FIFTH ISC WORKSHOP ON HPC APPLICATIONS IN PRECISION MEDICINE
June 2, 2022
9:00 am - 1:00 pm Central European Time
Program

9:00 am – 9:10 am **Welcome—Fifth ISC Workshop on HPC Applications in Precision Medicine (HAPM22)**
Charles Gillan, *Queen's University Belfast*
Eric Stahlberg, *Frederick National Laboratory for Cancer Research, USA*

9:10 am – 9:25 am **Addressing the Challenge of Drug Discovery with Machine Learning and Exascale Computing**
Agastya P. Bhati, Shunzhou Wan, and Peter V. Coveney, *University College London*

Presenters: Alex Wade, *University College London*
Moderator: Charles Gillan, *Queen's University Belfast*

Abstract: This talk will introduce an innovative workflow that couples machine learning (ML) and physics-based (PB) methods to accelerate the traditional process of computer-aided drug discovery. PB methods compensate for the sparsity of data for ML training, whereas ML methods yield progressively better predictions of ligand structures with active learning. Not only can the accuracy of predictions be improved through machine learning but, through the application of deep learning molecular generation methods, the relevant chemical space can be sampled, and the most relevant compounds identified. The generated compounds are first filtered based on their potential binding capabilities, followed by their pharmacokinetic properties and toxicity effects. ML approaches such as ATOM Modelling PipeLine (AMPL) can be used for the latter purpose. These properties are predicted based on binding affinities of the

compounds to protein targets which are linked to toxic responses and other side effects. This workflow is known as IMPECCABLE which involves performing compute-intensive MD simulations in tandem with much less expensive ML runs, all performed concurrently and in large numbers. The ensemble computing pattern deployed can be exploited for full utilisation of a supercomputer, which employs a high throughput "embarrassingly" parallel workload on a wide range of node counts. Therefore, as we move into an era of exascale computing, this workflow will scale to make use of the full machine and be able to perform larger computations, providing possible drug targets in a fraction of the current timeline.

9:25 am – 9:50 am **Porting the OpenCARP Cardiac Electrophysiology Simulation Framework to GPU Architectures**

Terry Cojean, Fritz Goebel, Marie Houillon, Hartwig Anzt, Axel Loewe, *Karlsruhe Institute of Technology*; Aurel Neic, *NumeriCor GmbH*

Presenters: Marie Houillon, *Karlsruhe Institute of Technology*
Moderator: Charles Gillan, *Queen's University Belfast*

Abstract: In order to understand cardiac arrhythmia, computer models for electrophysiology are essential. Yet, current models and computing resources are not powerful enough to model diseased hearts accurately. Achieving this will require the use of future exascale supercomputers and their specific architectures. In this paper, we achieve a first step towards this objective by porting the openCARP electrophysiology simulation framework to GPU architectures, from which future supercomputers will likely get most of their computational power.

9:50 am – 10:05 am **HPC Boosts Mathematical Models' Promises of Personalized Medicine**

Vincent Noël, *Institut Curie INSERM U900, Mines ParisTech, PSL Research University*; Javier Conejero, *Barcelona Supercomputing Center*;
Pablo Rodriguez-Mier, *Institute for Computational Biomedicine, Heidelberg University*; Laurence Calzone, *Institut Curie, INSERM U900, Mines ParisTech, PSL Research University*; Alfonso Valencia, Arnau Montagud, *Barcelona Supercomputing Center*.

Presenter: Vincent Noël, *Institut Curie INSERM U900, Mines ParisTech, PSL Research University*
Moderator: Charles Gillan, *Queen's University Belfast*

Abstract: Mathematical models of the biological processes that are deregulated in diseases show a high complexity not only because of the number of genes and pathways involved but also because of the numerous patients or samples to include in the simulations in order to be predictive. One way to address these issues is to combine High Performance Computer (HPC)-based methods to scale up the power of the computation with mechanistic and statistical modeling approaches. In the context of the PerMedCoE project, we have brought together computer scientists and modelers to define the needs and the methods that need to be developed to optimize the simulations of these computationally-demanding models. Two use cases were defined: the first one

describes a workflow that inputs omics data of cancer patients and outputs personalized combinations of drugs per patient based on a model of intracellular signaling pathways, and the second one aims at uncovering COVID-19-related mechanisms that explain the differences in severity among patients using personalized agent-based models of different cell types. These two use cases show examples of how to scale up personalized medicine diagnostic using HPC and envision possible clinical applications of such types of models.

10:05 am – 10:25 am **PhysiBoSS-X Allows for Drug Synergies Studies in Real-size Tumours Simulations**

Arnau Montagud, Miguel Ponce de Leon, Gaurav Saxena, Thaleia Ntiniakou, David Vicente, Alfonso Valencia, *Barcelona Supercomputing Center*

Presenter: Miguel Ponce de Leon, *Barcelona Supercomputing Center*
Moderator: Charles Gillan*, Queen's University Belfast*

Abstract: One of the desired objectives of personalised medicine is to study complex phenomena, such as cancer treatment [1] or finding novel optimised drug treatments [2], [3], in a patient-specific manner. There have already been different efforts to build surrogates of human tissue in personalised medicine [4], for instance, humanised patient-derived xenografts [5] and digital twins [6]. Multi-scale simulations, especially centre-based agent modeling, have proven their usefulness in many biological scenarios [7]–[10], even more so in combination with intracellular models, such as Boolean [11], [12], due to its realistic visualisation and ability to capture physics phenomena appropriately.

In spite of all these efforts, the scenarios studied by these tools are still quite simplistic and far from real-life examples [13]. To have models capable of simulating the evolution of clinically detectable tumours we need more large-scale modeling tools able to produce more realistic, real-sized simulations with complex micro-environments [14], [15]. These large-scale modeling tools need to take advantage of top-tier HPC clusters in an efficient and scalable manner.

These giga-scale simulations could help studying drug resistance against cancer therapies, as population-level dynamics, such as competition and cell-cell variability, play a key role in the evolution of drug resistance [16] or the environment architecture has been described to affect the cells' response to drugs [17], [18]. PhysiBoSS-X aims at addressing complex biological scenarios such as the study of drug synergies in real-size cancers in heterogeneous microenvironments. This tool builds upon several developments that allow for a truly personalised giga-scale simulation:

PhysiCell-X allows for agent-based simulations that take advantage of an HPC cluster in a single, monolithic run by decomposing the environment in sub-domains of equal size which are distributed using MPI library. Currently, PhysiCell [19] is only shared-memory parallelized using OpenMP, greatly limiting the execution of large-scale jobs in HPC clusters. PhysiCell-X assigns these sub-domains to different nodes and MPI+OpenMP are used to completely parallelize

the generic core kernels of PhysiCell [20] showing promising scalability in large 3-D problems with several hundred diffusible substrates and billion voxels.

PhysiBoSS [12] is an add-on that expands the PhysiCell agent-based functionalities with intracellular cell signaling using MaBoSS having a decoupled, maintainable and model-agnostic design. PhysiBoSS 2.0 allows for the integration of user-defined models and cells' specifications, mechanistic submodels of substrate internalisation with ODEs, and enables the study of drug synergies.

We have used PhysiBoSS-X to study drug treatment strategies based on the previously-reported TNF pulses [3] but scaling the size of the spheroid from ~103 initial cells to ~106 to test the scalability of our tool as well as to investigate how strategies optimised in smaller spheroids behave in tumours closer to real size. Our preliminary results show good scaling of the simulation run time, and the biological results suggest that the size of the spheroid is a key player in the effectiveness of a treatment strategy.

The PhysiBoSS-X source code, examples and documentation, are available under the BSD 3-Clause licence at https://gitlab.bsc.es/gsaxena/physicell_x.

10:25 am – 10:40 am **ATOM Consortium (Accelerated Therapeutics for Opportunities in Medicine)**
Presenter: Eric Stahlberg, *Frederick National Laboratory for Cancer Research*
Moderator: Charles Gillan, *Queen's University Belfast*

10:40 am – 10:55 am **Supporting Lung Protective Ventilation with Personalized Predictive Analytics in ICU Using HPC**

Murali Shyamsundar, *National Institute for Health and Care Research*; Charles J. Gillan, *Queen's University Belfast*

Presenters: Murali Shyamsundar, *National Institute for Health and Care Research*; Charles J. Gillan, *Queen's University Belfast*

Moderator: Eric Stahlberg, *Frederick National Laboratory for Cancer Research*

Abstract: Mechanical ventilation is a lifesaving tool and provides organ support for patients with respiratory failure. However, injurious ventilation due to inappropriate delivery of high tidal volume may lead to ventilator associated conditions and possible increased mortality. We report on our exploration of the viability of machine learning methods, using HPC, to generate personalized predictive alerts indicating violation of the safe tidal volume per ideal body weight threshold that is accepted as the upper limit for lung protective ventilation. We have developed a personalized clinical decision support tool that can predict tidal volume behaviour within 10% accuracy and compare alerts recorded from a real world system to highlight that our models would have predicted violations 1 hour ahead.

11:00 am – 11:30 am **Break**

11:30 am – 12:00 pm **Panel on Digital Twin in Medicine**
Rick Arthur, *GE Research*
Jeff Buchsbaum, *National Cancer Institute*
Crina Samarghitean, *AstraZeneca UK*
Leili Shahriyari, *University of Massachusetts*

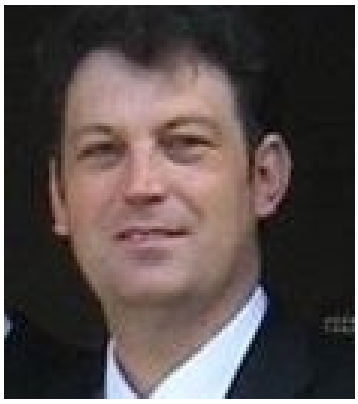
Eric Stahlberg, Moderator, *Frederick National Laboratory for Cancer Research*

12:00 pm – 1:00 pm **Open Discussion on High Performance Computing Applications in Medicine**
Co-Moderators:
Charles Gillan, *Queen's University of Belfast*
Eric Stahlberg, *Frederick National Laboratory for Cancer Research*

12:55 pm – 1:00 pm **Wrap up**

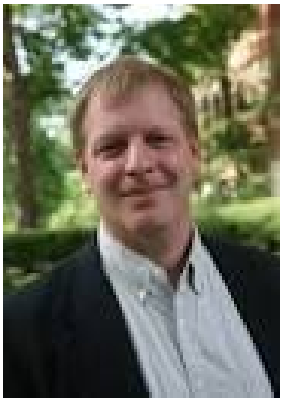
Organizing Committee
Eric Stahlberg – Frederick National Laboratory for Cancer Research
Charles Gillan – Queen's University Belfast
Jan Nygard – Cancer Registry of Norway
Thomas Steinke – Zuse Institute Berlin
Lynn Borkon – Frederick National Laboratory for Cancer Research
Petrina Hollingsworth – Frederick National Laboratory for Cancer Research

Presenter Bios



Charles Gillan, Queen's University Belfast
Dr. Gillan studied Applied Mathematics and Physics at Queen's University Belfast, completing his PhD, 1988, in the application of high performance computing to study low energy electron molecule scattering. He continued his research in computational chemistry as a post doc at the IBM Almaden Research Centre in San Jose.

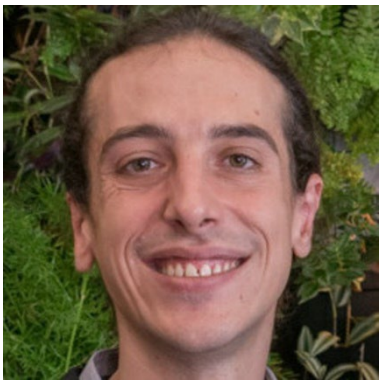
After a career in embedded software development in the telecommunications industry, he returned to work at the ECIT Institute at QUB in 2004. He continues his research in high performance computing applied to physics, chemistry, and more recently physiology and has published over fifty research papers. His current research applies machine learning and artificial intelligence (using HPC to train complex models) to predictive analysis of streams of physiological parameters received from patients in intensive care.



Eric Stahlberg, Frederick National Laboratory for Cancer Research
Eric Stahlberg serves as the director of Cancer Data Science Initiatives at the Frederick National Laboratory for Cancer Research (FNLCR). Joining the team at Frederick in 2011 to establish and lead the bioinformatics core supporting the NCI Center for Cancer Research, Dr. Stahlberg shifted his attention in 2014 to lead a new NCI CBIIT initiative to accelerate cancer research through applications of high-performance computing. Working collaboratively with NCI leadership Dr. Stahlberg helped established the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) collaboration between the NCI and the US Department of Energy as well as Accelerating Therapeutics for Opportunities in Medicine (ATOM), a public-private collaboration to dramatically increase the pace and success of new treatments. Driven to drive advances at the intersection of leading-edge science and computing, Dr. Stahlberg continues to build the cross-disciplinary community through efforts with the Computational Approaches for Cancer and HPC Applications of Precision Medicine workshops. In 2017, he was recognized as one of FCW's Federal 100. Stahlberg holds a Ph.D. in computational chemistry from the Ohio State University and bachelor's degrees in computer science, chemistry, and mathematics.

Alex Wade, University College London

Marie Houillon, Karlsruhe Institute of Technology
Marie Houillon completed her PhD in 2020 at the University of Strasbourg, where she has focused in particular on the development of scalable numerical methods for partial differential equations for electromagnetics and their implementation using HPC technologies. She is now working as a research software engineer at the Karlsruhe Institute of Technology within the European project MICROCARD. This project aims to develop a production-ready simulation platform that can simulate cardiac electrophysiology, using whole-heart models with sub-cellular resolution, on future exascale supercomputers.



Vincent Noël, Institut Curie INSERM U900, Mines ParisTech, PSL Research University

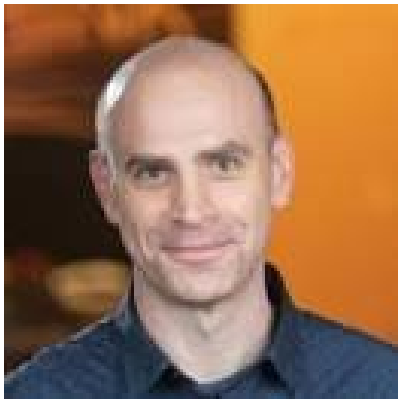
Vincent Noël is a researcher at the Computational Systems Biology of Cancer team of the U900 in Institut Curie since 2018. His research interests concern modeling of biological systems, from constructing and analyzing models to optimizing their simulations. He did his PhD in applied mathematics studying simplifications of ODE models and then did his first post-doc within a molecular biology unit building a model of Ras-MAPK signaling in tumor cells. He also developed tools to simplify the construction and analysis of models and the reproducibility of this work. He has been working on simulations of Boolean model with MaBoSS for several years and is a part of the PerMedCoE consortium working on scaling up simulation software and developing large-scale personalized medicine workflows.

Miguel Ponce de Leon, Barcelona Supercomputing Center

I am currently recognized postdoctoral researcher at the Computational Biology Group at the Life Science Departamente. My area of expertise is in the field of systems biology and scientific computation where most of my research has been on reconstruction and simulation of biological networks. Here at BSC my line of research is the development of systems biology approaches to personalized medicine, with a particular focus on cancer. We use different modeling approaches to integrate heterogeneous sources of information with two main objectives: 1) developing tools to assist in the decision-making process of choosing the most adequate therapy for specific patients given their unique genetic/background; and 2) improving our knowledge of basic cancer biology.

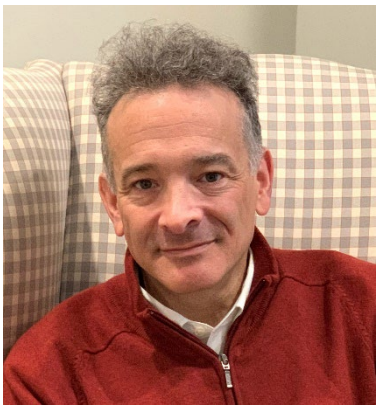
Murali Shyamsundar, National Institute for Health and Care

Dr. Murali Shyamsundar is a NIHR clinician Scientist Fellow/Senior Lecturer/Consultant in Intensive Care Medicine. His research programme includes development of novel pharmacotherapies to prevent and treat pulmonary injury and development of clinical decision support to improve translation of evidence to practice.



Rick Arthur, GE Research

Rick Arthur is a senior director and senior principal engineer at GE where he currently leads research and initiatives in computational methods and their application. Rick currently serves on the US Department of Energy Advanced Strategic Computing Advisory Committee (ASCAC) and co-chair of the AIAA Digital Engineering and Integration Committee cross-industry working group to develop concepts and standards for Digital Thread, Digital Twin, Ecosystem, Systems Modeling, etc. He is also co-chair of the US Council on Competitiveness Advanced Computing Roundtable.



Jeffrey Buchsbaum, National Cancer Institute

Jeffrey "Jeff" Buchsbaum, MD., Ph.D., A.M. is the Medical Officer in the Clinical Radiation Oncology Branch (CROB) in the Radiation Research Program of the National Cancer Institute. The CROB promotes and manages support for a portfolio of research grants and contracts that advance translational and clinical research in radiation therapy.

Dr. Buchsbaum's programmatic experience includes membership on teams conducting the development, evaluation, and management of multi-disciplinary research programs and consortia including photodynamic therapy, CTEP agent and radiation therapy, high-LET translational radiobiology, and other areas. He contributes to CTEP review, grants management, and unique opportunities for science associated with new technologies such as hadron therapy, biosensors, and the interface of missions across the USG where RRP science is a focus. His interests are both focused and broad - looking at quality assurance, pediatric radiation therapy, LINAC research, international collaborations, and late effects. He is the senior pediatric radiation oncologist seeing patients on the main NIH campus.

Dr. Buchsbaum completed a master's degree in computational physics focusing on the free electron laser's energy scaling in what should have been a senior year of college at Dartmouth. He then went to Johns Hopkins and completed an MD/PhD combined degree in molecular biophysics and biophysical chemistry under Jeremy Berg and discovered structural biology thinking as well as pediatric and radiation oncology along the way. He then completed formal clinical training at the Cleveland Clinic in radiation oncology, in which he is board certified, and developed a funded research program as a resident. He then went to St. Jude as faculty under Larry Kun and others developing translational skills including being on structural biology teams and CNS protocol teams. From Memphis his career included positions in Pennsylvania, Florida and most recently Indiana.

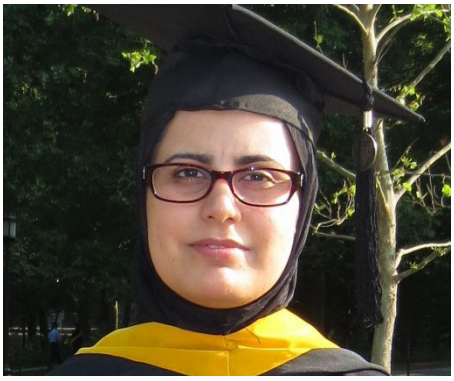
His final academic position before joining NCI was that of Professor in the Departments of Radiation Oncology, Pediatrics, Neurosurgery (School of Medicine), and Physics (School of Arts and Sciences) at Indiana University where he was a leader at the proton therapy center in Bloomington.

Crina Samarghitean, AstraZeneca

Dr. Crina Samarghitean joined AstraZeneca in 2019 as a Data Scientist in BioPharmaceuticals Medical (BPM), RWE Data& Analytics team. She collaborated with epidemiologists, clinicians, computer scientists, and health economists to derive insights and maximize the value of big data. In October 2020 Crina was promoted to the current role as an Associate Director of Data Digital Innovation (DDI) in the Oncology Business Unit, Medical Evidence & Alliances. Recently she organised an Advisory Board and a brainstorming workshop to get insights into Digital Twin ecosystem and different digital health platforms.

Prior to Crina working in the pharmaceutical industry, she spent 15 years in academia, government and healthcare settings acquiring an MD, MSc, and a PhD, followed by a post-doc at the Haematology Unit, University of Cambridge, UK. She has extensive training and practical experience in medicine, genomics, biomedical informatics, AI in healthcare, and academic entrepreneurship. The results of her research were presented in multiple publications, public lectures, conference presentations, and exhibitions, and received multiple awards.

As an AZ Mentor Crina is being part of different initiatives organised by AZ Emerging Innovations and Learning & Development R&D teams. For more information follow her on Twitter, LinkedIn, and ResearchGate.



Leili Shahriyari, University of Massachusetts

Leili's research focuses on mathematical and computational biology. Her lab develops frameworks to employ a combination of machine learning, statistical and mathematical techniques to arrive at personalized cancer treatments. Leili earned her MS in computer science and PhD in Mathematics from Johns Hopkins University. Subsequently, she was appointed as a Postdoctoral Scholar at UC Irvine in 2013. She then joined the Mathematical Biosciences Institute at The Ohio State University as an NSF-funded postdoctoral fellow in September 2014. She began her appointment at the University of Massachusetts Amherst in September 2019 following a year-long tenure track position at the University of Texas Arlington, where she was awarded the prestigious rising star grant from the UT system.