Newsletter Issue No. 7
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Welcome

Prof. Peter V Coveney
Principal Investigator & CompBioMed Coordinator

Welcome to our latest edition of the CompBioMed newsletter. I am pleased to announce that we have formally had the signature of the Commission on CompBioMed2 and we are looking forward to contining the innovative work we started in CompBioMed. In this edition of the Newsletter we are focussing on achievements, awards and articles from within the Centre of Excellence, a short round-up of our All-Hands Meeting and our website as well as describing our plans for events in the coming months including the CompBioMed Conference 2019 and webinars.

The organising committee for the conference has worked hard to put together an impressive group of invited speakers for each of the symposia. As you will see below, we have extended the deadline for both the abstract submission (initially to the 24th May, now to 29th May to make amends for the website going down for a couple of days) and the Early Bird registration (to the 31st July). We hope this will give people additional time to submit their abstracts and allow those that need to, time to apply for funding for the registration fee after they are informed of the decision on their proposed contribution.

This newsletter also features details of our partners Acellera and UPF (Universitat Pompeu Fabra) who were successful in two categories of the Drug Design Data Resource (D3R) Grand Challenge. They entered two applications for binding affinity prediction taken from their PlayMolecule suit of software, Kdeep and DeltaDelta, in addition to a docking tool (SkeleDock) that is still under development. More details can be found on page 3.

This month, having had the Grant Agreement for CompBioMed2 signed by the Commission, we are also promoting our current services, available via our website. In CompBioMed2 we plan to extend these services and build on the work we started in the first phase. I encourage you to take a look at these pages and others on our website.

On the back page we highlight the events that are coming up in the final months of CompBioMed. We have two finalised webinars (28th May and 27th June) and one more planned for September in addition to our HemeLB meeting at the end of May with the UKCOMES project.

We are very happy to be given the opportunity by the Commission to continue to build our Centre of Excellence and trust that we can shape the domain of computational biomedicine as it grows.

Deadline Extension

The CompBioMed Conference deadlines have been extended:

- **Call for Paper deadline: 29th May**
- **Early Bird Registration deadline: 31st July.**

This is to enable those that are accepted for an oral or poster presentation to register after the acceptance decisions have been made. We have also set up an EasyChair submission service for our abstract submissions and are looking forward to receiving an increasing number over the coming weeks.

Our various symposia now have numerous invited speakers and we are excited to be welcoming many well-known and high-profile speakers to the event. In the *Regulatory Science and in silico Trials* symposium we have Dr Tina Morrison from FDA and Dr Flora Musuamba from EMA. Together they will present work from both agencies on medical drug and device testing.

In the *From Quantum AI to the Virtual Human* Symposium we will be welcoming speakers from Google, Zapata, Microsoft and Atos to speak about their companies approach to quantum computing. In addition this symposium will feed into an event at the London Science Museum: *Future of Quantum Computing: From Quantum Intelligence to Virtual Humans*, on Wednesday 25th September at 19:30 - 20:30.

Publications

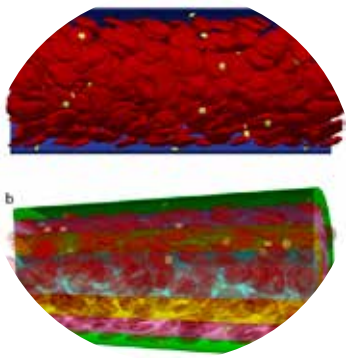
- L. Perez-Benito, N. Casajuana-Martin, M. Jimenez-Roses, H van Vlijmen, G. Tresadern, Predicting Activity Cliffs with Free-Energy Perturbation, *J Chem Theory Comput* (2019) DOI: 10.1021/acs.jctc.8b01290
- C. Llinas del Torrent, N. Casajuana-Martin, L. Pardo, G. Tresadern, L. Perez-Benito, Mechanisms Underlying Allosteric Molecular Switches of Metabotropic Glutamate Receptor 5, *J Chem Inf Model* (2019) DOI: 10.1021/acs.jcim.8b00924
- C. Llinas del Torrent, L. Perez-Benito, G. Tresadern., Computational Drug Design Applied to the Study of Metabotropic Glutamate Receptors, *Molecules* (2019) DOI:10.3390/molecules24061098
- M. Skalic, J. Jimenez, D. Sabbadin, G. De Fabritiis, Shape-based Generative Modeling for de-novo drug design, *J Chem Inf Model* (2019), DOI:10.1021/acs.jcim.8b00706
- D. W. Wright, S. Wan, C. Meyer, H. van Vlijmen, G. Tresadern, P. V. Coveney, Application of ESMACS binding free energy protocols to diverse datasets:Bromodomain-containing protein 4, *Scientific Reports* (2019) DOI: 10.1038/s41598-019-41758-1
- A. Potterton, F. S. Husseini, M. W. Y. Southey, M. J. Bodkin, A. Heifetz, P. V. Coveney, A. Townsend-Nicholson, Ensemble-Based Steered Molecular Dynamics Predicts Relative Residence Time of A2A Receptor Binders, *J Chem Theory Comput* (2019) DOI: 10.1021/acs.jctc.8b01270
- G. Zavodszky, B. van Rooij, B. Czaja, V. Azizi, D. de Kanter, A. G. Hoekstra,, Red blood cell and platelet diffusivity and margination in the presence of cross-stream gradients in blood flows, *Physics of Fluids* (2019) DOI: 10.1063/1.5085881
- A. Melis, F. Moura, I. Larrabide, K. Janot, R. H. Clayton, A. P. Narata, A. Marzo,, Improved biomechanical metrics of cerebral vasospasm identified via sensitivity analysis of a 1D cerebral circulation model *J Biomech* (2019) DOI: 10.1016/j.jbiomech.2019.04.019

News and Events Highlights

Physics of Fluids front cover

A paper written by our team at University of Amsterdam (UvA) has been selected for the front cover of the latest Physics of Fluids journal. The paper *Red blood cell and platelet diffusivity and margination in the presence of cross-stream gradients in blood flows* used their HemoCell modelling tool to investigate the diffusivity of cells and platelets. They conducted several blood flow simulations that enabled the evaluation of detailed diffusive behaviour of the cells. By comparing both single-cell and bulk properties to previous experimental data, the validity of the computations could be determined.

Through their work, they determined that the there were two competing processes taking place. An increase in the shear rate leading to an increase in collision frequency but a decrease in collision radius. They also recognised that there are still some aspects of the model that need to be reconciled to provide a fully-rounded model of cell diffusion through vessels.



Overall, this work provides a more accurate approximation of the cell collision frequency and displacement, enabling a better description of particle transport processes under the flow conditions of real blood vessels. It also suggests that in vascular blood flow the radial migration of cells towards the wall is primarily dependent on the local hematocrit gradient which could be important in the development of the platelet margination theory.

The full paper is available at:
https://doi.org/10.1063/1.5085881

To B(rexit) or not to B(rexit)...

As the UK becomes increasingly mired in the question of whether or not it will exit the European Union and if so how, it has become clear to many that if there is to be any certainty about the future of Britain and British institutions in a European context, individuals are going to have to act. In a bid to ensure that European funding for CompBioMed can and will continue, Coordinator of the project Prof Peter Coveney has secured a professorship by special appointment at the University of Amsterdam (UvA). The chair, in Applied HIgh Performance Computing at the Informatics Institute of UvA will run concurrently with his position as Professor of Physical Chemistry at University College London (UCL). In an article that he wrote for the *Times Higher Education* (https://www.timeshighereducation.com/opinion/uk-academics-should-not-rely-their-universities-save-them-brexit-fallout) he explains the reasons behind this move.

Domestic funding for HPC-related research in the UK has significantly decreased in recent years, whereas, funding from the European Union has steadily increased. The multidisciplinary teams that have been established from this funding have progressed their research and established collaborations that would otherwise have been impossible. The UK has benefited from this as much as any other European country.

While the UK government has promised to underwrite funding for UK co-investigators, there has been no explicit statement about those in the UK leading EU projects. If, as would be the case in a no-deal Brexit, the UK became a third country, there is no legal certainty about the status of coordinators. The uncertainty this creates, for the Centre of Excellence, CompBioMed, was a key factor in Prof Coveney seeking his Dutch appointment.

Some UK universities are looking to affiliate themselves with EU universities to aid in the continued participation in EU funded projects; however, there is no certainty that this course of action will be successful, and it behoves those in a suitable position of responsibilities to make their own decision.

All-Hands Meeting 2019

Our latest All-Hands Meeting took place in Oxford's St Anne's College on 29-30 May with an excellent collection of speakers and short meetings. On day 1 we had a full agenda of speakers from Core and Associate Partner and external participants in related fields explaining their latest work. We will be able to share some of this work on the website shortly.

On day 2 we held more of an internal meeting, discussing the work within each Work Package as we move to finalise the project. We held a technical meeting to further strengthen our collaborations within the project and a General Assembly to vote on matters pertinent to the project governance.

On day 2, the 3rd Innovation Advisory Board face-to-face meeting also took place. Seven members attended and we look forward to receiving the minutes from this meeting to put into action the ideas that resulted from this.

Software Hub

The CompBioMed Software Hub addresses the needs of the computational biomedicine research community, which can use the Hub to access the resources developed, aggregated and coordinated by CompBioMed. The CompBioMed User Guides are also located here and focus on the applications and services accessible through CompBioMed. They include technical instructions on how to access and run the applications, with examples coming from our network of developers and users within the consortium.

https://www.compbiomed.eu/services/software-hub/

HPC Allocations

CompBioMed has been granted allocations on several large scale HPC resources to support the work of the project which are shown on this webpage. Access to these resources is managed centrally. Anyone wanting to make use of an allocation on one or more of the available HPC resources should send an email to allocations@compbiomed.eu. Further instructions and a list of the allocations including notes for industry partners are available here:

https://www.compbiomed.eu/high-performance-computer-allocations/

SkeleDock & Kdeep win Drug Design Data Resource Grand Challenge 4

Alejandro Varela, MSc
PhD Student, Acellera

Davide Sabbadin, PhD
Post-Doc at UPF Computational Science Lab

Prof Gianni De Fabritiis,
Head of UPF Computational Science Lab
Acellera CEO & Founder

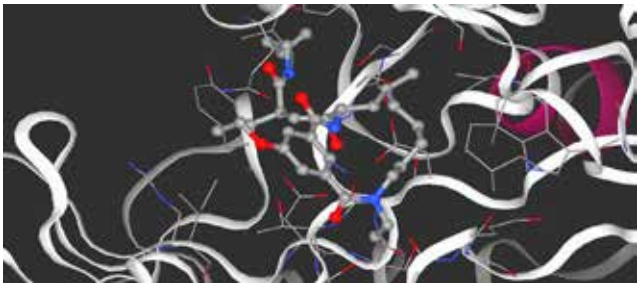
The Drug Design Data Resource (D3R) Grand Challenge is an annual, international competition which offers several tasks considered to be of great pharmaceutical interest. These tasks usually involve predicting the binding mode and affinity of a series of molecules in a given protein. Acellera and UPF's Computational Science Lab competed on this challenge using two Apps of PlayMolecule that make affinity predictions, i.e. Kdeep and DeltaDelta, together with a new docking tool to generate the poses, called SkeleDock (still under development).

If you use the Playmolecule platform, which is part of the CompBioMed solutions, you might already know about Kdeep and DeltaDelta. However, SkeleDock is still an in-house project which Acellera has started developing last summer. It is a docking protocol that takes advantage of previous structural knowledge to generate predictions. If the ligand-protein system for which you have to make a pose prediction is similar to some other, already crystallized complex, the tool searches for equivalent chemical moeites between the two and models the position of those moieites in your system so that they match the corresponding place in the cocrystal. Ideally, with some further minimization process, we can produce high quality poses, which one could then submit to Kdeep or DeltaDelta in order to get affinity predictions.

Internal tests at the end of last August showed promising results. However, when the D3R challenge was launched on the 4th of September, the modeling of macrocyles, which were present in the vast majority of the ligands in the challenge, had still not been considered yet. Modeling them was not an easy task. Our initial attempts were not what we expected: while the non-cyclic parts of the molecules did match the template that we provided, the cycles did not fit well; hence, the resulting poses were far away from the pose quality that we wanted. We worked on a temporary hack on the code to solve these issues and we were finally able to generate poses which, to our eyes, looked sensible. These poses were then used as input for Kdeep and DeltaDelta to predict binding affinities.

This March, the D3R organizers have announced the results for the different subchallenges of the competition. The submission from Acellera and UPF Computational Science Lab was ranked first in two of those subchallenges (BACE free energy prediction and BACE scoring, both in stage 2), as well as achieving 6th position (depending on which metric is used) in the pose prediction challenge among more than 80 participants. The median RMSD was 0.87 Å, where the template we used for most of the ligands [PDB code: 3K5C] has a resolution of 2.12 Å.

There were other tasks in which we participated where we did not perform as well; namely, those involving Cathepsin S. In this target, water molecules seem to play a very important role which, at this time, not SkeleDock nor Kdeep account for. We will work on these aspects to improve our tools and, hopefully, we might perform better next time. SkeleDock will soon be available on the Playmolecule platform and an article will be published with further details on the protocol we used. All results can be found at https://drugdesigndata.org/about/grand-challenge-4/bace#evaluation-results



CompBioMed Website - featured services

Training Repository

The Training Repository helps us to fulfil our objective to train future generations of scientists within the field of computational biomedicine. By running training courses on topics such as HPC use, software engineering and algorthm design, as well as training medical practitioners in the basic medical and clinical contexts of HPC simulation we hope to cover a wide range of backgrounds and abilities.

The training portal aims to be a sustainable open access educational and training resource for Computational Biomedicine, including HPC, and it displays

- the past and upcoming training events
- the training material developed for each course
- the training courses offered by our partners.

https://www.compbiomed.eu/training-3/

Visitor Programme

The Visitor Programme (formally 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 to adopt best practice software development tools and techniques by facilitating short internships within industrial organisations.

On this webpage we have a form which you can fill in if you are interested in taking part in this scheme (as a host or a visitor) along with a list of people who have already indicated some interest.

https://www.compbiomed.eu/innovation/visitor-programme/

Upcoming Events

CompBioMed Webinar Series:

8. The EOSC Digital Innovation Hub: open data services for biomedicine and business

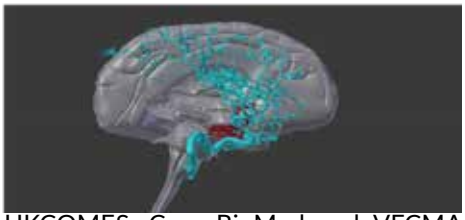
28 May 2019

An increasingly important part of computational biomedicine workflows is the sharing, processing and publishing of datasets. The European Open Science Cloud (EOSC) aims to provide a virtual environment with open and seamless services for storage, management, analysis and re-use of researhc data. This webinar will introduce the eOSC Digital Innovation Hub (DIH), which provides the primary mechanism for private organisations (start-ups, SMEs, large industry) to engage with the EOSC. Registration for the webinar is free: https://attendee.gotowebinar.com/register/170381819891912461

HemeLB: cardiovascular modelling and simulation with UKCOMES

University College London, UK,

29-30 May 2019



UKCOMES, CompBioMed and VECMA are hosting a meeting on "HemeLB: cardiovascular modelling and simulation in UKCOMES" centred around lattice Boltzmann simulations for blood flow. As part of the meeting researchers at UCL will introduce and demonstrate the use of their HemeLB application and the progress they have made towards simulating the whole arterial tree. There will be talks from other users of HemeLB in addition to alternative LB applications including Palabos and DL_MESO. Register: https://www.eventbrite.com/e/hemelb-cardiovascular-modelling-and-simulation-in-ukcomes-tickets-58284136421

CompBioMed Webinar Series:

9. EUDAT services for FAIR Data Management

27 June 2019

This presentation will show how the CompBioMed community can use EOSC services for managing active research data (i.e. data transfer, storage, and sharing) and for preserving final research data (i.e. data archiving and publishing). We will give a brief overview of the EUDAT Services and demonstrate how they operate and integrate with each other to meet the data management requirements of research communities and comply with the FAIR principles (**F**indable, **A**ccessible, **I**nteroperable and **R**eusable). Target audience: community researchers, data managers and the IT support people. Registration will open soon.

CompBioMed Conference 2019

The conference is rapidly taking shape. We have fifteen symposia under 3 general themes:

- **Biomedical Application**
  - Organ Modelling and Simulation
  - Molecular Medicine
  - Genomics
  - Immunology
  - Oncology
- **Methodology**
  - Multiscale Modelling
  - Role of Theory, Modelling and Simulation in Biomedicine
  - Machine Learning, Big Data and AI
  - Uncertainty Quantification
  - From Quantum AI to the Virtual Human
- **Technology & Outreach**
  - Education, Training & Public Awareness
  - Imaging and Visualisation
  - Regulatory Science and *in silico* Trials
  - Cloud and High Performance Computing
  - Innovation in Modern Biotechnology

We have now secured invited speakers for each of these symposia, which can be found on the website (https://www.compbiomed-conference.org/invited-speakers/). We are now receiving and assessing submitted abstracts to include in these events.

Once we have informed all our applicants of the outcome of these submissions, we will finalise the programme for the conference. It will run from 9am - 5pm each day. Following plenary talks we will have 3 parallel sessions, so there will be something to suit all interests.

Register now at: https://www.compbiomed-conference.org/registration/

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 Associate Partners, past and future events. We have an active and growing following on Twitter (@bio_comp), a user-forum on LinkedIn (CompBioMed) and we have our own YouTube channel (Computational Biomedicine), where you can watch live streaming of events and presentations at previous events and webinars, as well as our Virtual Humans film.

CompBioMed Coordinator:
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