**Supplementary Material: “Identifying the critical factors governing translaminar pressure differential through a compartmental model” by O.G. Kaskar, D. Fleischman, Y.Z. Lee, B.D. Thorp, A.V. Kuznetsov and L. Grace**

**S1. Derivation of equation for the intraocular compartment**

The change in the intraocular compartment volume is formulated according to ref. \(^{24}\)

\[
C_{98} \frac{d(P_9 - P_8)}{dt} + C_{\text{shell}} \frac{dP_9}{dt} = \frac{dV_{10}}{dt} + \frac{dV_9}{dt} \quad (S1)
\]

where \(C_{\text{shell}}\) is the compliance of the corneoscleral shell and the extraocular pressure, which is external to this membrane and is assumed to be constant. The two terms on the right-hand side are the rate of respective volume changes in the vascular and aqueous humor compartments.\(^{24}\)

**Intraocular vascular compartment**

\[
\frac{dV_{10}}{dt} = C_{ag} \frac{d(P_{\text{CRA}} - P_9)}{dt} + C_{vg} \frac{d(P_{11} - P_{\text{CRV}})}{dt} \quad (S2)
\]

\(P_{\text{CRA}}\) and \(P_{\text{CRV}}\) are the central retinal artery and central retinal vein pressures, respectively. The waveforms for \(P_{\text{CRA}}\) and \(P_{\text{CRV}}\) at the control state are fitted using discrete Fourier series from the data given by Guidoboni et al., \(^{23}\) where the pressures are formulated through an inverse problem based on blood velocity measurements in the central retinal artery and central retinal vein. \(C_{ag}\) and \(C_{vg}\) are the compliances associated with intraocular arteries and veins with the globe, respectively. Defining \(C_{bg}\) as the total compliance of the intraocular vascular compartment with the globe, \(C_{bg}\) can be found as the sum of the compliances associated with intraocular arteries and veins with the globe (\(C_{bg} = C_{ag} + C_{vg}\)).

Equation (S2) can then be rewritten as

\[
\frac{dV_{10}}{dt} = C_{ag} \frac{dP_{\text{CRA}}}{dt} + C_{vg} \frac{dP_{\text{CRV}}}{dt} - C_{bg} \frac{dP_9}{dt} \quad (S3)
\]

**Aqueous humor compartment**

\[
\frac{dV_9}{dt} = Q_{aq,\text{in}} - Q_{aq,\text{out}} \quad (S4)
\]

where \(Q_{aq,\text{in}}\) is assumed to be a constant while \(Q_{aq,\text{out}}\) is a function of the aqueous outflow facility (\(C_{tm}\)), uveoscleral outflow rate (\(Q_{uv}\)), IOP, and episcleral venous pressure (EVP).\(^{24}\)
We used equations (S3) and (S4) to rewrite equation (S1):

\[
(C_{g9} + C_{shell} + C_{bg}) \frac{dP_9}{dt} - C_{g9} \frac{dP_8}{dt} - C_{ag} \frac{dP_{CRA}}{dt} - C_{vg} \frac{dP_{CRV}}{dt} = Q_{aq.in} - Q_{aq.out} \tag{S5}
\]

The compliance of the lamina cribrosa \((C_{98} = C_{g9})\) between the optic nerve SAS and intraocular compartment is taken to be \(8.251 \times 10^{-15} \text{ m}^3/\text{Pa}\) \((1.1 \times 10^{-3} \text{ ml/mm Hg})\). The ocular compliance can be measured \textit{in vivo} by infusing fluid into the aqueous humor compartment and recording the associated change in IOP. Thus, the \textit{in vivo} globe compliance can be considered to be the sum of compliances of lamina cribrosa \((C_{98})\), corneoscleral shell \((C_{shell})\), and intraocular vascular compartment with the globe \((C_{bg})\). This makes the calculation of the compliance of the corneoscleral shell redundant as the summation \((C_{g9} + C_{shell} + C_{bg})\) appears in equation (S5) and using \(C_{g.in \, vivo} = C_{g9} + C_{shell} + C_{bg}\) the equation can be rewritten as:

\[
C_{g.in \, vivo} \frac{dP_9}{dt} - C_{g9} \frac{dP_8}{dt} - C_{ag} \frac{dP_{CRA}}{dt} - C_{vg} \frac{dP_{CRV}}{dt} = Q_{aq.in} - Q_{aq.out} \tag{S6}
\]

\(C_{g.in \, vivo}\) can be included in the model as given by equation (S7):

\[
C_{g.in \, vivo} = V_{g0}(\frac{C_1}{IOP} + C_2) \tag{S7}
\]

where \(V_{g0}\) is the average globe starting volume, which is considered to be \(6.500 \times 10^{-6} \text{ m}^3\) (6.5 ml), and \(C_1\) and \(C_2\) are empirical constants \(3.653 \times 10^{-5} \text{ Pa}^{-1} (4.87 \times 10^{-3} \text{ mmHg}^{-1})\) and \(2.925 \times 10^{-7} \text{ Pa}^{-1} (3.9 \times 10^{-5} \text{ mmHg}^{-1})\), respectively. \(C_{ag}\), which is the compliance of the arteries associated with the globe, is assumed to remain constant, while the net compliance of the blood with respect to the globe, given by \(C_{bg} = C_{ag} + C_{vg}\), is a function of IOP. The compliance \(C_{bg}\) can be separated into its respective arterial and venous compliance using a factor \(\omega = 0.7\). The \(C_{ag}\) is assumed to be constant with respect to changing IOP \((P_9)\), while \(C_{vg}\) is a function of IOP \((P_9)\), both calculated using equation (S8).
\[ C_{ag} = (1 - \omega)C_{bg0} \]

\[ C_{vg0} = \omega C_{bg0} \text{ and } C_{vg} = C_{vg0} + \Delta C_{bgg} \]

\[ C_{bg0} = V_{g0} \left( \frac{C_1}{P_9} + C_2 - \frac{1}{k P_9} \right) \]

In Eq. (S8) we assumed normal IOP, \( P_9 = 2,000 \times 10^3 \) Pa (15 mmHg) and the nondimensional globe stiffness, \( k = 312 \).

**S2. Sensitivity plots for all the 28 parameters**

Sensitivity coefficient plots for all the 28 parameters listed below:

| S. No. | Parameter                        |
|--------|----------------------------------|
| 1.     | \( R_{12} \)                     |
| 2.     | \( R_{23} \)                     |
| 3.     | \( R_{36} \)                     |
| 4.     | \( R_{45} \)                     |
| 5.     | \( R_{56} \)                     |
| 6.     | \( R_{511} \)                    |
| 7.     | \( R_{611} \)                    |
| 8.     | \( R_{58} \)                     |
| 9.     | \( C_{27} \)                     |
| 10.    | \( C_{24} \)                     |
| 11.    | \( C_{47} \)                     |
| 12.    | \( C_{56} \)                     |
| 13.    | \( C_{57} \)                     |
| 14.    | \( C_{51} \)                     |
| 15.    | \( C_{511} \)                    |
| 16.    | \( C_{ONS} \)                    |
| 17.    | \( C_{89} \)                     |
| 18.    | \( C_1 \)                        |
| 19.    | \( C_2 \)                        |
| 20.    | \( V_{g0} \)                     |
| 21.    | \( \omega \)                     |
| 22.    | \( k \) (nondimensional globe stiffness) |
| 23.    | \( C_{TM} \)                     |
| 24.    | \( Q_{aq.in} \)                  |
| 25.    | \( Q_{UV} \)                     |
| 26.    | \( Q_{CSF} \)                    |
| 27.    | \( Q_{lymph} \)                  |
| 28.    | \( EVP \)                        |
It can be seen from the figures below that the sensitivities for parameters $R_{12}, R_{23}, R_{611}, R_{58}$ and $Q_{\text{lymph}}$ are consistently greater than those for the other parameters. This might be indicative of the greater influence of these parameters on the RSAS pressure. Although greater variations with respect to the average values are seen for some other parameters (e.g., variations of sensitivity coefficients for parameters 11-15 in Table S1 as seen in figure S3), these variations are negligible in magnitude as compared to the more influential parameters such as $R_{12}, R_{23}, R_{611}, R_{58}$ and $Q_{\text{lymph}}$.

Fig. S1. Sensitivity coefficients for parameters 1-5.
Fig. S2. Sensitivity coefficients for parameters 6-10.

Fig. S3. Sensitivity coefficients for parameters 11-15.
Fig. S4. Sensitivity coefficients for parameters 16-20.

Fig. S5. Sensitivity coefficients for parameters 21-28.
S3. Explanation for CSF flow from RSAS into the SAS for the no lymphatic CSF outflow case

The model does take into account the possibility of outflow from the RSAS into the SAS. This depends on the combination of the values for the lumped resistance within the optic nerve SAS ($R_{58}$) and the outflow of the CSF through the optic nerve lymphatics ($Q_{lymph}$). The fact that the flow has been modeled as the pressure difference over the resistance to the flow allows the flow to occur in either direction between compartments, depending on the direction of the pressure gradient. For example, the figure S6 below shows the variation in the SAS pressure and RSAS pressure when there is no lymphatic outflow. It is seen that the RSAS pressure is greater than the SAS pressure for a particular time, indicating the CSF flow is moving from the RSAS compartment to the SAS compartment.

![Fig. S6. Pressure difference between the RSAS and SAS compartments.](image)

S4. Variation in RSAS pressure

The RSAS pressure variation for 10 different resistances for different outflow conditions are shown below:

It is seen that for low resistances, the outflow conditions have very little effect on the RSAS pressure, while conversely at high resistances, there is considerable variation in the RSAS pressures as the outflow conditions are changed. It is clear from the figures that for the condition of no lymphatic CSF outflow, the RSAS pressure is consistently greater than the reported range (represented by the shaded region) across all the resistances. The exact amount of lymphatic outflow from the optic nerve SAS in humans is unknown. However, previous studies have shown that the nasal lymphatics are the primary outflow tract when compared to the lymphatics in the optic nerve SAS. Using the fact that only a small portion of CSF drains out through the lymphatics in the optic nerve SAS, it can be seen from the figures below that for the optic nerve SAS resistance range from $1.600 \times 10^{12} - 1.900 \times 10^{12}$ Pa s/m$^3$, the curves displaying the RSAS pressure for 5-10% lymphatic CSF outflow bound the shaded region that depicts the range of reported RSAS pressure values. While it is possible for the RSAS pressure curves to lie within the reported range, for resistances that are not bound by $1.600 \times 10^{12} - 1.900 \times 10^{12}$ Pa s/m$^3$, an increased lymphatic CSF outflow, in the range of 10-25%, is seen. This increased CSF outflow through the lymphatics in the optic nerve SAS is contrary to studies that claim limited CSF outflow through this region.
Fig. S7. RSAS pressure values for different resistances and outflow conditions.