

Newsletter Issue No. 11 January 2021

Welcome

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I would like to start by wishing you all a very happy New Year, a year in which we hope to slowly get back to the usual ways of interacting. 2020 has been an incred-

ibly challenging year for all of us, but as with many difficult situations, we have continued to work and fortunately in many cases, to thrive.

In this issue, we celebrate, from our partners and collaborators, some of the achievements of 2020, some inspired by the pandemic and others a continuation of work that we have long been involved in.

In 2019 we held the inaugural edition of the Comp-BioMed Conference, during which selected abstracts were put forward for journal articles in the Royal Society Interface Focus. After a significant delay caused by the pandemic, we are delighted to have seen the publication of the two themed issues. Below you will find details of these and a list of articles from both editions. We are now planning for the 2nd iteration of the CompBioMed Conference in September 2021, which we have decided to hold online.

As part of the Royal Society's UK RAMP initiative for Rapid Assistance in Modelling the Pandemic (https:// royalsociety.org/topics-policy/Health%20and%20 wellbeing/ramp/), members of the consortium and the VECMA project have evaluated the uncertainty present

in the CovidSim code, an epidemiological code designed to predict the impact of the spread of the pandemic on a national population. It was influential in making the UK government enforce a national lockdown in March 2020. In this newsletter we take a look at this work and explain some of its most significant findings.

Further research includes the investigation of the effect of blood flow on thrombus formation through microfluidic devices by the University of Amsterdam. Also, the University of Bologna are leading a project on in silico trials to simulate 1000 patients monitored for 10 years for bone strength and risk of fall.

At SC20, we held a special session on our provision of access to HPC resources to undergraduate students to solve important biomedical problems. This work, which was a collaboration between two Core and one Associate Partner, ensures the use of cloud HPC computing facilities to students for interactive teaching, even through remote facilities. The session was attended by over 350 people.

We are pleased to announce that our Centre of Excellence continues to grow, with another 4 Associate Partners, and others in the process of being brought into the Centre. For more information on how to join, please see our website and contact us if you are interested.

CompBioMed theme issues in Interface focus

We announce that parts 1 & 2 of the one-theme issue on Computational Biomedicine have been pulished.

- Part I: Molecular Medicine (tinyurl.com/y3mstjcj) Hit-to-lead and lead optimization binding free energy cal-culations for G protein-coupled receptors, DOI: 10.1098/ rsfs.2019.0128
- On the faithfulness of molecular mechanics representations of proteins towards quantum-mechanical energy surfaces, DOI: 0.1098/rsfs.2019.0121
- How quickly can we predict trimethoprim resistance using al-
- chemical free energy methods?, DOI: 10.1098/rsfs.2019.0141 Large-scale binding affinity calculations on commodity compute clouds, DOI:10.1098/rsfs.2019.0133
- Rapid, accurate, precise and reproducible ligand-protein bind-
- ing free energy prediction, DOI: 0.1098/rsfs.2020.0007 The influence of base pair tautomerism on single point muta-tions in aqueous DNA, DOI: 10.1098/rsfs.2019.0120
- Quantum computing using continuous-time evolution, DOI:
- 10.1098/rsfs.2019.0143 Educating and engaging new communities of practice with high performance computing through the integration of teaching and research, DOI: 10.1098/rsfs.2020.0003

Part II: Organs and Systems (tinyurl.com/yxchwyoe) Haemodynamic flow conditions at the initiation of high-shear platelet aggregation: a combined in vitro and cellular in silico study,DOI: 10.1098/rsfs.2019.0126

- Digital blood in massively parallel CPU/GPU systems for the study of platelet transport, DOI: 10.1098/rsfs.2019.0116
- Coupling one-dimensional arterial blood flow to three-dimen-sional tissue perfusion models for in silico trials of acute ischaemic stroke, DOI: 10.1098/rsfs.2019.0125
- A porous circulation model of the human brain for in silico clinical trials in ischaemic stroke, DOI: /10.1098/rsfs.2019.0127
- Applicability assessment of a stent-retriever thrombectomy finite-element model, DOI: 10.1098/rsfs.2019.0123
- Electrophysiological and anatomical factors determine arrhythmic risk in acute myocardial ischaemia and its modulation by sodium current availability, DOI: 10.1098/rsfs.2019.0124
- The EurValve model execution environment, DOI: 10.1098/ rsfs.2020.0006
- Towards blood flow in the virtual human: efficient self-coupling of HemeLB, DOI: 10.1098/rsfs.2019.0119
- Analysis of mechanotransduction dynamics during combined mechanical stimulation and modulation of the extracellular-regulated kinase cascade uncovers hidden information within the signalling noise, DOI: 10.1098/rsfs.2019.0136
- Deep medical image analysis with representation learning and neuromorphic computing, DOI: 10.1098/rsfs.2019.0122

HemeLB aiming for exascale with POP

CompBioMed and its flagship code HemeLB had a presence via the Practical Hybrid Parallel Application Performance Engineering Tutorial during SC20. In the tutorial, Brian Wylie from the POP EU Centre of Excellence presented state-of-the-art performance tools for



leading-edge HPC systems founded on the community-developed Score-P instrumentation and measurement infrastructure, and demonstrated how they can be used for performance engineering of effective scientific applications based on standard MPI, OpenMP, hybrid combinations of both and increasingly common usage of accelerators

HemeLB was demonstrated as a benchmark software run on supercomputers SuperMUC-NG (MPI) and JUWELS/V100 (MPI+CUDA) in the presentation of the CUBE tools for interactive examination of analysis reports from Score-P runtime summarization and Scalasca automated event trace analysis.

HemeLB is a 3D macroscopic blood flow application based in the human arterial system and is developed by the team based at University College London led by Prof. Peter Coveney. The code is based on the lattice-Boltzmann method and is able to track fluid particles on a lattice grid with complex boundary conditions. HemeLB is the exascale flagship application for CompBioMed and has shown interesting scaling possiblities over the entire production partition of SuperMUC-NG. It has shown a 190x speed-up from 864 cores with 80% scaling efficiency to over 100,000 cores, with a final possibility to scale to >300,000 cores. The code is open-source with a test case available at www.hemelb.org.

Ensemble simulation best for COVID-19 epidemiological predictions

Computer modelling used to forecast Covid-19 mortality contains significant uncertainty in its predictions

SARS-CoV2 has rapidly spread worldwide since December 2019, and early modelling work of this pandemic has assisted in identifying effective government interventions. The UK government relied in part on the CovidSim model developed by Professor Neil Ferguson's team at the MRC Centre for Global Infectious Disease Analysis at Imperial College London, to model various non-pharmaceutical intervention strategies.

CovidSim, albeit a sophisticated model, contains a large degree of uncertainty in its predictions, due to its inherent nature. The model is subject to different sources of uncertainty, namely parametric uncertainty in the inputs, model structure uncertainty (i.e. missing epidemiological processes) and scenario uncertainty, which relates to uncertainty in the set of conditions under which the model is applied. A result of these combined types of uncertainty was the serious underestimation of the first wave.

Scientists from VECMA and CompBioMed analyzed CovidSim by undertaking an extensive parametric sensitivity analysis and uncertainty quantification of the publicly available code. From the over 900 parameters that are provided as input to CovidSim, a key subset of 19 was identified to which the code output is most sensitive. It was found that the uncertainty in the code is substantial, in the sense that imperfect knowledge in these inputs will be magnified to the outputs, up to the extent of ca. 300%. Most of this uncertainty can be traced back to the sensitivity of 3 parameters. Compounding this, the mod-



Figure: Showing the substantial uncertainty in predictions of cumulative deaths following initial spread of the COVID-19 pandemic in the UK

el can display significant bias with respect to observed data, such that the output variance does not capture this validation data with high probability. The large variance in the prediction of an outcome (coronavirus deaths, in this case) can be seen in the figure.

The team concluded that quantifying the parametric input uncertainty is not sufficient, and that the effect of model structure and scenario uncertainty cannot be ignored when validating the model in a probabilistic sense. What is more, the scientific teams call for a better public understanding of the inherent uncertainty of models predicting COVID-19 mortality rates, saying they should be regarded as "probabilistic" rather than being relied upon to produce a particular and specific outcome. They maintain that future forecasts used to inform government policy should provide the range of possible outcomes in terms of probabilities to provide a more realistic picture of the pandemic framed in terms of uncertainties.

VECMA and CompBioMed Principal Investigator Professor Peter Coveney noted: "There is a large degree of uncertainty in the modelling used to guide governments' responses to the pandemic and this is necessary for decision makers to understand. This is not a reason to disregard modelling. It is important that these simulations are understood in terms of providing a range of probabilities for different outcomes, rather than a single fixed prediction of COVID-19 mortality."

"Because of this uncertainty, future forecasts of the death rates of COVID-19 should be based not on an individual simulation, but on lots of different simulations of a code, each with slightly adjusted assumptions. Predictions based on this method, though still highly uncertain, will provide a more realistic picture of the pandemic."

Professor Coveney added: "Our findings are important for government and healthcare policy decision making, given that CovidSim and other such epidemiological models are – quite rightly – still used in forecasting the spread of COVID-19. Like predicting the weather, forecasting a pandemic carries a high degree of uncertainty and this needs to be recognised. Finally, our modelling has only been possible because Professor Neil Ferguson's team open sourced their code. Not all models being used in Government briefings are open in that way. We urge other research groups to follow Imperial's lead and adopt an open science approach."

Preprint available: https://www.researchsquare.com/ article/rs-82122/v3. Nature article: https://www.nature. com/articles/d41586-020-03208-1

New Associate Partners

Sano

Sano is a Teaming for Excellence centre which gathers experts in AI, computational biology, HPC and human physiology simulations, working together to create technology solutions and support for the precision medicine. They also carry out the Sano PhD program with partnering universities. For more information or collaboration



inquiries contact Karolina Tkaczuk (k.tkaczuk@sano.science).

Simula

Simula Research Laboratory is a non-profit research organization located near Oslo, Norway. The department of Computational Physiology focuses on biophysical modelling and simulation of the heart with the purpose of understanding the electrical and mechanical behaviour of the cardiac tissue both under healthy and diseased condi-

simula

tions. Contact point for Simula is Hector Martinez-Navarro, he works on cardiac physiology and has research interests in (1) myocardial ischemia and (2) diastolic dysfunction.

News and Results from Our Partners

Thrombus publication from UvA



Figure : Showing the methodology for measuring thrombus shrinkage through the microfluidic device

Towards Phase III in silico clinical trials

With the continuous population ageing in developed countries, an ever-growing interest is paid to elder pathology prevention and treatments; among these, osteoporosis is a first-class citizen, with over 8.9 million fractures caused every year. University of Bologna (https://www. unibo.it) is working with ANSYS (https://www.ansys.com), University of Sheffield (https://www.sheffield.ac.uk), and SURFsara Supercomputing Centre (https://www.surf.nl) to create a large-scale simulation of over 1000 patients followed for 10 years, to estimate pharmacological and/ or behavioural and routine interventions efficacy in reducing femur neck fracture risk. Starting from 100 real patients' CT scans collected by Sheffield Hospital, a virtual cohort of 1000 finite element models of femurs was generated, and for each single femur the risk of fracture Britt van Rooij, PhD alumnus of UvA supervised by Gábor Závodszky and Alfons Hoekstra, investigated the formation of occlusive thrombi formed under high flow shear rates in microfluidic devices. The results have been published in Nature Scientific Reports . The article is a result of a collaboration with Prof. David Ku of Georgia Institute of Technology. In this work, microfluidic devices are used to study the influence of the blood flow on in vitro growth and shrinkage of a clot. Experiments with whole blood and platelet-rich plasma at high shear rates (> 3,000 s-1) were performed in two microfluidic systems with a stenotic section. Both microfluidic systems occluded in the stenotic section. Significant different lag times, occlusion times and RPA rates have been obtained for whole blood and platelet-rich plasma. In addition, platelet aggregates seem to grow in a mountain-and-valley-like shape.

For more details, please visit: https://www.nature.com/ articles/s41598-020-74518-7

due to side fall in several different directions was evaluated. The finite element software from ANSYS was used to solve the femur-ground non-linear contact models. The synthetic cohort simulation required over 40k corehours on the Dutch national supercomputer Cartesius. The ambitious goal is to include in the simulation a bone

remodelling algorithm and to observe the possible evolutions of the population's fracture risk for 10 years, with and without treatments. The cohort simulation is expected to scale very well, due to the independence of the single femur models, and would allow compression of a 10-years cohort follow-up in less than a week of simulations.



Figure: Model of the femur neck on the virtual cohort

New Associate Partners

University of Sussex



The University of Sussex is a public research university located in Falmer, Sussex, England. The University received its Royal Charter in August 1961. The University has a diverse community of nearly 20,000 students, with around one in three being

EU and other overseas students, and over 1000 academics, representing over 140 different nationalities. Sussex counts 5 Nobel Prize winners, 15 Fellows of the Royal Society, 10 Fellows of the British Academy, 24 fellows of the Academy of Social Sciences and a winner of the Crafoord Prize among its faculty. Prof Maziar Nekovee is Dean of Sussex Zhejiang GongShang AI institute, Director of 6G Lab , Vice President of NetWorld 2020 European Technology Platform and founder of Quantrom Technologies Ltd. He joined the University of Sussex in 2017 after 20 years leading and working in mobile technology, telecom and consumer electronics R&D (Samsung, BT and Philips). His focus is as the intersection of communication, computing and AI technologies applied to the mobile, telecommunication and Healthcare and finance sectors.

The Institute for Experimental Medical Research

The Institute for Experimental Medical Research (IEMR) is part of the Oslo University Hospital and the Faculty of Medicine of the University of Oslo. The main research aim of the institute

is to identify the underlying pathophysiological mechanisms in heart failure and to discover novel treatment targets. The institute uses both clinical and basic research methods, complemented with in silico models of cardiac physiology, as they represent an alternative that overcomes ethical and technical limitations common in other experimental techniques. For more information or collaboration inquiries contact Hector Martinez-Navarro

Become an Associate Partner

If you are interested in becoming an Associate Partner of CompBioMed, please do check out our website to see the benefits. This is a free membership which allows for greater collaboration, regular updates of our work and events, and access to our services such as the Visitor Programme, Training repository and HPC allocations. Check it out: https://www.compbiomed.eu/associate-partners/



Institute for Experimental Medical Research

Sano Seminars

Every Monday at 2pm CET via Zoom



Sano is a centre dedicated to the advancement of computational medicine, sophisticated developing computer methods for the prevention, diagnosis and treatment of disease, to meet the overarching worldwide need for efficient. effective and streamlined healthcare. They invite everyone to participate in "Sano Computational Medicine Seminars". This is a series of lectures conducted by employees or guests from the Sano group.

Seminars are open to everyone, but we ask you to register before attending. More information at sano.science/events

News and Events CompBioMed CoE Training:

PATC Winter School 2020

Online, via Zoom 16-19 February 2021



The objetive of this course is to give a panorama on the use of hpc-based computational mechanics in Engineering and Environment through the projects BSC are carrying on. This panorama includes the basics of what is behind the main tools: computational mechanics and parallelization. The training is delivered in collaboration with the PerMedCoE and CompBioMed Centres of Excellence.

https://www.bsc.es/education/training/ patc-courses/online-patc-short-coursehpc-based-computational-bio-medicine/

CompBioMed Conference 2021

Building the Virtual Human: How to bring experimental research into your digital twin

15-17 September 2021



In September 2021, we will have our 2nd iteration of the CompBioMed Conference. With the uncertainty regarding the current pandemic and the effect of rolling out the vaccine, we have decided to hold this online using a virtual conference web platform.

Keep an eye on our conference website (compbiomed-conference.org) for up to date information and links to the registration and new landing page for the conference. This should be coming online in the next month.

CompBioMed HPC for Biomedical Researchers

More than 350 people attended the virtual presentation at Supercomputing 2020 featuring the work done in remote training of medical students by consortia members UCL and the University of Sheffield. This project, which took place over a 4-month period with a 6-week live course, introduced the students to HPC using the QIIME2 application (https://www.giime2.org) to analyse microbial diversity in a clinically-relevant example. Led by Andrea Townsend-Nicholson of UCL and Andrew Narracott of the University of Sheffield, the project outcome is a continued evolution of prior courses which were trained at on-site facilities. Out of this work CompBioMed not only has a complete remote course in QIIME2, it also has the nUCLeus cloud HPC education environment, a scalable cluster which is unfederated to a specific cloud platform. This cluster environment, built and managed by Associate Partner Alces Flight, will be positioned for future remote courses in QIIME2 and other, non-compute intensive applications.

The presentation covered everything from moving to remote training, to tuning the cluster environment for QIIME2, to tracking the scaling and spend of the cluster to keep future courses affordable and accessible to the consortia. Held in the HPC in Training session on November 17th this presentation was part of three specially selected projects on novel approaches to HPC education. This talk also included four students (now first-time authors at SC'20) who worked on the course and on the cluster.

This project's success was thanks to a great team and talented students. Course sponsor Guillaume Hautbergue of the University of Sheffield (USFD), HPC Foundation provider David Gregory of UCL, Test, Assessment and Sanity-Checker Marcellus Augustine of UCL. First-time Authors and Participants from USFD: Abdullah Ahmad, Joshua Palmer, Ailsa Jones, and Aaisha Sair. Cluster Build & Project Management, Cristin Merritt and Stu Franks of Alces Flight. Finally, we'd like to thank Art Hoti, a Year 4 MSci Biochemistry student at UCL who provided optimisation testing and student support to the project leaders. Watch the event here: https:// youtu.be/0qkv9xUgNb0

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 (in CompBioMed) and we have our

own YouTube channel (D Com- CompBioMed Coordinator: putational Biomedicine), where you can watch live streaming of events and presentations at previous events and webinars, as well as our Virtual Humans film (D https:// youtu.be/1FvRSJ9W734).

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