Newsletter Issue No. 4
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Welcome

Prof. Peter V Coveney
Principal Investigator & CompBioMed Coordinator

Welcome to our 4th CompBioMed Newsletter in which we are excited to announce more Associate Partners have joined our efforts and we have had great success with our *Virtual Humans* film.

We have been very busy over the last months since the last Newsletter and are pleased to introduce our updated and restructured website with news and information pages dedicated to our target user groups. We have also upgraded our Software Hub (compbiomed.eu/services/software-hub/) and are in the process of extended the list of services to include those of our Associate Partners. Within this Newsletter, you can read about some of the new software releases and updates that have recently been announced, as well as related awards won by members of CompBioMed. We have chosen a small selection of recent publications, but the full list can be found on our website (compbiomed.eu/media-social/publications/).

Please note that we have some exciting events upcoming, including our 4th Webinar introducing biomedical applications on HPC. We are particularly pleased that we will have the opportunity to show our *Virtual Humans* film at another public event at the Cheltenham Science Festival in the UK. In addition, it will be featured in a popular Dutch television programme on the future of science and technology. There are also many other interesting plans for additional showings of the film, repeating these public events across the world. Having released the film on YouTube in March, we have had over 5000 views to date and an overwhelmingly positive response to all showings.

CompBioMed has now reached its mid-term review, and we are busy preparing for our review meeting in Luxembourg later in June. We look forward to presenting our future plans to the reviewers and showing them the progress we have made to date. We intend to organise further workshops and training events in our final 18 months, and we will announce these on our website and in future newsletters.

Prizes and Awards

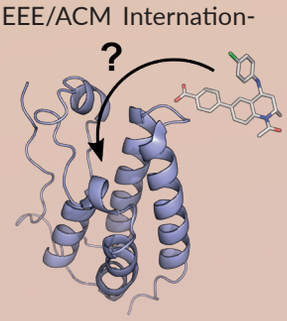
International 3Rs prize

Dr Elisa Passini, in the group of Professor Blanca Rodriguez and Dr Alfonso Bueno-Orovio, at the University of Oxford, has won the International 3Rs Prize for computer modelling that predicts human cardiac safety better than animal studies.

Their award-winning paper, in collaboration with Janssen Pharmaceutica, describes the use of human-based computer models that have proven to be more reliable in predicting the risk of drug-induced heart arrhythmias in humans than similar datasets conducted in animal studies.

SCALE award

The work of UCL and Rutgers (Associate Partner), executing and managing large and complex campaigns of ligand binding simulations (using the domain specific middleware, HTBAC), has won the 11th IEEE International Scalable Computing Challenge (SCALE 2018) at the IEEE/ACM International Symposium on Cluster, Cloud and Grid Computing (CCGrid) 2018 held in Washington DC. The prize rewards real-world poblem solving using computing that scales. This uses the HTBAC software described later in the newsletter (p2).



Publications

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- M. O. Bernabeu, M. L. Jones, R. W. Nash, A. Pezzarossa, P. V. Coveney, H. Gerhardt, C. A. Franco, PolNet: A Tool to Quantify Network-Level Cell Polarity and Blood Flow in Vascular Remodelling, *Biophys. J.* **2018,** DOI: 10.1016/j.bpj.2018.03.032
- D. Groen, R. A. Richardson, R. Coy, U. D. Schiller, H. Chandrashekar, F. Robertson, P. V. Coveney, Validation of patient-specific cerebral blood flow simulation using transcranial Doppler measurements, *Frotn. Physiol.*, **2018,** DOI: 10.3389/fphys.2018.00721

Software Releases and Updates

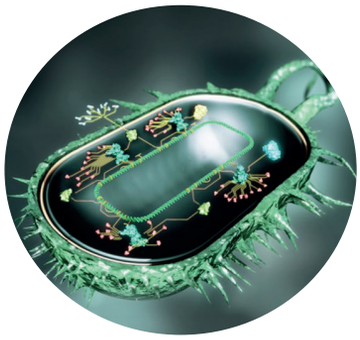
PolNet

PolNet is a software tool for the computer simulation of blood flow in realistic microvascular networks imaged with a wide variety of microscopy and clinical imaging techniques. To date, PolNet has contributed to a) uncovering the relationship between blood flow and blood vessel biology and its importance for correct vascularisation of tissues, and b) devleoping ways of predicting retinal vascular damage in diabetic retinopaty patients. PolNet facilitates the adoption of cutting-edge computer simulation technology by non-experts in the Biosciences. This software is featured in a recent paper published through a collaboration of UCL, with our Associate Partner at the Centre for Medical Informatics at the University of Edinburgh, in which the use and release of the software tool is outlined. https://doi.org/10/1016/j.bpj.2018.03.032

PolNet provides a complete workflow for image processing, three-dimensional vascular network reconstruction, and blood flow simulation with the HemeLB software. In addition, it provides tools for studying the relationship between the flow simulated and cellular/molecular readouts quantified in the same images. PloNet uses the Docker platform to facilitate deployment in experimental biology laboratories and hospitals. PolNet allows execution of HemeLB simulations on both commodity software and High Performance Computing resources. Ongoing work is aimed at enabling HemeLB execution on Cloud resources.

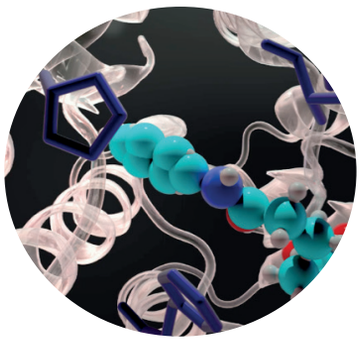
Visual GEC

Visual GEC is a software tool for designing engineered cells and simulating biochemical interactions (https://doi.org/10.1038/s41598-017-14415-8). The Genetic Engineering of Cells (GEC) software, developed by the Biological Computation team at Microsoft Research (Cambridge, UK), is a modelling tool that can be used to design and simulate synthetic genetic circuits. At the core is a domain-specific programming language for biochemical systems (LBS), originally developed at the University of Edinburgh. The tool supports stochastic and deterministic simulation of the temporal dynamics of chemical reaction networks, but also spatio-temporal dynamics via reaction-diffusion equations. Parameter inference can also be performed using Metropolis-Hastings Markov chain Monte Carlo with time-series data.



The software allows logical interations between potentially undetermined proteins and genes to be expressed in a modular manner. Programs can be translated by a compiler into sequences of biological parts, a process which relies on logic programming and prototype databases containing known biological parts and protein interactions. Programs can also be translated to reactions, allowing simulations to be carried out. The language is a first step towards the automatic translation of high-level behavioural designs to low-level DNA code.

https://www.microsoft.com/en-us/research/project/genetic-engineering-of-living-cells/



HTBAC

The efficacy of drug treatments depends on how tightly small molecules bind to their target proteins. Quantifying the strength of these interactions (the so called 'binding affinity') is a grand challenge of computational chemistry, surmounting which could revolutionize drug design and provide the platform for patient specific medicine. Recently, evidence from blind challenge predictions and retrospective validation studies has suggested that molecular dynamics (MD) can now achieve useful predictive accuracy (<= 1 kcal/mol). This accuracy is sufficient to greatly accelerate hit to lead and lead optimization. Translating these methodological advances into tools which can influence industrial and clinical decision making requires tools which facilitate the coordination of huge simulation campaigns (potentially incorporating many thousands of individual runs).

Our Scale 2018 award winning work (http://www.compbiomed.eu/wp-content/uploads/2018/05/scale2018-ccgrid.pdf) used our software HTBAC to manage calculations of the binding affinity of a range of drugs targetting the the BRD4 protein -- inhibitors of which have shown promising preclinical efficacy in pathologies ranging from cancer to inflammation. Our runs demonstrated the ability to use thousands of nodes to run coordinated batches of simulations. Furthermore, HTBAC allowed us to adapt the specifics of the runs to improve the efficiency of calculations looking directly at drugs binding affinities and more accurate computations of differences between closely related compounds.

Lightox

Lightox is a young SME founded in August 2016 but based on 8 years of research into novel compounds that have a unique function within cells. Lightox have developed a range of revolutionary tools for the interrogation, study and delivery across the therapeutics, diagnotics and life science tools industries. Prof Andrew Whiting, andy.whiting@lightox.co.uk, is the Chemistry Director of the company.

InSilicoTrials Technologies

InSilicoTrials is the first cloud-based platform with easy-to-use tools to perform computational modelling and simulation in pharmaceutical and medical devices development. Luca Emili, Luca.emili@promeditec.com, is CEO of InSilicoTrials and can be contacted for questions relating to the company

Towards Computational Cardiovascular Science in the Clinic

Dr Alfonso Bueno-Orovio
British Heart Foundation Intermediate Basic Science Research Fellow, Department of Computer Science, University of Oxford

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Dr Ernesto Zacur
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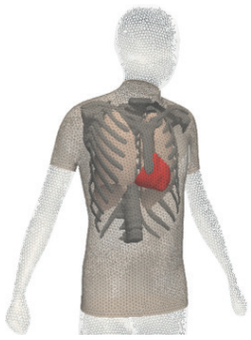
Wellcome Trust Senior Research Fellow in Basic Biomedical Sciences, Department of Computer Science, University of Oxford

CompBioMed is pushing the boundaries of modelling and high performance computing to achieve the ambitious goal of bringing these technologies closer to their translation to the biomedical and clinical settings. This is supported by solid scientific grounds, not only in the required technological infrastructures but especially in our current understanding of the underlying human physiology. In particular, investigations on the electrical activity of the human heart (cardiac electrophysiology) have one of the longest track records within the field of computational medicine, with more than half a century of history in the iteration between modelling and physiology in building new scientific knowledge with concomitant benefits for human health.

At the University of Oxford we are advancing the integration of modelling and simulation technologies with clinical imaging and electrophysiological recordings from patients affected by a variety of heart disease conditions. The constructed biophysically detailed models, both in terms of cardiac anatomy and electrical function, allow highly accurate reconstructions of the electric fields generated by the heart in the human body, in direct correspondence with the clinical electrocardiogram [1]. The use of such computational frameworks, together with advanced signal processing and machine learning techniques [2], is allowing us to augment the information we can obtain from these signals to improve diagnosis and to establish mechanistic links between abnormalities in electrical function and/or cardiac structure and the clinical manifestations of heart disease in these patients.

Further current developments of these methodologies at Oxford include state-of-the-art integration of clinical magnetic resonance imaging, imaging analysis and adoption of statistical atlases of the human body. Such an advanced approach grants us the feasibility of building fully personalised heart-torso anatomical models with complete reconstruction of the thoracic cavity (accounting for highly detailed heart anatomies, but also as an example ribs and lungs), directly from the clinical imaging studies of the patients [3]. The exploitation of such personalised human models, in close collaboration within CompBioMed with the Barcelona Supercomputing Centre, opens new prospects for scientific discovery and novel clinical applications. These involve, among others, the discrimination in clinical recordings between the contribution of each patient's specific anatomy and those arising from their disease state, the development of individualised score metrics for risk stratification, and therefore an improved tailoring of their pharmacological and electrical therapy. Such advances will lead to markedly improved outcomes for patients and enhance the health and wellbeing of citizens of the EU, also contributing to the financial sustainability of our health systems and optimisation of resources for adequacy of care.



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2. Lyon A, Ariga R, Mincholé A, Mahmod M, Laguna P, de Freitas N, Neubauer S, Watkins H, Rodriguez B. Front. Physiol. https://doi.org/10.3389/fphys.2018.00213. 2018.
3. Zacur E, Mincholé A, Villard B, Carapella V, Ariga R, Rodriguez B, Grau V. MICCAI Workshop in Bio-Imaging and Visualization for Patient-Customized Simulations, 2017.

CompBioMed Welcomes New Associate Partners

Dassault Systèmes

Dassault Systèmes, the **3D**EXPERIENCE Company, provides businesses and people with virtual universities to imagine sustainable innovations. Its **3D**EXPERIENCE Platform leverages the Company's world-leading 3D software applications to transform the way products are designed, produced and supported, enabling businesses to craft delightful customer experiences. Dr Steve Levine, Steven.LEVINE@3ds.com, is senior Director of Health and Life Science and Executive Director of the Living Heart Project of Dassault SIMULIA. Clint Davies Taylor, Clint.DAVIES-TAYLOR@3ds.com, is Sales Director for SIMULIA EuroNorth Academia and works very closely with the Life Sciences team at Dassault Systèmes coordinating their relationships with many leading Life Sciences Researchers in Europe

Diamond Light Source

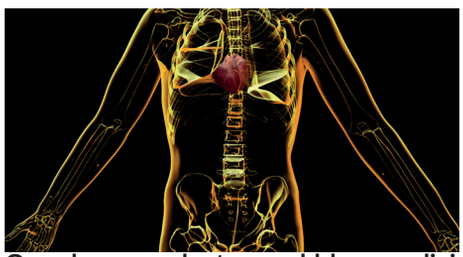
Diamond Light Source is the UK's synchrotron science facility. Diamond's state-of-the-art facilities and world class people act as agents of change, addressing 21st century challenges such as disease, clean energy and food security. Diamond research supports new medicines, technologies and advances throughout the sciences. Andrew Richards, andrew.j.richards@diamond.ac.uk, is the Head of Scientfic Computing at Diamond and can be contacted for questions and collaborations.

Upcoming Events

Webinar #4
Introduction to Biomedical Applications on HPC
7th June 2018

This webinar introduces the fundamental concepts and basic tools of HPC environments by Dr Gavin J. Pringle (EPCC), and includes an application example of flowing red blood cells in a vessel section by Dr Gabor Zavodszky (UvA). The whole talk forms a coherent unit providing a brief guide that takes you from the conceptual basics of HPC computing to an actual application. You can register for the webinar at: https://attendee.gotowebinar.com/register/6428440257819269379

Cheltenham Science Festival
IMAX screening and Q&A with the researchers
9th June 2018



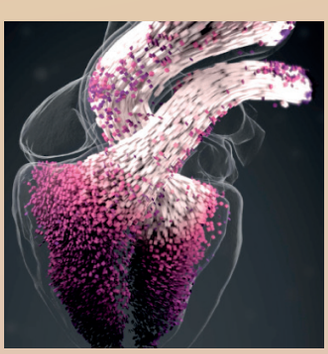
One day your doctor could have a digital version of you in a computer. It could be dissected, probed and explored in unprecedented detail to work out what is wrong and to help choose the best treatments for you as an individual. Roger Highfield talks to **Peter Coveney, Ana Mincholé** and **Andrea Townsend-Nicholson** who are bridging the fields of human biology, chemistry and computational science to pioneer this technology. https://www.cheltenhamfestivals.com/science/whats-on/2018/building-a-virtual-human/

CompBioMed BoF at
ISC-High Performance 2018
27 June 2018

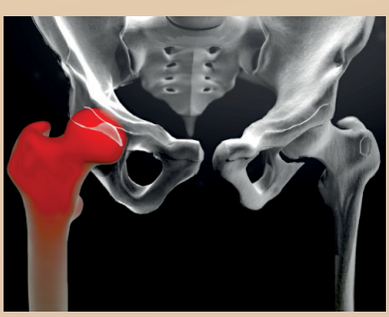
How do we bring HPC to medical SMEs, clinical researchers and hosptials? As we are nearing the exascale era, too few benefit from such computational power, and even fewer achieve excellence in HPC applicaiton delivery and use. By bringing together the biomedicine community and the HPC industry, we hope to help the community better embrace upcoming technologies, and help the industry better understand the needs. To feed the debate, all interested parties are welcome to atted and help paving the way to excellence.

"The Virtual Human" Film

On 9th March we released our Virtual Human film on YouTube: https://youtu.be/1FvRSJ9W734. We have released it on three different accounts to maximise visibility, and we have had over 5000 views to date. The film has been received with great enthusiasm at all events that it is shown and has enabled over one million twitter impressions. It has won awards and nominations at a number of science film festivals.



The film won the SCINEMA award for Technical Merit, an International Science Film Festival in Australia. The comment from the jury was "This film is a technically stunning example of the power and versatility of supercomputers, helping us see our body in ways we never have before." It has also been shortlisted in the AFO (Academic Film Olomouc) Festival of Science in the Short Film Competition.



As detailed above, we will be showing the film with Q&A from researchers in the field at the Cheltenham Science Festival in the UK.

The film will also feature on a popular Dutch television programme ("de wereld van morgen"), dedicated to innovation in the Netherlands. During the show the Dutch innovation prize will also be awarded by the second Dutch astronaut, Andre Kuipers, and we expect a very large audience for this programme.

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 (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.

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