Day 1 – Monday 26th March 2018
Doelenzaal, UvA University Library, Amsterdam

09:00	Peter V Coveney, Alfons Hoekstra	**Welcome and introduction to AHM agenda**
09:15	Emily Lumley (UCL)	Work Package 1 – Management
09:30	Alberto Marzo (USFD)	Work Package 6 – Empowering Biomedical Applications
09:50	Manuela Corsini (UvA) Hugh Martin (CBK)	Work Package 3 – Training & Dissemination
10.10	Gavin Pringle (UEDIN)	Work Package 4 – Innovation & Sustainability
10.25	Marco Verdicchio (SURFsara)	Work Package 5 – Resource & Infrastructure Support
10:40	Mariano Vazquez (BSC)	Work Package 2 – Biomedical Research Activities
11:00	*Break/ Tea and Coffee*	
11:15	Peter V Coveney/Alfons Hoekstra	Welcome all to AHM
11:20	**Invited Speaker: Prof Tim Elliott (University of Southampton)**	Computational modelling of antigen processing and presentation
11:50	Franck Chevalier (Acellera)	On demand Molecular Dynamics simulations for Drug Discovery
12:05	Phil Tooley (USFD)	There and back again: Large scale data transfer for HPC analysis
12:20	Luca Emili (InsilicoTrials)	Democratizing simulations in healthcare
12:35	*Lunch*	
14:05	Mariano Vazquez (BSC)	Spanish Research Network on Cardiac Computational Modelling (VHeart-SN)

14:20	Robin Richardson (UCL)	Exascaling of codes in CompBioMed
14:50	Jazmin Aguado (BSC)	Simulations for the biomedical realm on exascale systems
15:05	Ignacio Pagonabarraga (CECAM Director, E-CAM Technical Manager)	E-CAM: A path to extreme-scale computing for Industry and Academina
15:20	*Break/Tea and Coffee*	
15:35	Thierry Marchal (Avicenna Alliance)	Paving the way to *in silico* medicine: *in silico* clinical trial, digital twin, personalized healthcare
16:05	Robert Welch (University of Leeds)	FFEA: viscoelastic continuum simulations for biological macromolecules
16:20	General Assembly Meeting	
17:20	*End of day 1*	
18:30	*Dinner (costs not included)*	
Day 2 – Tuesday 27th March 2018 Doelenzaal, UvA University Library, Amsterdam		
09:00	WP2/5/6 Meeting	
10.00	WP3/4 Meeting	
11:00	*Break/ Tea and Coffee*	
11:15	**Invited Speaker: Prof Ralph Müller**	ETH Zurich: Cell-based in silico modelling of bone regeneration
11:45	Frits Prinzen (Maastricht University)	Mechanistic modelling for improving understanding mechanisms of heart failure
12:00	Clint Davies-Taylor (Dassault)	Virtual Human Modelling – who does Dassault Systèmes serve in Life Sciences?
12:15	Jose Pedro Ceròn Carrasco (UCAM)	When computational chemistry meets medicine: successful cases in drug discovery
12:30	Agastya Bhati (UCL)	Uncertainty Quantification in “Exact” Free Energy Methods
12:45	*Lunch*	
	Parallel sessions during Innovation Advisory Board Meeting (14:00 – 17:00)	

14:15	Julien Favier, (Aix-Marseille University)	Complex wall boundary conditions in lattice Boltzmann simulations
14:30	Marco Verdicchio (SURFsara)	SURFsara, compute and data services for researchers
14:45	Francesc Levrero (University of Oxford)	HPC simulations of human hearts in health and disease
15:00	Adria Perez (UPF)	Applying machine learning in MD simulations and drug discovery
15:15	Jonas Lätt (University of Geneva)	Flow diverters to treat cerebral aneurysms
15:30	*Break/Tea and Coffee*	
15:45	Laura Perez Benito (Janssen)	Update on predicting binding energies
16:00	Marco Stijnen (LifeTec Group)	Predicting surgical and percutaneous coronary interventional outcome to support clinical decision making
16:15	Gerald Mathias (LRZ)	Life Science Application Support: BioLab @LRZ
16:30	Alex Heifetz (Evotec)	Identifying Inter-Helical Interactions Involved in GPCR Structure-Function and the Forces that Determine Ligand Residence Time
16:45	Andy Whiting	Lightox: A journey from curiosity-driven retinoid signalling pathway studies to spinout
17:00	Alfons Hoekstra (UvA)	Blood cells in the Supercomputer, towards large scale cell based blood flow modelling.
17:15	*Meeting Ends*	

Tim Elliott, University of Southampton

MHC-I molecules play a central role in the immune response to viruses and cancers. They present peptides on the surface of affected cells, for recognition by cytotoxic T cells. Determining which peptides are presented, and in what proportion, has profound implications for developing effective treatments. However, our ability to predict peptide presentation levels is currently limited. Existing prediction algorithms focus primarily on the binding affinity of peptides to MHC-I, and do not predict the relative abundance of individual peptides on the surface of antigen presenting cells *in situ* which is a critical parameter for determining the strength and specificity of the ensuing immune response. We have developed and experimentally verified a mechanistic model for predicting cell-surface presentation of competing peptides. The method explicitly models key steps in the processing of intracellular peptides, incorporating both peptide binding affinity and intracellular peptide abundance. We use the resulting model to predict how the peptide repertoire is modified by interferon-γ, an immune modulator well known to enhance expression of antigen processing and presentation proteins.

Franck Chevalier, Acellera

High Performance Computing resources combined with efficient sampling allow us to study and understand macroscopic events on a microscopic scale like ligand binding. Access to those resources and the need for complex protocols may limit their use. We have developed a range of powerful tools to democratize the use of MD for Drug Discovery.

Reference:

M. J. Harvey and G. De Fabritiis. AceCloud: Molecular Dynamics Simulations in the Cloud. J. Chem. Inf. Model. (2015) 55 (5), pp 909–914.

Phil Tooley, University of Sheffield,

We report on the recent demonstration of the transfer of large datasets from archival storage at the Diamond Light Source (DLS) facility to the Archer HPC and their subsequent analysis. The data transfer is performed over the public internet using encrypted parallel FTP marshalled by the Globus data management system. Performance and scalability are analyzed and we discuss potential improvements to the workflow. The frameworks used are common to many large scale experimental facilities and HPC installations and we discuss the potential for reuse and development of our current implementation into a more widely deployable framework for data analysis workflows both within CompBioMed and the larger light source user community.

Luca Emili, InsilicoTrials

InSilicoTrials is a cloud-based platform built to provide healthcare companies and researchers with an integrated and easy-to-use tool to perform computational testing during the development and validation process of new medical devices and drugs. InSilicoTrials aims to reach a new collaboration paradigm in healthcare R&D, engaging clinical and research centers to safely commercialize their data and know-how (virtual patients, model templates and simulation tools), and helping medical and pharmaceutic companies to significantly reduce efforts to create and translate IP during pre-clinical, clinical, regulatory approval and health technology assessment (HTA) process. InSilicoTrials' vision is to democratize simulations in healthcare, lowering entry barriers in terms of investment and knowledge level required, and finally resulting in an increased pace of innovation and reduced time-to-market for new products and treatments.

Mariano Vazquez, VHeart-SN, BSC

The VHeart-SN aims at enhancing collaboration among several Spanish groups with an ample experience in the field of cardiac computational modeling. The objective of the network is to accelerate the development, implementation and application of computational models in clinical practice, helping in the design of more efficient and safe personalized therapies.

Robin Richardson, UCL

The approaching era of so-called exascale computing brings with it the feasibility of performing (quantifiable) predictions of very large and complex systems in the computational biomedicine domain. However, there are significant challenges around how most effectively to exploit such a class of supercomputers. This presentation will discuss the different approaches one can take, algorithmically and by workflow, illustrated by a selection of CompBioMed's most promising candidate codes for "exascalability".

Jazmin Aguado, Barcelona Supercomputing Center.

Exascale systems are biomedical simulations at organ level are about to reach their confluence. This will unleash an unprecedented prediction power.... providing our codes are prepared and exascale systems can admit them. At this scale, even energy efficiency will be decisive. This talk addresses several of these issues.

Ignacio Pagonabarraga, CECAM Director, E-CAM Technical Manager

In this presentation I will describe the goals and activities carried out by E-CAM, one of the Centers of Excellence funded within H2020. I will focus on activities being developed and that can have overlap with the interests of CompBioMed, especially in the area of meso- and multi-scale modelling. CECAM coordinates E-CAM. Hence, I will also briefly describe CECAM's mission and the activities carried out by CECAM that can be of potential interest for CompBioMed.

Thierry Marchal, Secretary General, Avicenna Alliance,

The current “one size fits all” approach to healthcare fails to recognize the significant differences between the bodies and behaviors of different patients. This creates inefficiencies and cost overruns — but it also affects the quality of care provided. By personalizing the specific treatment to each patient, healthcare will become more affordable for patients and more profitable for providers due to increased efficiency. In silico medicine, the adoption of predictive computer models, is the most promising technology to accelerate and amplify healthcare innovation making medicine safer, cheaper and more effective.

Robert Welch (University of Leeds)

Fluctuating Finite Element Analysis (FFEA) treats globular macromolecules as viscoelastic continuum objects - deformable 3D meshes - which fluctuate under thermal noise. At the cost of some detail, this technique us to simulate mesoscale (5nm to 1μ m) protein complexes and biological processes on the μ s timescale. This talk will briefly discuss the FFEA algorithm and its applications to systems such as Cytoplasmic Dynein dynamics, Fibrinogen aggregation and force transmission in the Kinetochore.

Ralph Müller, ETH Zurich

A validated fracture healing model has the potential to reduce the need for animal testing when developing drugs and biomaterials. Current *in silico* models of bone regeneration lack the fidelity of physiological processes or are limited spatially making comparison to *in vivo* data for validation difficult. In regeneration, woven bone is produced and remodeled to the structured lamellar bone. The remodeling process is mechanically driven, thus an accurate representation of woven bone is crucial for *in silico* models, in which discrete mechanically sensitive cells are modeled. State-of-the-art *in silico* models of bone regeneration model tissue as a continuum. As part of the lecture, a novel fracture healing model on the microstructural level will be presented. The focus will be on investigating the effect of initial mesenchymal stem cell (MSC) density and osteoblast polarization on callus microstructure. As a geometric input for the simulations including nine cell types and tissue vascularization, *in vivo* micro-CT images of mice undergoing osteotomy were used. Results show polarization of osteoblasts was crucial for creating a porous microstructure. Pore size qualitatively depended on the initial population size, with fewer cells creating a finer structure in the regenerated bone.

Acknowledgements

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Frits W. Prinzen; Joost Lumens, Depts of Physiology and Biomedical Engineering, Maastricht University

The CircAdapt lumped parameter model of cardiac mechanics and the entire circulation has been developed in our center. It has proven to predict effects of various pathologies (pulmonary hypertension, right and left ventricular failure, dyssynchrony) and potential novel therapies. The model studies also allows to investigate the mechanism of disease in arrhythmogenic right ventricular cardiomyopathy (ARVC: primarily structural rather than electrical) and to develop novel biomarkers based on strain imaging. The almost real time computation on a conventional desktop computer allows to create populations of patients based on variation of myocardial tissue properties and circulatory conditions and test the optimal therapy in silico.

Clint Davies-Taylor, Dassault Systémes

Life Sciences for Dassault Systemes covers 3 segments – medical devices, Pharma/biotech, and patient care - that have hitherto been quite distinct, at least in terms of computational tools and technologies. However, all segments are ultimately concerned with patient health and satisfaction, and this presentation will demonstrate how Virtual Human Modelling R&D at Dassault Systemes is developing solutions for all 3 segments and in the process deepening, diversifying, and democratizing the use of simulation in healthcare

Jose Pedro Cerón Carrasco, UCAM

In this talk, we will review how one can use theoretical tools to design better drugs. We will be first focused on the application of Herceptin, an antibody that selectively recognizes the Her2/neu over-expressed protein of breast cancer cells, as a drug-carrier molecule. Next discuss other possible approaches to do less damage in normal cells, as photoactivated chemotherapy, an interesting strategy to control over the drug activation process. Other successful cases in the framework of anticoagulants, Parkinson, Fabry and Zika will be also presented.

Agastya Bhati, University College London

The so-called exact free energy methods, also known as alchemical methods, have gained much importance recently from several reports of improved ligand-protein binding affinity predictions based on their implementation using molecular dynamics simulation. A large number of variants of such methods implementing different accelerated sampling techniques and free energy estimators are available, each claimed to be better than the others in its own way. However, the key features of reproducibility and the quantification of the associated uncertainties in such methods have barely been discussed. Here, we apply a systematic protocol for uncertainty quantification to a number of popular exact free energy methods, covering both absolute and relative free energy predictions. We show that a reliable measure of error estimation is provided by ensemble simulation which applies irrespective of the free energy method. The need to use ensemble methods is fundamental and holds regardless of the duration in time of the molecular dynamics simulations performed.

Julien Favier, Aix Marseille University

The numerical simulation of biological flows often requires the implementation of complex wall boundary conditions including flexible, porous and in multicomponent fluid flows. The presentation will present recent implementations in that context using lattice Boltzmann and immersed boundary methods.

Marco Verdicchio, SURFsara

The mission of SURFsara is to support research in the Netherlands by the development and provision of advanced ICT infrastructure, services and expertise. Among SURFsara's customers are all of the Dutch universities, a number of large research, educational and government institutions, and the business community. In this presentation we will describe the main services SURFsara provides in the areas of High Performance Computing, Cloud Computing, Data Services and Visualisation and how they have been used to enable grand challenge applications.

Francesc Levrero, University of Oxford

We present the full pipeline of multi-scale ventricular electromechanical simulations of the human heart. Patient-specific biventricular meshes consisting of more than 30M elements are created from clinical MRI sets of images. These meshes are then used to simulate the fully coupled electrical and mechanical components of a heartbeat, with spatial scales ranging from sub-cellular (ionic channels) to organ levels. The resulting displacement maps are then compared to those obtained from tagged-MRI sequences.

Adria Perez, UPF

In the last few years, ML applications have grown exponentially. One of the main factors driving this growth is the broad popularization of a particular type of ML called deep neural networks. The application of deep neural networks in computational biology is steadily increasing. Our work has been focused on applying the recent advances in machine learning to structural biology and MD simulations, in order to create fast and effective tools for computer-aided drug design and to overcome the current limitations of MD simulations and improve their performance.

Jonas Lätt, University of Geneva

We have developed a new way to represent flow diverters, as those used to treat cerebral aneurysms, without the need to resolve the scale of the struts. This saves a lot of computation time, while maintaining an acceptable accuracy. We will also shortly summarize our other research activities in computational biomedicine, which include a new approach to the modelling of deformable RBC and the strategies adopted to achieve HPC simulations of fully resolved blood flow

Laura Perez Benito, Janssen

At Janssen we have been investigating the use of binding energy prediction calculations for several years. Part of this work has involved free energy perturbation studies. We will give an update on our progress in this area

Marco Stijnen, LTG

In clinical decision making, knowing pre-operatively what the expected outcome of different interventions might be and choosing the correct one, is not always an easy thing to do. We intend to build a software toolchain that would be able to compare the expected outcome of a coronary bypass surgery with that of a stenting procedure, including an (un)certainty analysis and based on clinical measurements as input to the model. We aim to exploit this software to support clinical decision making as a service to the clinical end users.

Gerald Mathias, LRZ

The Biolab application support group at the Leibniz Supercomputing Centre (LRZ) helps users to bring their projects to the SuperMUC HPC system. The talk will give an overview of the Biolab activities and show possible starting points for collaboration.

Alexander Heifetz, Evotec UK,

GPCRs comprise the single largest class of proteins against which therapeutic compounds in clinical use have been developed. However, these drugs only target approximately 50 of the 800 GPCRs in the human genome. Expansion of the range of GPCR targets available for the generation of effective therapeutics would provide an enhanced approach to the treatment of cardiovascular, neurological, endocrine and many other disorders.

Today, the key questions in GPCR drug discovery are: 1) What are the structural features responsible for 'gluing' together the seven helices of the GPCR bundle and how do these affect ligand binding, receptor flexibility and activation? 2) What are the forces that most affect the time that small molecules remain bound (residence time, RT) to the target receptor? RT is considered to be one of the most critical properties for the therapeutic efficiency of a drug.

Evotec (UK) Ltd and University College London (UCL) joined forces in the framework of CompBioMed, with the support of the BBSRC, to address these key questions. We integrated a suite of computational and experimental tools designed to address the issues related to GPCR structure and function. We use steered molecular dynamics (SMD) to calculate the forces that affect the residence time of various adenosine receptor ligands. We have also applied the Fragment Molecular Orbital (FMO) quantum mechanical method for the analysis of 33 GPCR crystal structures to identify the inter-helical tertiary interaction network. FMO offers a considerable computational speed-up over traditional QM methods, especially when combined with DFTB, allowing us to apply our method to the structure of an entire GPCR. This primary analysis revealed a consensus network of >30 inter-TM interactions mediated by 50 topologically equivalent amino

acids, providing a proof of concept that a conserved inter-helical interaction network exists and affects GPCR structure-function.

Andrew Whiting, Lightox,

Professor Andy Whiting will briefly talk about ongoing research interests related to retinoid signalling pathways and in silico ligand design to study ligand-retinoid acid receptor (RAR) interaction versus the downstream biological effects. These academic interests have led to the development of a new spinout company, Lightox Ltd., who are looking at applications of related compounds in fluorescence imaging, photodynamic therapy (PDT) and neurodegenerative diseases.

Alfons Hoekstra, University of Amsterdam,