Modélisation multi-échelle des fluides biologiques : aspects théoriques et numériques

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Journée thématique « multi-échelles » en génie électrique

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Context and medical background

Glaucoma:

Degeneration of the optic nerve and death of retinal ganglion cells leading to irreversible vision loss.

Normal vision

Advanced glaucoma

http://www.drnrr.com/glaucoma

Question:

What is the cause of this degeneration?

Standard clinical evaluations:

- intraocular pressure (IOP) *via* Goldmann tonometer;
- visual functions *via* visual field test.

A multi-factorial disease:

- elevated IOP is a recognized risk factor, however the establishment of optimal IOP levels for patients is still controversial;
- numerous other risk factors in the literature: age, gender, genetic factors, diabetes, blood pressure *etc.*

Today's Talk:

Mathematical and computational models for biofluids:

- Complex multiphysics and multiscale phenomena.
- Develop innovative methods for analyzing contributions of IOP and non-IOP risk factors for glaucoma, on an individual-specific basis.

Outline:

- **Part I. A new splitting approach** to numerically solve geometric multiscale problems. **First-order** and **second-order** approximations.
- **Part II. A multiscale model** coupling hemodynamics, biomechanics and fluid dynamics in the eye. Development of the **Ocular Mathematical Virtual Simulator**.

Conclusions and outlook: relationship between **neurodegenerative disorders** in the brain and in the eye.

Mathematical modeling: 3D description of the fluid flow through a large vessel

Blood: homogeneous, incompressible fluid, with "standard" Newtonian behavior, unsteady Navier-Stokes equations:

$$\begin{aligned} \rho \frac{\partial \mathbf{u}}{\partial t} - 2\mathbf{div}(\mu \mathbf{D}(\mathbf{u})) + \rho(\mathbf{u} \cdot \nabla)\mathbf{u} + \nabla p &= \mathbf{0}, \quad \text{in } \Omega \times I \\ \mathrm{div}(\mathbf{u}) &= 0, \quad \text{in } \Omega \times I \end{aligned}$$

$+$ Initial and boundary conditions,

where:

- $\mathbf{u}$ and p velocity and pressure of the fluid;
- $\mathbf{D}(\mathbf{u}) = \frac{1}{2}(\nabla \mathbf{u} + \nabla \mathbf{u}^T)$ strain rate tensor;
- $\boldsymbol{\sigma}(\mathbf{u}, p) = -p\mathbf{I} + 2\mu\mathbf{D}(\mathbf{u})$ Cauchy stress tensor;
- ρ and μ density and dynamic viscosity of the fluid.

Mathematical modeling: 3D description of the fluid flow through a deformable porous media

Balance equations: conservation of mass of fluid phase and of linear momentum for the fluid+solid mixture, respectively:

$$\zeta_t + \nabla \cdot \mathbf{v} = S \quad \text{and} \quad \nabla \cdot \mathbf{T} + \mathbf{F} = \mathbf{0} \quad \text{in } \Omega \times (0, T)$$

Constitutive equations:

$$\begin{array}{l} \text{total stress: } \mathbf{T} = \mathbf{T}_e(\mathbf{u}) + \delta \mathbf{T}_v(\mathbf{u}_t) - \alpha p \mathbf{I} \\ \text{discharge velocity: } \mathbf{v} = -\mathbf{K} \nabla p \\ \text{fluid content: } \zeta = c_0 p + \alpha \nabla \cdot \mathbf{u} \end{array} .$$

$+$ Initial and boundary conditions, where:

- $\mathbf{u}$ the solid displacement, p the Darcy fluid pressure;
- λ_e and μ_e are the elastic parameters, and λ_v and μ_v are the viscoelastic parameters (Kelvin-Voigt);
- $\mathbf{K}$ the permeability tensor, α is the Biot-Willis coefficient, S is a net volumetric fluid production rate, $\mathbf{F}$ is a body force per unit of volume.

Mathematical modeling: reduced 0D description

Main idea: circuit-based representation of the cardiovascular system, analogy between **electric** and **hydraulic** networks.

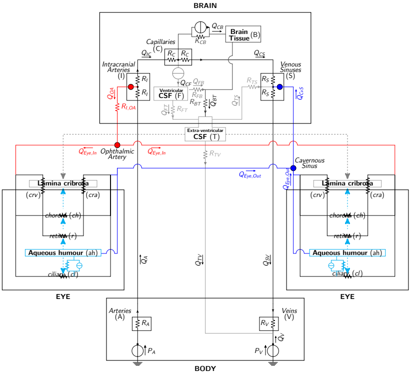
Hydraulic	**Electric**
Pressure	*Voltage*
Flow rate	*Current*
Volume	*Charge*
Blood viscosity	Resistance R
Blood inertia	Inductance L
Wall compliance	Capacitance C

Objective: Provide a **systemic view**, while maintaining a relatively accessible mathematical complexity and low computational costs.

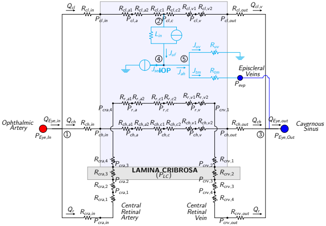
Mathematical model: Kirchhoff laws for the nodes (conservation of current/flow rate) and for closed circuits (conservation of the voltage/pressure) $\Rightarrow$ **system of differential algebraic equations**:

$$\frac{d\boldsymbol{y}_m}{dt} = \underline{\underline{\boldsymbol{A}}}_m(\boldsymbol{y}_m, t)\boldsymbol{y}_m + \boldsymbol{r}_m(\boldsymbol{y}_m, t), \quad m \geq 1.$$

A new 0D model for the coupled eye-cerebral system



0D coupled model for the Body-Brain-Eyes system.



Applications:

Glaucoma: MS et al. *Mathematical modeling of aqueous humor flow and intraocular pressure under uncertainty: towards individualized glaucoma management*, JMO 2016.

Microgravity: F. Salerni et al. *Biofluid modeling of the coupled eye-brain system and insights into simulated microgravity conditions*, PLoS One 2019.

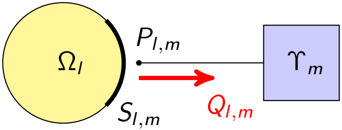
UQ and SA: L. Sala et al. *Uncertainty propagation and sensitivity analysis: results from the Ocular Mathematical Virtual Simulator*, MBE 2021.

Multiscale approach: coupling of reduced (0D) and distributed (3D) fluid flow models

Why?

- Reliable method for computing correct boundary conditions at the artificial boundaries of a region of interest **OR**
- Rough description of the whole system + zoom in a specific region of interest.

Coupling conditions: continuity of the pressures and fluxes.



Coupling between a Navier-Stokes region Ω_l and a lumped circuit Υ_m via the interface $S_{l,m}$.

$$\Big(- p_l \underline{\boldsymbol{I}} + \mu \nabla \boldsymbol{v}_l \Big) \boldsymbol{n}_{l,m} = -P_{l,m}(t) \boldsymbol{n}_{l,m}(\boldsymbol{x}) \quad \text{for} \quad \boldsymbol{x} \in S_{l,m} \quad \text{and} \quad t \in (0,T),$$

$$Q_{l,m}(t) = \int_{S_{l,m}} \boldsymbol{v}_l(\boldsymbol{x},t) \cdot \boldsymbol{n}_{l,m}(\boldsymbol{x}) dS_{l,m} \quad \text{for} \quad t \in (0,T),$$

where $P_{l,m}$ is the pressure at the node of the circuit sitting on $S_{l,m}$ and $Q_{l,m}$ contributes as source/sink for the circuit Υ_m.

Numerical approximation of the coupled problem: two strategies

Implicit - Monolithic approach:

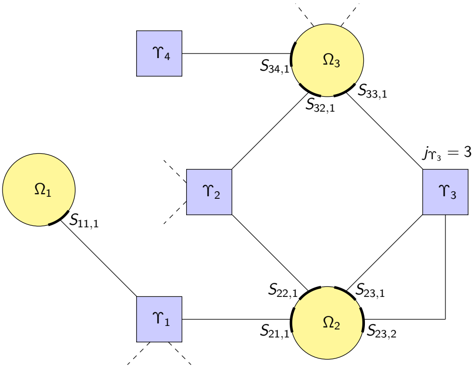
- the coupled problem is solved in one block
- same solver and time discretization
- unconditionally stable
- fully coupled matrix might be ill-conditioned (needs of preconditioning)

Explicit - Splitting approach:

- split coupled problem in two or more blocks (PDEs and ODEs)
- need for sub-iterations between blocks
- use existing solvers for solving subproblems separately (separate non-linearities)
- stability and convergence issues due to splitting

A. Quarteroni, S. Ragni, A. Veneziani *Comput Vis Sci.* (2001), A. Quarteroni, A. Veneziani *SIAM MMS* (2003), C. Bertoglio, A. Caiazzo, M.A. Fernandez *SIAM SciComp* (2013), M. E. Moghadam et al. *JCP* (2013), **A. Quarteroni, A. Veneziani, C. Vergara** *CMAME* **(2016)**, C. Grandmont, S. Martin *M2AN* (2021) *etc.*

A new energy-based splitting scheme for the Stokes-ODE coupled problem



Geometrical architecture of the coupled system.

L. Carichino, G. Guidoboni, MS, *Energy-based operator splitting approach for the time discretization of coupled systems of partial and ordinary differential equations for fluid flows: the Stokes case*, JCP 2018.

Mathematical setting: a Stokes-ODE coupled problem

Stokes system + boundary and interface conditions:

$$\begin{aligned}
\boldsymbol{v}_l &= \boldsymbol{0} && \text{on } \Gamma_l \times (0, T) \\
\Big(-p_l \underline{\underline{\boldsymbol{I}}} + \mu \nabla \boldsymbol{v}_l\Big)\boldsymbol{n}_l &= -\overline{p}_l \boldsymbol{n}_l && \text{on } \Sigma_l \times (0, T) \\
\Big(-p_l \underline{\underline{\boldsymbol{I}}} + \mu \nabla \boldsymbol{v}_l\Big)\boldsymbol{n}_{l,m} &= -P_{l,m}(t)\boldsymbol{n}_{l,m}(\boldsymbol{x}) && \text{on } S_{l,m} \times (0, T) \\
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\end{aligned}$$

+ circuit equations:

$$\frac{d\boldsymbol{y}_m}{dt} = \underline{\underline{\boldsymbol{A}}}_m(\boldsymbol{y}_m, t)\boldsymbol{y}_m + \boldsymbol{r}_m(\boldsymbol{y}_m, t)$$

+

$$\boldsymbol{r}_m(\boldsymbol{y}_m, Q_{l,m}, P_{l,m}, t) = \boldsymbol{s}_m(\boldsymbol{y}_m, t) + \boldsymbol{b}_m(Q_{l,m}, P_{l,m}, t)$$

where:

$\boldsymbol{s}_m(\boldsymbol{y}_m, t)$: contributions of sources and sinks for the circuit;

$\boldsymbol{b}_m(Q_{l,m}, P_{l,m}, t)$: contributions from the Stokes-circuit connections.

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\frac{d\boldsymbol{y}_m}{dt} = \underline{\underline{\boldsymbol{A}}}_m(\boldsymbol{y}_m, t)\boldsymbol{y}_m + \boldsymbol{r}_m(\boldsymbol{y}_m, t)
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$+$

$$
\boldsymbol{r}_m(\boldsymbol{y}_m, Q_{l,m}, P_{l,m}, t) = \boldsymbol{s}_m(\boldsymbol{y}_m, t) + \boxed{\boldsymbol{b}_m(Q_{l,m}, P_{l,m}, t)}
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Operator splitting approach for the time discretization

Time step Δt, $t^n = n\Delta t$, $\varphi^n = \varphi(t = t^n)$ for any general expression φ.

Step 1

For each $l \in \mathcal{L}$ and $m \in \mathcal{M}$, given $\boldsymbol{v}_l^n$ and $\boldsymbol{y}_m^n$, solve

$$\begin{aligned}
\boldsymbol{\nabla} \cdot \boldsymbol{v}_l &= 0 && \text{in } \Omega_l \times (t^n, t^{n+1}) \\
\rho \frac{\partial \boldsymbol{v}_l}{\partial t} &= -\nabla p_l + \mu \Delta \boldsymbol{v}_l + \rho \boldsymbol{f}_l && \text{in } \Omega_l \times (t^n, t^{n+1}) \\
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\end{aligned}$$

with the initial conditions

$$\boldsymbol{v}_l(\boldsymbol{x}, t^n) = \boldsymbol{v}_l^n(\boldsymbol{x}) \text{ in } \Omega_l \text{ and } \boldsymbol{y}_m(t^n) = \boldsymbol{y}_m^n$$

the boundary conditions

$$\begin{aligned}
&\boldsymbol{v}_l = \boldsymbol{0} && \text{on } \Gamma_l \times (t^n, t^{n+1}) \\
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and set

$$\boldsymbol{v}_l^{n+\frac{1}{2}} = \boldsymbol{v}_l(\boldsymbol{x}, t^{n+1}),\ \ p_l^{n+1} = p_l(\boldsymbol{x}, t^{n+1}) \text{ and } \boldsymbol{y}_m^{n+\frac{1}{2}} = \boldsymbol{y}_m(t^{n+1}).$$

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Step 2

For each $l \in \mathcal{L}$ and $m \in \mathcal{M}$, given $\boldsymbol{v}_l^{n+\frac{1}{2}}$ and $\boldsymbol{y}_m^{n+\frac{1}{2}}$, solve

$$\begin{aligned} \rho \frac{\partial \boldsymbol{v}_l}{\partial t} &= \boldsymbol{0} && \text{in } \Omega_l \times (t^n, t^{n+1}) \\ \frac{d\boldsymbol{y}_m}{dt} &= \underline{\underline{\boldsymbol{A}}}_m(\boldsymbol{y}_m, t)\, \boldsymbol{y}_m + \boldsymbol{s}_m(\boldsymbol{y}_m, t) && \text{in } (t^n, t^{n+1}) \end{aligned}$$

with the initial conditions

$$\begin{aligned} \boldsymbol{v}_l(\boldsymbol{x}, t^n) &= \boldsymbol{v}_l^{n+\frac{1}{2}}(\boldsymbol{x}) && \text{in } \Omega_l \\ \boldsymbol{y}_m(t^n) &= \boldsymbol{y}_m^{n+\frac{1}{2}} \end{aligned}$$

and set

$$\boldsymbol{v}_l^{n+1} = \boldsymbol{v}_l(\boldsymbol{x}, t^{n+1}) \quad \text{and} \quad \boldsymbol{y}_m^{n+1} = \boldsymbol{y}_m(t^{n+1}).$$

Splitting scheme features

Main idea: sub-steps are designed so that the energy at the semi-discrete level mirrors the behavior of the energy of the full coupled system.

R. Glowinski *Handbook of Numerical Analysis: Numerical methods for Fluids (Part 3)* (2003).

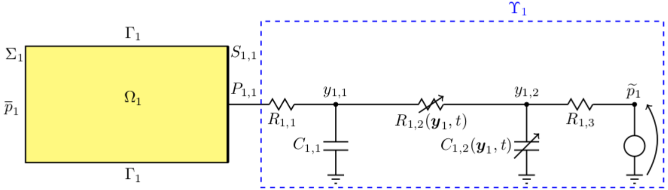
Salient features:

1. solve in a **separate step** potential **nonlinearities** in the 0D network.
2. **flexible** on the choice of the numerical method and discretization for each sub-step.
3. **unconditionally stable**, independently on the numerical method and discretization chosen in each sub-step.

   $\rightarrow$ see energy considerations.
4. **first-order accuracy** in time.

   $\rightarrow$ see numerical results.

Example



Coupled problem:

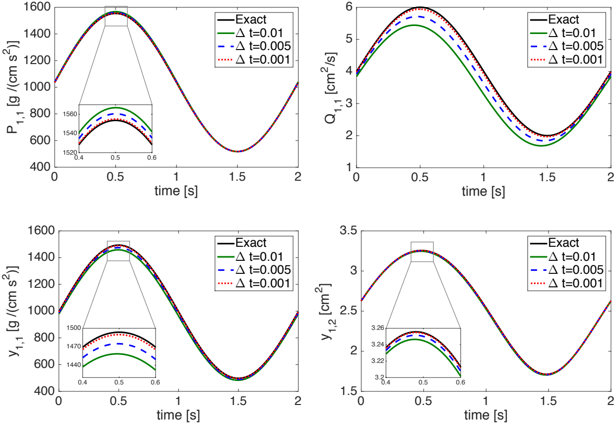
- 2D Stokes system in Ω_1, unknowns: velocity $\boldsymbol{v}_1$, pressure p_1;
- Lumped circuit Υ_1, unknowns: nodal pressure $y_{1,1}$, nodal volume $y_{1,2}$.

Nonlinearities:

$$R_{1,2}(\boldsymbol{y}_1, t) = \overline{R}_{1,2} + \frac{\alpha_0}{1 + \alpha_1 e^{-\alpha_2 y_{1,1}}} \text{ (autoregulation)},$$

$$C_{1,2}(\boldsymbol{y}_1, t) = \frac{\overline{C}_{1,2}}{1 + \gamma_1 y_{1,2}} \text{ (nonlinear compliance)}.$$

Example: numerical results



Comparison between the exact solution and the corresponding numerical approximation for **interface quantities** (up) and **0d unknowns** (bottom), for three time steps

$$\Delta t = 0.01,\ 0.005,\ 0.001.$$

Order of convergence in time

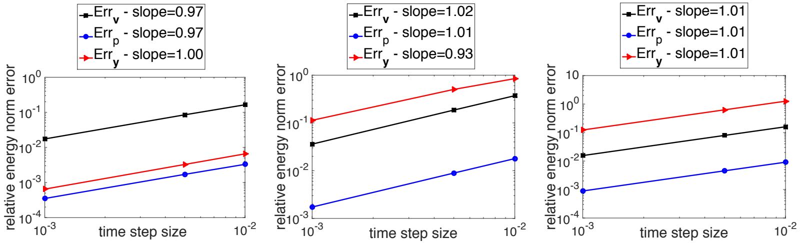
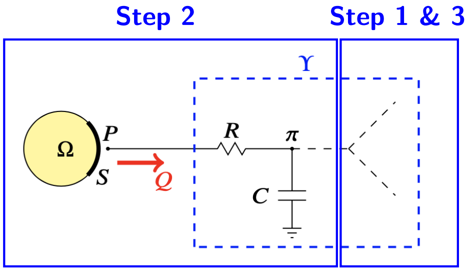


Figure: Plot of the energy norm errors, in logarithmic scale as a function of the global time step $\Delta t = 0.01,\ 0.005,\ 0.001$ for three examples considered in JCP 2018.

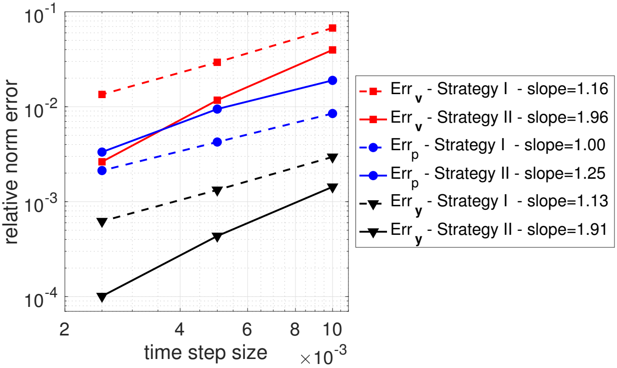
Second order operator splitting



Step 1 $\mathcal{A}_1$ = non-linear lumped ODEs system
Step 2 $\mathcal{A}_2$ = Stokes problem in Ω coupled to the resistive connections
Step 3 $\mathcal{A}_1$ = non-linear lumped ODEs system

Step 1, **Step 2** and **Step 3** communicate **ONLY** via the initial conditions
$\Rightarrow$ **no subiterations**

Second-order splitting algorithm: numerical results



Example 1, linear case, global time step $\Delta t = 0.01,\ 0.005,\ 0.0025$.

Strategy I: $\Delta t_1 = \Delta t_3 = \Delta t/5$ and $\Delta t_2 = \Delta t$;

Strategy II: $\Delta t_1 = \Delta t_2 = \Delta t_3 = \Delta t/5$.

L. Carichino, G. Guidoboni, MS. *Second-order time accuracy for coupled lumped and distributed fluid flow problems via operator splitting: a numerical investigation*, Numerical Mathematics and Advanced Applications ENUMATH 2019, LNCS 2021.

Part II: A multiscale model coupling hemodynamics, biomechanics and fluid dynamics in the eye.

Si vous êtes intéressés par les détails sur cette partie, n'hésitez pas à me contacter directement à

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Conclusions and future directions

- First steps in deriving a **multiscale model** of ocular fluid dynamics are achieved, numerous innovative mathematical and numerical questions into play:
  - design of a **new partitioned scheme** for the time discretization of a coupled PDE-ODE problem;
  - multiple connections allowed;
  - both **first-order** and **second-order** accurate in time versions are proposed.

- Models are carefully **validated** against medical data and **clinical** applications are proposed.

- A mathematical model to study the interplay between **intracranial pressure**, **blood pressure** and **intraocular pressure** is both challenging and very meaningful in terms of clinical applications.

Guidoboni, Sacco, S, Sala, Verticchio-Vercellin, Siesky, Harris. *Neurodegenerative disorders of the eye and of the brain: a perspective on their fluid-dynamical connections and the potential of mechanism-driven modeling.*, Frontiers in Neuroscience (2020).

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Thank you for you attention!