CompBioMed

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Welcome

Prof. Peter V Coveney
Principal Investigator & CompBioMed Coordinator

I would like to wish all our readers a very happy 2018, and welcome you to our Newsletter. We have had a very busy and productive 2017, and now look forward to another year. Since our previous newsletter our flagship "Virtual Humans" IMAX film was released at the end of September, we have started the CompBioMed webinar series, and welcomed more Associate Partners. In addition various partners have published important papers, some of which are described below.

We were delighted by the high turn-out for our IMAX film at our Associate Partner the London Science Museum at the end of September (which you can read about below). The tickets were sold out ahead of time, and we had a full and engaged audience who gave positive feedback on the event. We have since shown the film at the Imagine Science Film Festival in October, and we are planning to show the film, with presentations and Q&A session at the Cheltenham Science Festival in June. This will hopefully be repeated in other countries in collaboration with our partners in the future, so keep a close eye on the Science Museums near you.

Looking ahead, we are planning for our annual All-Hands Meeting in Amsterdam at the end of March, during which we will again have two guest speakers (Prof Tim Elliott, University of Southampton, and Prof Ralph Mueller, ETH Switzerland). We plan to hear from our Core and Associate Partners, and to hold our 2nd Innovation Advisory Board Meeting. After this meeting, we shall hold a joint Workshop with the Spanish Network of Excellence, Virtual Heart, during which we will be investigating cardiovascular and blood flow modelling with members of both projects.

We have also started our Webinar series, and we will be announcing the remaining webinars very shortly. Our first webinar, *HPC simulations of cardiac electrophysiology using patient specific models of the heart (using CHASTE and Alya)*, took place on 22nd November and we had a good turnout, if you would like to watch it, it is on our YouTube channel or website, http://www.compbiomed.eu/compbiomed-webinar-1/. Our second webinar, *Introduction to Cloud computing for the VPH*, will be taking place on 30th January. You can find out more and register here: http://www.compbiomed.eu/compbiomed-webinar-2/.

"The Virtual Human" IMAX Event

On Wednesday 27th September, we unveiled our film - "Virtual Humans" - at the Science Museum IMAX theatre in London in front of an audience of 400.

To create truly personalised medicine, doctors dream of the day when they can create a digital Doppelgänger of you, one that can be a guinea pig, crash test dummy and a drug trial volunteer all rolled into one. That way they can perfect medical treatments on your virtual clone before they try them out on you.

Speakers prepare for the Science Museum Lates IMAX event.

Virtual organs are already taking shape as a result of efforts by many groups worldwide, including severnal in the CompBioMed Centre of Excellence. Our projecthas enabled these medical simulations through access to supercomputers such as ARCHER, the UK national supercomputer; Marenostrum, at the Barcelona Supercomputing Centre (BSC), Spain; and SuperMUC at the Leibniz Supercomputing Centre, Germany.

The movie premier was part of the Science Museum Lates series. The hour-long feature described recreating a human being *in silico*, including the IMAX film which was composited on the Marenostrum supercomputer at BSC. The film showed stunning simulations on aspects of computational biomedicine using several of the largest supercomputers in Europe.

The Science Museum Lates events take place once a month and feature a different theme each month. Typically, they attract 4,000-7,000 people, and the CompBioMed film at the IMAX cinema proved to be a very popular attraction. The free tickets were available to reserve before the event, and sold out in the days leading up to the event.

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Publications

- R. Eccleston, P. V. Coveney, and N. Dalchau, Host genotype and time dependent antigen presentation of viral peptides: predictions from theory, *Sci Rep-UK*, 7 (1), 14367, **2017**
- J. J. Luna, M. Skalic, G. Martinex-Rosell, G. De Fabritiis, K_{DEEP}: Protein-ligand absolute binding affinity prediction via 3D-convolutional neural networks, *J Chem Inf Model*, Just Accepted, 10.1021/acs.jcim.7b00650
- A. Lyon, A. Minchole, J. P. Martinez, P. Laguna, B. Rodriguez, Computational techniques for ECG analysis and interpretation in light of their contribution to medical advances, *J Roy Soc Interface*, 15 (138), **2018**
- R.C.Eccleston, S. Wan, N. Dalchau, P.V. Coveney, The role of multiscale protein dynamics in antigen presentation and T Lymphocyte recognition, *Front Immunol*, 8 (797), **2017**

HPC-Europa 3 Memorandum of Understanding

The HPCEuropa3 project runs from May 1st 2017 to April 31st 2021 and aims at maintaining high-quality service to transnational access. Transnational access allows researchers to visit the most advanced HPC infrastructures available in Europe for European research. The project is based on a program of visits, with researchers visiting HPC centres and/or scientific hosts who mentor them scientifically and technically.

The visitors are:

1. Funded for travel, accommodation and subsistence
2. Provided with an amount of computing time suitable for the approved project.

The calls for applications are issued 4 times per year and published online at www.hpc-europa.eu. The next deadline is 28th February 2018

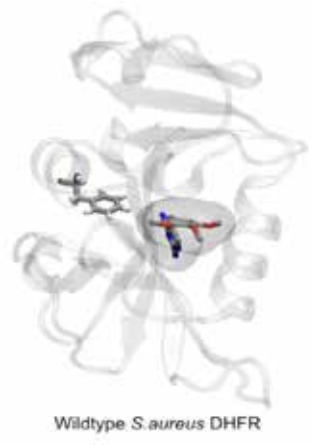
A close collaboration between CompBioMed and HPCE3 is very desirable as the HPCE3 project is going to serve as a starting point for the applicants in their natural evolution towards future deployment of HPC exascale infrastructures, while CompBioMed promotes the uptake and exploitation of high performance computing within the biomedical modelling community

Predicting whether individual bacterial protein mutations confer antibiotic resistance

Dr Phil Fowler

Senior Researcher in the Modernising Medical Microbiology group, Nuffield Department of Medicine, University of Oxford

Everyone appreciates the threat to modern medicine posed by the rise of antibiotic resistance and the resulting urgent need to develop new classes of antibiotics. What is less well understood is that new, faster diagnostic methods are at least as important as new drugs in sustaining our ability to treat bacterial infections.



Wildtype *S.aureus* DHFR

The traditional approach to determining which antibiotics can be used to treat an infection is to grow (culture) a sample and then expose it to a panel of antibiotics and determine which prevent further growth. Whilst there have been important advancements in imaging and automation, Alexander Fleming would have understood this method.

There is, however, a coming technological revolution in clinical microbiology. One of the most promising approaches is to sequence the whole genome of the infecting pathogen and, having compared to a reference genome, look up any encountered mutations in a panel of key genes and infer their effect on a panel of antibiotics. This is potentially faster, more reproducible, is getting cheaper all the time, and you also get epidemiological data for free.

Nor is this fantasy; since March 2017, all patients with suspected Tuberculosis in England have routinely had their sputum sample sequenced and an antibiogram inferred by Public Heath England [1]. Such a whole-genome sequencing (WGS) clinical microbiology service has one key weakness; it cannot return a result for mutations that have not been encountered enough times to allow them to be classified.

Researchers at the Oxford NIHR Biomedical Research Centre, led by Philip Fowler, are developing methods using molecular simulation that are able to predict the effect of individual mutations on the action of an antibiotic. The hypothesis on which the method is based is that mutations in a bacterial target protein confer resistance by abrogating the binding of the antibiotic whilst, crucially, not materially affecting the binding of the natural substrate. This boils down to calculating the effect of the mutation on the antibiotic and substrate binding free energies. Since the antibiotic often competes with the substrate this is a difficult and subtle problem and so faster, but less necessarily less accurate, methods of calculating free energies are ineffective.

Philip Fowler presented results from a preliminary study on the action of trimethoprim in S. aureus at the recent CompBioMed & BioExcel Free Energy Workshop at UCL. He showed how large numbers of short replica-exchange thermodynamic integration calculations were able to not only predict which mutations conferred resistance (and which did not) but also that the calculations were reproducible, a necessary condition if the results of this method are ultimately to be included in any clinical microbiology service.

1. Walker TM, Cruz ALG, Peto TE, Smith EG, Esmail H, Crook DW. Tuberculosis is changing. Lancet Infec Dis 2017; 17: 359–61.

Qatar Robotic Surgery Centre, Hamad Medical Corporation

QRSC is a centre dedicated to producing technological innovations through research, development and training (i.e. skills development) in the delivery of surgical care and interventions. As the focus of the centre is clinical, it is an ideal partner to work with CompBioMed. Senior contact point is Dr Abdulla Al-Ansari (aalansari1@hamad.qa)

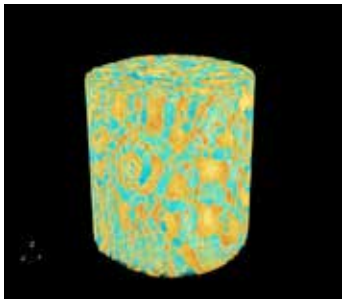
DiaVita, Life Science

DiaVita Ltd is based in Varna, Bulgaria and addresses recent advances in data mining, machine learning, and predictive analytics of the growing volume of heterogeneous health data that is emerging from both real-time, on-line and offline systems, and that exists in a variety of formats, types and dimensions. Dr Dimiter Dimitrov mailto:dimiter@diavita.org is the main contact.

Bridging the gap: Pushing the boundaries of simulations to understand Atrial Fibrillation

Dr Jazmin Aguado-Sierra

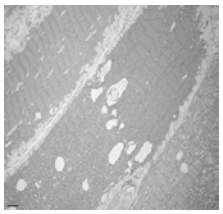
Senior Research Assistant at Barcelona Supercomputing Centre.

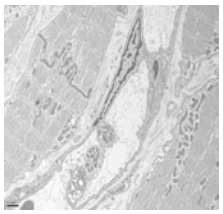


Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with a high prevalence, affecting up to 1.5% of the population in the developed world1. The molecular, electrophysiological and structural changes leading to atrial fibrillation progression from paroxysmal to persistent have not been described in detail. Oxidative stress, atrial dilatation, calcium overload, inflammation, microRNAs and myofibroblast activation are all thought to be involved in AF-induced atrial remodel-ling1. The extracellular matrix is affected and thus conduction propagation is also affected in a hetero-geneous manner, leading to progression of the arrhythmia.

The Computer Applications in Science and Engineering Department of the Barcelona Supercompu-ting Center, with support from CompBioMed, in collaboration with the Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III in Madrid (CNIC), Spain recently made measure-ments at the European Synchrotron Radiation Facility, Beamline ID16A, to obtain 3-dimensional images at the nano-scale resolution of the atrial tissue of human donor hearts and an experimental pig protocol of atrial fibrillation. The aim, is to visualize the arrhythmic substrate to study the structural remodelling underlying atrial fibrillation progression from in-vivo models and human donors to cre-ate the most detailed existing computer simulations of electrophysiology employing the exact tissue structure. The project has a multi-disciplinary, multicenter and translational design that enables us to generate both, an in vivo pig model, based on rapid atrial pacing that resembles clinical progression of AF, and to study isolated Langendorff-perfused human hearts from donors to correlate the propa-gation dynamics identified in the animal model with those present in the human heart.

Full 3-dimensional high resolution, transmural images of the progression stages of AF of intact tissue had never been achieved. Firstly, because the experimental model is complex, time consuming and costly. And secondly, because the computational power to process and simulate in high detail the tissue microstructure was unavailable, and even now, only capable of running in supercomputers. The quantification of the subtle changes in structure of the intact tissue can bring into light some of the mechanisms of progression of the disease. Heterogeneous transmural remodelling has been related to atrial fibrillation sustenance, therefore the need of imaging the transmurally intact tissue3 using syn-chrotron radiation.





The team aims to segment the tissue structure to create finite element detailed models of the tissue in health and at various stages of AF to create electrophysiology simulations using Alya. The tissue sim-ulations will provide a quantitative/structural decision tool to support parameter estimation for com-putational models of electrophysiology and mechanics for clinical and patient-specific applications.

The study is being led by Dr. Jazmín Aguado-Sierra from BSC. Dr. José Jalife, Dr. David Filgueiras and José Manuel Alfonso Almazán from CNIC designed and created the experimental animal protocol under grant number SAF2016-80324-R.

Dr. Constantine Butakoff, from the Universitat Pompeu Fabra is in charge of the image processing and segmentation. The preliminary results shown in figure 1 were obtained after a tissue freeze-substitution protocol performed by Dr. Cristina Patiño at the Centro Nacional de Biotecnología of Madrid.

1. Jalife J, Kaur K. Trends in Cardiovascular Medicine, August 2015, 25(6), pp 475-484.

CompBioMed Welcomes New Associate Partners

Microsoft

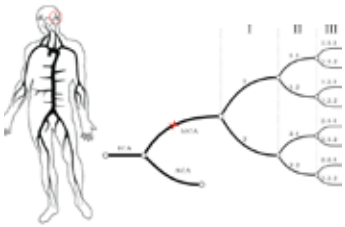
Microsoft have already sponsored our Cloud HPC event in April 2017 and "The Virtual Human" IMAX event at the Science Museum in September. Among other activities, Microsoft will facilitate access to the Microsoft Azure HPC cloud service. Microsoft Research not only performs research within Microsoft but collaborate in and supports research around the world well beyond the company itself. Principle contact with Microsoft is Dr Kenji Takeda (kenji.takeda@microsoft.com), Director of the Microsoft Azure for Research program.

Institute of Molecular Biology, National Academy of Sciences of Armenia.

The bioinformatics group work in computational biology. The group is focused on development and application of algorithms aimed at integration and systems level analysis of high-throughput *omics* data to understand processes guiding pathomechanisms of complex human disorders. Contacts for this Partner are Dr Arsen Arakelyan (arakelyanaa@zoho.com) and Dr Lilit Nersisyan (txgt.lilit.nersisyan@gmail.com)

Upcoming Events

Webinar #2 Introduction to Cloud Computing for the VPH 30th January 2018



What is a cloud environment and how can it help your research? We give an overview and demonstrate for the 1D blood flow model openBF. The webinar will be delivered by SURFsara and University of Sheffield. You can register at: https://attendee.gotowebinar.com/register/4269795464897031682

CompBioMed Training: Winter School 2018, BSC, Barcelona 14-16 February 2018

The objective of this course is to give a panorama on the use of HPC-based computational mechnanics in Engineering and Environment through the projects BSC are carrying out. More information can be found by following the link on our events website: http://www.compbiomed.eu/events-2/

CompBioMed All-Hands Meeting UvA, Amsterdam 26-27 March 2018

The CompBioMed All-Hands Meeting organised at the University of Amsterdam will take place over two days. We invite Core and Associate Partners to get involved and a number of other European projects will be represented as we report on and discuss how the project is shaping up. https://wp.me/P87tNu-mW

CompBioMed & VHeart Joint Workshop UvA, Amsterdam 28 March 2018

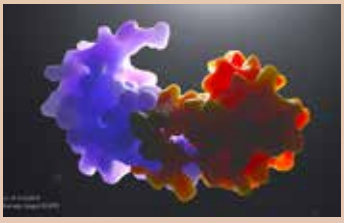
CompBioMed are joining the Spanish Network of Excellence, VHeart for a one-day Workshop on Cardiovascular Modelling, Solid-fluid Interactions and Biomedical Flows. A mixture of speakers are arranged from both projects, and it promises to be a fruitful and interesting event. https://wp.me/P87tNu-s8

"The Virtual Human" IMAX Event

(continued from front page)

The event started with the film; the leaders of the research groups whose work was shown each gave a 5-minute presentation, followed by questions to the panel from the Director of External Affairs of the Science Museum, Dr Roger Highfield, before the audience were invited to ask questions of the panel. The panel consisted of:

- Prof Peter Coveney (UCL), consortium lead who spoke on simulating how drugs work in the body
- Prof Blanca Rodriguez (Oxford University) on virtual hearts
- Prof Marco Viceconti (Sheffield University), a key player in the Virtual Physiological Human Initiative
- Prof Alfons Hoekstra (University of Amsterdam), on virtual blood vessels and more.



Production of the film started 9 months before this event, and involved numerous Core and Associate Partners within the project. Led by University College London and directed at Barcelona Supercomputing Center by Guillermo Marin and Fernando Cuchietti, the diverse computational models were incorporated to take the audience through the simulation of various aspects of the human body, and from there to the future possibility of creating a virtual human.

The film has been shown and is planned to be shown at various film festivals. The film is available for members of the consortium with a password that can be provided by e.lumley@ucl.ac.uk. More information on this event can be found at:

http://www.compbiomed.eu/how-to-build-the-virtual-human/

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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