CompBioMed

Newsletter Issue No. 10
August 2020

Welcome

Prof. Peter V Coveney
Principal Investigator & Comp-BioMed Coordinator

Welcome to our Covid-19 themed Newsletter edition. With the pandemic hitting the world this year, CompBioMed Centre of Excellence has been well placed to set up a number of cutting edge research projects on the deadly disease and aid where we can in the dissemination of news and results from around the world.

As you will see, we have also created dedicated pages on our website which help to track our work, in addition to a blog that allows us to explain in more accessible language the work that is happening and how this could impact the spread and treatment of the virus.

BSC has been using their Alya code to investigate the cardiotoxicity of drugs associated with the treatment of Covid-19, determining how they could affect both male and female hearts.

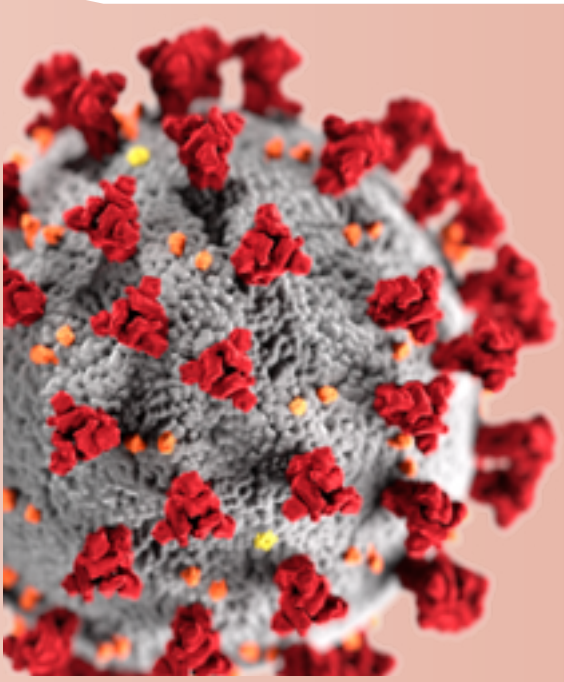
UCL is working with LRZ and our International Partners in the US to screen billions of drug candidates for possible lead compounds. This work has been substantially assisted by the opportunity to run many of these calculations on SuperMUC-NG through a very major allocation dedicated to this research.

The pandemic has changed many things about the way that we communicate and work. However, we have managed to conduct numerous meetings during this time, and the use of on-line tools has enabled us to make such events accessible to our followers. Take a look at our website for the many activities we have participated in and watch some of our fascinating talks.

In addition, our latest webinar has just aired. If you missed it, or want to check back on anything it is on our website and YouTube. Our next webinar is planned for September, and will focus on Machine Learning and Artifiical Intelligence methods being employed in our search for suitable drug candidates.

We have not abandoned our other areas of research though. In this issue, we report on work from the University of Geneva which establishes new ways of determining bloodflow more accurately with important ramifications for future software, which could affect theirs and other codes and simulations.

It is my hope that all our readers are staying safe during this time, and we trust we will see you all again in the not too distant future.



CompBioMed and Coronavirus

Coronavirus webpages

In response to the international pandemic, CompBioMed reacted fast to join the research community in investigating possible treatments and vaccines. To aid in these activities, we produced and developed a number of new pages on our website which details, not only our own activities, but links to other research worldwide. In these pages, we include details of the work being conducted in addition to some informatory pages for those less familiar with the key concepts behind virology.

In addition, we are keeping up to date with resources from across Europe, which we link on our resources page, giving our researchers and those wee are working with, the opportunity to find the most up to date work in this field from one place.

There is also a new blog every week detailing a specific example of resaerch from within our own group and further afield. These blogs explain in clear, easy to understand language, the research for all those that are inerested.

News and Publications

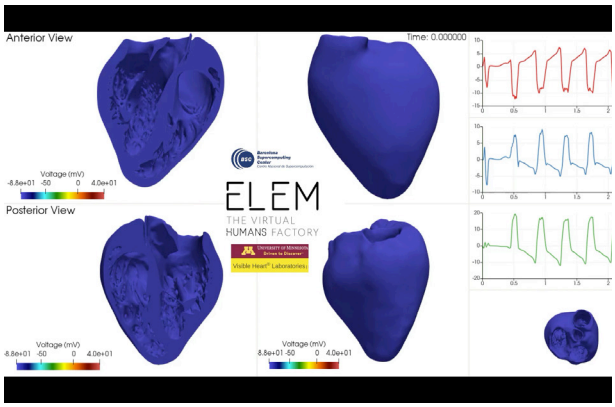
Peter Coveney has been asked by the UK Royal Society's RAMP (https://epcced.github.io/ramp/) initiative to undertake a detailed analysis of an epidemiological code from the perspective of sensitivity analysis and uncertainty quantification. In collaboration with the VECMA project (vecma.eu) and through the use of the VECMA toolkit (link) , the team is investigating the code for robustness and repeatability.

Peter Coveney was an invited speaker with Rick Stevens (Argonne National Lab) and Matsuoka Satoshi (RIKEN) at theISC 2020 Digital event, as part of a one-off plenary session on "COVID-19, supercomputing and AI" in June 2020.

- **A. Santiago, M. Zavala-Ake, R. Borrell, G. Houzeaux, M. Vazquez, HPC compact quasi-Newton algorithm for interface problems, *J. Fluid Struct.* (2020), DOI:10.1016/j.jfluidstructs.2020.103009**
- **R.Pons, A.Guala, J.F.Rodríguez-Palomares, J.C.Cajas, L.Dux-Santoy, G.Teixidó-Tura, J.J.Molins, M.Vázquez, A.Evangelista and J.Martorell,Fluid–structure interaction simulations outperform computational fluid dynamics in the description of thoracic aorta haemodynamics and in the differentiation of progressive dilation in Marfan syndrome patients *Royal Society.* (2020), DOI:10.1098/rsos.191752**
- B.Czaja, M.Gutierrez ,G.Závodszky, D.de Kanter, A.Hoekstra, O.Eniola-Adefeso, The influence of red blood cell deformability on hematocrit profiles and platelet margination, *PLoS Comput Biol. (2020), DOI: 10.1371/journal.pcbi.1007716*

Cardiotoxicity: supercomputer-based *in silico* studies with Alya Red

Making COVID-19 treatments safer for your heart.



A large dose of Chloroquine produced a LBBB (Left Bundle Branch Block) on a normal male heart under stress

Depending on the patient's underlying conditions and the dosages administered, anti-malarial and antibiotic drugs can have cardiotoxic effects by prolonging the QT interval [1,2]. It has been reported that drugs like azithromycin, hydroxychloroquine are QRS prolonging drugs that have weak proarrhythmic effects at effective dosages [3,4]. It is, however, unknown if the effect of using both drugs in combination may increase their arrhythmic risk for patients being treated for COVID-19. Moreover, COVID-19 can have fatal consequences for people with underlying cardiovascular disease and cause cardiac injury even in patients without underlying heart conditions. High-fidelity cardiac computational models provide unique means to model heart function and assess drug cardiotoxicity in considerable detail.

ELEM Biotech (ELEM - http://elem.bio) is engaged in a special initiative, together with the Barcelona Supercomputing Center (BSC-CNS - http://www.bsc.es) to use Alya Red [5], the supercomputers-based cardiac in-silico platform to assess the drug dosage and potential interactions between antimalarial drugs to provide guidance for their use in the clinic. The study is being performed on MareNostrum IV, the BSCs supercomputer, led by Dr. Jazmin Aguado-Sierra and Dr. Mariano Vázquez.

[1] Hancock and Baranchuk. 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4040726/
[2] Simpson, Kovacs, and Stecker. 2020. https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-du e-to-hydroxychloroquine-azithromycin-treatment-for-covid-19
[3] Chorin, Dai, Shulman et al. 2020. https://doi.org/10.1101/2020.04.02.20047050
[4] Vicente, Zusterzeel, Johannesen et al. 2019. https://doi/epdf/10.1002/cpt.1303
[5] Santiago, Aguado-Sierra, Vázquez et al.. 2018. https://doi/abs/10.1002/cnm.3140

This study is complementary to efforts such as WHO's "Solidarity" in which the efficacy of the drugs used in COVID-19 treatments is tested. In our supercomputer-based *in silico* trial, we address the cardiac safety of the drugs, especially when administered in combination, for patients with different underlying conditions.

"COVID-19 has infected a very wide demographic. Males and females are observed to have different risks and propensities to drug-induced cardiac arrhythmias. We aim to study the effect of antimalarial drugs on various human hearts with a variety of comorbidities that may be present in the infected population. These comorbidities include gender, ischemia, metabolite imbalances, and structural diseases." says Jazmin Aguado-Sierra.

The electrophysiological model employed is a state of the art mathematical model used as the basis for the US Food and Drug Administration's (FDA) CiPA initiative (https://cipaproject.org/), by the. The results are being validated against published data regarding the pro-arrhythmic behavior of the drugs. A varying set of interaction mechanisms between drugs will be explored and an approximate interaction space can be mapped. The main objective is to provide quantitative guidance for the treatment of COVID-19 using these antimalarial drugs.

For instance, our results show how a conduction left bundle branch block may occur as an effect from action potential duration lengthening, due to chloroquine. This effect may occur especially during stress (at a heart rate of 150bpm) particularly at a high dose (3 µM concentration in plasma). Following this initially interesting result, BSC is now involved in a more ambitious and far-reaching study.

Thanks to ELEM's Alya Red's potential and BSC's expertise and computational reach, we are opening the door towards delivery of valuable medical evidence that could prevent life-threatening incidents in patients treated for COVID-19 where a classical clinical study woul d take months, and weeks, even to only get approved and started.

PRACE has granted 8M core hours to run the simulations required in this project through a COVID-19 specific call. Patients should follow their doctor's instructions and not use antimalarial drugs exceptt with clear medical advise. We will continue providing support and information using virtual patient

Associate Partners

Kuano

Kuano provides innovative quantum and AI solutions for molecular design. The flagship offering of the company is the Nautilus platform, which combines quantum simulation and machine learning to facilitate the design of highly efficient inhibitors based on target chemistry. Kuano also provides services ranging from strategic understanding of the impact of quantum technologies to full turnkey inhibitor design projects.Dr David Wright is the CTO of Kuano and will be the contact between them and CompBioMed

KUANO

Istituto Italiano di Tecnologia (IIT)

Istituto Italiano di Tecnologia (IIT) is a Foundation financed by the State to conduct scientific research in the public interest, for the purpose of technological development. IIT is under the supervision of the Ministry of Economy and Finance and the Ministry of Education, University and Research. IIT aims to promote excellence in basic and applied research and to foster the development of the national economy. The main contact point is Prof Sauro Succi, Senior Research Executive.

iit
ISTITUTO ITALIANO DI TECNOLOGIA

Computational Drug Discovery

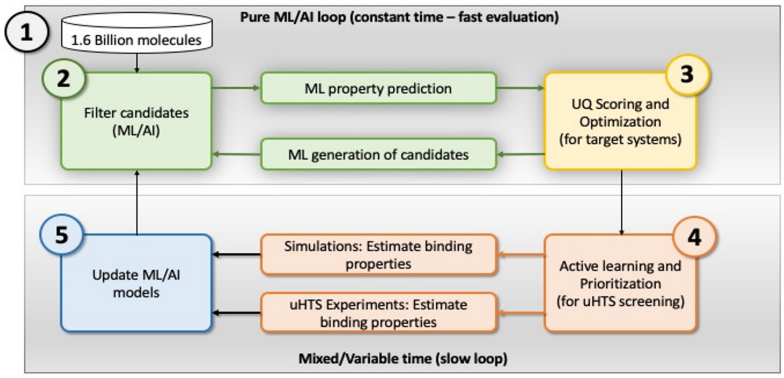
Part of the CompBioMed effort against coronavirus aims to accelerate the development of antiviral drugs by modelling proteins that play critical roles in the virus life cycle in order to identify promising drug targets. Our work is developing machine learning (ML), deep learning (DL) and artificial intelligence (AI) techniques to:
1) identify and build accurate three-dimensional structural models of the SARS-CoV-2 proteome by closely integrating experimental structural and systems biology datasets,
2) accelerate adaptive conformational sampling of the viral proteins to potentially identify novel binding sites/pockets that can be targeted by small molecules,
3) rapidly filter, rank, and search for small molecules across widely available chemical libraries, and to integrate virtual screening (computational drug discovery techniques) techniques with experimental high throughput screening, and
4) enable multi-scale, multi-resolution simulations of the SARS-CoV-2 viral envelope, and specific proteins.

Across various supercomputing facilities in the US and Europe, three collections of drug candidates are being screened for inhibitor activity:
1) Known and licensed drugs for quick repurposing opportunities (e.g., DrugBank),
2) Library of 100M known small molecules that are drug like (e.g., PubChem) and
3) Large-scale libraries (e.g., Enamine, ZINC) with billions of compounds that could be manufactured quickly for testing.

Our primary initial targets are existing drugs that are currently in manufacturing pipelines and can be repurposed quickly. There are a number of compounds that are now being suggested by these models and we are making them available to community wet labs for experimental testing and screening.

Our multi-level screening approach uses fast machine learning and docking methods to provide an initial ranking of drug compounds. This ranking is refined by using methods that take the protein response into account as well as the initial protein states. These methods include machine learning driven sampling as well as accelerated dynamics methods to sample the protein and protein-ligand complex phase space. The CCS group is carry out more advanced binding free energy prediction calculations on thousands of compounds selected by this workflow. These computationally intensive calculations will be carried out the supercomputers Summit, Frontera, Longhorn, Theta, SuperMUC-NG, and Scafell Pike (at Hartree Centre, an Associate Partner). Use of these supercomputers has been enabled by the unique collaboration between the consortium on coronavirus and CompBioMed2.

Prof Coveney's Centre for Computational Science (CCS) at UCL is seeking to identify promising inhibitors of COVID-19 targets through assessing the potential to reposition existing drugs in combination with machine learning alongside so-called deep-drive applications of molecular dynamics and artificial intelligence methods. We are interested in additional contributors to this effort, in particular from those with expertise in machine learning and generative methods for compound discovery, and physics based methods for calculating binding free energies.



A schematic of the closed loop active learning strategy identify compounds that can be used as leads to mitigate the effect of COVID-19..

Associate Partners

Zapata Computing:

Founded in 2017 and based on technology developed at Harvard University, Zapata Computing is the leading enterprise software company for quantum solutions. Zapata's software platform Orquestra offers workflows and quantum algorithms for the next generation of high-performance computing in industries such as pharmaceutical, oil & gas, finance, aerospace. Zapata works with leading Fortune 500 companies and has raised over $25m from investors such as Comcast Ventures, Prelude Ventures, Pitango Ventures, BASF Ventures, Robert Bosch Ventures, The Engine. Witold Kowalczyk is the Director of European Business Development for Zapata Computing.

Deep Learning Partnership:

Deep Learning Partnership aims to become a market leader in the drug design and personalised medicine space through the application of quantum computers to simulate molecular processes directly. We work with pharmaceutical companies to develop custom algorithms and software in order to accelerate the drug discovery process. We also work with companies to accelerate research and development in other areas such as energy, materials science and high temperature superconductivity using quantum computers. The main point of contact for CompBioMed is Peter Morgan, CEO of Deep Learning Partnership.

University of Warwick

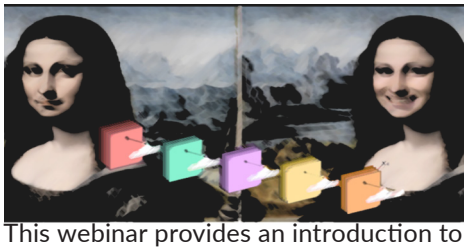
Warwick University is one of the leading UK university in STEM research. The Department of Statistics with approx. 45 faculty is very research-active, hosts the Centre for Research in Statistical Methodology (CRiSM) and is a founding member of the Alan Turing Institute for data science. Dr. Ritabrata Dutta works on the applications of statistical methodology in the domain of epidemiology, meteorology, population genetics, and complex biomedical processes. He has worked with Swiss National Supercomputing Centre to optimally use Approximate Bayesian Computation using High performance computing (ABCpy) and been recently funded by UK Reaserch Initiative to develop an optimal lockdown strategy for COVID-19. The contact at University of Warwick is Dr Ritabrata Dutta, Assistant Professor at the Department of Statistics

Upcoming Events

CompBioMed Webinar #12

Getting started with Deep Learning: A gentle introduction and working example

7 July 2020



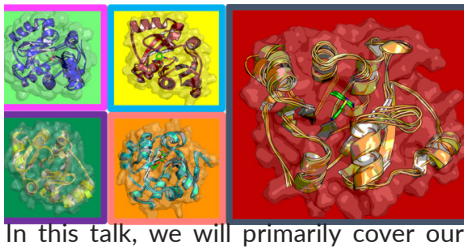
This webinar provides an introduction to Machine Learning (ML), and more specifically, Deep Learning. Using computer vision as an example, this seminar elaborates on the working principles of topics such as convolutional neural networks, network architectures, or transfer Learning. This webinar is aimed at students with no previous experience with Deep Learning. The only requirement is the ability to read and write Python code.

If you missed it you can watch it here: https://www.compbiomed.eu/training-3/

CompBioMed Webinar #13

Emerging drug discovery challenges for SARS-CoV-2 with artificial intelligence driven molecular dynamics

16 September 2020



In this talk, we will primarily cover our ongoing efforts in using AI/ML techniques in addressing the COVID-19 pandemic. We outline how we have been using AI/ML strategies in (1) elucidating the molecular mechanisms by which drugs/ small molecules interact with the SARS-CoV-2 proteome, and (2) driving multi-scale molecular simulations to accelerate the sampling of 'rare' events in the conformational landscape of these proteins. More information is coming soon here: https://www.compbiomed.eu/training-3/

Past Events

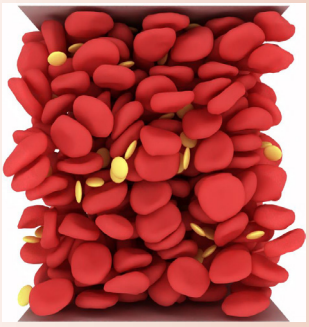
Catch up with videos from our past events online

https://www.compbiomed.eu/events-2/

Due to the Covid-19 pandemic, we are not organising any events in the near future, however, you can catch up with all our past events on our website and on YouTube. Some examples include:

- ML meets Modelling and Simulation
- Incubator Activities
- All-Hands Meeting
- Various CompBioMed/PRACE Advanced Training Centre Winter School courses

Anomalous Platelet Transport



The transport of platelets in blood is commonly assumed to obey an advection-diffusion equation. Kotsalos *et al.*[1] has overturned this view, by showing that the random part of their velocity is governed by a fat-tailed probability distribution, usually referred to as a Levy flight. Although for small spatio-temporal scales it is hard to distinguish it from the generally accepted "cell-enhanced" Brownian motion, for larger systems this effect is dramatic as the standard approach underestimates the flux of platelets by several orders of magnitude, undermining in particular the validity of current platelet (PLT) function tests.

In their study, the University of Geneva team has shown, with the support of numerical experiments (cellular blood flow simulations[2,3] and stochastic models), along with previous experimental evidence[4], that platelets exhibit anomalous transport, i.e. their velocities follow fat-tailed distributions, and more specifically power laws with exponents (α) that lead to infinite/undefined variance and moments above (α ≤ 2, Levy flights). Contrary to the common practice of modelling platelet transport as a red blood cell-enhanced Brownian motion (i.e. as a Gaussian random walk), their statistical analysis redefines platelet transport physics. The proposed stochastic models, based on fat-tailed velocity distributions, show that platelets deposit on the vessel walls 2 to 10 times more than suggested by the standard models. Hence, they conclude that this reinterpreted platelet transport physics could be adapted to next generation PLT function tests, increasing their clinical readiness and accuracy, but also may provide a disruptive view on the study of various phenomena related to platelet behaviour.

1. Kotsalos, C., Zouaoui Boudjeltia, K., Dutta, R., Latt, J. & Chopard, B. arXiv: 2006.11755 (2020).
2. Kotsalos, C., Latt, J. & Chopard, B. Journal of Computational Physics 398, 108905. issn: 10902716 (Dec. 2019).
3. Kotsalos, C., Latt, J., Beny, J. & Chopard, B. (accepted for publication). arXiv: 1911.03062 (2020).
4. Chopard, B. et al. Royal Society Open Science 4, 170219. issn: 2054-5703 (Apr. 2017).

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 (https://youtu.be/1FvRSJ9W734).

CompBioMed Coordinator:
Peter V. Coveney (p.v.coveney@ucl.ac.uk)

Project Manager:
Emily Lumley (e.lumley@ucl.ac.uk

This Centre of Excellence has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712.