligands with their targets and hence binding strength. This was the final example of how progress is being made in meeting the complex challenges of providing actionable computational predictions of protein-ligand binding affinities.

The meeting concluded with a wide ranging panel discussion. Topics included the interplay between computational drug design and synthesis, the relationship between molecular simulation and sequencing, and the utility of blind tests (such as SAMPL) for driving improvements in the field. In particular, a lot of discussion revolved around the need to focus on difficult cases and develop standard benchmark calculations across the field. One of the most valuable parts of the discussion was how it stimulated conversations between researchers from academic and commercial pharmaceutical backgrounds.

A number of informative posters were also presented with three prizes appointed by a judging committee to:

1. Fiona Naughton, University of Oxford, UK
Interactions of pleckstrin homology domains with phosphyatidylinosiitol phosphate lipids: structures and energetics through simulation
2. Matteo Aldeghi, MPI, Goettingen, Germany
Bromodomains as a test system for absolute binding free energy calculations
3. Wojciech Kopec, MPI, Goettingen Germany
Free energy calculations in K^+ channels: force field vaildation and selectivity

CompBioMed Welcomes New Associate Partners

ITMO University

ITMO University in St. Petersburg has received a Russian federal grant to improve its world ranking by 2020. The Institute of Translational Medicine was established as an innovative hub for joint R&D and educational activities in biomedical technologies. For scientific queries contact Dr Andrew Svitenkov (svitenkov@yandex.ru) or Sergey Kovalchuk (sergey.v.kovalchuk@gmail.com). For organisational matters please contact Mrs Anna Bilyatdinova (a.bilyatdinova@gmail.com)

Academic Computing Centre Cyfronet AGH

The DICE team at ACC Cyfronet AGH has more than 10 active years working within computational biomedicine and the Virtual Physiological Human (VPH) (http://dice.cyfronet.pl/). Marian Bubak (bubak@agh.edu.pl) is adjunct at the Institute of Computer Science and ACC Cyfronet AGH, Krakow, and a Professor of Distributed System Engineering at University of Amsterdam.

Norton Straw Consultants

Norton Straw is an SME with a team of specialist scientists, mathematicians and engineers engaged in numerical modelling and computational simulation across a range of industry domains. The main contact for this partner is Dr Ed Kay (edward.kay@nortonstraw.com)

Innovation Activities

Innovation Exchange Programme

The Innovation Exchange Programme promotes and monitors internships between academia, healthcare and industry in the field of biomedical computing. In this programme, experts from the research community spend time embedded within industrial organisations looking for assistance, applying the latest research techniques in their software. Likewise it assists academic software developers in adopting best practice software developent tools and techniques by facilitating short internships within industrial organisations.

Opportunities can be arranged via the CompBioMed website (http://www.compbiomed.eu/innovation/innovation-exchange-programme/) and are open to both internal and external stakeholders. The only requirement is that at least one participant (visitor or host) has to be a CompBioMed Partner (Core or Associate). Visits may be funded through the Transnational Access research visit programme organised by HPC-Europa project, which started its 3rd phase in June 2017 and will last for 4 years. Visit the HPC-Europa3 website for more details (http://www.hpc-europa.org)

Innovation Advisory Board

Our Centre of Excellence's Innovation Advisory Board, or IAB, is designed to review and comment on our Innovation Plan, which adapts as we progress. They also review our IP Registry, assess the impact of our activities, and advise on innovation, collaboration, disseminating, exploitation and our incubator activities.

The IAB is made up of a number of invited members, currently from across Europe and USA, and each Board meeting will be attended by a subset of the IAB members, depending on availability. Attendance is face-to-face only, and the aim is to have these meetings at least once per year, probably around our annual All Hands Meetings.

The membership of the Board is not closed and we are interested in recommendations for new members, from both within and without CompBioMed. You may propose yourself if you are interested in joining.

Keynotes and Invited Speakers

Alexander Heifetz, Evotec Ltd, UK "Accurate assessment of protein-ligand interaction energy in seconds with quantum mechanics" at 6th World Congress on Medicinal Chemistry and Drug Design, June 8th Milan, Italy

Alfonso Bueno-Orovio, University of Oxford, UK "Sudden death in the young: Decoding cellular profiles of hypertrophic cardiomyopathy." at the Ion Channel Symposium, Denmark 31 May - 2 June.

Peter V Coveney, University College London, UK "Rapid, Accurate & Reliable Binding Affinity Calculations for Drug Discovery" at International Supercomputing Conference in High Performance Computing (ISC-HPC) 2017, June 20th, Frankfurt

Peter V Coveney, University College London, UK "Big Theory for Big Data" at New York Scientific Data Summit, August 8th, New York City.

"The Virtual Human" IMAX event

The CompBioMed IMAX event is part of the Science Museum Lates series. The hour-long feature will describe recreating a human being *in silico*, including IMAX film composited on the Marenostrum supercomputer at the Barcelona Supercomputing Centre (BSC). The video will show stunning simulations on aspects of computational biomedicine using supercomputers.

The performance will take place between 19:30-20:30 for an audience of up to 400 members of the general public. Typically, Lates events attract between 4,000 - 7,000 people, and we expect intense competition from participants to attend. It is recommended that members of the general public who are planning to attend, get their tickets (free of cost) at http://my.sciencemuseum.org.uk/single/SYOS.aspx?p=121972.

In addition to the IMAX film, "The Virtual Human" feature will contain short presentations from the following four speakers:

- Prof Peter V Coveney (UCL) on simulating how drugs work in the body
- Prof Alfons Hoekstra (University of Amsterdam), on virtual blood vessels and more (as can be read about in the article on page 2)
- Prof Blanca Rodriguez (Oxford University), on virtual hearts
- Prof Marco Viceconti (Sheffield University), a key player in the Virtual Physiological Human initiative

This will be followed by a discussion including questions from the audience, chaired by Dr Roger Highfield (Science Museum)

Find CompBioMed online

Our website (www.compbiomed.eu) is full of all the latest news and information about CompBioMed, including further information on our Partners and Associates and past events. We have an active and growing following on Twitter (@bio_comp), a user-forum on LinkedIn (user-forum) and we have recently made our own YouTube channel (Computational Biomedicine), where you can watch live streaming of events and presentations at previous events.

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