



COMPUTATIONAL MODELING OF INTRAVITREAL DRUG DELIVERY IN VITRECTOMISED EYES

Jyoti Kathawate
M.S. Candidate

Faculty Advisor: Prof. Sumanta Acharya

ABSTRACT

In recent years, significant advances have been made in optimizing the delivery of drugs to target tissues within the eye and in providing effective drug doses to these tissues. The eye is generally divided into two parts: the anterior and the posterior segment. Anterior segment of eye includes cornea, anterior chamber, iris, crystalline lens, and ciliary body. Posterior segment of the eye include the vitreous body, retina, and choroid. Currently, the treatment of posterior segment disease is limited by the difficulty in delivering effective doses of drugs to target tissues in the posterior eye. Four approaches may be used to deliver drugs to the posterior segment—topical, systemic, intravitreal, and periocular. Many drugs have a narrow concentration window of effectiveness and may be toxic at higher concentrations; so the ability to predict local drug concentration is necessary for proper drug delivery. An intravitreal injection provides the most direct approach to delivering drugs to the tissues of the posterior segment, and therapeutic tissue drug levels can be achieved. Intravitreal injections, however, have the inherent potential side effects of retinal detachment, hemorrhage, endophthalmitis, and cataract. Intravitreal injection of drugs into the vitreous chamber is sometimes employed to achieve high drug concentration in the vitreous and retina. However, repeated injections are needed to maintain the effective range for a certain period of time since the half-life of drugs in the vitreous is relatively short. Repeated injections may cause discomfort to the patient and may lead to complications such as vitreous hemorrhage, infection, and lens or retinal injury.

One of the most recent developments in eye surgery has been the introduction of the surgical procedure called vitrectomy. Trans pars plana vitrectomy (TPPV) is used to treat many different retinal disorders such as proliferative diabetic retinopathy (including vitreous hemorrhage), macular hole, intraocular infections (endophthalmitis), etc., where the vitreous is removed and replaced with vitreous substitutes that have properties similar to the liquid being removed from the eye. Silicone oil, fluorosilicone oil, perfluorocarbon liquid, etc., are the most commonly used vitreous substitutes [1]. Retinal tears are often associated with age-related liquefaction and

shrinkage of the vitreous body. These vitreous substitutes can be used intra-operatively to push a detached retina to its normal position and to restore the volume of the vitreous cavity. A study by Hegazy et al. [4] has shown that the concentration of drug that is non-toxic when injected into a normal eye can be toxic if used to treat a vitrectomised eye. Knowledge of drug distribution following injection, therefore, is very important in order to maximize the therapeutic benefits while minimizing damage to tissues due to high local concentration.

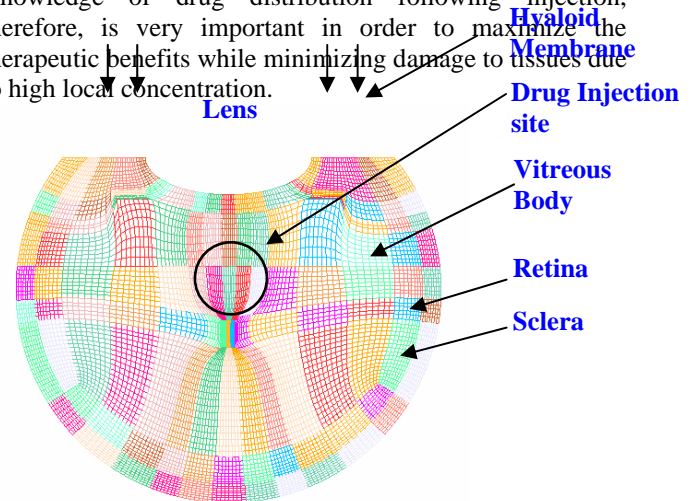


Figure [1]: Computational domain of vitreous chamber

The goal of the present work is to simulate intravitreal drug delivery in the presence of vitreous substitutes. Limited information on intravitreal drug distribution in the normal eye is available from the studies by Friedrich et al. [2], Stay et al. [3], Xu [5], but there is no information available on how drug is transported in the presence of vitreous substitutes that have different transport properties. A parameter of specific interest is the diffusivity of the drug since different drugs are characterized by different scalar diffusivity. In the present study different intravitreal substitutes like silicone oil, fluorosilicone oil and perfluorocarbon liquids are considered and drug distribution as a function of time is examined. Both direct injection of drugs and injection of a time released drug distribution i.e., bio-degradable drug injection are studied. Another problem associated with the vitreous is the liquefaction of the vitreous humor. In addition to vitreous

substitutes, water as a vitreous fluid is studied, since, in human aging brings important changes in the rheological characteristics and the volume of the liquid vitreous proportionally increases in older people. This has been observed with slit lamp investigation carried out by Eisner [6] with direct measurement of the liquid vitreous in formalin-fixed eyes. Thus, the liquefied vitreous is expected to lead to fluid circulation and the abolishment of gradients in the drug concentration within the liquefied portion which leads to reduced half life of the drug in the vitreous chamber.

RESULTS

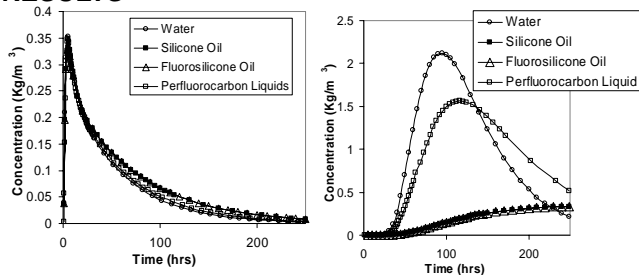


Figure [2]: Concentration at the center of the retinal surface for direct drug injection with Diffusion coefficient (a) $D=6 E-10 \text{ m}^2/\text{s}$ and (b) $D=1 E-11 \text{ m}^2/\text{s}$

Fig. 2 shows the concentration plot for the direct injection of the drug at the center of retinal surface with respect to time for different vitreous substitutes. As seen in the fig. 2(a) for drugs with high diffusion co-efficient, the mass of the drug in the vitreous chamber increases quickly after the injection but decays fast as the drug is absorbed by the retina. It is seen in fig. 2(b), that the amount of accumulation of the drug in the vitreous is increased significantly because of the slower diffusion process. It is also noted that the drug reaches to its peak concentration of 2.125 Kg/m^3 at $t=95 \text{ hrs}$ in the case of water. The drug diffuses slowly in the case of silicone and fluorosilicone oil, reaches the peak concentration of 0.337 Kg/m^3 which is only 16% of the peak concentration reaching the retina as compared to the case of water.

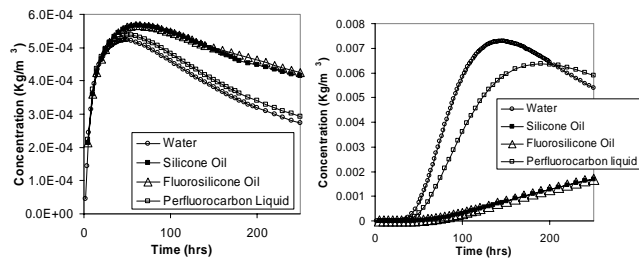


Figure [3]: Concentration at the center of the retinal surface for Bio-degradable injection with Diffusion coefficient (a) $D=6 E-10 \text{ m}^2/\text{s}$ and (b) $D=1 E-11 \text{ m}^2/\text{s}$

Fig. 3 shows the concentration plot for the bio-degradable injection of the drug at the center of retinal surface with

respect to time for different vitreous substitutes. As seen in fig. 3(a), the mass of the drug in the vitreous chamber increases slowly after the injection but decays after $t=2$ days as drug is absorbed by the retina. When compared to direct injection, it is seen that in the case of biodegradable injection with water as vitreous substitute only 0.15% of peak concentration drug reaches center of the retinal surface. In the previous case of direct injection where the transport of the drug is without the controlled release, the drug reached the peak of concentration at 5 hrs whereas in this case the drug reached the peak concentration at 48 hrs which shows that the residence time in the vitreous of polymer system is 9.6 times longer than that of the normal injection. Fig. 3(b) shows that for water, the drug is accumulated in the vitreous till 7th day and then decreases as it is absorbed by the retinal surface. In the previous case of direct injection with drugs with low diffusion coefficient for water, the drug reached the maximum of concentration of 2.125 Kg/m^3 at 95 hrs whereas in this case the drug reached the maximum concentration of $7.28 E-3 \text{ Kg/m}^3$ at 144 hrs which shows that the residence time for low diffusivity drug in the vitreous of polymer system is 1.5 times longer than that of the normal injection and it is also seen that in this case only 0.34 % of peak concentration compared to the case of direct injection is attained.

REFERENCES

1. Colthrust M.J., Williams R.L., Hiscott P.S., Grierson I., 2000, "Biomaterials used in the posterior segment of the eye, Biomaterials, 21, pp. 649-665.
2. Stuart Friedrich, Yu-Ling Cheng, and Bradley Saville, 1997, "Finite Element Modeling of Drug distribution in the vitreous humor of the rabbit eye", Annals of Biomedical Engineering, 25, pp. 303-314.
3. Matthew Stay, Jing Xu, Theodore W. Randolph and Victor H. Barocas, 2003, "Computer Simulation of Convective and Diffusive transport of controlled release drugs in the vitreous humor. Pharmaceutical Research, 20, pp. 96-102.
4. Hegazy H.M., Kivilcim M., Peyman G. A., Unal M. H., Liang C., Molinari L. C., Kazi A.A., 1999, "Evaluation of Toxicity of intravitreal ceftazidime, vancomycin, and ganciclovir in a silicone oil-filled eye", Retina, 19, pp.553-557.
5. J. Xu., 1999, "Controlled release and the concentration distribution of the drug in the vitreous humor", M.S. Thesis, University of Colorado.
6. Eisner, G., 1976, "The anatomy and biomicroscopy of the vitreous body", Documenta Ophthalmologica Proceedings Series. New Development in Ophthalmology, pp. 87-104.