Advancing Treatment of Retinal Disease through *in silico* Trials

Rémi Hernandez[1,2], Paul A. Roberts[3], Wahbi K. El-Bouri[1,2]

[1] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital Liverpool, UK

[2] Department of Cardiovascular and Metabolic Medicine, University of Liverpool, UK

[3] Centre for Systems Modelling and Quantitative Biomedicine, University of Birmingham, UK

Summary

The retina has been described as an accessible part of the brain. It's convenient location at the back of the eye facilitates the use of non-invasive techniques to obtain micro-resolution *in vivo* images detailing its structure. As such, it provides the modelling community with a wealth of opportunity to develop, calibrate and validate clinically valuable computational models. These models provide useful insights into the mechanisms at play in the retina that might not be experimentally tractable and relate them across various spatial and temporal scales. Whilst many models of the retina have been developed, the translation into formal *in silico* trials remains slow.

In this review, we will summarise the state-of-the-art in retinal *in silico* models in health and for various retinal pathologies and associated treatments. Whilst covering a range of subtypes of *in silico* models, we will address the major retinal diseases and most common treatment options. Additionally, we will discuss *in silico* models of therapeutics and administration routes that are still under development. In this way, we will give the reader an understanding of the potential of *in silico* models for both development and optimisation of treatment. Finally, we will present previous successful applications of *in silico* trials in order to highlight the gaps that need to be closed before running such trials for the retina.

Abstract

In a globally aging society, treating retinal diseases to prevent sight loss is an increasingly important challenge. The retina is the layer of tissue at the back of the eye that contains light-sensitive cells that make vision possible. This tissue is one of the most metabolically active of the human body, rendering it sensitive to any changes in its environment. Thanks to the configuration of the eye, the retina can be relatively easily examined *in situ*. Owing to recent technological development in scanning devices, much progress has been made on understanding the physiology of the retina in health and disease. However, treatment options remain limited and are often of low efficiency and efficacy.

In recent years, the concept of *in silico* clinical trials has been adopted by many, smaller, pharmaceutical companies to optimize and accelerate the development of therapeutics. *In silico* trials rely on the use of mathematical models based on the physical and biochemical mechanisms underpinning a biological system. With appropriate simplifications and assumptions, one can generate computer simulations of various treatment regimens, new therapeutic molecules, delivery

strategies and so forth, rapidly and at virtually no cost. Such simulations have the potential not only to hasten the development of therapies and strategies but also to optimise existing therapeutics.

The retina can provide some of the richest *in vivo* data in the human body in health and disease and, as such, a wealth of opportunities for validation of *in silico* models and translation to *in silico* clinical trials. Additionally, the growing body of experimental and clinical studies on retinal diseases provides the scientific understanding necessary to develop accurate *in silico* models. This paper reviews the state-of-the-art in mathematical modelling of the retina in health and disease, highlights challenges to developing *in silico* clinical trials and proposes a plan of action to overcome them.

Outline

1) Introduction
2) Retinal physiology and therapeutic approaches
    a) Physiology
        i) Health
        ii) Disease
    b) Therapeutic strategies
        i) Surgery
        ii) Drug based
        iii) Other
3) Mathematical modelling
    a) Primer
    b) Linking imaging to modelling
4) Retinal tear and retinal detachment
    a) Laser surgery
    b) Surgical repair
    c) Cryotherapy
5) Retinal haemodynamics, vascular disease, neovascular AMD and diabetic retinopathy
    a) Retinal haemodynamics
        i) Healthy retina
        ii) Ageing and diseased retina
    b) Anti-VEGF
    c) Laser treatment
6) Non-neovascular AMD, retinis pigmentosa and retinal oxygenation
    a) Immunotherapies and complement system-targeting therapies
    b) Senotherapeutics
    c) Ocular gene therapy
    d) Retinal transplantation and stem cell therapies
7) Drug delivery to the retina
    a) Intravitreal injections
    b) Sub-retinal injections
    c) Implants/port-delivery
    d) Systemic administration
8) *In silico* clinical trials
    a) Current state of affairs
    b) Verification, validation and uncertainty quantification

c) Successful application(s) of *in silico clinical* trials
d) Gaps to application to the retinal disease
e) Suggestions for future research

9) Conclusions

Why is this review important?

The retina provides some of the richest *in vivo* data in humans and hence provides a wealth of opportunities for validated *in silico* trials. Whilst there are many mathematical models of the retina in health and disease, the current literature does not provide clear applications of these models within an *in silico* clinical trials framework. Owing to the potential *in silico* trials have in retinal disease treatment, we believe this review will be useful in gathering the currently available models, identifying gaps in the translation to *in silico* trials, and demonstrating the next steps for developing *in silico* clinical trials for retinal diseases.

Relevant Recent Reviews

1. Handa, J.T., Bowes Rickman, C., Dick, A.D. et al. A systems biology approach towards understanding and treating non-neovascular age-related macular degeneration. Nat Commun 10, 3347 (2019). https://doi.org/10.1038/s41467-019-11262-1

2. Arciero, J., Carichino, L., Cassani, S., & Guidoboni, G. (2019). Mathematical Modeling of Blood Flow in the Eye. Modeling and Simulation in Science, Engineering and Technology, 101–157. https://doi.org/10.1007/978-3-030-25886-3_5

3. Paul A. Roberts, Eamonn A. Gaffney, Philip J. Luthert, Alexander J.E. Foss, Helen M. Byrne, Mathematical and computational models of the retina in health, development and disease, Progress in Retinal and Eye Research, Volume 53, 2016, Pages 48-69, ISSN 1350-9462, https://doi.org/10.1016/j.preteyeres.2016.04.001.

4. Kim HM, Woo SJ. Ocular Drug Delivery to the Retina: Current Innovations and Future Perspectives. Pharmaceutics. 2021 Jan 15;13(1):108. doi: 10.3390/pharmaceutics13010108. PMID: 33467779; PMCID: PMC7830424.

5. Linsenmeier RA, Zhang HF. Retinal oxygen: from animals to humans. Prog Retin Eye Res. 2017;58:115-151. doi:10.1016/j.preteyeres.2017.01.003

6. Luthert, P.J, Serrano, L., and Kiel, C., 2018. Opportunities and Challenges of Whole-Cell and -Tissue Simulations of the Outer Retina in Health and Disease. *Annu. Rev. Biomed. Data Sci.*, 1:131. https://doi.org/10.1146/annurev-biodatasci-080917-013356

7. Repetto R & Tweedy JH. Biomechanics of the vitreous humour. In Biomechanics of the Eye, Roberts CJ, Dupps WJ & Downs JC eds., Kugler Publications (2018) ISBN: 9789062992508