**Final Report: Cardiac Physiome Project**

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**Theme and background information**

The Cardiac Physiome project is an international effort to build biophysically based multi-scale mathematical models of the heart. Effective methods for analyzing model complexity are an important and fundamental mathematical requirement for the success of this project. Specifically, techniques are needed for determining the appropriate level of detail, exploiting model inheritance and defining standards for the constituent electrical, mechanical and vascular classes of cardiac model.

Our overall goal for the four week workshop was to facilitate the development and application of modelling and algorithmic expertise to cardiac physiological problems, to establish new ways of contributing to the Physiome framework. To do this we aimed to promote interactions between mathematically focussed scientists seeking to work at the life sciences interface and multi-scale modellers and selected experimental specialists. Within specific classes of cardiac model the goal was to outline a specific set of criteria for the model elements. Specific examples of criteria included enforcement of conservation laws, parameter sensitivity which is consistent with experimental observations, and establishing the level of model complexity which is supported by the data and required to capture function. Using these criteria we used the environment of the workshop to collectively review the current techniques and outline the opportunities and needs for novel mathematical techniques to assess models. Within this over arching framework the following issues for the Cardiac Physiome project were addressed:

Where are the computational bottle-necks in multi-scale simulations, and what numerical analysis and visualisation tools will improve the throughput and interpretation of computational simulation for the Physiome?

Which mathematical tools are most appropriate to quantify stability and parameter sensitivity in increasingly complex models of physiological systems?

How much complexity is required at a given level (e.g. cell) for integrating into simulations of function at higher level (e.g. tissue), and what sort of analysis can be used to establish the level of complexity required for a specific simulation?

What are the mathematical and computational criteria that models or sub-groups of models should conform to for different functions? How can these be promoted and enabled within the community?

What should be the form and function of model data bases and ontologies for different model classes? How can they enable robust model testing and accelerate the iterative refinement within the research community?

To address these issues within the multi-scale and multi-physics framework, each of the first three weeks was organized to focus on a particular scale/physics relevant to the overall theme of the workshop. The specific focus and goal of each of these weeks was:

Focus Week 1 Sub-cellular Modelling**:** To review the characterisation of subcelluar measurement with biophysically based models of subcellular components including: channel and exchanger functions, signalling and transduction pathways. These discussions and presentations for this week were based on:

- Which mathematical tools are most appropriate to quantify stability and parameter sensitivity in increasingly complex models of physiological systems?
- How much complexity is required at a given level (e.g. cell) for integrating into simulations of function at higher level (e.g. tissue), and what sort of analysis can be used to establish the level of complexity required for a specific simulation?
- What are the mathematical and computational criteria that models or sub-groups of model should conform to for different functions? How can these be promoted and enabled within the community?

Focus Week 2 Excitation and Contraction: To investigate frameworks and methods used to couple models of excitation and mechanics at both cell (ODE) and tissue scales (PDE). The influence and interdependence of these two phenomena were discussed along with mathematical and computational tools. Specific issues covered were:

- *Modelling*: Models of excitation (cell and tissue), phenomenology of excitation propagation during normal beats and arrhythmias, and models of force development and tissue deformation. Influence of tissue mechanics on activation during normal beats and arrhythmias. Potential for patient specific models.
- *Mathematics and computation*: Parameter identification and parameter sensitivity in models of excitation and contraction. Relative merits of different numerical schemes

Focus Week 3 Coronary Vascular Fluid Dynamics: To investigate frameworks and methods to describe the flow and transport properties of the coronary vasculature, and to consider how these models link to the cell and tissue models considered in weeks 1 and 2. Areas which were discussed and presented were:

- *Physiology*: Coronary vascular mechanical structure and topology
- *Vascular mechanics and transport*: Mechanostransduction, mass transport processes, regulation, angiogenesis and vascular remodelling
- *Modelling*: Modelling from large vessels through to microvasculature, fluid-structure interactions. A particular focus was given to the level of complexity that should be incorporated at each level of modelling.
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- *Mathematics and computation*:, Lumped parameter models, network models, continuum models with a focus on homogenisation, coupling at different scales (large vessels to microvasculature),

The fourth week was run as a much larger workshop with approximately 140 participants presenting research findings from their own work in the form of talks and posters. Many the questions and discussion topics developed during the first three weeks were echoed in both the formal and informal discussion time during the meeting.

**Structure**

The structure of each of the first three weeks was run with the following template:

Monday: Introduction from all new participants. Each new participant presented 2 slides covering their research focus and the strengths and weaknesses in their areas/approach. These slides were then pinned on the notice board on the mezzanine level for the remainder of the meeting. This was followed by a review talk, and dinner in Cambridge

Tuesday: Modelling issues talk followed by 2-3 short talks given by early career participants.

Wednesday: Informal discussion and work. 4-6 pmsocial activities

Thursday: Informal discussion and work

Friday: Interface talk connecting the topic of the current week with the spatial or physical scale of the upcoming week.

A detailed program with talk titles and presenters can be found at:
http://www.newton.ac.uk/programmes/CPP/

As outlined above the final week was held as a five day conference with approximately 140 participants covering the full spectrum of cardiac physiome research topics, scales and experimental-mathematical approaches. To complement a very full talk program, 2 commented poster sessions were very well attended. In addition to attracting many of the leading international researchers contributing to Cardiac Physiome related research, as the organizers, we were very pleased at the number of early career attendees at the meeting. A detailed outline of the talk program can be found at:

http://www.newton.ac.uk/programmes/CPP/cppw01p.html

The schedule of poster presentations is at:

http://www.newton.ac.uk/programmes/CPP/CPPW01_poster1.pdf

and

http://www.newton.ac.uk/programmes/CPP/CPPW01_poster2.pdf

**Outcome and achievements**

Comments fed back through the scientific reports, and also informally at the meeting, have been uniformly positive. People have indicated a number of discussions which they expect to lead to new collaborations, although inevitably not all interactions can be documented. Specific examples include: T Secomb organised a visit to Oxford at the end of August, S Sherwin discussions about expanding his fluids research to electrophysiology, S Niederer discussions with A Young about data source for cardiac models, N Smith discussions about validation with F van de Vosse about collaboration on the validation of fluid mechanical cardiac models.

As highlighted by a number of participants, the unique opportunity provided by the Newton Institute building and environment was the time and opportunity to deeply

critique the current state of the field with collective input from many leaders in the field. This was summarised by one participant

"*Discussions revolved around model building, validation, and standardisation. In building a model, decisions have to be made on the structure and hence the processes to include. Moreover, it is not clear what data should be used to build the model and which to validate it with. This holds especially true since available data is obtained under various conditions, so they are not compatible. Hence it is questionable how a model that was fitted to one set of data could be applied to another range of parameter values. An outcome of this discussions was the wish for standardised experiments, so that any ambiguity can be minimised. From a modeller's perspective, reproducing simulations from other groups is a major issue. To resolve it, suggestions for publicly available data bases were voiced, where all code, meta data and other information should be made accessible and at the same time adhere to a given standard. In conclusion, the first week was a stimulating time, which did not only highlight the achievements of the field, but more importantly pointed to future challenges that we face. I highly welcomed the critical scrutiny that was applied to many questions."*

**Publications**

The collective input and contributions of attendees throughout the meeting is currently being organised in a special issue of Progress in Biophysics and Molecular Biology which we are currently editing (expected publication date is March 2010). Significant progress was made on writing much of the content for these articles while still at the Newton meeting such that they are currently close to being ready for submission.

1. The Cardiac Physiome and cellular modeling (title to be updated) Corresponding author Nic Smith

2. The Cardiac Physiome and tissue modeling (title to be updated) Corresponding author Richard Clayton

3. The Cardiac Physiome and mechanics modeling (title to be updated) Corresponding author Nic Smith

4. The Cardiac Physiome and vascular modeling (title to be updated) Corresponding author Sarah Waters

5. The Cardiac Physiome and data (title to be updated) Corresponding author Peter Hunter

**Proposal for a one week follow up meeting in 2011**

The success of the program has provided real momentum to our field and, if available, we would like to take the opportunity to use any available funding to run a 1 week follow up meeting in Oxford 8$^{th}$ to 10$^{th}$ of July 2011. We would aim to use funding to attract leading international speakers and once again support early career participation. Given the interest in the 2009 workshop we anticipate between 150-200 attendees and would follow a similar format as the meeting held in the last week of the CPP programme.