

Welcome

Prof. Peter V Coveney
 Principal Investigator & CompBioMed Coordinator



As we head into our final year of CompBioMed, we welcome the news that our Centre of Excellence has secured funding for a further four years through the recent call for new Centres of Excellence in High Performance Computing. This of necessity obliged us to spend a considerable amount of time and effort assembling a major bid during the first few months of this year but the hard work paid off and we are delighted with the outcome.

This means we can plan for the succession and capitalise on the opportunity provided to grow our plans for sustainability into the longer term. These plans are based on continuing and growing interest from the three sectors we work with, academia, industry and clinical. Each has diverse needs which we are able to serve. And CompBioMed has already overseen the creating of two start up companies, ELEM Biotech and EnsembleMD, which are both featured in the newsletter.

Our Centre of Excellence will grow to include the Leibniz Rechenzentrum in Garching near Munich as a core partner. LRZ brings in anticipated access to the exascale through a combination of both German

national and European exascale computing plans over the next several years. We also welcome two new third parties, Argonne National Laboratory in Chicago and Rutgers University in New Brunswick, both in USA, led by Rick Stevens and Shantenu Jha respectively. Argonne expects to house an exascale machine by 2021, well within the lifetime of the extended CompBioMed project, while Rutgers will provide ongoing support in workflow management on emerging exascale architectures.

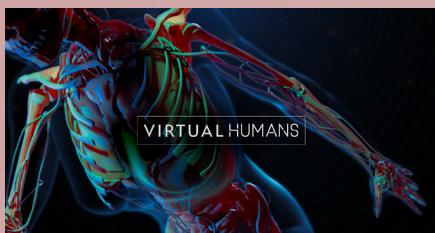
We would like to use this opportunity to introduce a highly relevant and a related EU funded FET HPC project, VECMA, which is working on Verification, Validation and Uncertainty Quantification within HPC applications. More information can be found on their website: www.vecma.eu.

We are looking forward to exhibiting our Centre of Excellence at the upcoming VPH2018 conference with a training course and booth, in which we will host the Virtual Human film and demos from our research exemplars. We are still extending our software hub with examples of new and existing software from our Associate Partners, and you can see some examples in this edition of the Newsletter.

CompBioMed2 and FocusCoE

In March this year we were particularly busy finalising the CompBioMed2 proposal for the 2018-2020 call from the Commission for Centres of Excellence. In July we found that we were successful in this bid, and we have been working towards putting

the Grant Agreement in place. We are excited to start this second phase of our project, which will give us a chance to make more progress on all the great research and collaborations that we have started in CompBioMed1.



We would like to thank all our Core Partners who worked so hard to put the proposal together, and make it as strong as possible. In addition we would like to thank all our Associate Partners, and poten-

tial Associate Partners who added their support to the bid through their letters of support. We are looking forward to the future of CompBioMed.

In addition to this, UCL was also involved in a Coordination and Support action bid, known as FocusCoE. We are happy to say that this was also successful, and will work with CompBioMed and all the other CoEs to ensure that they run more efficiently and adopt common practices within the HPC environment. The placement of UCL within this CSA project will ensure that CompBioMed is well represented.



Publications

- R. Dutta, B. Chopard, J. Latt, F. Dubois, K.Z. Boudjeltia, A. Mira, "Parameter Estimation of Platelets Deposition: Approximate Bayesian Computation with High Performance Computing" *Front Physiol*, 2018, DOI: 10.3389/fphys.2018.01128
- M. Skalic, A. Verela-Rial, J. Jimenez, G. Martinez-Rosell, G. De Fabritiis, LigVoxel: Inpainting binding pockets using 3D-convolutional neural networks, *Bioinformatics*, 2018, DOI: 10.1093/bioinformatics/bty583
- A. Perez, G. Martinez-Rosell, G. De Fabritiis, Simulations meet machine learning in structural biology, *Curr Opin Struc Biol*, 2018, DOI: 10.1016/j.sbi.2018.02.004
- F. Sacco, B. Pain, O. Lehmkuhl, T.L. Illes, P.A. Iaizzo, G. Houzeaux, M. Vazquez, C. Butakoff, J. Aguado-Sierra, Evaluating the roles of detailed endocardial structures on right ventricular haemodynamics by means of CFD simulations, *Int J Numer Meth Biomed Engng*, 2018, DOI: 10.1002/cnm.3115
- D.S.M. Boulanger, R.C. Eccleston, A. Phillips, P.V. Coveney, T. Elliot, N. Dalchau, A mechanistic model for predicting cell surface presentation of competing peptides by MHC class I molecules, *Front Immunol*, 2018, DOI: 10.3389/fimmu.2018.01538
- S. Succi, P.V. Coveney, Big Data: the End of the Scientific Method?, *Phil Trans R Soc (Series A)*, in press 2018, arxiv.org/abs/1807.09515

tions Decrease the Wall Shear Stress and Increase the Intra-Ventricular Pressure Drop in CFD Simulations, *Front in Physiol*, 2018, DOI: 10.3389/fphys.2018.00458

• F. Sacco, B. Pain, O. Lehmkuhl, T.L. Illes, P.A. Iaizzo, G. Houzeaux, M. Vazquez, C. Butakoff, J. Aguado-Sierra, Evaluating the roles of detailed endocardial structures on right ventricular haemodynamics by means of CFD simulations, *Int J Numer Meth Biomed Engng*, 2018, DOI: 10.1002/cnm.3115

• D.S.M. Boulanger, R.C. Eccleston, A. Phillips, P.V. Coveney, T. Elliot, N. Dalchau, A mechanistic model for predicting cell surface presentation of competing peptides by MHC class I molecules, *Front Immunol*, 2018, DOI: 10.3389/fimmu.2018.01538

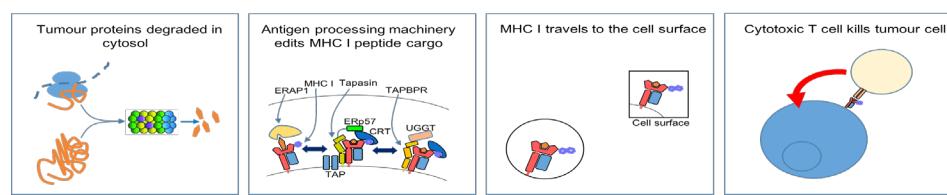
• S. Succi, P.V. Coveney, Big Data: the End of the Scientific Method?, *Phil Trans R Soc (Series A)*, in press 2018, arxiv.org/abs/1807.09515

A Mechanistic Model for Predicting Cell Surface Presentation of Competing Peptides by MHC Class I Molecules

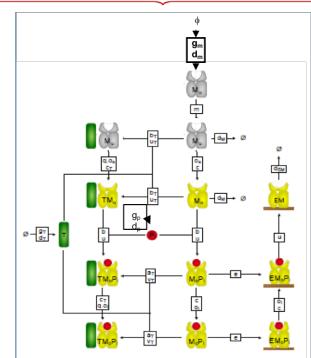
The processing and presentation of cellular antigens to cytotoxic T lymphocytes (CTL) lies at the heart of protective immune responses to infections and cancer, be they natural or induced by vaccination.

In a previous collaboration, the Elliott group at the Centre for Cancer Immunology at the University of Southampton, and the Phillips/Dalchau group at Microsoft Research Cambridge (both Associate Partners of CompBioMed) have built and experimentally validated a computational model that describes the antigen processing and presentation pathway. The team has subsequently started working with Prof Coveney's group (the Centre for Computational Science) at UCL, where Dr Ruth Eccleston further developed the model in a manner that can be used to predict the likelihood of a viral or cancer antigen being presented to CTL. This capability is a very valuable addition to the armoury of predictive tools that underpin vaccine development for infection and cancer.

CTL recognise peptide fragments of proteins (selected for presentation from a vast pool of candidates generated from the natural turnover of cellular proteins, including viral proteins in infected cells) and presented at the surface of cells bound to MHC I molecules. Inside the cell therefore, the function of MHC I is to select peptides for presentation, and this is assisted by the peptide-loading complex (PLC) in the ER which comprises newly assembled MHC I:beta2-microglobulin (b2m), tapasin, ERp57,



Antigen processing and presentation involves a complex series of intracellular events that regulate the generation and selection of peptide epitopes that are presented to killer T cells.



calreticulin and TAP (the transporter associated with antigen presentation).

The paper, which appeared in *Frontiers in Immunology* last month (July 2018) models the contribution to antigen presentation of a) the intracellular abundance of the source-protein, b) competition between peptides, c) the binding affinity of individual peptides for MHC I and d) the action of intracellular cofactors known to assist peptide loading of MHC I. Computationally intense model-fitting to experimental data delivered a predictive, mechanism-based algorithm as well as a mathematical abstraction that is well suited to transcriptomic big-data.

This is important because currently there is no quantitative model to predict the relative abundance of different peptide:MHC I complexes at the surface of antigen presenting cells, virus infected cells or cancer cells - and the Elliott group have previously shown that it is the abundance of specific peptide:MHC I that determines CTL immunodominance to both vaccines and cancer.

The model will therefore augment correlative algorithms designed to predict the presentation of specific peptides, and which are currently the only instrument available to vaccinologists resolved to provoking CTL responses to viral epitopes, and more

recently to epitopes generated from the cancer mutanome - the thousands of coding mutations that are found in individual tumours that could be seen by patient CTL. Be-

cause the Elliott/Dalchau model incorporates mechanistic knowledge of the antigen processing pathway, it could be used to predict the outcome (levels of presentation) under different physiological conditions - such as cytokine milieu. In fact the study, incorporating the work from the UCL group, accurately predicted the antigen presentation outcome when antigen presenting cells were cultured in the presence of interferon-gamma: a signature cytokine of cancers that respond well to immunotherapy.

Article written by **Prof Tim Elliott**

Original Paper: *Front. Immunol.*, 05 July 2018 | <https://doi.org/10.3389/fimmu.2018.01538>



EnsembleMD

tancy, software, tools and services for the rapid, accurate and reliable prediction of measurable macroscopic properties from molecular dynamics. Our flagship product is designed to facilitate the calculation of drug binding affinities, thereby reducing the cost and time to market in drug development for our key clinets in the Pharma industry. CTO of EnsembleMD is Stefan Zasada: s.zasada@ensemblemd.com

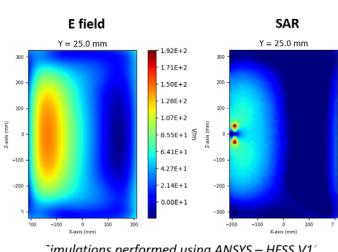
Pie Medical Imaging BV

Pie Medical Imaging (PMI) develops software for quantitative analysis in cardiology and radiology and is well-known for its product CAAS (Cardiovascular Angiographic Analysis System). PMI is a world leader in cardiovascular image analysis. Director of Research & Development, Jean-Paul Aben (JeanPaul.Aben@pie.nl), is the contact person with PMI



PIE MEDICAL IMAGING

Software Releases and Updates



InSilicoMRI

InSilicoMRI provides a framework to predict the overheating of a medical device during an MRI scan. The software allows evaluation of the radiofrequency (RF) safety analysis of a passive device exposed to a 3T MRI birdcage coil field following the directives of ASTM F2182 standard. The simulation calculates the EM fields, SAR, and thermal heating after 900 s of RF exposure.

This application uses Microsoft Azure cloud services to run the simulation.

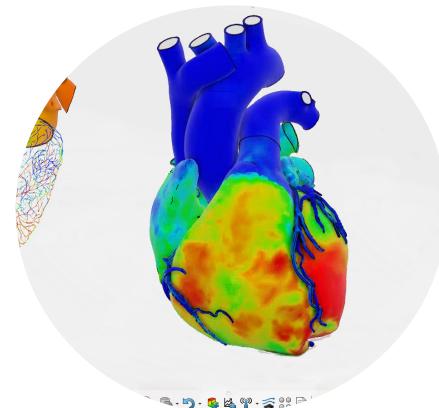
The software is developed in a collaboration between InSilicoTrials, ANSYS and FDA, to support the broadening use of computer modelling and simulation for electromagnetic safety analysis prior to medical device submission. It can be accessed at <https://insilicomri.com>

Living Heart Human Model

The SIMULIA Living Heart Human Model is a high-fidelity multiphysics model of a healthy, 4-chamber adult human heart and proximal vasculature. The dynamic response of the Living Heart is governed by realistic electrical, structural, and fluid (blood) flow physics. With this model, medical professionals, researchers, and device manufacturers will be able to rapidly conduct virtual experiments in a highly realistic 3D environment. The Living Heart can readily be used to study cardiac defects or disease states and explore treatment options by modifying its geometry, loading or electromechanical properties. In

addition, medical devices can be inserted into the model to study their influence on cardiac function, validate their efficacy, and predict their reliability under a wide range of operating conditions.

Living Heart Human Model is part of the Living Heart Project run by Dassault Systemes. All relevant links can be found: <https://wp.me/P87tNu-K3>



Virtual Assay

Virtual Assay

The Virtual Assay software provides a framework to run *in silico* drug trials in populations of human cardiac cell models for predictions of drug safety and efficacy. Virtual Assay starts with well-understood human cellular biology models and modulates the variables to generate a range, or population, of models which will respond differently to the same inputs. These populations

are then calibrated against experimental data, retaining only those models in Calibrated Model Populations range with experimental observations. Once calibrated, these populations can be used to analyse the effects of different pharmaceutical agents on cellular response at the population level.

Virtual Assay was developed by the Computational Cardiovascular Science Group at University of Oxford. More information can be found: <http://www.cs.ox.ac.uk/ccs/virtual-assay>

CompBioMed Welcomes New Associate Partners



ANSYS

ANSYS is the global leader in engineering simulation, a technology bringing clarity and insight to

their customer's most complex design challenges through the broadest portfolio of fast accurate and reliable simulation tools. ANSYS technology enables organisations in all industries to imagine high-quality, innovative and sustainable product designs that have an accelerated time to market.

Thierry Marchal, thierry.marchal@ansys.com, is the Global Industry Director for Healthcare. He leads the medical devices, pharmaceutical and biotech strategy of ANSYS through the *in silico* and personalised medicine evolution by closely interacting with industrial innovators and SMEs, academic leaders and governmental and regulatory authorities such as the FDA and the EMA.

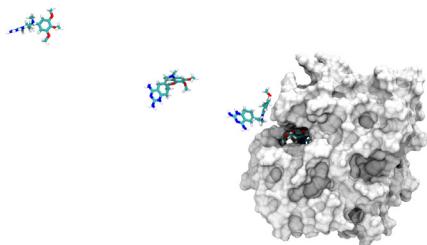
Medtronic

Medtronic is the world's largest medical technology company, offering an unprecedented breadth and depth of innovative therapies to fulfil their mission of alleviating pain, restoring health and extending life. With a global reach that extends to more than 160 countries, they have a deep understanding of many universal healthcare challenges. Frederic Turquier, frederic.turquier@medtronic.com, is Director of R&D for Surgical Innovations and is the principle contact for the company within the CompBioMed project.



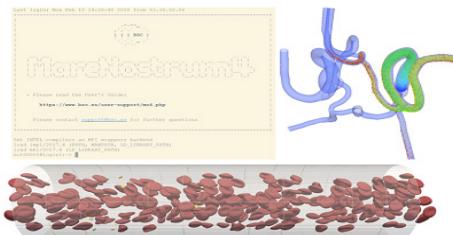
Upcoming Events

Webinar #5
High Throughput Molecular Dynamics for Drug Discovery
25th October 2018



Molecular dynamics (MD) simulations are used to capture dynamic processes of proteins across different timescales, with atomistic detail. The recent software and hardware innovations have decreased the computational cost of classical MD simulations, which can now be performed in high-throughput simulations, and we will show how to easily prepare and set up a system to study protein-ligand binding and compute its binding properties. Registration will open soon: <http://www.compbioemed.eu/compbioemed-webinar-5/>

CompBioMed Pre-Course,
HPC for the VPH, VPH2018,
Zaragoza, Spain
4th September 2018



The course will provide a practical introduction to HPC usage for biomedical applications. The lectures target early phase researchers and aim to provide a short and concise introduction to HPC programming. All lectures are hands-on using Barcelona's MareNostrum supercomputer. This course is now fully booked, however, we will report on the results and hope to have recordings available soon after. For more information: <http://vph-conference.org/pre-courses/course-b/>

CompBioMed Booth at
VPH 2018,
Zaragoza, Spain
5th - 7th September 2018



CompBioMed will be hosting a booth during the VPH conference. At the booth you will be able to watch the Virtual Human film and we will host three demos of the work that we are doing within CompBioMed during the lunch breaks.

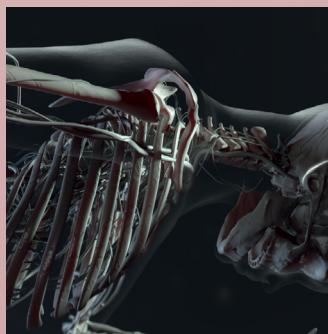
5th: Neuromusculoskeletal research, University of Sheffield (Pinaki Bhattacharya)

6th: Cardiac research, University of Oxford (Hector Martinez-Navarro)

7th: Drug Targeting research, University College London (Robin Richardson)

ELEM Biotech

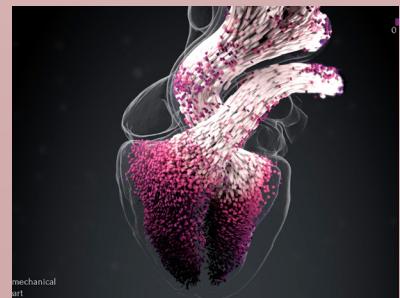
BSC's spinoff company, ELEM Biotech, has been born under the auspices of CompBioMed to commercialise, on a Cloud-Deployed Software-as-a-Service basis, the use of the HPC-based simulation code Alya for biomedical research. ELEM will become a Virtual Humans Factory, where *in-silico* trials can be



performed thanks to a specifically designed user interface. Although ELEM's first target will be the cardiovascular and respiratory domains, its vision is to progressively move to all organs and systems. Alya has a strong record in the efficient use of massively parallel computational resources and all this power will be put directly in the hands of clinicians, biologists and engineers from different realms: clinics, medical de-

vices, pharma and CROs. At ELEM, they create the most incredible software technology dedicated to replicating human physiology on supercomputers. They encapsulate medical knowledge into modelling and simulation tools for medical professionals. Working on tissues, organs and complex human models, clinicians, biomedical engineers and biotechnologists can test, validate and develop new medical treatments in a safe, reliable and replicable environment: *insilico* virtual humans.

The website is under construction, and can be found at <http://www.elem.bio>



Find CompBioMed online

Our website (www.compbioemed.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](https://twitter.com/bio_comp)), a user-forum

on LinkedIn ([CompBioMed](https://www.linkedin.com/company/compbio-med/)) and we have our own YouTube channel ([Computational Biomedicine](https://www.youtube.com/user/ComputationalBiomedicine)), where you can watch live streaming of events and presentations at previous events and webinars, as well as our Virtual Humans film.

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