Dynamics of the vitreous humour induced by eye rotations: implications for retinal detachment and intra-vitreal drug delivery

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Anatomy of the eye
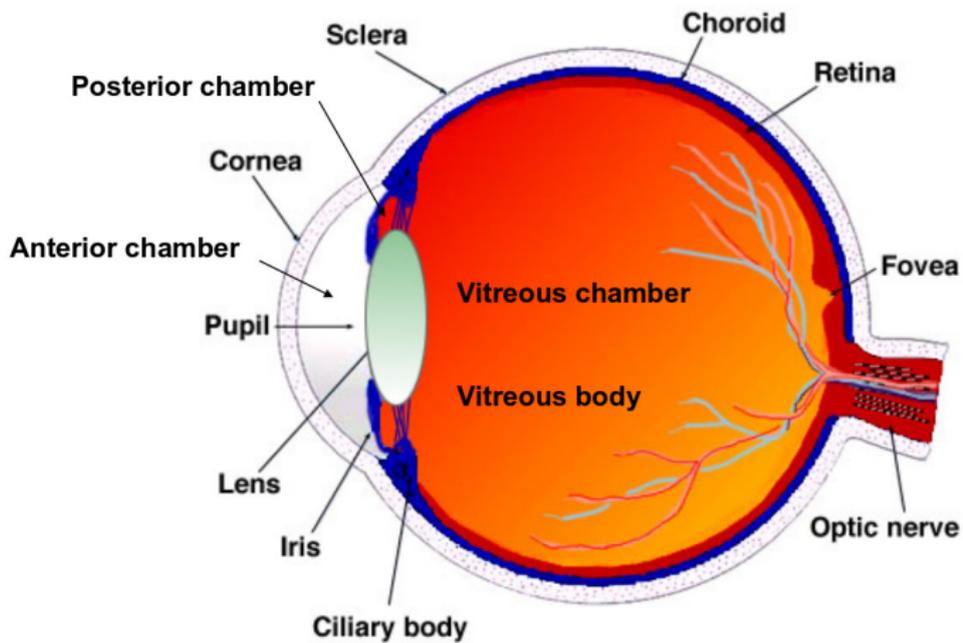
Vitreous characteristics and functions

Vitreous composition

The main constituents are

- Water (99%);
- hyaluronic acid (HA);
- collagen fibrils.

Its structure consists of long, thick, non-branching collagen fibrils suspended in hyaluronic acid.

Normal vitreous characteristics

- The healthy vitreous in youth is a gel-like material with **visco-elastic mechanical properties**, which have been measured by several authors (**???**).
- In the outermost part of the vitreous, named **vitreous cortex**, the concentration of collagen fibrils and HA is higher.
- The vitreous cortex is in contact with the **Internal Limiting Membrane (ILM)** of the retina.

Physiological roles of the vitreous

- **Support function for the retina** and filling-up function for the vitreous body cavity;
- **diffusion barrier** between the anterior and posterior segment of the eye;
- establishment of an **unhindered path of light.**

Vitreous ageing

With advancing age the vitreous typically undergoes significant changes in structure.
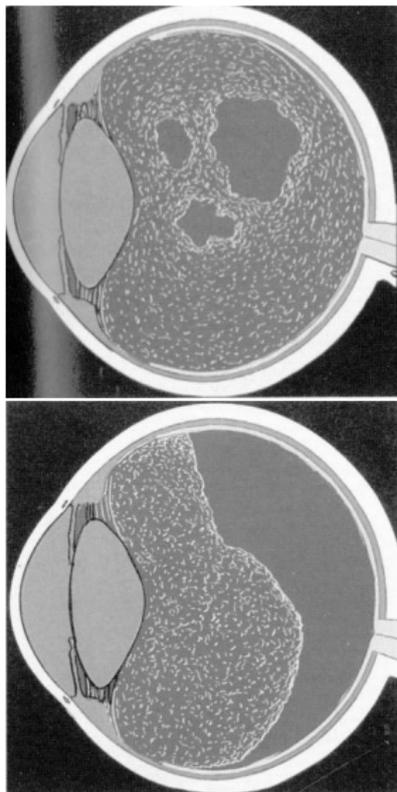
- Disintegration of the gel structure which leads to **vitreous liquefaction (synchisys)**. This leads to an approximately linear increase in the volume of liquid vitreous with time. Liquefaction can be as much extended as to interest the whole vitreous chamber.
- Shrinking of the vitreous gel **(syneresis)** leading to the detachment of the gel vitreous from the retina in certain regions of the vitreous chamber. This process typically occurs in the posterior segment of the eye and is called **posterior vitreous detachment (PVD)**. It is a pathophysiologic condition of the vitreous.

Vitreous replacement

After surgery **(vitrectomy)** the vitreous may be completely replaced with tamponade fluids:

- silicon oils water;
- aqueous humour;
- perfluoropropane gas;
- . . .

Partial vitreous liquefaction
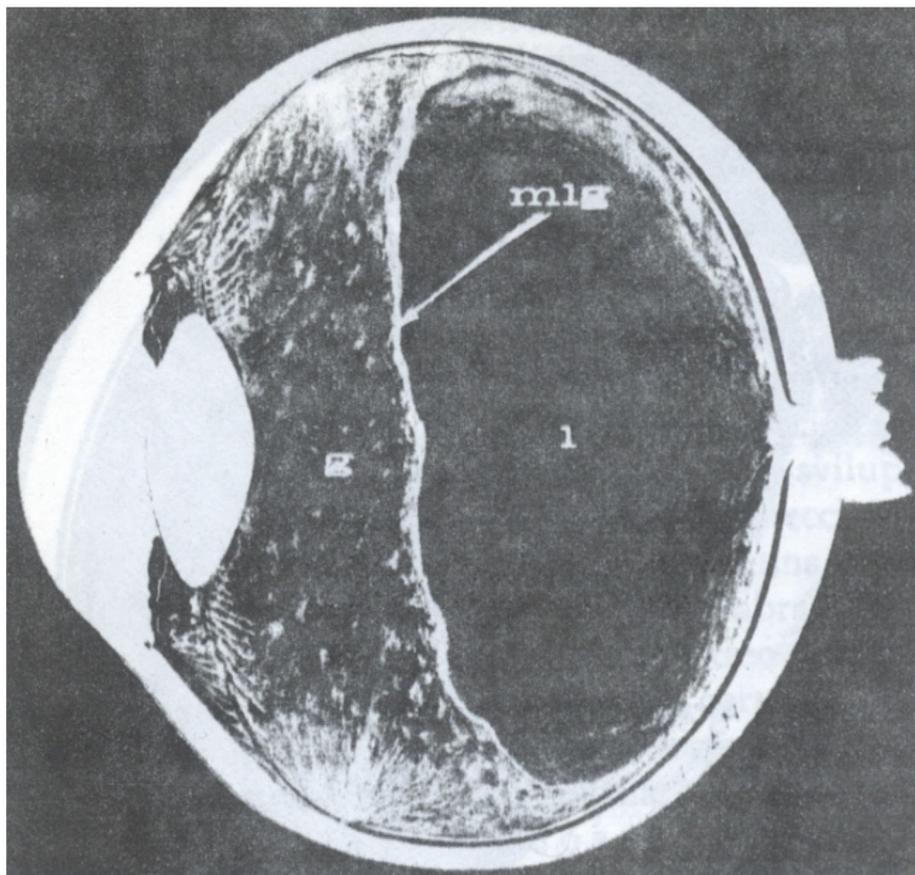
Motivations of the work

Why research on vitreous motion?

- Possible connections between the mechanism of **retinal detachment** and
  - the shear stress on the retina;
  - flow characteristics.
- Especially in the case of liquefied vitreous eye rotations may produce effective **fluid mixing**. In this case **advection may be more important that diffusion** for mass transport within the vitreous chamber.
  Understanding diffusion/dispersion processes in the vitreous chamber is important to predict the behaviour of drugs directly injected into the vitreous.

Retinal detachment
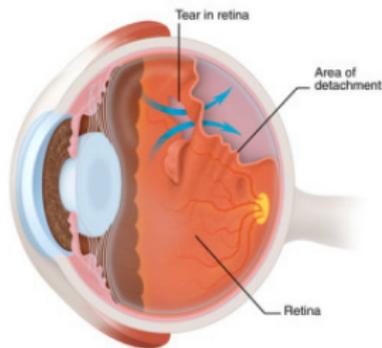
**Posterior vitreous detachment (PVD)** and vitreous degeneration:

- more common in myopic eyes;
- preceded by changes in vitreous macromolecular structure and in vitreoretinal interface → possibly mechanical reasons.

- If the retina detaches from the underlying layers → loss of vision;
- **Rhegmatogeneous retinal detachment:** fluid enters through a retinal break into the subretinal space and peels off the retina.
- **Risk factors:**
  - myopia;
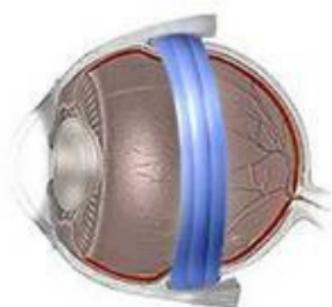 - posterior vitreous detachment (PVD);
  - lattice degeneration;
  - ...

Scleral buckling and vitrectomy

Scleral bluckling
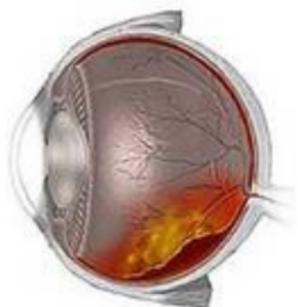
Before   After

Scleral buckling is the application of a rubber band around the eyeball at the site of a retinal tear in order to promote reachtachment of the retina.
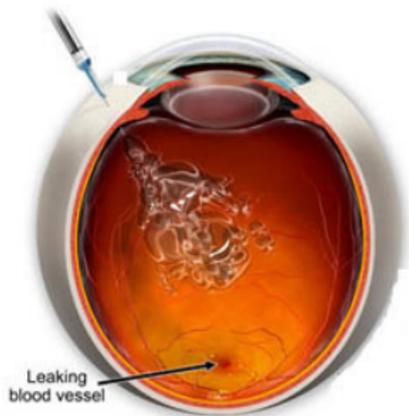
Vitrectomy

The vitreous may be completely replaced with tamponade fluids: silicon oils, water, gas, ...

Intravitreal drug delivery

It is difficult to transport drugs to the retina from 'the outside' due to the tight blood-retinal barrier $\rightarrow$ use of **intravitreal drug injections.**

Leaking
blood vessel

The effect of viscosity

Main working assumptions

- **Newtonian fluid**
  The assumption of purely viscous fluid applies to the cases of
  - vitreous liquefaction;
  - substitution of the vitreous with viscous tamponade fluids .

- **Sinusoidal eye rotations**
  Using dimensional analysis it can be shown that the problem is governed by the following two dimensionless parameters

$$\alpha = \sqrt{\frac{R_0^2 \omega_0}{\nu}} \qquad \qquad \textbf{Womersley number},$$

$$\varepsilon \qquad \qquad \textbf{Amplitude of oscillations}.$$

- **Spherical domain**

Theoretical model I

?

Scalings

$$\mathbf{u} = \frac{\mathbf{u}^*}{\omega_0 R_0}, \quad t = t^* \omega_0, \quad r = \frac{r^*}{R_0}, \quad p = \frac{p^*}{\mu \omega_0},$$

where ω_0 denotes the angular frequency of the domain oscillations, R_0 the sphere radius and μ the dynamic viscosity of the fluid.

Dimensionless equations

$$\alpha^2 \frac{\partial}{\partial t}\mathbf{u} + \alpha^2 \mathbf{u} \cdot \boldsymbol{\nabla}\mathbf{u} + \boldsymbol{\nabla}p - \nabla^2\mathbf{u} = 0, \qquad\qquad \boldsymbol{\nabla} \cdot \mathbf{u} = 0, \qquad (1)$$

$$u = v = 0, \quad w = \varepsilon \sin\vartheta \sin t \qquad\qquad (r = 1), \qquad (2)$$

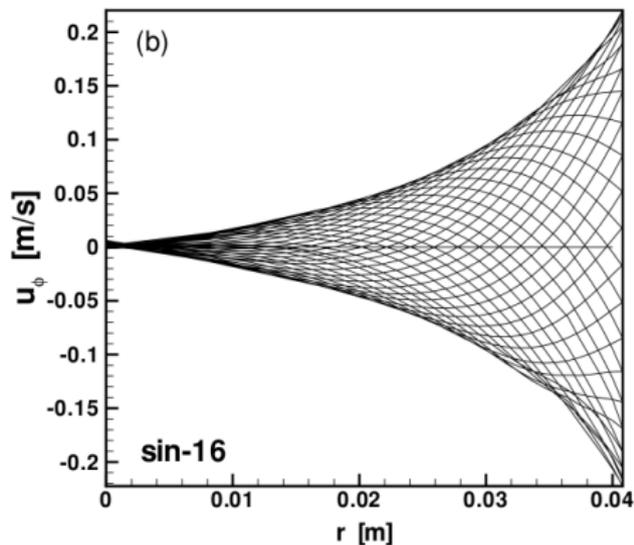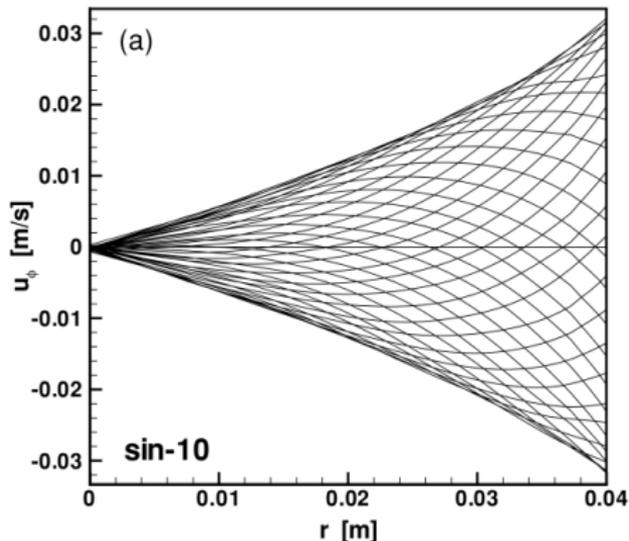where ε is the amplitude of oscillations. **We assume $\varepsilon \ll 1$.**

Asymptotic expansion

$$\mathbf{u} = \varepsilon\mathbf{u}_1 + \varepsilon^2\mathbf{u}_2 + \mathcal{O}(\varepsilon^3), \quad p = \varepsilon p_1 + \varepsilon^2 p_2 + \mathcal{O}(\varepsilon^3).$$

Since the equations and boundary conditions for u_1, v_1 and p_1 are homogeneous the solution is $p_1 = u_1 = v_1 = 0$.

Theoretical model II

Velocity profiles on the plane orthogonal to the axis of rotation at different times.

- Limit of small α: **rigid body rotation;**
- Limit of large α: formation of an **oscillatory boundary layer at the wall.**

Experimental apparatus I

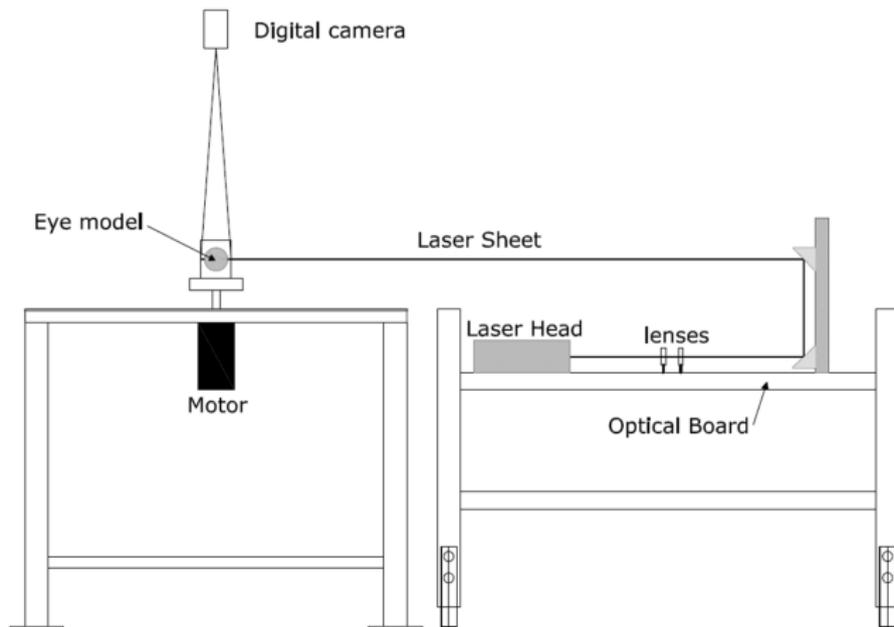**?**, Phys. Med. Biol.
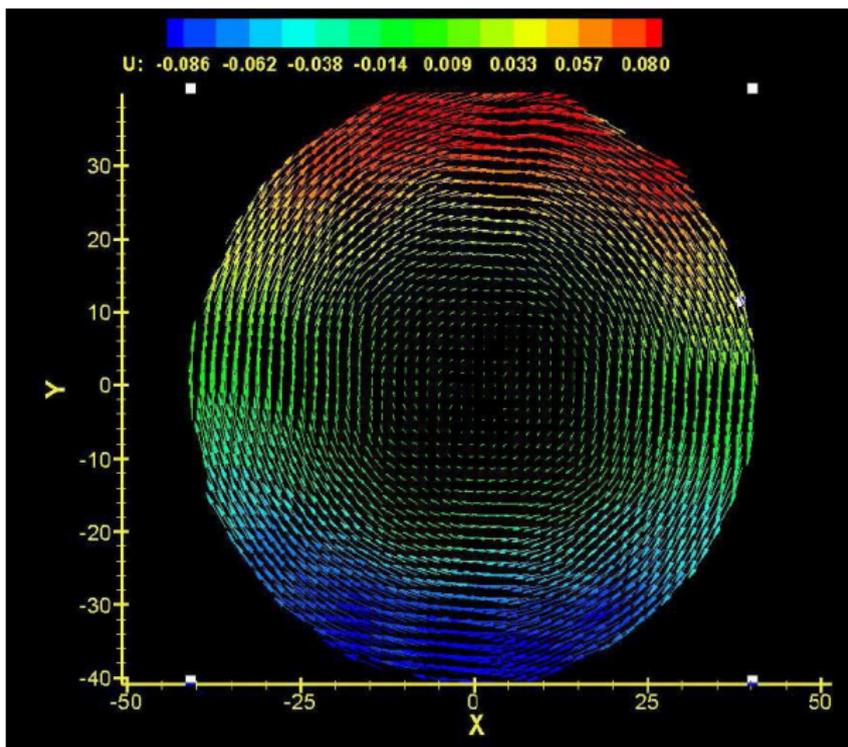The experimental apparatus is located at the University of Genoa.

- Perspex cylindrical container.
- Spherical cavity with radius $R_0 = 40$ mm.
- Glycerol (highly viscous Newtonian fluid).
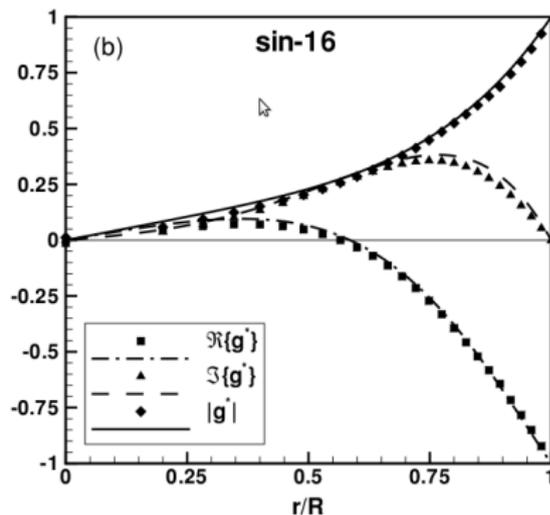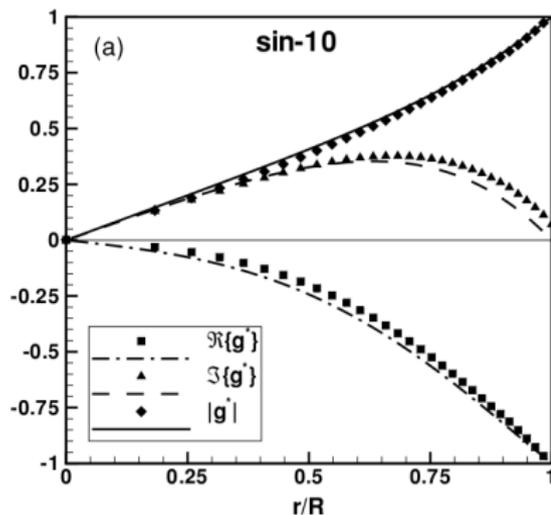
Experimental apparatus II

Experimental measurements

Typical PIV flow field

Comparison between experimental and theoretical results

Radial profiles of $\Re(g_1)$, $\Im(g_1)$ and $|g_1|$ for two values of the Womersley number α.

The case of a viscoelastic fluid I

- As we deal with an sinusoidally oscillating linear flow we can obtain the solution for the motion of a viscoelastic fluid simply by replacing the real viscosity with a **complex viscosity.**
- In terms of our dimensionless solution this implies introducing a **complex Womersley number.**
- Rheological properties of the vitreous (complex viscosity) can be obtained from the works of **?**, **?** and **?**.
- It can be proved that in this case, due to the presence of an elastic component of vitreous behaviour, the system admits natural frequencies that can be excited resonantly by eye rotations.

Formulation of the problem I

The motion of the fluid is governed by the momentum equation and the continuity equation:

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} + \frac{1}{\rho}\nabla p - \frac{1}{\rho}\nabla \cdot \mathbf{d} = 0, \tag{3a}$$

$$\nabla \cdot \mathbf{u} = 0, \tag{3b}$$

where **d** is the deviatoric part of the stress tensor.

Assumptions

- We assume that the velocity is small so that nonlinear terms in (??) are negligible.
- For a linear viscoelastic fluid we can write

$$\mathbf{d}(t) = 2 \int_{-\infty}^{t} G(t - \tilde{t})\mathbf{D}(\tilde{t})d\tilde{t} \tag{4}$$

where **D** is the rate of deformation tensor and G is the relaxation modulus.

Therefore we need to solve the following problem

$$\rho\frac{\partial \mathbf{u}}{\partial t} + \nabla p - \int_{-\infty}^{t} G(t - \tilde{t})\nabla^2\mathbf{u} \ d\tilde{t} = 0, \tag{5a}$$

$$\nabla \cdot \mathbf{u} = 0, \tag{5b}$$

Relaxation behaviour I

We assume that the solution has the structure

$$\mathbf{u}(\mathbf{x}, t) = \mathbf{u}_\lambda(\mathbf{x})e^{\lambda t} + c.c., \qquad p(\mathbf{x}, t) = p_\lambda(\mathbf{x})e^{\lambda t} + c.c.,$$

where $\mathbf{u}_\lambda, p_\lambda$ do not depend on time and $\lambda \in \mathbb{C}$.
It can be shown that the deviatoric part of the stress tensor takes the form

$$\mathbf{d}(t) = 2\int_{-\infty}^{t} G(t - \tilde{t})\mathbf{D}(\tilde{t})d\tilde{t} = 2\mathbf{D}\frac{\tilde{G}(\lambda)}{\lambda}, \tag{6}$$

where

$$\tilde{G}(\lambda) = G'(\lambda) + iG''(\lambda) = \lambda \int_0^\infty G(s)e^{-\lambda s}ds$$

is the complex modulus.

- G': **storage modulus;**
- G'': **loss modulus;**

This leads to the eigenvalue problem

$$\rho\lambda\mathbf{u}_\lambda = -\nabla p_\lambda + \frac{\tilde{G}(\lambda)}{\lambda}\nabla^2\mathbf{u}_\lambda, \quad \nabla \cdot \mathbf{u}_\lambda = 0, \tag{7}$$

which has to be solved imposing **stationary no-slip conditions** at the wall and **regularity conditions** at the origin.

Relaxation behaviour II

This eigenvalue problem can be solved analytically by expanding the velocity in terms of vector spherical harmonics and the pressure in terms of scalar spherical harmonics (**?**).
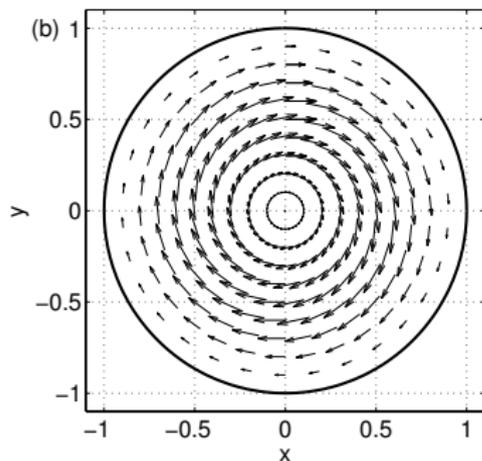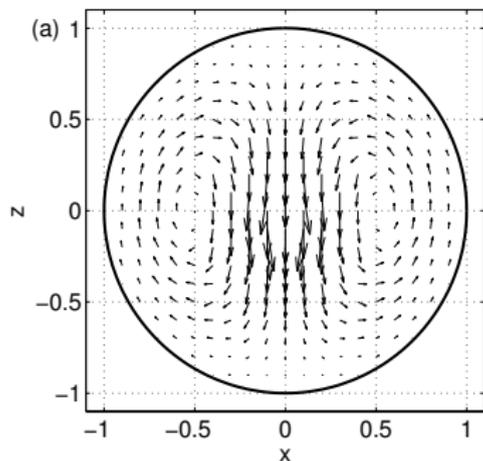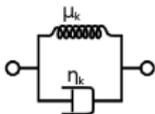

Spatial structure of the first two **eigenfunctions.**

Relaxation behaviour III

In order to determine the **eigenvalues** it is necessary to specify the model for the vitreous humour viscoelastic behaviour.
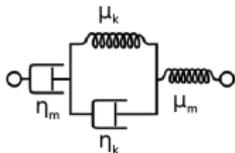
Two-parameter model

- dashpot: ideal viscous element
- spring: ideal elastic element

$$\tilde{G}(\lambda) = \mu_K + \lambda\eta_K.$$

Four-parameter model

$$\tilde{G}(\lambda) = \frac{\lambda\eta_m\mu_m(\mu_K + \lambda\eta_K)}{(\mu_m + \lambda\eta_m)(\lambda\eta_m\mu_m/(\mu_m + \lambda\eta_m) + \mu_K + \lambda\eta_K)}$$

Some conclusions

- For all existing measurements of the rheological properties of the vitreous we find the **existence of natural frequencies of oscillation.**
- Such frequencies, for the least decaying modes, are within the range of physiological eye rotations ($\omega = 10 - 30$ rad/s).
- The two- and the four-parameter model lead to qualitatively different results:
  - **Two-parameter model:** only a finite number of modes have complex eigenvalues;
  - **Four-parameter model:** an infinite number of modes have complex eigenvalues.
- **Natural frequencies could be resonantly excited by eye rotations.**
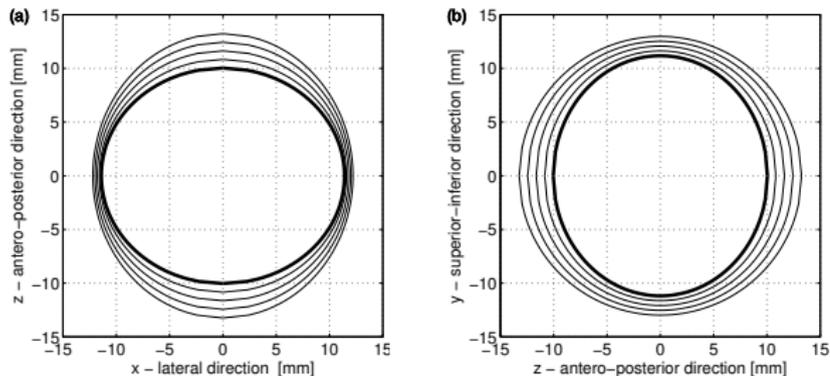
The effect of the geometry I

Myopic Eyes

In comparison to emmetropic eyes, myopic eyes are

- larger in all directions;
- particularly so in the antero-posterior direction.

Myopic eyes bear **higher risks of posterior vitreous detachment and vitreous degeneration** $\rightarrow$ increased the risk of rhegmatogeneous retinal detachment.

The shape of the eye ball has been related to the degree of myopia (measured in dioptres D) by **?**, who approximated the vitreous chamber with an ellipsoid.

$$\text{width} = 11.4 - 0.04D,$$
$$\text{height} = 11.18 - 0.09D,$$
$$\text{length} = 10.04 - 0.16D.$$

(a) horizontal and (b) vertical cross sections of the domain for different degrees of myopia.

Formulation of the mathematical problem

Meskauskas et al., submitted to Invest. Ophthal. Vis. Scie.

Equation of the boundary

$$R(\vartheta, \varphi) = R_0(1 + \delta R_1(\vartheta, \varphi)),$$

where

- R_0 denotes the radius of the sphere with the same volume as the vitreous chamber;
- δ is a **small parameter** ($\delta \ll 1$);
- the maximum absolute value of R_1 is 1.

Expansion

We expand the velocity and pressure fields in therms of δ as follows
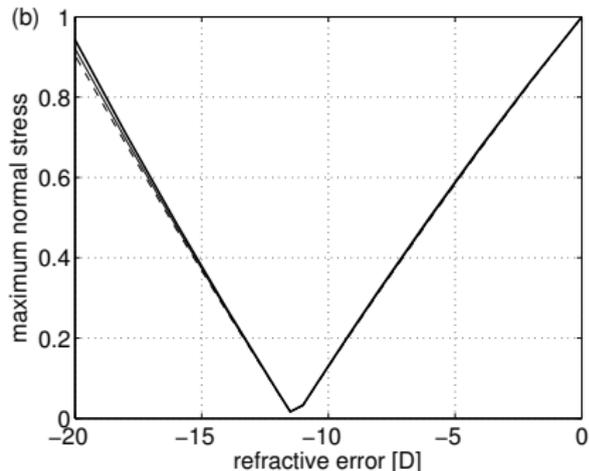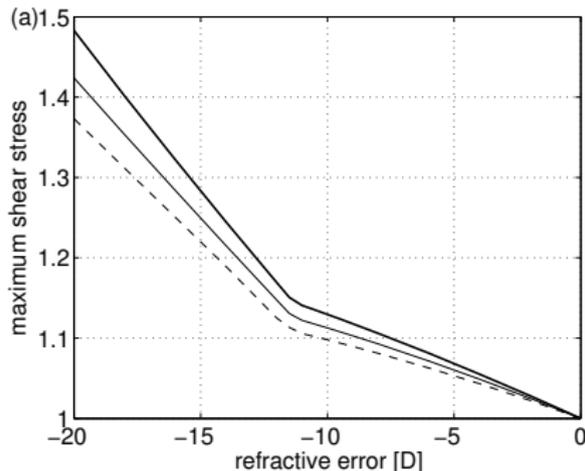
$$\mathbf{U} = \mathbf{U}_0 + \delta \mathbf{U}_1 + \mathcal{O}\left(\delta^2\right), \qquad P = P_0 + \delta P_1 + \mathcal{O}\left(\delta^2\right).$$

Solution

The solution at the order δ can be found analytically expanding R_1, $\mathbf{U}_1$ and P_1 in terms of spherical harmonics.

Myopic eyes I

Maximum stress on the retina as a function of the refractive error

Maximum (over time and space) of the (a) tangential and (b) normal stress on the retina as a function of the refractive error in dioptres. **Values are normalised with the corresponding stress in the emmetropic (0 D) eye.** The different curves correspond to different values of the rheological properties of the vitreous humour taken from the literature.

Non-linear effects and implications for fluid mixing

Back to viscous fluids . . .
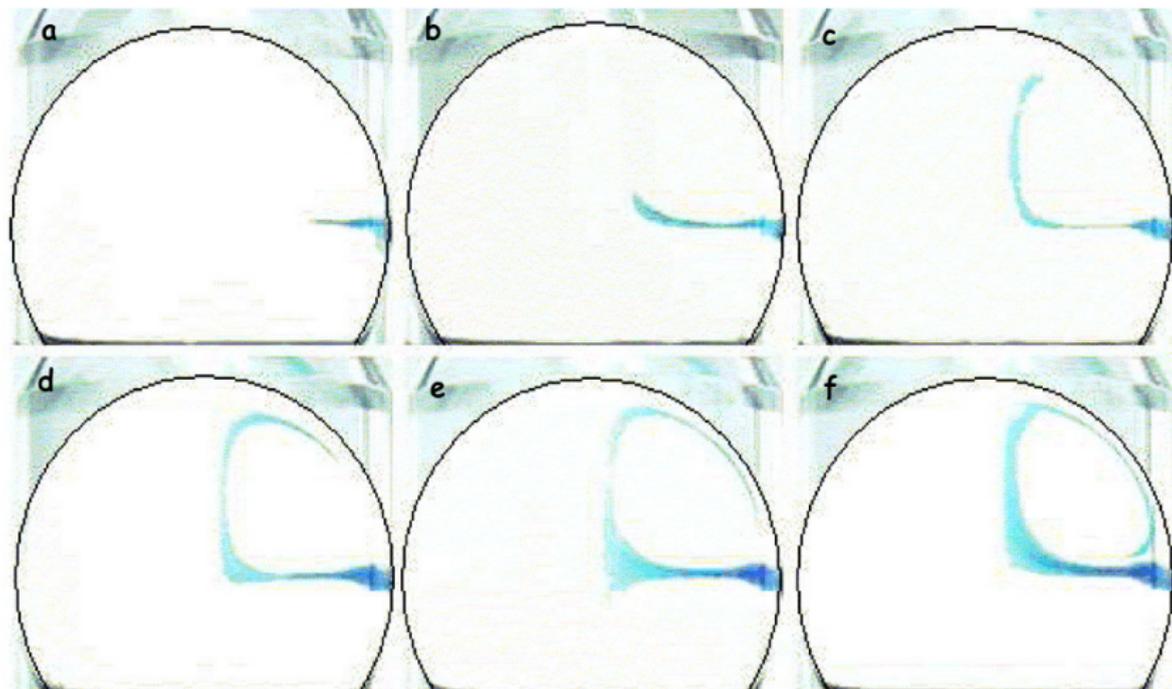
Flow visualisations on planes containing the axis of rotation.

Theoretical model I

Second order solution

$$\mathbf{u} = \varepsilon \mathbf{u}_1 + \varepsilon^2 \mathbf{u}_2 + \mathcal{O}(\varepsilon^3), \quad p = \varepsilon p_1 + \varepsilon^2 p_2 + \mathcal{O}(\varepsilon^3).$$

We decompose the velocity $\mathbf{u}_2$ and the pressure p_2 into their **time harmonics** by setting

$$\mathbf{u}_2 = \mathbf{u}_{20} + \left\{ \mathbf{u}_{22} e^{2it} + c.c. \right\}, \quad p_2 = p_{20} + \left\{ p_{22} e^{2it} + c.c. \right\}, \quad \mathbf{u}_1 \cdot \boldsymbol{\nabla} \mathbf{u}_1 = \mathcal{F}_0 + \left\{ \mathcal{F}_2 e^{2it} + c.c. \right\},$$

where $\mathbf{u}_{20}$, $\mathbf{u}_{22}$, p_{20}, p_{22}, $\mathcal{F}_0$ and $\mathcal{F}_2$ are independent of time.

### Governing equations for the steady component

$$\nabla^2 \mathbf{u}_{20} - \boldsymbol{\nabla} p_{20} = \alpha^2 \mathcal{F}_0, \qquad\qquad \boldsymbol{\nabla} \cdot \mathbf{u}_{20} = 0, \qquad\qquad (8a)$$

$$u_{20} = v_{20} = w_{20} = 0 \qquad\qquad (r = 1). \qquad\qquad (8b)$$

Comparison between experimental and theoretical results I

- The steady streaming flow can be directly measured experimentally by cross-correlating images that are separated in time by a multiple of the frequency of oscillation.
- This procedure filters out from the measurements the oscillatory component of the flow.
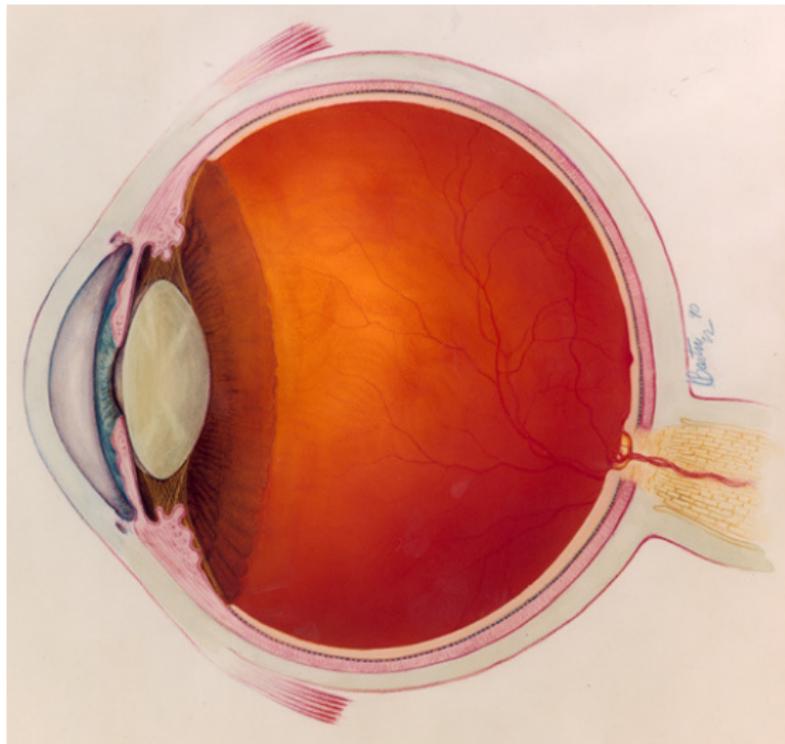
?, J. Fluid Mech.

Numerical

Experimental
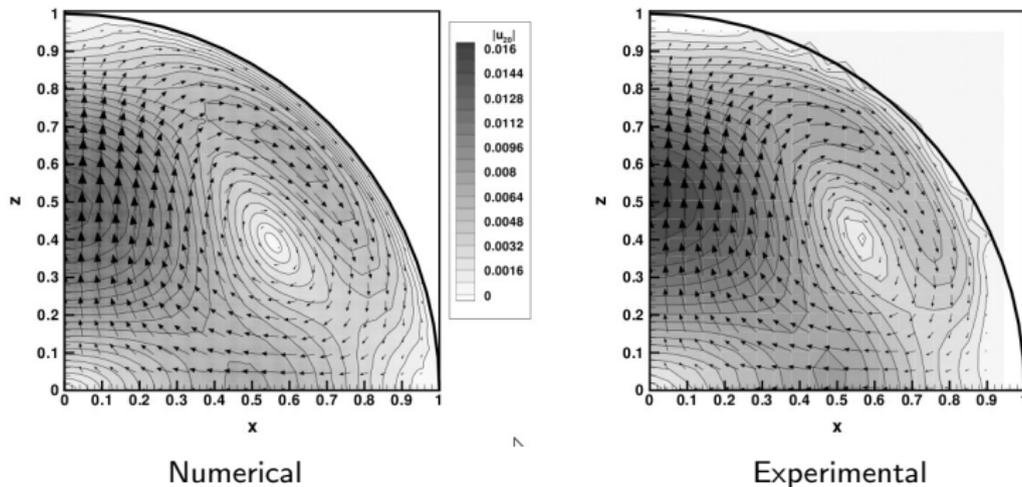
Effect of the geometry on the steady streaming

Non-sphericity of the domain

- The antero-posterior axis is shorted than the others;
- the lens produces an anterior indentation.

What is the effect of the geometry on the steady streaming?

Theoretical model I

?, Biomech. Model. Mechanobiol.

We assume small amplitude sinusoidal torsional oscillations

$$\beta = -\varepsilon \cos(\omega_0 t^*) \qquad \varepsilon \ll 1.$$

Scaling

$$\mathbf{u} = \frac{\mathbf{u}^*}{\omega_0 R_0}, \quad t = t^* \omega_0, \quad (r, R) = \frac{(r^*, R^*)}{R_0}, \quad p = \frac{p^*}{\mu \omega_0}.$$

Dimensionless governing equations

$$\alpha^2 \left(\frac{\partial}{\partial t} - \varepsilon \sin t \frac{\partial}{\partial \varphi} \right) \mathbf{u} + \alpha^2 (\mathbf{u} \cdot \nabla) \mathbf{u} + \nabla p - \nabla^2 \mathbf{u} = 0, \tag{9a}$$
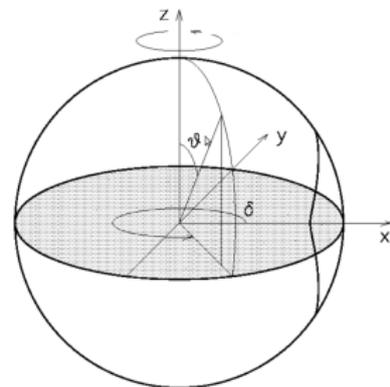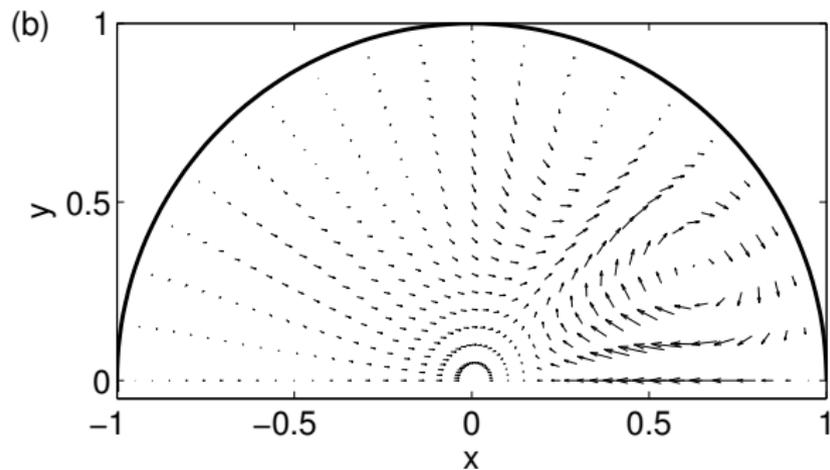
$$\nabla \cdot \mathbf{u} = 0, \tag{9b}$$

$$u = v = 0, \ w = \varepsilon R \sin \vartheta \sin t \qquad\qquad [r = R(\vartheta, \varphi)], \tag{9c}$$

Shape of the domain

We write the function $R(\vartheta, \varphi)$ describing the shape pf the domain as

$$R(\vartheta, \varphi) = 1 + \delta R_1(\vartheta, \varphi), \qquad \delta \ll 1.$$
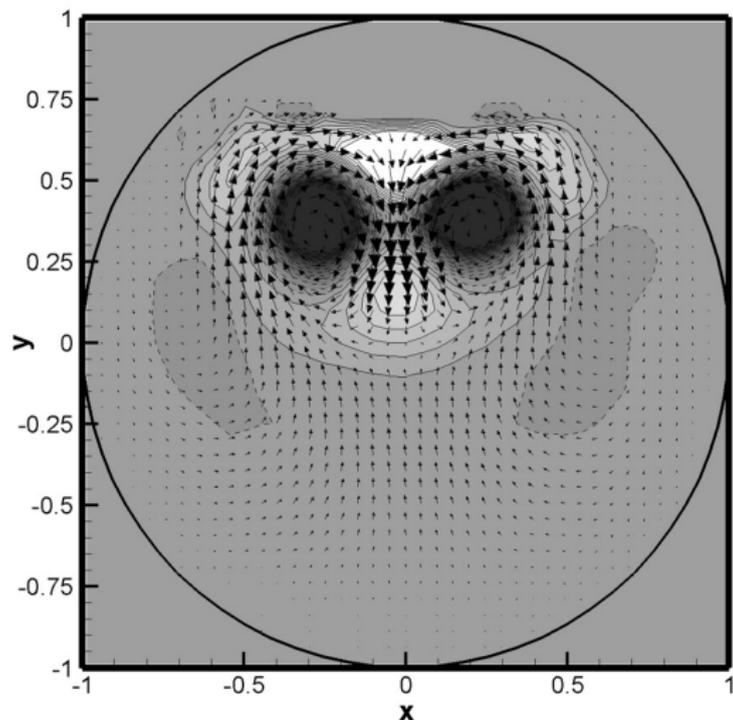
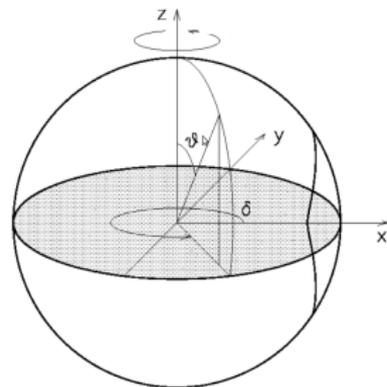## Theoretical model II

(b)

Perturbation of the steady streaming flow on the equatorial plane

Experimental measurement of the steady streaming flow

$\alpha = 3.8$

Steady streaming flow on the equatorial plane.

Conclusions

- Eye movements during reading: $\approx$ 0.16 rad, $\approx 63\ s^{-1}$ (**?**).
- Kinematic viscosity of the vitreous: $\nu \approx 7 \times 10^{-4}$ m^{2}s^{-1} (**?**).
- Eye radius: $R_0 = 0.012$ m.
- Womersley number: $\alpha = 3.6$.
- Streaming velocity: $U = \varepsilon^2 \delta \max(|\mathbf{u}_{21}^{(0)}|) \approx 6 \times 10^{-5}$ m s^{-1}.
- Diffusion coefficient of fluorescein: $D \approx 6 \times 10^{-10}$ m s^{-1} (Kaiser and Maurice, 1964)
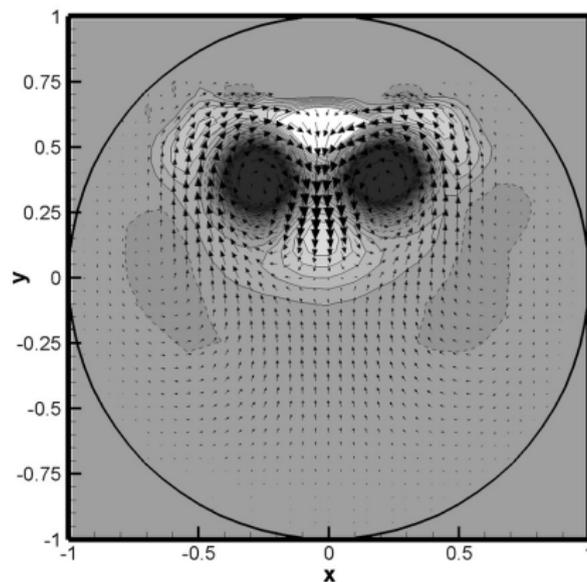
Peclèt number: $Pe \approx 1200$.
In this case advection is much more important than diffusion!

Work in progress 1

**Julia Meskauskas, Rodolfo Repetto and Jennifer Siggers**

- **Steady streaming in a viscoelastic fluid.**
- **Stress on the retina during real eye movements.**

Work in progress 2

Amabile Tatone, Rodolfo Repetto

- **Motion of the vitreous after Posterior Vitreous Detachment.** The gel phase is modelled as a hyperelastic viscous solid, the liquefied vitreous as a viscous fluid. Interaction using the ALE approach.
- **Quasi static shrinking of the vitreous.**

Movie 2

Movie 2
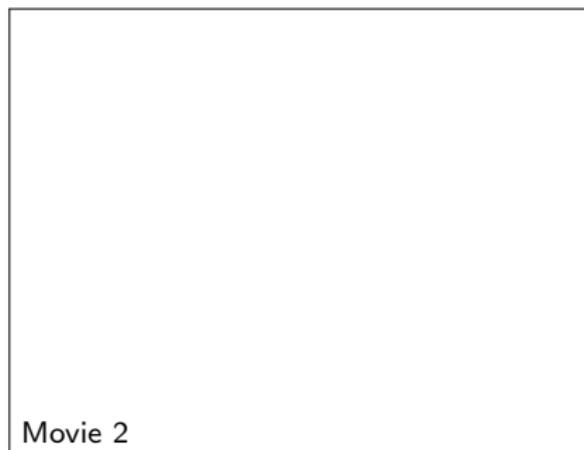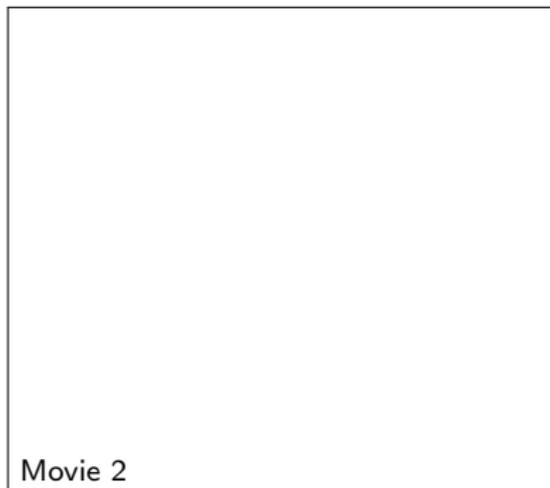
Work in progress 3

Jan Pralits, Krystyna Isakova, Rodolfo Repetto

- **Stability of the interface between a tamponade fluid and the acqueous humour, after vitrectomy.** Understanding the basic mechanisms leading to the formation of oil emulsions.
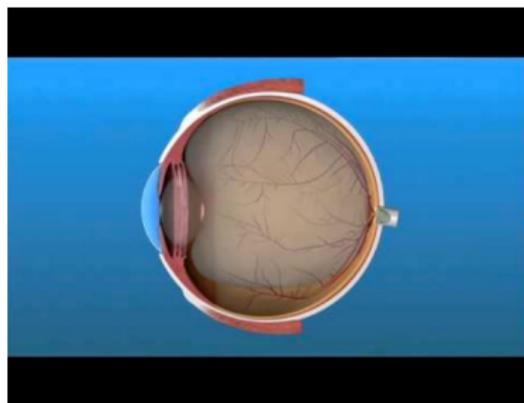
Movie 2

References I

D. A. Atchison, N. Pritchard, K. L. Schmid, D. H. Scott, C. E. Jones, and J. M. Pope. Shape of the retinal surface in emmetropia and myopia. *Investigative Ophthalmology & Visual Science*, 46(8):2698–2707, 2005. doi: 10.1167/iovs.04-1506.

T. David, S. Smye, T. Dabbs, and T. James. A model for the fluid motion of vitreous humour of the human eye during saccadic movement. *Phys. Med. Biol.*, 43:1385–1399, 1998.

R. Dyson, A. J. Fitt, O. E. Jensen, N. Mottram, D. Miroshnychenko, S. Naire, R. Ocone, J. H. Siggers, and A. Smithbecker. Post re-attachment retinal re-detachment. In *Proceedings of the Fourth Medical Study Group, University of Strathclyde, Glasgow*, 2004.

B. Lee, M. Litt, and G. Buchsbaum. Rheology of the vitreous body. Part I: viscoelasticity of human vitreous. *Biorheology*, 29:521–533, 1992.

J. Meskauskas, R. Repetto, and J. H. Siggers. Oscillatory motion of a viscoelastic fluid within a spherical cavity. *Journal of Fluid Mechanics*, 685:1–22, 2011. doi: 10.1017/jfm.2011.263.

C. S. Nickerson, J. Park, J. A. Kornfield, and H. Karageozian. Rheological properties of the vitreous and the role of hyaluronic acid. *Journal of Biomechanics*, 41(9):1840–6, 2008. doi: 10.1016/j.jbiomech.2008.04.015.

R. Repetto, A. Stocchino, and C. Cafferata. Experimental investigation of vitreous humour motion within a human eye model. *Phys. Med. Biol.*, 50:4729–4743, 2005. doi: 10.1088/0031-9155/50/19/021.

References II

R. Repetto, J. H. Siggers, and A. Stocchino. Steady streaming within a periodically rotating sphere. *Journal of Fluid Mechanics*, 608:71–80, August 2008. doi: 10.1017/S002211200800222X.

R. Repetto, J. H. Siggers, and A. Stocchino. Mathematical model of flow in the vitreous humor induced by saccadic eye rotations: effect of geometry. *Biomechanics and Modeling in Mechanobiology*, 9(1):65–76, 2010. ISSN 1617-7959. doi: 10.1007/s10237-009-0159-0.

T. Rossi, G. Querzoli, G. Pasqualitto, M. Iossa, L. Placentino, R. Repetto, A. Stocchino, and G. Ripandelli. Ultrasound imaging velocimetry of the human vitreous. *Experimental eye research*, 99C:98–104, Apr. 2012. ISSN 1096-0007. doi: 10.1016/j.exer.2012.03.014. PMID: 22516112.

K. Swindle, P. Hamilton, and N. Ravi. In situ formation of hydrogels as vitreous substitutes: Viscoelastic comparison to porcine vitreous. *Journal of Biomedical Materials Research - Part A*, 87A(3):656–665, Dec. 2008. ISSN 1549-3296.