Opportunities for agent based modeling of retinal stem cell transplantation

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Late stage blindness and visual impairment (BVI) affects over 400 million adults worldwide. These disabilities severely impact the ability of adults to function independently, reduce their quality of life, and worsen socio-economic burdens on health care systems. Importantly, the World Health Organization projects worldwide BVI from degenerated retina to more than double by the year 2050 (Bourne et al., 2021). To understand the clinical problem, consider Figure 1A depicting the retina’s seven neuronal cell types that interconnect across three nuclear layers. Retinal photoreceptors of the outer nuclear layer (ONL) are light sensitive neurons that absorb and convert photons into bioelectrical signals. Photoreceptors synapse with neurons in the inner nuclear layer, which in turn synapse with neurons of the retinal ganglion layer to transduce photonic signals through the optic nerve to the brain. Degeneration or dysfunction in any of these neuronal components can disrupt the visual circuitry and result in BVI.

BVI lacks an effective cure since retinal neurons cannot self-repair. Moreover, BVI is often progressive, as synaptic dysfunction can propagate along the retina’s interconnected networks. Recent advances in regenerative medicine offer new promise to restore vision through cell replacement therapy, in which cells are transplanted into adult tissue to replace damaged or dysfunctional neurons (Gasparini et al., 2019). During transplantation, stem or progenitor cells are inserted into the host retina, where in order to restore vision, they must navigate to areas of damage, achieve functional positioning within the host laminae, and create synaptic connections with healthy, native cells. Photoreceptors are attractive targets for replacement therapy, both because of their proximity to the subretinal space (Figure 1A) used for surgery and because their functionality requires a single synaptic connection with adjacent bipolar cells. However, contemporary transplantation studies have demonstrated variable success, as the biological mechanisms underlying each of the neuronal processes required for regeneration are complex and incompletely understood (Gasparini et al., 2019). While there have been a number of in vivo and in vitro studies conducted to understand these mechanisms (Mishra et al., 2019), few groups have utilized the power of in silico approaches for the advancement of vision restoration.

Opportunities for computational modeling: Computational modeling provides the potential to evaluate both individual and collective roles of replacement cells in regeneration by mechanistically and quantitatively simulating key cellular processes. Agent based modeling (ABM) in particular defines individual cells as autonomous “agents” that are programmed to follow a set of interaction “rules,” which themselves mimic either established biological mechanisms or behaviors newly obtained from in vivo experiments. In this way, complex, multi-component processes and interactions can be analyzed to improve both structure and function of replacement cells.

The ABM approach simulates both individual and collective behaviors in sufficient detail to predict both local behaviors and global scale tissue or organ phenomena. As shown schematically in Figure 1B, the biological structure of organisms can be deconstructed into hierarchical components: An organism is comprised of organs, the organ of tissues, the tissues of cells, and the cells are regulated by molecular mechanisms. The architecture of ABM mirrors this hierarchy, but from bottom up, rather than from top down. Agents, representing cells, operate according to rules, producing population, aggregate, and ultimately tissue- or organ- level behaviors (Glen et al., 2019). The resulting simulations can then be validated in a variety of ways including using in vitro microfluidic platforms or in vivo/ex vivo methods such cyrosectioning, imaging, or live cell tracking.

In order to meaningfully predict cell replacement behaviors, a modeling approach must veridically describe migration of injected cells into an adult tissue environment. Several well-known methods have been used to model cellular migration; these include Monte Carlo simulations, Finite Element and other discretized models as reviewed in (Masuzzo et al., 2016). Each of these approaches has an important place: Monte Carlo models obtain ultimate states (e.g., cell positions) by randomly altering variables to identify the lowest energy or most likely state. Finite Element models mechanically simulate each part of a cell in response to external stresses. Other discretized models (e.g., Potts, or Cellular Automata) apply ad hoc rules to mimic cell behaviors. These methods, however, do not easily lend themselves to comprehensively modeling cells as individual entities, whose behaviors change depending on environmental cues. Thus migration occurs in response to mechanical, chemical and electrical cues, which are not easily (if at all) incorporated into other modeling methods – yet by defining each cell to be an agent, its shape, directionality, metabolic activity and other features essential to migration can easily be individually specified and modified according to external cues.

Moreover, each cell in an ABM model is specified by a small number of parameters (defining shape, mechanical properties etc.,) and so large-scale simulations can be developed in an efficient manner. Other models (e.g., Finite Element or Cellular Automata), by contrast, either require large numbers of components for every cell, and so tend to be slow and cumbersome, or provide only qualitative, coarse scale data. Either approach significantly limits the ability of simulations to capture either individual or collective changes in cell shape, velocity, and force interactions with other cells (Rajagopal et al., 2018).

By contrast, ABM can provide a comprehensive model of migration – as well as differentiation, deformation, chemical gradient response, etc. – over a heterogeneous range of scales and architectures (Glen et al., 2019). In particular, ABMs can include important details such as progenitor and native receptor expressions, cytoskeletal trafficking and alignment, and both
Agent based modeling (ABM) provides underexplored opportunities to enrich cell replacement therapies in the adult retina. ABMs model the biomechanics involved in key processes and inform future research and clinical directions in a transparent way. ABM advantages–spatial architecture: To illustrate how ABMs achieve the flexibility and verisimilitude needed to model cell replacement in the retina, consider Figure 1C, where we provide a visual representation of a retinal photoreceptor that is modeled as a column of overlapping spherical agents. By specifying agent placement, separation, compressive and bending stiffness, etc., we can model any shape and mechanical response desired. In the ONL of the retina, columnar photoreceptors have lengths 20–30 μm and diameters 1–2 μm and are configured in a tightly packed arrangement with center-to-center distances as little as 2 μm. This leaves nanometer spaces for replacement cells to migrate (Wells-Gray et al., 2016), yet transplanted cells are introduced into the subretinal space as 10 µm-diameter spherical agents. By specifying agent relative sizes of agents, or by spawning new agents as the cell shape evolves. Moreover as shown in the inset to Figure 1D, force balances required for forward migration can be accurately modeled, with stronger adhesion ahead and weaker behind, as mediated by cadherin trafficking within the cell and stimulated by chemotactic gradients (Lauffenburger and Horwitz, 1996). Additionally, ABMs more naturally represent these force balances than more abstract numerical discretization of differential equations whose values change discontinuously across material interfaces. This facilitates analysis of changes in retinal tissue structure, such as the bending stiffness of the photoreceptor cells, and the cellular morphological changes that result from interactions between transplanted and native cells. All these advantages provide a clear cut framework for understanding the biomechanics involved in key processes and inform future research and clinical directions in a transparent way.

ABM advantages–heterogeneity: ABM models readily incorporate heterogeneity, allowing simulations to include and differentiate between replacement stem cells and the retina’s highly specialized native cells, each of which have different mechanical, migratory and chemical response behaviors. This is especially important for the complex retinal network comprised of multiple neuronal types and subtypes (Masland, 2001), and stem cell derived retinal neurons could result in mixed cell populations. Such phenotypic differences may impact transplantation outcomes based on their communication with other cells, how they form synaptic connections, or their adhesion properties. Unlike a differential equation, which describes a whole group of cells to generally behave similarly based on a set of desired parameters, ABMs simulate and track individual cells, which are dependent on local cell-cell interactions and cell-matrix interactions. This individualized tracking of agent experiences and factors that impact how a cell behaves over time enables simulations with a level of detail that would often get lost in continuum equations. This tracking ability facilitates the prediction of useful migration
parameters related to transplantation including the net distance and path distance of transplanted stem cells as well as the cellular displacement of native cells needed to accommodate replacements. Additionally, the heterogeneity of agents increases the flexibility of how agents might be defined. For example, the computational agent to biological cell ratio is most commonly 1:1. However, this ratio can be changed to an N:1 ratio, where N number of agents are used to define a single cell, such as a photoreceptor, shown in Figure 1C. Modeling photoreceptors and stem cells in this way facilitates unique exploration of the viscoelastic properties and binding stiffness of photoreceptors as well as the morphological changes of stem cells as they undergo migration within such limited spacing (see Figure 1D) (Wells-Gray et al., 2016).

ABM advantages–stochasticity: The processes involved in replacement cell evolution, including differentiation, proliferation and chemotactic migration are all intrinsically stochastic. Indeed, adhesion-mediated migration as illustrated in Figure 1D would never occur without bonds being formed and broken, and cellular dynamics have long been observed to be highly intermittent in studies ranging from neurogenesis to wound healing. Stochastic elements are arguably essential to developing systems as cells must explore their host environment for the optimization of tissue structure and functionality. Agent based models readily incorporate a great number of agents, types, and parameters for exploration, a shortcoming as a result is that the simulation becomes computationally expensive as the model complexity increases, and too many inputs can result in incomprehensible or trivial results. As Robert Millikan has put it, scientific progress walks forward on two feet: theory and experiment. Advancement of cell replacement therapies depends on better theories, and we propose that agent based modeling is a valuable tool to visually and transparently develop these theories and so improve experimental outcomes.

Conclusion: Late onset blindness and visual impairment is a debilitating and currently incurable disability that affects millions of people worldwide. Replacement of dysfunctional neurons with stem cells offers newfound promise to restore vision but this promise is currently unrealized, in large part by a lack of understanding of precisely how transplanted cells behave in a host retinal architecture. ABM is advantageous for the study of retinal transplantation because it reduces the expense and technical expertise required to conduct animal studies, cryosectioning, and imaging within enucleated specimens and tissues. Further, ABM enables analyses of cell behaviors and morphological changes at time points in between sectioned specimens as well as cells and/or tissues that provide critical information for time dependent processes. While ABM allows modelers to incorporate a great number of agents, types, and parameters for exploration, a shortcoming as a result is that the simulation becomes computationally expensive as the model complexity increases, and too many inputs can result in incomprehensible or trivial results. As Robert Millikan has put it, scientific progress walks forward on two feet: theory and experiment. Advancement of cell replacement therapies depends on better theories, and we propose that agent based modeling is a valuable tool to visually and transparently develop these theories and so improve experimental outcomes.

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