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CompBioMed

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1 Version Log

Version	Date	Released by	Nature of Change
V0.1	11/01/2018	Gavin J. Pringle	Draft of template
V1.0	14/02/2018	Gavin J. Pringle	First Draft
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2 Contributors

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3 Acronyms and Definitions

Acronyms	Definitions
CoE	Centre of Excellence
KPI	Key Performance Indicator
HPC	High Performance Computing
SME	Small and Medium Enterprise
MoU	Memorandum of Understanding
cPPP	contractual Public-Private Partnerships
ETP4HPC	European Technology Platform for High Performance Computing
FDA	Food and Drug Administration
EMA	European Medical Association
LTG	LifeTec Group
GPCR	G-protein coupled receptor
HGMP	Hierarchical GPCR modelling protocol
EGFR	Epidermal Growth Factor Receptor
FMO-DFTB	Fragment Molecular Orbit – Density Functional Tight-Binding
ISBA	*In Silico* Binding Assay
CADD	Computer-aided drug design
BoF	Birds of a Feather
EC	European Commission
BTK	Bruton's tyrosine kinase
FEP	Free Energy Perturbation
MD	Molecular Dynamics
IAB	Innovation Advisory Board
IEP	Innovation Exchange Programme

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4 Executive Summary

Our CompBioMed Centre of Excellence has around 30% of our Core Partners are from Industry, and a current total of 33 Associate Partners, and this report discusses our joint collaborations to further innovation in the field of personalised medicine. This report contains detailed discussion on the Core Partners collaborative efforts with the Centre as a whole. Further, significant progress has been made in bringing in new Associate Partners as we currently have 33, with many more expected in the following 18 months. We have established, revised and improved our Centre's 'incubation' activities, in collaboration with SMEs and other industrial stakeholders, to ensure our results are nurtured on the road to the marketplace. Our Centre has created strong links to the ETP4HPC Association, as part of the HPC cPPP, which established a mechanism for the HPC industry to interact with the computational biomedicine community, whether in academia, hospitals or SMEs. Our Innovation Exchange Programme has been created and is actively seeking to bring together individuals with visits to industrial companies to and from academic centres. Finally, our Innovation Advisory Board contains members from industry, particularly SMEs, from both within CompBioMed and, more importantly, from outwith CompBioMed.

5 Introduction

The importance of industrial collaboration to CompBioMed cannot be understated, given it is one of the key elements of success for our Centre of Excellence. We have closely collaborated with industry to create and implement a strong sense of innovation, thereby enabling the Centre to sustain itself well into the future. We have begun to provide a centre of information, a hub of ideas and a place where medical professionals can access both HPC computing resources and advice from HPC professions. To this end, ComBioMed works closely with its many and various industrial stakeholders, our current main stakeholders being our Core or our Associate Partners.

This report describes our engagement with industrial stakeholders, specifically our Core and Associate Partners. We also discuss our progress in developing our engagement with the wider community, via our work with the cPPP on High Performance Computing and the ETP4HPC Association, our Innovation Exchange Programme, and our Innovation Advisory Board.

Our Core Partners are funded by our Centre of Excellence and are the legal entities that sign the Grant Agreement and have the responsibility for the proper implementation of the action. They contribute directly to the implementation of the research, transfer of knowledge and training activities by supervising, hosting, training and/or seconding staff members. At present, around 30% of our Core Partners are from Industry, and these are listed in detail below, where we describe the Partner, the official role in the project, and summarise their activities to date.

To date, we have attracted 33 Associate Partners to join our Centre of Excellence. The benefits of being an Associate Partner are described in Section 6.2. Associate Partners are partners who have agreed to co-align themselves with CompBioMed and are listed at the following webpage: http://www.compbiomed.eu/associate-partners/. Significant progress has been made, in this regard, as we have gathered many new Associate

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Partners throughout the first 18 months of the CompBioMed project and expect the number to increase substantially over the next 18 months.

To bring in external industrial partners, we actively maintain tasks to promote, attract and involve them through the following activities.

We coordinate the Centre's 'incubation' activities with SMEs and other industrial stakeholders, wherein we monitor novel ideas via our IP Register, determine suitable candidates for entry into the Innovation Management Process, then where appropriate nurture them on the road to the marketplace.

The contractual Public Private Partnership on High Performance Computing (HPC cPPP) entered into force in January 2014 to develop an ambitious research and innovation strategy for technologies and usage and applications (pillars a & c) of the European HPC strategy along with training, education and skills development the pillars. The private partner in the cPPP is the industry association European Technology Platform for High Performance Computing (ETP4HPC).

The HPC cPPP's main goals and high-level objectives are to:

- Develop the next generation of HPC technologies, applications and systems towards exascale
- Achieve excellence in HPC applications delivery and use

The HPC cPPP brings together both the technology providers and the end users via the ETP4HPC Association and the Centres of Excellence. CompBioMed, as one of the Centres of Excellence, has created links to the ETP4HPC to establish a forum and mechanism for the HPC industry to interact with computational biomedicine community, whether in academia, hospitals or SMEs. This is described in more detail below.

Our Innovation Exchange Programme, or IEP, actively seeks to bring together individuals with visits to industrial companies to and from academic centres. This is also presented in greater detail in Section 8.1.

The Innovation Advisory Board, or IAB, contains members from industry, particularly SMEs, which are not only from Core and Associate Partners, but also, and more importantly, from outwith CompBioMed altogether. This ensures a constant interrogation, discussion and flow of ideas into our Centre to help us learn, develop and remain at the forefront of our field.

A WP4 teleconference is held at least once per month, wherein the current and future industrial collaborations are discussed. Each Core Partner is represented, and actively engages with all aspects of the meetings, including the Innovation Panel wherein all novel news of the last month is discussed, ranging from any new IP to be recorded and perhaps progressed through the incubator, to journal/conference articles to items reported in the Press. This ensures a nurturing sense of innovation is maintained and we plan to roll this Innovation Panel across all work packages.

Lastly, many industrial bodies also interact with CompBioMed via

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- engagement with Core or Associate Partners,
- through companies employing CompBioMed HPC resources,
- companies participating in CompBioMed workshops,
- company guest presenter at seminars/meetings.

The remainder of this Report describes each of our industrial Core Partners and the status of their involvement. It then describes the Associate Partners, our work with ETP4HPC, and the progress made by our IEP. Finally, we describe some ongoing efforts to improve industrial engagement, monitoring and suggests future improvements currently under consideration.

6 CompBioMed Industrial Partners

6.1 Core Partners

This section lists the Industrial CompBioMed Core Partners, first providing an overview of each company, second describing their role in the project and, thirdly, presenting their progress to date.

CBK Sci Con Limited

CBK's key contributions to the project include support for project management, where CBK works as an integral part of the project management team at UCL providing complementary experience from commercial industry perspectives alongside UCL's research management expertise. CBK is the lead partner co-ordinating the project's quality assurance planning, data management planning and the final public reporting. The project quality assurance system and its procedures were developed with all core partners under CBK's lead during the first 6 months of the project, as was the project's approach to data management. Both areas were formally reported at this time.

As a partner in the team supporting the management of dissemination activities, CBK has developed the CompBioMed online presence principally via a unique website created for the project. The website has both external and internal access facilities and functions that facilitate the storage of key documents and dynamic interchange of project information to partners and to the public. All configurable documents are stored in their latest form in an "intranet" section of the website with viewing access enabled for the core partners. There is progressively less restricted access to facilitate the engagement of wider stakeholders in science and medicine, through to direct engagement with the public via news, events (& booking) and a knowledgebase. The project website was set up before the project started with the website release deliverable (D3.1) submitted at M3 detailing the public release of the website. The functionality of the website is regularly reviewed and developed as its use increases and the project output information builds.

CBK has a substantial presence in the overall dissemination and closely related training team. The company led the team in the development of the plan for dissemination, the public plan being published at the 3-month point. Subsequently CBK has led and continues to lead the co-ordination of the dissemination activities and produces all materials necessary in support of these activities. This has resulted in substantial

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success in promulgating the results and knowhow to a wider scientific and public community. Where seen to be beneficial, CBK has co-ordinated the application of additional effort to achieve a significant boost to the dissemination of project information. A key example of this is the development of a film showing the state of the art of HPC use in biomedicine, that formed the basis of an IMAX cinema showing to the public at the Science Museum in London in 2017. This film and the material captured in recording the event is now being further developed for wider distribution at science orientated public events. The project training plan was developed early in the project and CBK is one of the core partners involved in the coordination of training activities, including help with workshop materials, facilities and organising events.

The management of innovation is led by the University of Edinburgh and CBK is a partner in the innovation management team, also providing one of its directors to sit on the Innovation Advisory Board. CBK led the development of the plan for managing the processes within the project aimed at supporting the scientific research teams to best exploit the project results for maximum impact. The formal plan was issued 6 months into the project and encompasses the project's approach to identifying new knowhow and tools and then providing support in assessing their exploitation potential, whether this be academic, societal or commercial potential. To date this support has taken the form of advice for specific exploitation routes, enhanced dissemination to appropriate stakeholder groups, commercial advice for software commercialisation and early help in assessing how knowhow may be bundled to support provision of consultancy services. In addition, a specific new training module which serves to educate medical students in the use of HPC simulation is currently being assessed for its commercial potential. The project has a task which focuses on incubator coordination. Bringing its experience of university incubation and acceleration, CBK contributed to the development of the approach which aims to facilitate collaborations between research partners and commercialisation parties for results which have a high commercial growth potential.

LifeTec Group

LifeTec Group (LTG) is playing a substantial role in our Innovation and Sustainability work package, particularly in the future precommercial activities. The main tasks of LTG in this project are the development and application of cardiovascular in silico models and tools and to combine them with the models of other participants, to create workflows, pipelines and interfaces.

LTG is involved in business development for the CoE by working on the Innovation Plan, which established mechanisms to actively promote in silico methods to e.g. the pharmaceutical industry. The Innovation Plan is a live document which is maintained throughout the life of our Centre. Further, LTG is also contributing to the development of the sustainability plan to ensure the Centre adheres to in silico regulatory procedures (FDA for US and EMA for EU) and incorporates relevant regulatory procedures into the CoE's portfolio.

LTG have explored some of the cardiovascular software models that are available within the consortium. Discussions with clinicians have been held to explore their interest and needs for a cardiovascular simulation tool that they would be beneficial to the clinical decision-making process as well as allows for an exploitation opportunity towards the end of the project.

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To date, LTG has envisioned a tool to provide clinical decision support as a service, based upon the infrastructure currently provided by CompBioMed. More specifically, discussions with clinicians have identified a challenge in the decision-making process to treat difficult coronary stenosis either by bypass surgery or by placing a stent. A simulation that can predict the outcome of both interventions as well as present the accuracy of said prediction, would be very helpful in the decision-making process and would reduce the cost of treating complications. The idea is that relatively (computationally) cheap 1D models with input from patient specific data will provide quick results of both interventional strategies, and that running many cases in parallel allows for a population of results that not only provides a result but also an assessment of the expected accuracy of the result.

The 1D models may also be used as a tool to provide inlet or outlet boundary conditions for more complex 3D cardiovascular models, such as to incorporate such 3D local simulations into a larger vascular computational environment. Collaborations with consortium partners on such interactions will be beneficial for the integration of different software tools.

Acellera

Acellera is playing a substantial role in three work packages, namely Biomedical Research Activities (WP2), Innovation and Sustainability (WP4), and Empowering Biomedical Applications (WP6). Acellera provide technology and knowhow for large-scale molecular simulations and analysis. They participate in the following research activities within the Molecular-based Medicine theme: Molecular simulation of the transport properties and mechanism of gating, to decipher the key factors controlling selectivity; Fragment-based drug design for GPCR targets; rational antibody design for EGFR inhibitors.

Since the beginning of the project, Acellera participated in the dissemination of the project news and promoted the use of *in silico* methods in Industry and non-profit entities by participating and organising events, but especially by its effective marketing activity. This activity is illustrated by the organisation of workshops, its participation in the winter school (at BSC (14-16 February 2018, Barcelona)), and the organisation of exclusive webinars for CompBioMed partners as well as for our customers.

Strong in its expertise in biomolecular interactions, Acellera developed innovative methods to predict small molecule interaction with protein target, especially with GPCR, in the following publication:

- Dopamine D3 receptor antagonist reveals a cryptic pocket in aminergic GPCRs, Sci. Rep. 2018; 8:897.

Acellera's ISBA protocol has been optimized and is ready to initiate collaboration among CompBioMed partners. Moreover, they provide free access through its platform PlayMolecule.org to promote the use of *in silico* methods for drug discovery and molecular medicine projects.

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Finally, Acellera has produced the following seven CompBioMed-related publications since the start of our Centre.

- N. Ferruz, S. Doerr, M. A. Vanase-Frawley, Y. Zou, X. Chen, E. S. Marr, R. T. Nelson, B. L. Kormos, T. T. Wager, X. Hou, A. Villalobos, S. Sciabola and G. De Fabritiis, Dopamine D3 receptor antagonist reveals a cryptic pocket in aminergic GPCRs in Sci. Rep., 2018, 8, Article number: 897, DOI: 10.1038/s41598-018-19345-7
- G. Martinez-Rosell, T. Giorgino and G. De Fabritiis, PlayMolecule ProteinPrepare: a web application for protein preparation for molecular dynamics simulations in J. Chem. Inf. Model., 2017, 57 (7), pp 1511–1516, DOI: 10.1021/acs.jcim.7b00190
- S. Doerr , M. J. Harvey, F. Noé and G. De Fabritiis, HTMD: High-throughput molecular dynamics for molecular discovery in J. Chem. Theory Comput., 2016, 12 (4), pp 1845–1852, DOI: 10.1021/acs.jctc.6b00049
- M. J. Harvey and G. De Fabritiis, Acecloud: Molecular Dynamics Simulations in the Cloud in J. Chem. Inf. Model., 2015, 55 (5), pp 909–914, DOI: 10.1021/acs.jcim.5b00086
- M. Harvey, G. Giupponi and G. De Fabritiis, ACEMD: Accelerated molecular dynamics simulations in the microseconds timescale in J. Chem. Theory Comput., 2009, 5 (6), pp 1632–1639, DOI: 10.1021/ct9000685
- Kapoor, G. Martinez-Rosell, D. Provasi, G. De Fabritiis and M. Filizola, Dynamic and Kinetic Elements of μ-Opioid Receptor Functional Selectivity in Sci. Rep., 2017, 7, Article number: 11255, DOI: 10.1038/s41598-017-11483-8
- G. Martínez-Rosell, T. Giorgino and G. De Fabritiis, PlayMolecule ProteinPrepare: A Web Application for Protein Preparation for Molecular Dynamics Simulations in J. Chem. Inf. Model., 2017, 57 (7), pp 1511−1516, DOI: 10.1021/acs.jcim.7b00190

Evotec

Evotec (UK) Ltd, as a leading industrial application partner, is responsible for four key objectives: adaptation of hierarchical GPCR modelling protocol (HGMP) to HPC platform, developing of the new HGMP-HPC based tools / plugins that require high scale calculations, testing and application of HGMP-HPC integrated technology in real drug discovery cases within the CoE and to make it available to third parties seeking assistance from the CoE and/or from Evotec, and dissemination of the results of this work to our partners in academia and in pharma & biotech companies in order to stimulate follow-on research. Evotec has also published the outcome of this work in peer-reviewed journals and at scientific conferences.

Evotec (UK) Ltd has established a close collaboration with UCL (group of Prof Andrea Townsend-Nicholson). In the framework of this collaboration, they developed computational methodology to rationalize the receptor-ligand binding and drug-candidates' residence time [1, 2]. This methodology is based on integration between HGMP (Hierarchical GPCR modelling protocol) and FMO-DFTB (novel and rapid quantum mechanical method [2]). The method was tested by Evotec (UK) Ltd and feedback provided (this is ongoing). Further computational and experimental validation of the method is initiated

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Dissemination and training: Evotec gave an oral presentation at two high profile international conferences: ACS Annual Conference in Washington (August 2017) and 6th World Congress on Medicinal Chemistry in Milan (June 2017)

Evotec (Alex Heifetz) provided a training session in the CompBioMed & BioExel Free-Energy Workshop, London, 31 May 2017; and at the CompBioMed winter school in Barcelona in February 2018 on the subject of 'Introduction to Computer-Aided Drug Design (CADD) and GPCR Modelling' illustrated by examples from real drug discovery projects. Videos of both these sessions are available via the CompBioMed YouTube channel.

Publications: The translation of knowledge was performed by the following four publications, including a book 'Computational Methods for GPCR Drug Discovery' recently (2018) published by Springer [4].

- Potterton, A.; Heifetz, A.; Townsend-Nicholson, A., Synergistic Use of Gpcr Modeling and Sdm Experiments to Understand Ligand Binding. Methods Mol Biol 2018, 1705, 335-343.
- Morao, I.; Fedorov, D. G.; Robinson, R.; Southey, M.; Townsend-Nicholson, A.; Bodkin, M. J.; Heifetz, A., Rapid and Accurate Assessment of Gpcr-Ligand Interactions Using the Fragment Molecular Orbital-Based Density-Functional Tight-Binding Method. J Comput Chem 2017, 38, 1987-1990.
- Heifetz, A.; Southey, M.; Morao, I.; Townsend-Nicholson, A.; Bodkin, M. J., Computational Methods Used in Hit-to-Lead and Lead Optimization Stages of Structure-Based Drug Discovery. Methods Mol Biol 2018, 1705, 375-394.
- Heifetz, A., Computational Methods for GPCR Drug Discovery. Springer ed.; Springer: Germany, 2018; Vol. 1705, p 454.

Bull

Bull has been deeply involved in the Innovation and Sustainability work package coordinating the collaboration between CompBioMed and the cPPP on High Performance Computing, via the ETP4HPC. They have been active in the partnership and we have established connections with three individuals: Marcin Ostasz, Hugo Falter and Jean-Pierre Panziera. On top of regular exchanges with them, Hugo Falter made a presentation at our Kick-Off meeting in October 2016. Further, Bull is actively seeking to establish collaboration with at least two more ETP4HPC centres.

CompBioMed and ETP4HPC are proposing a BoF at the upcoming ISC18. If it is accepted, Marcin Ostasz will represent the ETP4HPC there. This work is described in more details below. The collaboration is also visible by the presence of one CompBioMed individual to all the cPPP Board Meetings since the beginning of the project. In collaboration with the other CoEs and via ETP4HPC, CompBioMed has provided comment and input to the text of the EC's 2018-20 calls during their development. Further, ETP4HPC are advertising CompBioMed events through their website. Bull plans to seek collaboration with other Industrial Partners out with ETP4HPC.

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Lastly, Bull is heavily involved in Task 2.6 Upscaling of CompBioMed Production Applications for Future HPC Platforms and in Innovation and Sustainability (WP4). Bull intends to provide access to an "on-demand" HPC production infrastructure with dedicated portal and provide expertise. They contribute to best practice recommendations for efficient resource usage and solution upscaling toward the exascale.

Janssen Pharmaceutica NV

Janssen's interests are in developing and using advanced molecular simulation methods to optimize lead compounds in discovery programs. Such methods, if proven robust and accurate could have a profound impact on the way drug discovery is performed. They would permit reliable computational triaging of very close analogue molecules greatly improving efficiency. Also, this would lead to high-confidence design of synthetically more challenging molecules leading to better drugs in new chemical space. Also, we envisage the accurate prediction of compound binding for targets that have mutated residues. This latter application can be of value in diagnostics, by predicting the best possible compound for a patient clinically (personalised medicine), but is also of use in discovery, where mutated targets occur regularly in antibacterials, antivirals, and oncology compounds.

Janssen have been working with collaborators, particularly the group of Prof. Peter Coveney at UCL, and internally to improve the computational prediction of the binding energy of small molecules to protein targets. In collaboration with UCL, multiple datasets, provided by Janssen from drug discovery targets such as BRD4, PDE2, BACE etc, have been assessed with different theoretical methods to calculate the binding free energy. Methods that are being considered include ESMACS and TIES approaches from the UCL groups, as well as FEP implementations performed by Janssen with Schrodinger and GROMACS software. Most calculations are now finished, and the final analysis stages are being entered. Decision points will follow where more datasets are expected into the more promising approaches. This work has been performed with the involvement of several people in Janssen and makes use of Janssen internal hardware as well as hardware accessed via this CompBioMed project. Regarding this latter point, scientists from Janssen, Laura Perez and Gary Tresadern, attending a full-day visit to the SURFsara HPC in Amsterdam on 27th February to perform a detailed analysis of how to scale-up their calculations on the HPC resource there. The meeting was a success with excellent advice from Marco Verdicchio helping Janssen to immediately run binding energy calculations, in a pre-competitive evaluation manner, in a larger throughput.

Further to the collaborative work mentioned above, Janssen have been performing internal evaluations on other projects and difficult datasets. Results are encouraging but one recently completed validation study revealed that relative FE binding methods can still struggle with typical drug discovery datasets, Perez-Benito et al Sci Rep, 2018 In press. Regarding difficult datasets, recent activities in Janssen also include compiling GPCR based datasets for use with binding free energy calculations. The focus on GPCR modelling, which is also something of direct interest to Janssen, as they have a long history of GPCR drug discovery programs, many of which have led to marketed drugs. They currently have several active drug discovery programs on GPCRs for which no structure has been solved and building the expertise on the proposed hierarchical GPCR

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modelling protocol in subtask 2.3.2 will be of immediate use. Bioactivity data was collected from existing Janssen legacy projects for CRF1, DOR, OX2, A2A amongst others. Initial free energy calculations are underway and will be the subject of future comparisons.

Other areas of CompBioMed related work inside Janssen include applying molecular dynamics simulations (with GROMACS) to understand the functional effects of specific mutations on GPCRs, a member of the metabotropic glutamate receptor family.

Binding kinetics of small molecules to targets can be a means to improve the pharmacodynamic effect, or to reduce the systemic exposure while retaining full target engagement. Janssen are interested in this area, for instance a recent marketed Janssen drug, ibrutinib, uses covalent attachment to the target BTK for an extremely slow off rate. We regularly measure binding kinetics to differentiate the compounds in discovery programs. In some cases, a fast-off rate is desired, such as with antipsychotics and the D2 receptor. The ability to predict the binding kinetics of compounds is still in its infancy and using molecular dynamics-based methods to do this is of interest to Janssen. The ability to predict the binding kinetics of compounds is still in its infancy, and therefore the activities in subtask 2.3.3 are of great interest and practical use to Janssen

The Medical Devices arm of Johnson and Johnson would also benefit from the proposed activities in the cardiovascular space as described in the Biomedical Research Activities work package. Our current collaborators at Janssen are involved in active discussions to determine how this can be implemented in the future. Janssen do not yet have active programs around flow simulation in stents but are interested in lesion formation in the heart and have done some computational work around those aspects.

The use of high performance computing in these areas is something Janssen are exploring actively, with internal and external resources. They realize that it is essential to have access to quality software and hardware, and the project is certainly being highly valuable for them in that respect. It has become clear that their main strategy for this will be to access external resources, as this provides the best flexibility and cost effectiveness. They are therefore highly interested in developing new options for external access to high performance computing through this H2020 project.

Summary:

- Janssen has been actively collaborating with UCL on calculation of free energies of binding on public and on Janssen internal compound sets (targets BRD4 and PDE2). A manuscript is being co-written. Furthermore, the use of GROMACS for Free Energy Perturbation, or FEP, is actively being pursued. Results are being compared to previously run calculations with Schrodinger's FEP+ software. Janssen are initiating efforts to model difficult GPCR datasets.
- Extensive Molecular Dynamics calculations are run with GROMACS to a current drug discovery project: understanding the effect of specific mutation in Glutamate receptors (class C GPCRs). and apply
- Active interaction with SURFsara is ongoing to set up FEP and MD calculations using GROMACS software on the Cartesius HPC infrastructure.

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- Janssen has been a partner in two successful bids for HPC resources led by UCL: 32M core hours on SuperMUC in 2017-19, and on DoE Titan in an INCITE award worth around 100M core hours between 2018-2019. These grants are for work on binding affinity prediction.

Finally, Janssen have had the following CompBioMed-related paper accepted for publication

- Pérez-Benito L, Keränen H, Van Vlijmen H, Tresadern G. Predicting Binding Free Energies of PDE2 Inhibitors. The Difficulties of Protein Conformation. Sci. Rep., accepted.

6.2 Associate Partners

As noted earlier, CompBioMed has been very successful in attracting new collaborators, as represented by the current 33 Associate Partners, and their number is growing rapidly.

Associate Partners are encouraged to participate in CompBioMed meetings and events throughout the project, which gives them the opportunity to join our full network of partners and help steer the future of computational biomedicine through their influence on the actions of our Centre. Associate Partners also get complete access to the training provided by CompBioMed.

The list of benefits for Associate Partners includes:

- access to and provision of project resources including HPC facilities
- access to and provision of software
- access to and provision of training materials
- invitations to project meetings
- invitations to our workshops
- invitations to our training events
- listing as an associate partner on the CompBioMed website
- participation in our Innovation Exchange Programme
- participation in Incubator Coordination
- possible participation in our Innovation Advisory Board

There is no formal process involving paperwork required to allow Associate Partners to join; however, we may require an NDA to be signed for the purposes of some CompBioMed meetings where IP is involved.

Our Associate Partners include institutions from industry, academia, medical hospitals and HPC Centres, and they benefit from their association with CompBioMed by either being engaged with a Core or another Associate Partner. Further, they may use CompBioMed resources or allow CompBioMed members to employ their resources, where these include HPC and HPDA resources or simply exploiting CompBioMed's growing information hub.

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The list of current Associated Partners is presented via the CoE webpage http://www.compbiomed.eu/associate-partners/

The list of Associate Partners currently stands at 33, and includes the following partners from Industry; Avicenna Alliance, Convergence Pharmaceuticals, GSK, DNAnexus, Oxford Biomedical Research Centre, Alces Software, Electric Ant Lab BV, Norton Straw Consultants, Pozlab (Poznan), Qatar Robotic Surgery Centre (Hamad Medical Corporation), Microsoft, DiaVita (Life Science), Dassault Systems, Lightox and Medtronic

7 CompBioMed's Collaboration with the cPPP ETP4HPC

The cPPP on HPC brings together both the technology providers and the end users via the ETP4HPC Association and the Centres of Excellence. CompBioMed, as one of these Centres of Excellence, has created its own links to the ETP4HPC to establish a forum and mechanism for the HPC industry to interact with computational biomedicine community, whether in academia, hospitals or SMEs.

ETP4HPC is the European Technology Platform (ETP) in the area of HPC. It is an industry-led think tank comprising of European HPC technology stakeholders: technology vendors, research centres and end users. The main task of ETP4HPC is to define research priorities and action plans in HPC technology provision (i.e. the provision of supercomputing systems). They issue and maintain a Strategic Research Agenda as a mechanism to help the European Commission define the contents of the HPC Technology Work Programmes. ETP4HPC also acts as the "one voice" of the European HPC industry in relation with the European Commission and national authorities. ETP4HPC was formed in October 2011.

Regarding general collaborative efforts, our Centre has attended all the HPC cPPP board meetings since CompBioMed started in October 2016. Reciprocally, Hugo Falter, of the ParTec Cluster Competence Center and the ETP4HPC Association, gave a presentation at our Centre's kick-off meeting. Further, in response to requests from ETP4HPC, as the HPC cPPP coordinator, we have also made significant contributions to the EC's Work Programme 2018-2020 in the area of High Performance Computing.

Regarding particular collaborative efforts, Bull has established a working relationship with three key contacts of ETP4HPC, namely H. Falter , M. Ostasz of the Barcelona Supercomputer Center (BSC), and Jean-Pierre Panziera (ATOS). .

Bull is continually meeting new contacts and is planning to expand beyond the identified networks. Specifically, Bull plan to meet with Jesus Carretero, of the University Carlos III of Madrid – a member of ETP4HPC, and Sabri Pllana, of Linnaeus University, Sweden. Further, we have approached various institutions associated with ETP4HPC to become Associate Partners

Finally, CompBioMed is provisionally planning to have a strong presence at the upcoming ISC18 conference in Germany. To this end, a proposal has been submitted to host a Birds-of-a-Feather session, or BoF. This BoF promises to be a very exciting

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opportunity that will permit a more open discussion between a wide range of participants, with focus on SMEs and other industrial/medical companies. A meeting which aims to be much less restrictive than an ISC Workshop, and we hope to extend our reach to publicise CompBioMed, and attract new industrial collaborations through our many existing routes, i.e. as becoming Associate Members, a member of our IAB, attending our All Hands Meetings, workshops, presentations, etc.

This BoF is being organised by a CompBioMed Core Partner, namely Bull with strong support from members of the ETH4HPC themselves. Members of both ETP4HPC and six of CompBioMed's Core Partners will be in attendance, including Bull, an ATOS company, SURFsara, Barcelona Supercomputing Centre, LifeTec Group, Janssen Pharmaceutica, and EPCC of The University of Edinburgh. Our ISC18 BoF application is included in Annex A below, and all successful BOFs will be notified on the 4th of April.

8 Innovation Exchange Programme and the Innovation Advisory Board

Industrial collaboration is strongly encouraged, fostered and extended via two of the Innovation and Sustainability WP4 activities, namely the Innovation Exchange Programme and the Innovation Advisory Board.

8.1 Innovation Exchange Programme

Our Centre's Innovation Exchange programme, or IEP, permits the technology transfer between academia, healthcare and industry in the field of biomedical computing by fostering a mentoring programme, whereby experts from the research community spend time embedded within industrial organisations looking for assistance, applying the latest research techniques in their software. This mentoring programme is enabled via short internships within industrial organisations.

The associated work package, Innovation and Sustainability (WP4), and the sister work package, Training and Dissemination (WP3), work together to develop mentoring programme opportunities, which will be posted on the ComBioMed website, and will be open to both internal and external stakeholders. These visits nurture best practice in software development and techniques, and we anticipate that this will foster mentoring relationships and establish collaborations between the participating sites.

Our initial plan for visits were from academia to industry; however, after consultation within the associated work package, Innovation and Sustainability, we have decided to extend the remit of the IEP: parties form industry can visit academia, and parties from industry can visit other industrial institutions, and parties from academia can visit other academic institutions. Our only limitation is that one of the participants, either the visitor or the target institution, must be one of the CompBioMed partners.

Our plans include:

- holding conferences/seminars between academia and industry, in collaboration with CompBioMed Training and Dissemination;
- at least 5 participants in the IEP from European countries and regions with fewer HPC resources;

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- design and implement an extension to our web-based hub in our website, namely http://www.compbiomed.eu/innovation/innovation-exchange-programme/, where
    - visitors can post their wish to visit anyone
    - hosts can post their wish to host anyone

Clearly this programme requires extensive advertising, and, to this end, we advertise our IEP through the publicity channels of both CompBioMed and VPH, namely Newsletters, LinkedIn, Twitter, Facebook, etc. It is worth noting that VPH advertises our IEP via their website, their monthly newsletter (which has over 8000 contacts), and via their VPH social media networks.

All past, current and future visitors are noted and displayed on our website at http://www.compbiomed.eu/innovation/innovation-exchange-programme/current-and-planned-exchanges/

The table presented in Annex B is a snapshot of our IEP at the time of writing which currently lists twenty visits.

Our Centre has limited funds to support visitors, and we work closely with Core, Associate Partners and third parties who can provide financial support to the programme, such as the HPC-Europa3 project. To date, we have formed a Memorandum of Understanding, or MoU, between CompBioMed and the HPC-Europa3 Project, shown in Annex B, and visitors have already started to exploit this opportunity.

The HPC-Europa3 Project offer grants for travel, accommodation, subsistence and computing time at one of the HPC centres, for visits lasting between 3 and 13 weeks in total. The HPC Centres within HPC-Europa3 are as follows: CINECA (Italy), EPCC (UK), BSC (Spain), HLRS (Germany), SURFsara (Netherlands), CSC (Finland), GRNET (Greece), and KTH (Sweden).

The visitors can be hosted at either the HPC centres themselves, or the visitor can be hosted at a site of their choice, provided the visit is mutually agreed, be it an industrial organisation, an academic department; however, the visit must be paired with one of the HPC Centres listed above.

HPC-Europa3 has 4 calls per year, with funding for visits lasting between 3 weeks and 3 months. (For more information, please see the HPC-Europa3 website: http://www.hpc-europa.eu/.)

8.2 Innovation Advisory Board

Our Centre's Innovation Advisory Board, or IAB, has moved from strength to strength. We started with around 14 IAB members for the first meeting and now, to date, we currently have 20 IAB members. The members include academics specialising in HPC and professional sustainable software practices, practicing medics from hospitals and universities, alongside members from Industry, particularly SMEs. The members come

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from both our Core and Associate Partners but, most importantly, also from outwith CompBioMed altogether.

All IAB members sign NDAs upon attendance and present their own personal views which may be different to the views of their home intuitions.

IAB members from industry come from the following industrial companies, in no particular order: Microsoft Azure, Amazon AWS, EvoTec (UK) Ltd, Vertex Pharmaceuticals, Merck, Neuravi Ltd, CADREM Ireland Ltd, and Medtronic Plc.

The first IAB meeting was held at UCL in London on the 30th of May 2017. Six of the then fourteen members were in attendance, along with four CompBioMed staff members.

What follows is a description of the 1st IAB Recommendations:

Create a Forum:

- specialists/practitioners can learn what is out there
- provide translation/terminology service
    - clinicians don't understand biotech who, in turn, don't understand hpc
- Offer consultancy for
    - data management
        - storage/movement
    - connecting with other groups
    - FAQs
        - pre-clinical studies
        - how to get results quickly
- "ask an expert" button for real-time interaction

Provide a directory of services

- lists of contacts, groups, information, providers
- exhaustive list of CBM resources
    - codes, platforms, models, paradigms, etc.
    - list of associated experts
    - public domain
        - perhaps a second one is needed for internal use only

Create CompBioMed Ambassadors

- Informed and empowered members to attend conferences

Offer speed-up of existing software

- web browser app that looks like familiar UI
- front-end to cloud HTC/HPC
- Time to solution reduced by 50% is not good enough
    - Reduce from hours to minutes

Shift focus

- More on SMEs, less on practitioners
    - Focus on early results

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    - Clinicians will be slow to employ CompBioMed results
- More on Models, less on HTC/HPC
    - General workshops are simply too general
    - Model-specific workshops
        - Speed of compute is key, however
        - Underlying code not of interest
- More on HTC, less on HPC

Miscellaneous

- Offer Solutions as a Service
    - Not "Software as a Service" or "HPC as a Service"
    - Create pictorial representations for end-users
    - Then align representations with our CoE's objectives
- Need clear statement of data security
    - Critical to Business Model
    - All centres signed up to GDPR
- Consider expanding CoE's range of interest
    - Virtual reality for training purposes?
    - Machine learning plus medicinal chemistry for post-simulation validation

We have addressed these proposals in turn and have adapted accordingly. Specifically, we are in the process of creating the User Forum, as outlined above. A Directory of Services is being created as part of a general, ongoing process to improve our website. CompBioMed Ambassadors may not exist with that name, but we have our members attending a wide variety of conferences, armed with a relevant slide deck. Moreover, we organise booths at various conference. We do not currently plan to help speed-up existing software, as this is within the domain of a sister CoE, namely POP: www.pop-coe.eu/.

Regarding shifting our focus: we *are* introducing our concepts to medical students, and introducing ideas to clinicians; however, this is not our focus. We have several SMEs within our Associate Partners, and we focus on their needs. Further, we believe that CompBioMed has a very wide area of interest: i.e. we have had an HPC-related conference on Cloud and HPC, but equally we held a dedicated model-related workshop on Free-Energy considerations. We will consider model-related topics when we organise further workshops. Lastly, as our membership is very wide, we have members already working on both High Throughput Computing (HTC), as well as HPC.

Regarding offering Solutions as a Service: we acknowledge this is an area which requires more effort. To this end, Marco Viceconti (USFD) produced a public report which outlines our Solutions and End-users. Furthermore, we are actively collecting this information from our Associate Partners.

Data security is already a key consideration both for user and the providers at CompBioMed's HPC Centres. As such, those that are handling sensitive/patient data have the necessary security in place, and we have ensured that they are aware of the GPDR requirements. Moreover, within our Associate Partner, DNAnexus cloud gives additional security for commercially sensitive and personal data, and we are working with them, alongside Birmingham City University who is also an expert in data security.

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9 Further collaborative avenues

Many industrial bodies interact with CompBioMed not only via the mechanisms described above, but also through many other routes. These include engagement with Core or Associate Partners, or through companies employing HPC resources provided by Core or Associate Partners. We also interact with the wide community via invited attendance to our All-Hands meetings, and via our attendance to workshops, webinars, and seminars.

Further, many individuals from several industrial bodies subscribe to the CompBioMed Newsletter. (The list of these bodies is currently under construction, verification is being sought, and some may be withheld for reasons of confidentially.)

9.1 Key Performance Indicators

One method of monitoring our success in industrial collaboration fall under the management of our Key Performance Indicators, or KPIs. Of the thirteen KPIs, four of them relate to engagement with our industrial collaborators.

There are two KPIs regarding the impact on innovation, specifically: five of our industrial customers will report saving in development costs of ≥ €25K per annum, and our industrial customers will report saving in development costs of at least €200k per annum. At this stage, we have no reported savings; however, we are confident that this will is viable, given the current achievements from our SME Core Partners, presented in Section

One of the our KPIs monitors our IEP, specifically it aims to include five participants from European countries and regions with fewer HPC resources. This KPI has already been surpassed in our first 18 months.

Finally, the KPI which monitors the engagements of industrial companies requires that at least twenty companies, where at last one third are SMEs, have accessed CompBioMed services. This too has already been surpassed in our first 18 months.

9.2 Events

Finally, for this Section, we list our past events which have attracted attendance from at least 100 individuals from Industrial companies. (The number of attendees from Industry are given in square brackets.)

Past Event

- 3-4 October 2016 – CompBioMed KO Meeting – UoL, London [9]
- 11-12 April 2017 – CompBioMed All-Hands Meeting – BSC, Barcelona [9]
- 27th April 2017 – Cloud & High Performance Computing in Biomedicine – UCL, London [37]
- 16th May 2017 – CompBioMed at PRACEdays 2017 – BSC, Barcelona [3]
- 31st May 2017 – CompBioMed & BioExcel Free-Energy Workshop – UCL, London [15]
- 27th September 2017 – "CompBioMed's Cloud HPC Workshop", Cristin Merritt, Alces Flight Ltd (UK), UCL, London [0]

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- 27th September 2017 – "The Virtual Human" IMAX film at the Science Museum Lates event, Science Museum, London [20]
- 22nd November 2017 – CompBioMed Webinar Series: HPC Simulations of Cardiac Electrophysiology [3]
- 30th January 2018 – CompBioMed Webinar Series: Introduction to cloud computing for the VPH. [0]
- 19 March 2018 – CompBioMed Webinar Series: Lattice Boltzmann method for CompBioMed (incl. Palabos) [4]

Future Events

- 26-27 March 2018 – CompBioMed All-Hands Meeting, UvA, Amsterdam
- 28 March 2018 – CompBioMed & VHeart Joint Workshop, UvA, Amsterdam

10 Conclusion

Industrial collaboration is a keystone to the success of our Centre of Excellence, and its importance cannot be understated.

This Report has given an overview of the collaborations that CompBioMed has with industry in general, where we have shown an increased awareness of CompBioMed within Industry through our ever-expanding list of 33 Associate Partners, through to our Incubator services; the Innovation Exchange Service, which currently monitors twenty visits, to our Innovation Advisory Board which grew from fourteen members at the 1st IAB, to twenty members for the upcoming 2nd IAB at the All-Hands meeting, in Amsterdam on the 26th-27th March, 2018. Furthermore, we had at least 79 attendees to our workshops and meetings from industrial bodies.

Moreover, within the HPC cPPP, our CompBioMed Centre of Excellence and the ETP4HPC Association, are collaborating well, both via Board Meeting attendance, and personal one-to-one collaborations, where early fruits from the latter has resulted in a joint ISC18 BoF proposal.

At this mid-point, we have clearly demonstrated that our Core Partners are fostering innovative advances throughout the Centre. Our strategy to introduce further industrial (as well as academic) Associate Partners into the Centre is ensuring that we can work on new innovations in the field, as well as to more effectively support the planned research of all our Partners. New Associate Partners (from all sectors) have often joined after collaborations with one of our Core Partners, indicating that our research and partnerships are strong ambassadors of the Centre. As our reputation grows, we will continue to actively seek further industrial partners to strengthen and build our Centre as we look ahead to producing our Sustainability Plan.

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Annex A: ISC18 BoF Application

Title of the BoF session: The Computational Biomedicine Community and the HPC Industry: working together to advance personalised medicine

BoF organizer/speaker information: six of CompBioMed's Core Partners: Bull, an ATOS company, SURFsara, Barcelona Supercomputing Centre, LifeTec Group, Janssen Pharmaceutica, and EPCC, of The University of Edinburgh, with close support from the ETP4HPC.
The persons quoted this after already have guaranteed their presence:
Peter Coveney from UCL (University College of London)
Cristin Merritt from Alces Flight
Marcin Ostasz from BSC (Barcelona Supercomputing Center), on behalf of ETP4HPC
Gavin Pringle from EPCC of the University of Edinburgh
Marco Verdicchio from SURFsara
Dieter Kranzlmüller from LRZ (Leibniz Supercomputing Centre)
Benjamin Pajot from Atos, Bull technologies

Short abstract: How to bring HPC to medical SMEs, clinical researchers and hospitals? As we are nearing the exascale era, too few benefit from such computational power, and even fewer achieve excellence in HPC application delivery and use. By bringing together the biomedicine community and the HPC industry, we hope to help the community better embrace upcoming technologies, and help the industry better understand the needs: fault tolerance, data and compute resources, access mechanism (such as urgent computing, on-demand computing, advanced reservation…), computing power, code efficiency. Which feature is critical for Biomedicine? Is Industry aware of it, and what answers are planned in the future? Overall, how to bring these improvements to the people who diagnose, to the drug discoverer, or even to your doctor? As a Centre of Excellence working towards the advancement of computationally based modelling and simulation within biomedicine using large-scale and cloud computing resources, CompBioMed is a significant contributor to this debate, with experience to share, especially through its three exemplar research areas: cardiovascular, molecularly-based and neuro-musculoskeletal medicine. To complete the picture, we hope industry stakeholders will share their vision of a complex area involving so many different areas of expertise. To feed the debate, all interested parties are welcome to attend and help paving the way to excellence.

Topic area (as listed in the call for research papers):

- HPC Applications
- Exascale computing
- Domain-specific architectures
- Trends in the HPC chip market
- Job management
- Productivity improvement
- Data intensive applications
- Convergence of simulations and big data
- Workflow management

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- Industrial simulations

One to five keywords: computational biomedicine, exascale, personalised medicine

Maximum intended fraction of time spent for presentations: 15 minutes only: 5 minutes for introduction of CompBioMed, 5 minutes for introduction of ETP4HPC, 5 for the introduction of the BoF itself.

Description of approach to make the BoF interactive: gathering a panel of experts to lead the room-wide discussion and to collect details of interested parties.

Targeted audience: HPC industry stakeholders & the computational biomedicine community

Estimated number of attendees: 50

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Annex B: Current List of Visitors promoted/monitored by IEP

This following table is a snapshot of our IEP at the time of writing, which currently lists twenty visits, where the possible nature of transfers can be Learning from Host, Learning from Visitor, Studentship, Undergraduate Training, Secondment, or Collaboration. Further, the level of visitor can be UG (Undergraduate), PhD, PD (Postdoc), Ac (Academic), or Ind (Industrial).

Host institution	Visitor Institution	Duration	Nature of transfer	Level of visitor
Barcelona Supercomputing Center (BSC)	University of Oxford	2 weeks	Collaboration	PhD
Medtronic	BSC	2 months	Collaboration	PhD student
Flinders University (AU)	University of Sheffield	3 months	Collaboration	PhD student
Evotec	University College London (UCL)		Studentship	PhD
CBK	University College London (UCL)		Studentship	PhD
UCL	Evotec	2 years (ongoing)	Secondment	Snr Scientist (Ind)
Leiden University	Janssen	6 months		
UCL	Zayed University (ZU)	Ongoing (Started October 2017)	Studentship	PhD
UCL	Merck	Ongoing	Collaboration	PD
University of Alberta Edmonton	University of Oxford	2 weeks	Collaboration	PhD
University of Oxford	University of Bologna	6 months	Studentship	Master Student
University of Oxford	University of Bologna	4 months	Collaboration	PhD
University of Oxford	Barcelona Supercomputing Center (BSC)	1 week	Collaboration	PhD
University of Oxford	Fraunhofer – Chalmers Research Centre	1 week	Collaboration	PhD
University of	Queensland	2 weeks	Collaboration	Ac

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Oxford	University of Technology			
University of Oxford	Queensland University of Technology	1 month	Collaboration	PhD
University of Oxford	Washington University in St. Louis	1 month	Collaboration	Ac
University of Oxford	Food and Drug Administration	1 week	Collaboration	PhD
University of Oxford	Queensland University of Technology	6 weeks	Collaboration	Ac
University of Oxford	UCL	1 week	Collaboration	PhD

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Annex C: CompBioMed and HPC-Europa Memorandum of Understanding

Memorandum of Understanding

Between COMBIOMED and HPCE3
Version 0.2; 01 October 2017

1. Project Information

1.1. COMBIOMED

CompBioMed is a user-driven Centre of Excellence in Computational Biomedicine, to nurture and promote the uptake and exploitation of high performance computing within the biomedical modelling community. Its user communities come from academia, industry and clinical practice. CompBioMed has innovation at the forefront of its aims, promoting interdisciplinary entrepreneurial opportunities driven by our users' needs. Its industrial partners participate fully in the Centre's activities from the outset, with the number of associate partners expected to grow continuously over the lifetime of the Centre.

1.2. HPCE3

The HPCE3 project that run from May 1st 2017 to April 31st 2021 aims at maintaining the persistency of a high-quality service of transnational access to the most advanced HPC infrastructures available in Europe for European research. The project is based on a program of visits, in the form of traditional transnational access, with researchers visiting HPC centres and/or scientific hosts who mentor them scientifically and technically.
The visitors are:

1. Funded for travel, accommodation and subsistence, and
2. Provided with an amount of computing time suitable for the approved project.

The calls for applications are issued 4 times per year and published online at **www.hpc-europa.eu**

1.3. Common participants

SURFsara, BSC and EPCC are partners both of CompBioMed and HPCEuropa3 and can naturally act as liaisons between the two parties for administrative and technical collaboration.

2. Purpose

A close collaboration between CompBioMed and HPCE3 is very desirable as HPCE3 project is going to serve as a starting point for the applicants in their natural evolution towards future deployment of HPC exascale infrastructures, while ComBioMed promotes the uptake and exploitation of high performance compu-

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ting within the biomedical modelling community. The purpose of this MoU is to formalize the collaboration between the two parties.

3. Objectives

The high-level objectives of the collaboration are as follows:

- The HPCE3 Transitional Access programme visits could be used for collaboration with CompBioMed
- Both parties can actively disseminate the essential information and calls from each partner.
- Trainings - HPCE3 applicants can become CompBioMed training participants.

4. Joint Work Plan

The framework of the joint work plan is as follows:

1. Training **Parties involved:** CompBioMed: WP3 HPCE3: TA **Description of work:** CompBioMed organizes different training for use of HPC in biomedical modelling. HPCE3 TA can advertise and encourage the visitors to attend these events. **Milestones:** M1.1: CompBioMed to periodically communicate about the upcoming events with HPCE3
2. Dissemination **Parties involved:** CompBioMed: WP3 HPCE3: WP3 **Description of work:** HPCE3 will send dissemination material to CompBioMed as well as announcements of application calls. HPCE3 will also disseminate all the necessary information provided by CompBioMed. **Milestones:** M2.1: Disseminate the provided material M2.2: Disseminate the call announcements
3. Collaborative visits **Parties involved:** CompBioMed: WP4 HPCE3: WP3 **Description of work:** CompBioMed researchers can use the opportunities provided by HPCE3 for collaborative visits

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Milestones:
M3.1: Several visitors from CompBioMed to apply for HPCE3 programme

5. Schedule

Milestone	Time Due	Description
M1.1	30/04/2021	CompBioMed to communicate the up-coming event to HPCE3 on periodical bases
M2.1	31/10/2017	Start the dissemination of HPCE3
M2.2	31/10/2017	Start the dissemination of HPCE3 calls
M3.1	31/10/2021	Several applications from CompBio-Med

6. Contacts

	CompBioMed	HPCE3
Main	Stefan Zasada UCL stefan.zasada@ucl.ac.uk +44-20 7679 5300	Debora Testi CINECA d.testi@cineca.it +39-3939761599
Secondary		Lilit Axner KTH lilit@kth.se +46 8 790 78 19

7. Signatures

The following agree to the terms and conditions of the MoU:

P. V. Coveney

Peter V. Coveney
CompBioMed project coordinator

Date:

Paola Alberigo

Paola Alberigo
HPCE3 project coordinator

05/10/17
Date:

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