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Bifurcation analysis of a photoreceptor interaction model for Retinitis Pigmentosa

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Retinitis Pigmentosa (RP) is an inherited disease affecting both the rod photoreceptors and cone photoreceptors in the retina. Particularly puzzling to researchers is that all manifestations of RP are caused by mutations in the rods, which cause them to die first, yet cone death always follows. The cones are necessary for daylight vision and acuity while the rods are responsible for night vision. Thus it is crucial to find a way to stop the demise of the cones. Unfortunately, patients typically come to the doctor and are diagnosed with RP once their daylight vision is beginning to be lost, which is often far into the disease progression. While numerous therapies exist that can slow the progression of RP, there is no cure for it.

We present a mathematical model of photoreceptor interactions, trophic and renewal processes, that aims to predict how a patient suffering from RP can go from a state in which all the photoreceptors are alive to one of complete blindness. The mathematical analysis focuses on the stability of the equilibrium solutions and limit cycles of the model and on tracking emergence of different regimes of stability in the empirical parameter space. The model predictions of various mathematical pathways to blindness is consistent with numerous different disease progressions experimentally observed in RP patients as well as the various animal models of the disease.

More specifically, a first analysis of the model examined stability of equilibrium solutions and saw the progression of the disease represented mathematically as a series of transcritical bifurcations leading to blindness as certain key parameters changed. Our more recent analysis focuses on identifying Hopf bifurcations, the emergence of stable limit cycles and the co-existence of multiple stable modes. Our numerical results identified the existence of alternate stable solutions that are present for lower nutrient levels corresponding to the patient being closer to blindness. Stable limit cycles can be interpreted physiologically periodic variations in the levels of outer segment discs, due to their rhythmic shedding and renewal. Hence locating stable limit cycles, or other non-equilibrium stable attractors, could give insights into potential mechanisms to slow or stop the disease. Furthermore, existence of regimes of equilibrium/cycle bistability suggests that identifying RP in its early stages could avoid permanent blindness.

We discuss the need to focus on additional parameter ranges in which the life of the photoreceptors may be prolonged. Current experimental research is focusing on ways to increase the supply of glucose and nutrient uptake into the cell. Our work supports the importance of nutrients in preventing the disease from progressing, and may suggest other areas of parameter space that could be explored empirically. This line of research is also crucial in the developing field of designing retinal implants (in which photoreceptors are transplanted into an RP retina) since it can provide sets of initial conditions that would sustain one or more types of photoreceptors, even after blindness had occurred.