Roadmap towards a virtual eye

Proceedings of the short conference
'Towards a virtual eye'
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Organised by
Peter S. Stewart, University of Glasgow
Jennifer H. Tweedy, University of Bath

Supported by the Macular Society

1 OVERALL OBJECTIVE

Computational modelling provides an attractive way to understand and quantify the behaviour of tissues and organs in the human body, For example, this approach has been used to build large-scale models of the human heart capable of testing therapeutic interventions (*e.g.* the Physiome Project, the Living Heart Project, Cardiac CHASTE).

Our aim is to create an *in silico* model of the human eye that can be used for clinical decision making, which we term the **Virtual Eye**. Although modelling the specialised anatomy of the eye requires context-specific models, the underlying principles of cell biology and soft tissue/fluid mechanics apply more widely, enabling the translation of aspects of computational models of other tissues into our framework.

We intend that this Virtual Eye will have sufficient predictive power to inform selection of therapeutic interventions on an individual basis informed by imaging, genetics and assays of peripheral blood. It could also be used for testing potential effects of drugs. The long-term goal is to reduce the burden of vision loss by providing a simple tool for clinical use, capable of predicting patient-specific outcomes from particular treatment protocols.

This short document seeks to present a potential high-level implementation plan for the initiative.

2 SUMMARY OF MEETING IN BATH

With the generous support of the Macular Society, we recently held a meeting to discuss and plan the project. Twenty-five delegates attended, mostly from the UK, including 4 clinicians, 11 mathematicians, 5 engineers, 2 biologists and 3 representatives from the Macular Society.

The meeting began with participant introductions and visionary talks by clinicians on the potential scope of the Virtual Eye project and what it might achieve. Prof Peter Hunter of the Auckland Bioengineering Institute gave a presentation on the modelling framework used for the Physiome Project. All elements of the meeting were followed by opportunities for discussion and contribution from the delegates. We spent some time developing an idealised mathematical model of the mechanism underlying central serous retinopathy and controlling choroidal thickness, and concluded with a discussion on future steps.

3 ORGANISATION AND MODE OF WORKING

We are in the process of forming an **international consortium** supported by diverse funding that is consolidated around **large-scale core funding** to sustain the project.

We will take advantage of developments in distributed working/electronic notebooks/version control to allow the entire consortium to access, in real-time, all the strands of work as they progress.

The eye will be sub-divided into a number of functional tissues units (FTUs), which themselves can be subdivided into smaller units. We anticipate that individual models for FTUs will be developed in a coherent and cohesive manner, so that segments of code can be inserted into the master in a 'plug-and-play' type manner.

As far as possible, we intend that each version of the model will be developed to address a specific medical question.

The project will be made available to the academic community following completion of particular milestones. There is also the possibility of making some versions available in real time to foster 'crowd' engagement in problem solving and solution development. Selected versions will also be made available to the clinical community for prototype testing and interface development.

As the project develops it will require high-level management to ensure the constituent parts fit together. In particular, we need to make arrangements for:

(a) Progress monitoring;

(b) A consortium agreement between the Universities represented;

(c) IP sharing;

(d) IT infrastructure for the consortium (distinct to IT for modelling);

(e) Managing code quality and code verification;

(f) Compliance with regulations for *in silico* testing of medical devices.

4 PROGRAMMES AND WORK-PACKAGES

Work on the large-scale project will be divided into three work-packages (WPs), each with a series of sub-packages. There will be tight coupling between all packages:

WP1 (Sec. 4.1) will involve requirements gathering to inform the model building and validate the final product.

WP2 (Sec. 4.2) will involve identification of core modelling tasks to build the overall framework within which the smaller scale components will be placed

WP3 (Sec. 4.3) will involve building/adapting detailed models for individual components of the eye which will then be integrated into the larger-scale framework constructed in WP2.

In the following sections, we consider each WP in turn.

4.1 WP1: REQUIREMENTS GATHERING

We will acquire data to inform and validate our modelling. We aim to collate a central repository using a number of sources. The sub-packages include:

(a) Data curation from published work to determine physiological parameters required for modelling/validation: some parameters will have been directly measured while others must be inferred from whole animal physiology;

(b) Machine learning parameter estimation for prediction of parameters that are not otherwise available. This will include enzyme and transporter kinetic parameters *etc*;

(c) Imaging, including tomography (OCT, OCTA), fundus auto fluorescence, fundus fluorescein angiography;

(i) Acquisition device development;

(ii) Segmentation of images;

(iii) Meshing of segmented images into suitable formats;

(iv) Field mapping;

(d) Blood-based analyses;

(e) Genetics;

(f) Cell biology signalling cascades.

4.2 WP2: CORE MODELLING PROGRAMME

We will develop a large-scale modelling framework within which the more detailed models of individual components can be embedded. These core modelling tasks include:

(a) Development of an integrative programming environment that will incorporate all the various modelling approaches we are likely to need (continuum, particle-based *etc*);

(i) There are likely to be efficiencies in building off current work (such as CHASTE, OPENCMISS *etc*) and using existing mark-up languages (such as OpenCOR, CellML, SBML *etc*);

(ii) Model coupling (Application Programming Interfaces, bond graph formulation *etc*);

(iii) Multi-scale time and space solutions (for instance a major challenge to capture natural history processes over decades);

(b) Verification, Validation and Uncertainty Quantification;

(i) Contemporary, robust approaches to software testing;

(ii) Ensemble modelling approaches using different methods;

(iii) Feedback to WP1 for available data or specific experiments required for validation;

(c) Core modelling tools (software and hardware);

(i) Bond graphing;

(ii) Hypergraphs;

(iii) Integrated conservation laws (energy, charge, momentum and mass balance);

(iv) Spatial representations (continuum mechanics and metabolite transfer);

(v) Biological process simulation;

(vi) Scaling to meet complexity demands;

(d) Prototype model development - from the very beginning we are striving for whole eye models, no matter how simple, that will provide the basis for incremental increases in sophistication.

4.3 WP3: DETAILED MODELLING PROGRAMME

The final virtual eye model will include detailed models for individual components of the human eye, including:

(a) Mechanical model of layers of the eye (including choroid and retina with scope to incorporate vascular tone *etc*);

(b) Connective tissue properties (to inform point (a) above) with particular focus on elastin and collagen cross-linking;

(c) Whole eye blood flow dynamics;

(d) Whole eye fluid dynamics and ion balance;

(e) Whole eye blood-tissue transfer;

(f) Whole eye cell and tissue metabolism including detailed mitochondrial modelling;

(g) Whole eye energy flows;

  (i) Coupling to metabolism;
  (ii) Cell work;

(h) Whole eye tissue and ECM aging changes;

(i) Pathological process modules;

  (i) Mitochondrial failure;
  (ii) ECM changes;
  (iii) Oxidative stress;

(j) Disease modules, including:

  (i) Glaucoma;
  (ii) Diabetes;
  (iii) Age-related macular degeneration (AMD);
  (iv) Central serous retinopathy (CSR);

(k) Physiological process modules, including:

  (i) Cellular homeostasis (including outer segment turnover);
  (ii) Phototransduction;
  (iii) Retinal ganglion cell projection;

(l) Coupled optical effects.

A List of participants:

Edward Adams, UCL
Atrayee Bhattacharya, University of Glasgow
Dr. Jessica Crawshaw, University of Oxford
Dr. Mariia Dvoriashyna University of Oxford
Dr. Wahbi El-Bouri, University of Liverpool
Prof. Alex Foss, University of Nottingham
Prof. Eamonn Gaffney, University of Oxford
Dr. David Garway-Heath, Moorfields Eye Hospital
Dr. Cameron Hall, University of Bristol
Remi Hernandez, University of Liverpool
Dr. Ruoyu Huang, Univerisity of Strathclyde
Prof. Christina Kiel, University of Pavia
Prof. Phil Luthert, UCL/Moorfields Eye Hospital
Prof. Gary Misson, Aston University
Dr. Stella Prins, UCL
Dr. Paul Roberts, University of Birmingham
Dr. Tamsin Spelman, University of Cambridge
Dr. Peter Stewart, University of Glasgow
Dr. Jennifer Tweedy, University of Bath
Dr. Heather Yorston, University of Edinburgh
Dr. Moussa Zouache, University of Utah
Dr. Vladimir Zubkov, University of Brighton

Also, from the Macular Society: Clare Bryce-Smith, Sarah Clinton and Geraldine Hoad.