Progress in Retinal and Eye Research 53 (2016) 48–69

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

Mathematical and computational models of the retina in health, development and disease

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ARTICLE INFO

Article history:
Received 19 December 2015
Received in revised form
5 April 2016
Accepted 5 April 2016
Available online 7 April 2016

Keywords:
Oxygen
Neuroglobin
Photoreceptors
Angiogenesis
Retinitis pigmentosa
Choroidal neovascularisation

ABSTRACT

The retina confers upon us the gift of vision, enabling us to perceive the world in a manner unparalleled by any other tissue. Experimental and clinical studies have provided great insight into the physiology and biochemistry of the retina; however, there are questions which cannot be answered using these methods alone. Mathematical and computational techniques can provide complementary insight into this inherently complex and nonlinear system. They allow us to characterise and predict the behaviour of the retina, as well as to test hypotheses which are experimentally intractable. In this review, we survey some of the key theoretical models of the retina in the healthy, developmental and diseased states. The main insights derived from each of these modelling studies are highlighted, as are model predictions which have yet to be tested, and data which need to be gathered to inform future modelling work. Possible directions for future research are also discussed.

Whilst the present modelling studies have achieved great success in unravelling the workings of the retina, they have yet to achieve their full potential. For this to happen, greater involvement with the modelling community is required, and stronger collaborations forged between experimentalists, clinicians and theoreticians. It is hoped that, in addition to bringing the fruits of current modelling studies to the attention of the ophthalmological community, this review will encourage many such future collaborations.

Contents

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http://dx.doi.org/10.1016/j.preteyeres.2016.04.001
1350-9462/

1. Introduction

The retina is a complex and highly structured tissue. Covering the inner surface of the back of the eye, it captures incident light, generating electrochemical signals, which, after some initial processing, are transmitted to the brain via the optic nerve, giving rise to visual perception. As such, it is arguably the most important means by which we gain information about the world around us.

The last two decades have seen a rapid increase in the use of mathematical and computational modelling techniques in the biological sciences, due, in part, to an increase in computational resources. These methods have been applied to a plethora of systems, across a range of spatial and temporal scales, from the ecological, through to the molecular scale and from the evolutionary timescale to the rapid firing of neurons (Keener and Sneyd, 2009a,b; Murray, 2002, 2003). As a consequence, a wealth of insights have been generated that would have been difficult, and in many cases impossible, to achieve through the use of experimental or diagnostic techniques alone.

The revolution in mathematical and computational biology has not left eye and retinal research untouched, with a host of models exploring the biomechanics of the eye (Burd and Regueiro, 2015; Ethier et al., 2004; Grytz and Meschke, 2010; Grytz et al., 2011; Ruberti et al., 2011), glaucoma (Band et al., 2009; Burgoyne et al., 2005; Harris et al., 2013; Sigal and Ross Ethier, 2009), flow within the aqueous and vitreous humours (Siggers and Ethier, 2012; Stewart et al., 2014) and the dynamics of the tear film (Braun, 2012; Braun et al., 2015; King-Smith et al., 2008). A number of models of the retina have also been developed, though modelling in this area has been less extensive than that devoted to other aspects of the eye. The purpose of this review is to highlight insights that have been gained from theoretical studies of the retina and to stimulate further modelling work and theoretical/experimental collaborations in this area.

Whilst experimental and clinical studies can reveal many of the physiological and biochemical details of the retina, there are limits to the questions that can be answered using these techniques alone. Mathematical and computational modelling allows us to extend these horizons in at least three ways. Firstly, it allows us to understand and predict the behaviour of systems which involve *nonlinearities*, such as those generated by feedback mechanisms in biochemical reaction networks, or those which arise in the mechanics of fluid flow (see Sections 3.3 and 5.1.1 for examples). The sensitivity of the system to alterations in each component can be tested, and the range of qualitative behaviours that it may exhibit, together with the conditions under which they are realised, may be determined. Thus, by placing a problem in a modelling framework, we gain insight into why a system behaves as it does, when it does. Secondly, modelling allows us to *isolate mechanisms*, or manipulate a system, in ways that may not be possible experimentally. An example of this is discussed in Section 5.1.3, where oxygen toxicity is assumed to be the only cause of photoreceptor death in retinitis pigmentosa. Lastly, modelling allows examination of a *wider range of scenarios* than would be possible experimentally, since *in silico* (computer simulation) studies are not subject to the same financial and time constraints as those performed *in vivo* or *in vitro*. This is seen clearly in Section 5.2, where the effects of a range of inter-cell adhesivities on the progression of choroidal neovascularisation are investigated.

How, then, can mathematical and computational models be integrated with experimental and clinical studies? In Fig. 1, we sketch out the basic contours of this relationship. We begin with the system to be modelled and all that is known about it. Upon this foundation, and guided by a set of well-defined questions, we build our theoretical model. In so doing, we make a series of *simplifying assumptions*, including only those features of the system which are thought to be significant and of relevance to the questions under consideration. The nature of the system and the questions we bring to it will also influence the type of model we develop (see Section 2 for a discussion of model types). Having formulated our model, we use *mathematical analysis* and/or *computational simulations* to derive solutions. Comparing these solutions with our current knowledge, we find that the model is either successful or unsuccessful in replicating its known behaviours. If unsuccessful, the model is revised and fresh solutions generated; if successful, the model is then used to make *predictions* that lie outside our knowledge domain, in an attempt to answer our earlier questions. These predictions may then be tested experimentally. If the experiments match with model predictions then we may have some confidence that we have answered our questions, whilst if they do not, then we must revise our model and compare it once more with known system behaviour, returning to an earlier point in the *modelling/experiment cycle*. Insight is gained at two main stages during this process. Firstly, insight is gained at the *benchmarking* stage (see Fig. 1), which reveals whether or not the mechanisms included in the model are sufficient to replicate known behaviour. Secondly, insight is gained when experimental/clinical studies confirm model predictions (see Fig. 1).

The above description does not perfectly represent the approach taken in all of the modelling studies presented below, but it serves as a basic framework. Depending upon what data are available, it may be difficult to benchmark the model and many modelling predictions are left to gather dust without experimental confirmation. It is important to note that it is unhelpful to simply characterise models as either right or wrong, since any model is a *simplified representation of reality* and hence always, in some sense, wrong. A more fitting way of classifying them would be as *useful* or *useless*. A model is useful if it replicates current data enabling us to make predictions, or if it fails to replicate current data, but in such a way as helps us to identify missing or unwarranted features of the model. It is useless if it fails in both of these respects.

The process of constructing a mathematical model is itself