Exeter College Oxford Summer Programme

Computational Medicine:
shaping the future of healthcare with digital twins and in silico trials

Course Description

This course aims to serve as an introduction to multidisciplinary biomedical research. Specifically, the course will provide you with an understanding of multiple facets of computational medicine applied in the context of cardiovascular research. For this, state-of-the-art computational techniques in cardiac research will be explained and demonstrated, as well as current shortcomings in the field fueling future research opportunities. In silico trials represent a crucial part of the course, since experiments in human-based computational models and simulations represent a novel and exciting opportunity that overcomes limitations imposed by traditional paradigms in vivo or in vitro. In addition, the digital twin in healthcare is an ambitious vision that attempts to improve the safety and efficacy of diagnosis and treatment for individuals by using a digital representation of the specific patient. All in all, the course serves as a platform for discovering where novel computational techniques intersect with medical science, for the benefit of personalised medicine.

Syllabus Overview

Lecture 1. Introduction to Computational Medicine
Lecture 2. Anatomy & Physiology
Lecture 3. Integration with Experimental & Clinical Cardiology
Lecture 4. Modelling Anatomy
Lecture 5. Modelling & Simulation of Cellular Dynamics
Lecture 6. Modelling & Simulation of Whole Organ Dynamics
Lecture 7. Modelling Complex Dynamics
Lecture 8. Verification, Validation and Uncertainty Quantification
Lecture 9. The Digital Twin Vision
Lecture 10. In Silico Trials for Therapy Testing
Lecture 11. How to write a paper
Lecture 12. Final project

The course comprises 12 lectures, 6 seminars, and 4 tutorials. It requires the students to read in advance to gain an understanding of the contents to be discussed. The course will help to sharpen analytical skills, improve abilities to critically interpret primary scientific data, improve confidence in academic debate, and develop presentation skills. It will also give students a chance to learn to write clearly and

advocate ideas during our debates (tutorials). This course is suitable for students who have a strong interest in and curiosity about new technologies applied to healthcare and biomedical research. There are no prerequisites, but some knowledge of mathematics, computer science and/or human biology would be an advantage. The course will require that you read in advance of each lecture and will aim to be interactive and stimulate you to debate the ideas presented.

Teaching Methods and Assessment

• 12 x 1.25hr Lectures (15hrs)

• 6 x 1.25hr Seminars (7.5hrs)

• 4 x 1.25hr Tutorials (5hrs)

Twice weekly lectures will present the key points of the topics. A weekly seminar will focus in-depth on research techniques and provide opportunities to read, interpret, discuss, and criticise scientific literature. Tutorials will allow students to discuss research methods and results obtained in fruitful discussions. In addition, students will be expected to give a short oral presentation on a particular primary research article relevant to the topics discussed in the course.

Assessments:
Final assessment: An essay of no more than 3,000 words (35%), a written exam (35%), an oral presentation (20%) and participation in seminar/tutorial discussions (10%).

Lecture Schedule:
The course is divided into the following lectures. You can find a brief description of every lecture and recommended literature.

1. **Introduction to Computational Medicine**

In this lecture, the course will be introduced to the students. We will describe the current state-of-the-art in the field of computational medicine, and introduce important concepts, such as the *digital twin*, and how to apply modelling and simulation, or machine learning techniques to improve current diagnosis and treatment strategies.

Machine Learning for the ECG Diagnosis and Risk Stratification of Occlusion Myocardial Infarction at First Medical Contact
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9915770/

What determines the optimal pharmacological treatment of atrial fibrillation? Insights from in silico trials in 800 virtual atria
https://pubmed.ncbi.nlm.nih.gov/37475475/

2. Anatomy & Physiology

In this lecture, basic anatomy and physiology will be introduced which will serve as the basis in the subsequent lectures.

Dr Klabunde's excellent website, you can check a few topics of interest and read them
https://cvphysiology.com/

My recommendation:
https://cvphysiology.com/arrhythmias/a008
https://cvphysiology.com/cad/cad001

ECG basics
https://en.ecgpedia.org/index.php?title=Basics

3. Integration with Experimental & Clinical Cardiology

The interface between computational medicine and experimental and clinical cardiology offers an ideal framework to study how the techniques presented can bring tangible advantages to medical sciences.

Computationally guided personalized targeted ablation of persistent atrial fibrillation
https://pubmed.ncbi.nlm.nih.gov/31427780/

The role of computational methods in cardiovascular medicine: a narrative review
https://pubmed.ncbi.nlm.nih.gov/38323181/

4. Modelling Anatomy

Computational medicine techniques often require the use of personalised data, such as digital versions of an organ, to conduct computer-based analysis based on the specific anatomy. Patient-specific anatomies can be reconstructed from medical imaging techniques, such as magnetic resonance and computer tomography.

A rule-based method to model myocardial fiber orientation in cardiac biventricular geometries with outflow tracts
https://pubmed.ncbi.nlm.nih.gov/30721579/

5. Modelling & Simulation of Cellular Dynamics

It is possible to model and simulate the behaviour of certain cells, such as neurons and cardiomyocytes (cardiac cells), and their electric activity. In this lecture, we will

introduce a series of techniques to simulate biophysically detailed cell dynamics to conduct computational experiments modelling drug action and disease.

A model for human ventricular tissue
https://pubmed.ncbi.nlm.nih.gov/14656705/

Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block
https://pubmed.ncbi.nlm.nih.gov/31868580/

6. **Modelling & Simulation of Whole Organ Dynamics**

As a continuation of the previous lecture, we will incorporate the cellular models into tissue and organ models to simulate physiology at the whole organ level.

High arrhythmic risk in antero-septal acute myocardial ischemia is explained by increased transmural reentry occurrence
https://pubmed.ncbi.nlm.nih.gov/31728039/

7. **Modelling Complex Dynamics**

Using the cardiac ventricles as an example, we will investigate how modelling and simulation can be used to tackle research questions in the field of cardiac arrhythmias and to assess cardiotoxic drug effects triggered by certain drug therapies.

8. **Verification, Validation and Uncertainty Quantification**

How can you ensure that your computational framework can be trusted for something as impactful as health sciences? This lecture will tackle the question, and their legal, scientific and technical implications.

In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products
https://pubmed.ncbi.nlm.nih.gov/31991193/

9. **The Digital Twin Vision**

Personalised medicine aims to deliver safe, effective and cost-efficient healthcare by tailoring diagnosis and treatments to patients. The Digital Twin is an ambitious approach that exploits computational techniques to achieve that purpose and will become more and more present in future years.

The 'Digital Twin' to enable the vision of precision cardiology

https://pubmed.ncbi.nlm.nih.gov/32128588/

10. In Silico Trials for Therapy Testing

Biomedical research is traditionally based on animal and clinical experiments. However, alternative approaches are gaining relevance, due to the benefits they represent. In silico trials are based on computer-based simulations and aim to reduce, refine and replace animal experiments in the preclinical stages of therapy development. Pharmaceutical and medical device companies are increasingly interested in this approach, and we will introduce them in this lecture.

Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity
https://pubmed.ncbi.nlm.nih.gov/28955244/

11. How to write a paper

Producing interesting research outputs is only the beginning. The design of a sound research study and the effective communication of results is vital. This lecture is an introduction to research dissemination.

12. Final project

The last lecture is the culmination of the course. The students will have the opportunity to present their final project to the rest of the class. It is expected that the students will design, conduct and communicate a well-constructed and scientifically sound research project by applying technique(s) presented in the course to their newly acquired knowledge of cardiology.

Datasets of interest

- PhysioNet (number of biomedical datasets containing ECG, MRI, and other data modalities)

https://physionet.org/about/database/

- Papers With Code datasets (enter a search term of interest, e.g. 'ECG' or a disease)

https://paperswithcode.com/datasets?

- NHS Cardiovascular Disease Prevention Audit (CVDPREVENT)

https://www.cvdprevent.nhs.uk/home

- Rodero meshes (1000 virtual cardiac meshes)

https://zenodo.org/records/4506930

- Edgar ECG imaging dataset

https://www.ecg-imaging.org/edgar-database

- ML for drug-induced cardiotoxicity (dataset available on request)

https://pubmed.ncbi.nlm.nih.gov/32508633/

- MedalCare-XL: 16,900 healthy and pathological synthetic 12 lead ECGs from electrophysiological simulations

https://www.nature.com/articles/s41597-023-02416-4