Model Order Reduction and Sensitivity Analysis for complex heat transfer simulations inside the human eyeball

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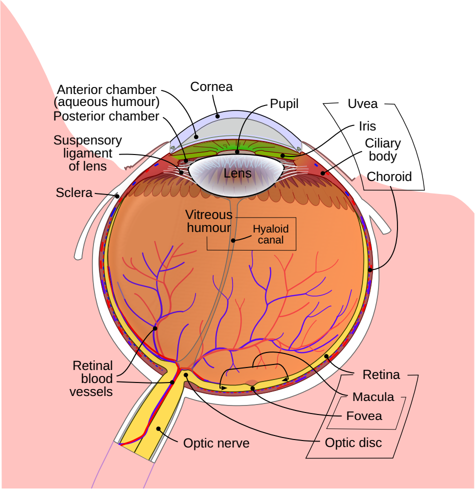
Introduction



Rhcastilhos, from Wikipedia

- Need to understand ocular **physiology** and **pathology**,
- **Heat transfer** has an impact on the distribution of drugs in the eye[a],
- Complexity to perform **measurements** on a human subject[b], mostly available on the surface[c].

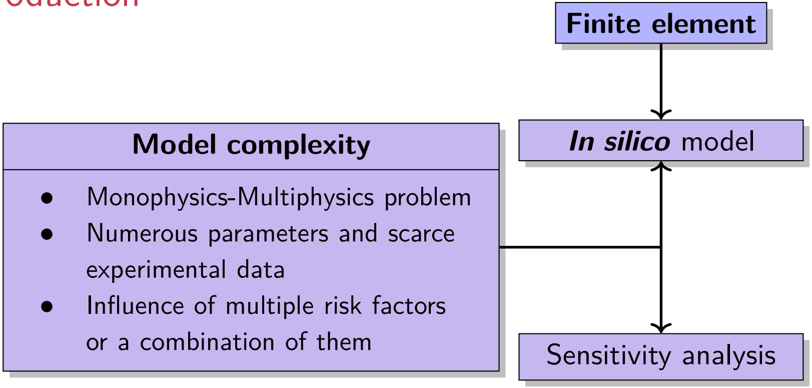
[a] Bhandari et al., J. Control Release (2020)
[b] Rosenbluth et al., Exp. Eye Res. (1977)
[c] Purslow et al., Eye Contact Lens (2005)

Introduction

Model complexity

- Monophysics-Multiphysics problem
- Numerous parameters and scarce experimental data
- Influence of multiple risk factors or a combination of them

Introduction



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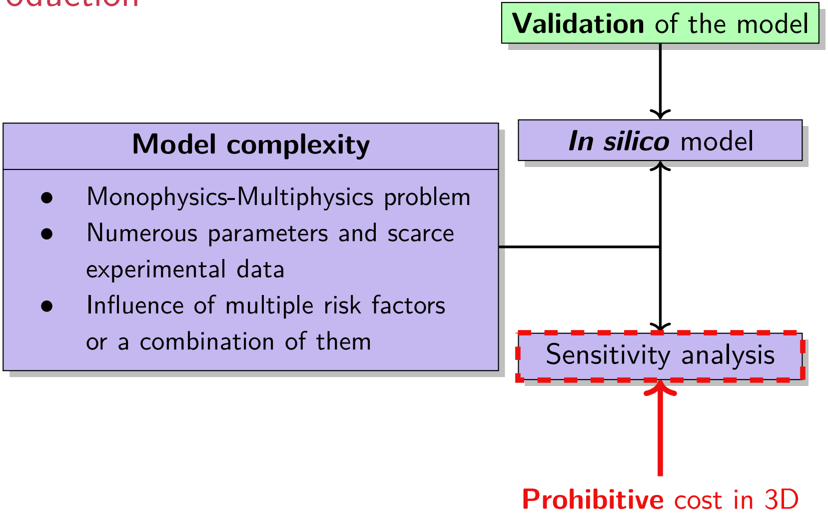
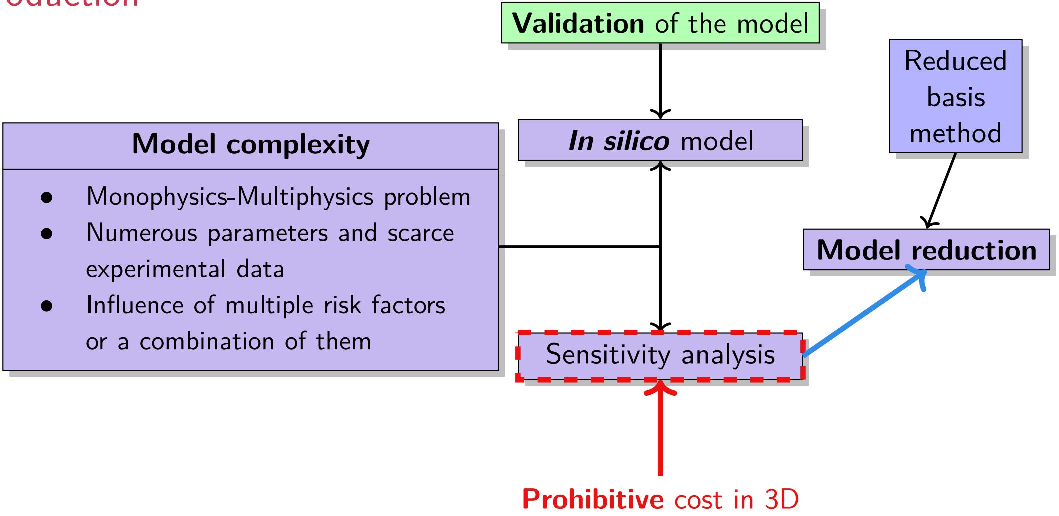
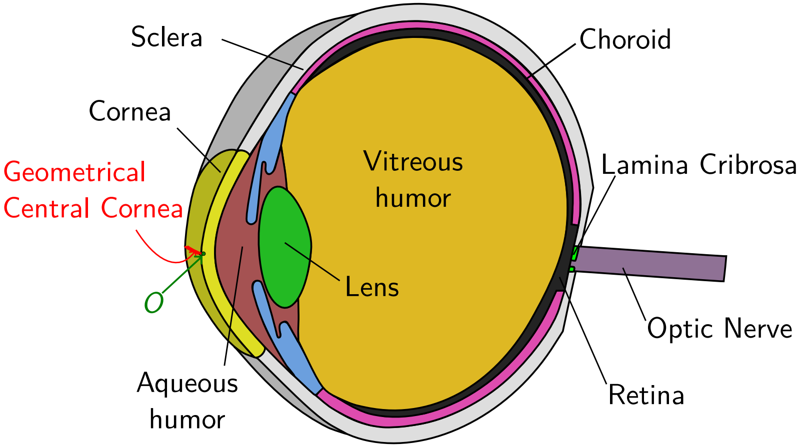


Introduction



Three dimensional biophysical modeling

Geometrical model[1]



[1] Lorenzo Sala et al. "The ocular mathematical virtual simulator: A validated multiscale model for hemodynamics and biomechanics in the human eye". In: *International Journal for Numerical Methods in Biomedical Engineering* (), e3791.

Biophysical model[2]

$$\rho_i C_{p,i} \frac{\partial T_i}{\partial t} - \nabla \cdot (k_i \nabla T_i) = 0 \qquad \text{over } \Omega_i$$

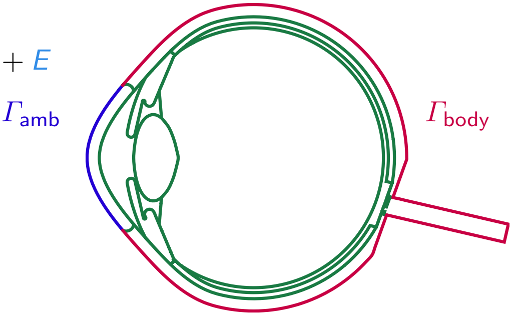
where :

- i is the region index (Cornea, Aqueous Humor, Vitreous Humor, Sclera, Iris, Lens, Choroid, Lamina, Retina, Optic Nerve),
- T_i [K] is the temperature in the volume i,
- t [s] is the time,
- k_i $[\mathrm{W\,m^{-1}}K^{-1}]$ is the thermal conductivity, ρ_i $[\mathrm{kg\,m^{-3}}]$ is the density and $C_{p,i}$ $[\mathrm{J\,kg^{-1}}K^{-1}]$ is the specific heat.

[2] J.A. Scott. "A finite element model of heat transport in the human eye". In: *Physics in Medicine and Biology* 33.2 (1988), pp. 227–242; Ng, E.Y.K. and Ooi, E.H. "FEM simulation of the eye structure with bioheat analysis". In: *Computer Methods and Programs in Biomedicine* 82.3 (2006), pp. 268–276.

Biophysical model $\mathcal{E}_{\text{lin}}$

- Interface conditions : $\begin{cases} T_i = T_j \\ k_i(\nabla T_i \cdot \boldsymbol{n}_i) = -k_j(\nabla T_j \cdot \boldsymbol{n}_j) \end{cases}$ over $\partial\Omega_i \cap \partial\Omega_j$
- Robin condition on Γ_N : $-k\dfrac{\partial T}{\partial \boldsymbol{n}} = h_{\text{bl}}(T - T_{\text{bl}})$
- Linearized Neumann condition[a] on Γ_N :
  $$-k_i\frac{\partial T_i}{\partial \boldsymbol{n}} = h_{\text{amb}}(T_i - T_{\text{amb}}) + h_r(T_i - T_{\text{amb}}) + E$$



$h_r = 6\,\text{Wm}^{-2}\text{K}^{-1}$

[a] J.A. Scott. "A finite element model of heat transport in the human eye". In: *Physics in Medicine and Biology* 33.2 (1988), pp. 227–242

Parameter dependent model

Symbol	Name	Dimension	Baseline value	Range
T_{amb}	Ambient temperature	[K]	298	[283.15, 303.15]
T_{bl}	Blood temperature	[K]	310	[308.3, 312]
h_{amb}	Ambient air convection coefficient	$[\mathrm{W\,m^{-2}\,K^{-1}}]$	10	[8, 100]
h_{bl}	Blood convection coefficient	$[\mathrm{W\,m^{-2}\,K^{-1}}]$	65	[50, 110]
E	Evaporation rate	$[\mathrm{W\,m^{-2}}]$	40	[20, 320]
k_{lens}	Lens conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	0.4	[0.21, 0.544]
k_{cornea}	Cornea conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	0.58	–
$k_{\mathrm{sclera}} = k_{\mathrm{iris}} = k_{\mathrm{lamina}} = k_{\mathrm{opticNerve}}$	Eye envelope components conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	1.0042	–
$k_{\mathrm{aqueousHumor}}$	Aqueous humor conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	0.28	–
$k_{\mathrm{vitreousHumor}}$	Vitreous humor conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	0.603	–
$k_{\mathrm{choroid}} = k_{\mathrm{retina}}$	Vascular beds conductivity	$[\mathrm{W\,m^{-1}\,K^{-1}}]$	0.52	–
ε	Emissivity of the cornea	[–]	0.975	–

Geometrical parameters may be involved, but we will not consider them in this work.

Present work: focus on parametric analysis

Parameter	Minimal value	Maximal value	Baseline value	Dimension
T_{amb}	283.15	303.15	298	[K]
T_{bl}	308.3	312	310	[K]
h_{amb}	8	100	10	$[\mathrm{W\,m^{-2}}K^{-1}]$
h_{bl}	50	110	65	$[\mathrm{W\,m^{-2}}K^{-1}]$
E	20	320	40	$[\mathrm{W\,m^{-2}}]$
k_{lens}	0.21	0.544	0.4	$[\mathrm{W\,m^{-1}}K^{-1}]$

Table 1: Range of values for the parameters

- We set $\mu = (T_{\mathrm{amb}}, T_{\mathrm{bl}}, h_{\mathrm{amb}}, h_{\mathrm{bl}}, E, k_{\mathrm{lens}}) \in D^{\mu} \subset \mathbb{R}^6$, a **parameter**.
- $\overline{\mu} \in D^{\mu}$ is the baseline value of the parameters.

Mathematical and computational framework

Finite Element results [3]

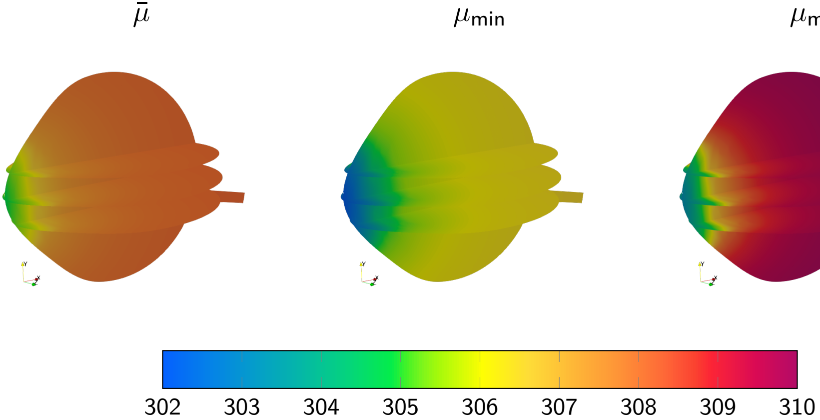
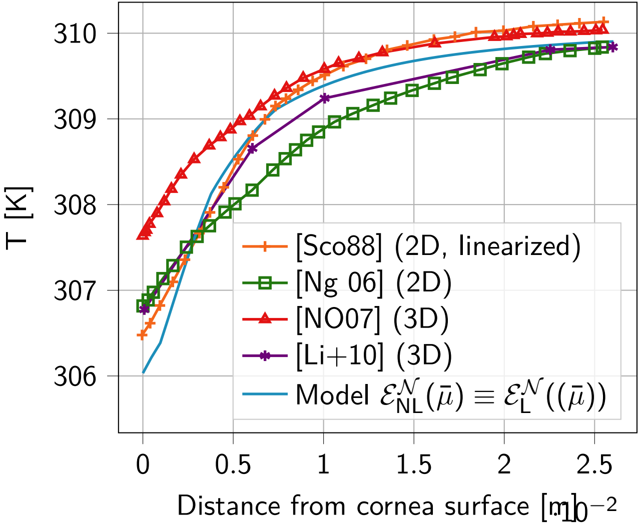
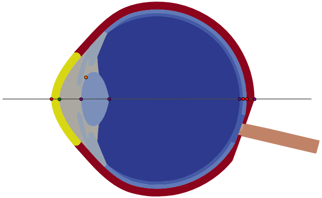


Figure 1: Distribution of the temperature [K] in the eyeball from the linear model $\mathcal{E}_{\text{L}}(\mu)$.

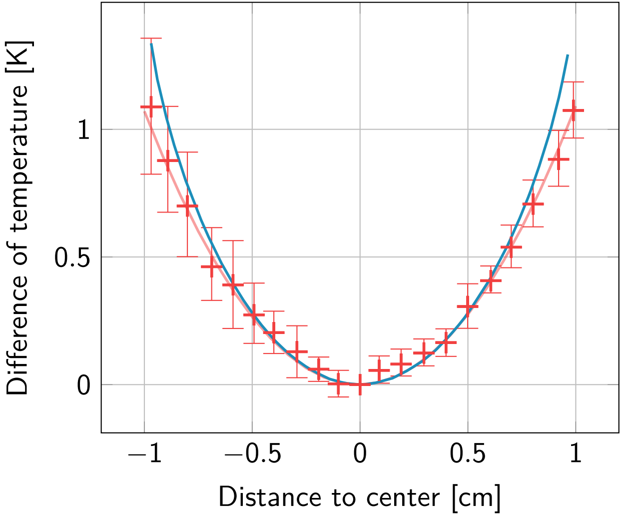
[3] Computed with the open-source library Feel++: github.com/feelpp/feelpp

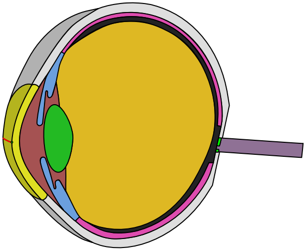
Validation and comparison with previous studies





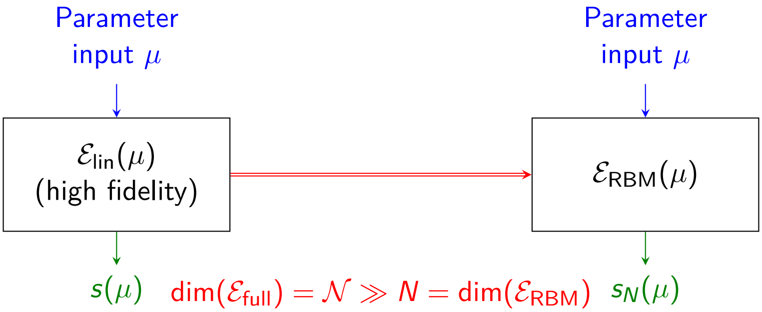
Validation: measured values over the GCC



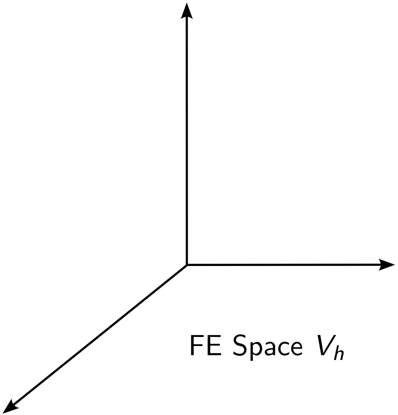


Model Order Reduction

- **Goal:** replicate input-output behavior of the high fidelity model $\mathcal{E}_{\text{lin}}$ with a reduced order model $\mathcal{E}_{\text{RBM}}$, by means of an **efficient** and **stable** procedure.



Reduced Basis Method[4]



- High fidelity model: $\mathcal{E}_{\text{lin}} : \mu \mapsto T^{\text{fem}}(\mu)$,

[4] C. Prud'homme et al. "Reliable Real-Time Solution of Parametrized Partial Differential Equations: Reduced-Basis Output Bound Methods ". In: *Journal of Fluids Engineering* 124.1 (Nov. 2001), pp. 70–80.

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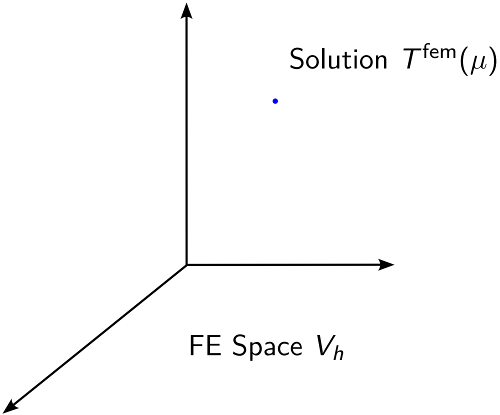

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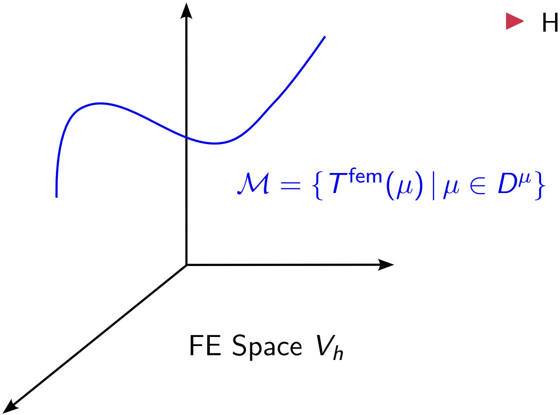

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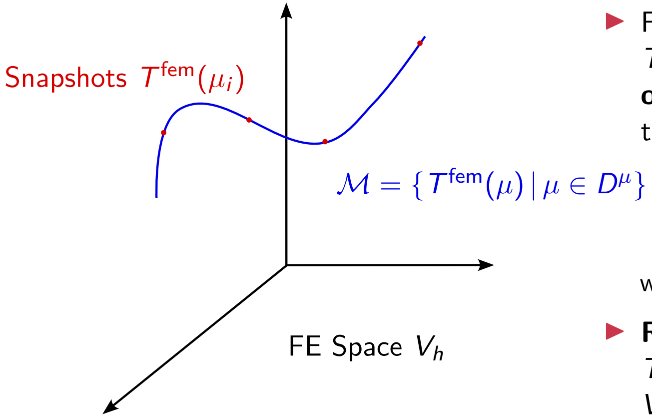

- From a set of **snapshots** $T^{\text{fem}}(\mu_1), \cdots, T^{\text{fem}}(\mu_N)$ computed **only once (*offline stage*)**, we define the **reduced functional space**:

$$V_N = \text{span}(\xi_1, \cdots, \xi_N)$$

where $\xi_i = T^{\text{fem}}(\mu_i)$, is orthonormalized.

- **Reduced solution (*online stage*):** $T^{\text{rbm},N}(\mu)$ solution of the PDE on V_N.

[4] C. Prud'homme et al. "Reliable Real-Time Solution of Parametrized Partial Differential Equations: Reduced-Basis Output Bound Methods ". In: *Journal of Fluids Engineering* 124.1 (Nov. 2001), pp. 70–80.

Reduced Basis Method

Problem considered

Given $\mu \in D^\mu$, evaluate the output of interest

$$s_N(\mu) = \ell(\boldsymbol{T}^{\mathrm{rbm},N}(\mu); \mu)$$

where $\boldsymbol{T}^{\mathrm{rbm},N}(\mu) \in V$ is the solution of

$$a(\boldsymbol{T}^{\mathrm{rbm},N}(\mu), v; \mu) = f(v; \mu) \quad \forall v \in V_N$$

- *Snapshots matrix:* $\mathbb{Z}_N = [\xi_1, \cdots, \xi_N] \in \mathbb{R}^{\mathcal{N} \times N}$,

Reduced Basis Method

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- *Snapshots matrix:* $\mathbb{Z}_N = [\xi_1, \cdots, \xi_N] \in \mathbb{R}^{\mathcal{N} \times N}$,
- Projection onto V_N: $\underline{\underline{\boldsymbol{A}}}_N(\mu) := \mathbb{Z}_N^T \underline{\underline{\boldsymbol{A}}}(\mu) \mathbb{Z}_N \in \mathbb{R}^{N \times N}$ and $\boldsymbol{f}_N(\mu) := \mathbb{Z}_N^T \boldsymbol{f}(\mu) \in \mathbb{R}^N$,

Reduced basis resolution

Input: $\mu \in D^\mu$,

- Construct $\underline{\underline{\boldsymbol{A}}}_N(\mu)$, $\boldsymbol{f}_N(\mu)$ and $\boldsymbol{L}_{N,k}(\mu)$,
- Solve $\underline{\underline{\boldsymbol{A}}}_N(\mu) \boldsymbol{T}^{\text{rbm},N}(\mu) = \boldsymbol{f}_N(\mu)$,
- Compute outputs $s_{N,k}(\mu) = \boldsymbol{L}_{N,k}(\mu)^T \boldsymbol{T}^{\text{rbm},N}(\mu)$.

Output: Numerical solution $\boldsymbol{T}^{\text{rbm},N}(\mu)$ and outputs $s_{N,k}(\mu)$.

Affine decomposition

- We want to write $\underline{\underline{\boldsymbol{A}}}(\mu) = \sum_{q=1}^{Q_a} \beta_A^q(\mu) \underline{\underline{\boldsymbol{A}}}^q$, and $\boldsymbol{F}(\mu) = \sum_{q=1}^{Q_f} \beta_F^q(\mu) \boldsymbol{F}^q$.
- Compute and store $\underline{\underline{\boldsymbol{A}}}_N^q = \underbrace{\mathbb{Z}_N^T \underline{\underline{\boldsymbol{A}}}^q \mathbb{Z}_N}_{\text{independent of } \mu}$ and $\boldsymbol{F}_N^q = \mathbb{Z}_N^T \boldsymbol{F}^q$.
- Hence $\underline{\underline{\boldsymbol{A}}}_N(\mu) = \sum_{q=1}^{Q_a} \beta_A^q(\mu) \underline{\underline{\boldsymbol{A}}}_N^q$ and $\boldsymbol{F}_N(\mu) = \sum_{q=1}^{Q_f} \beta_F^q(\mu) \boldsymbol{F}_N^q$.

Affine decomposition

- We want to write $\underline{\underline{A}}(\mu) = \sum_{q=1}^{Q_a} \beta_A^q(\mu)\underline{\underline{A}}^q$, and $F(\mu) = \sum_{q=1}^{Q_f} \beta_F^q(\mu) F^q$.
- Compute and store $\underline{\underline{A}}_N^q = \mathbb{Z}_N^T \underline{\underline{A}}^q \mathbb{Z}_N$ and $F_N^q = \mathbb{Z}_N^T F^q$.
- $a(T, v; \mu) = \sum_{q=1}^{4} \beta_A^q(\mu) a^q(T, v)$ with

$$
\begin{aligned}
\beta_A^1(\mu) &= k_{\text{lens}} & a^1(T,v) &= \int_{\Omega_{\text{lens}}} \nabla T \cdot \nabla v \, \mathrm{d}x \\
\beta_A^2(\mu) &= h_{\text{amb}} & a^2(T,v) &= \int_{\Gamma_{\text{amb}}} T v \, \mathrm{d}\sigma \\
\beta_A^3(\mu) &= h_{\text{bl}} & a^3(T,v) &= \int_{\Gamma_{\text{body}}} T v \, \mathrm{d}\sigma \\
\beta_A^4(\mu) &= 1 & a^4(T,v) &= \int_{\Gamma_{\text{amb}}} h_r T v \, \mathrm{d}\sigma + \sum_{i \neq \text{lens}} k_i \int_{\Omega_i} \nabla T \cdot \nabla v \, \mathrm{d}x
\end{aligned}
$$

Affine decomposition

- We want to write $\underline{\underline{\boldsymbol{A}}}(\mu) = \sum_{q=1}^{Q_a} \beta_A^q(\mu)\underline{\underline{\boldsymbol{A}}}^q$, and $\boldsymbol{F}(\mu) = \sum_{q=1}^{Q_f} \beta_F^q(\mu)\boldsymbol{F}^q$.
- Compute and store $\underline{\underline{\boldsymbol{A}}}_N^q = \mathbb{Z}_N^T \underline{\underline{\boldsymbol{A}}}^q \mathbb{Z}_N$ and $\boldsymbol{F}_N^q = \mathbb{Z}_N^T \boldsymbol{F}^q$.
- $f(v;\mu) = \sum_{p=1}^{2} \beta_F^p(\mu) f^p(v)$

$$\beta_F^1(\mu) = h_{\text{amb}}\, T_{\text{amb}} + h_r\, T_{\text{amb}} - E \qquad f^1(v) = \int_{\Gamma_{\text{amb}}} v \,\mathrm{d}\sigma$$

$$\beta_F^2(\mu) = h_{\text{bl}}\, T_{\text{bl}} \qquad f^2(v) = \int_{\Gamma_{\text{body}}} v \,\mathrm{d}\sigma$$

Offline / Online procedure

Offline:

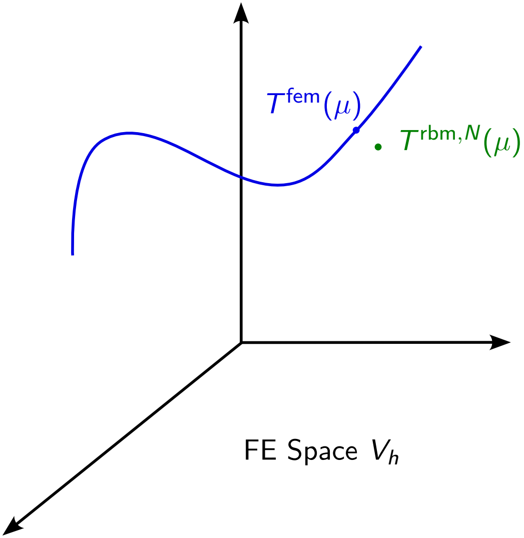
- Solve N high-fidelity systems depending on $\mathcal{N}$ to form $\mathbb{Z}_N$,
- Form and store $\boldsymbol{F}_N^p(\xi_i)$
- Form and store $\underline{\underline{\boldsymbol{A}}}_N^q(\xi_i)$

Online: independant of $\mathcal{N}$

Given a new parameter $\mu \in D^\mu$,

- Form $\underline{\underline{\boldsymbol{A}}}_N(\mu) : O(Q_a N^2)$,
- Form $\boldsymbol{F}_N(\mu) : O(Q_f N)$,
- Solve $\underline{\underline{\boldsymbol{A}}}_N(\mu)\boldsymbol{T}^{\mathrm{rbm},N}(\mu) = \boldsymbol{F}_N(\mu) : O(N^3)$,
- Compute $s_N(\mu) = \boldsymbol{L}_N(\mu)^T \boldsymbol{T}^{\mathrm{rbm},N}(\mu) : O(N)$.

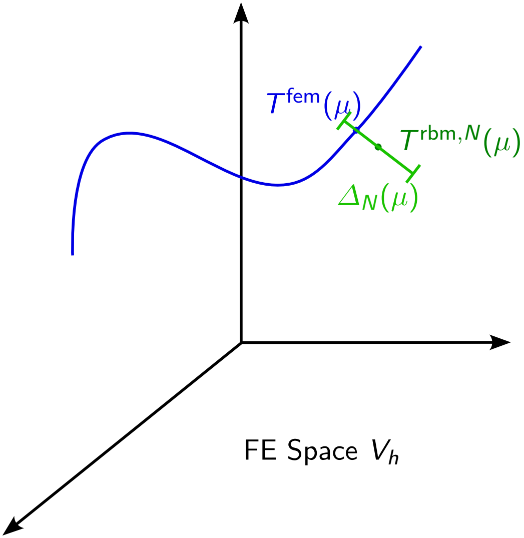
Error bound $\Delta_N(\mu)$



For $\mu \in D^\mu$, we define the error:

$$e(\mu) = T^{\text{fem}}(\mu) - T^{\text{rbm},N}(\mu)$$

Error bound $\Delta_N(\mu)$



For $\mu \in D^\mu$, we define the error:

$$e(\mu) = T^{\text{fem}}(\mu) - T^{\text{rbm},N}(\mu)$$

We require this error bound to be:

- **rigorous**: $\|e(\mu)\|_X \leqslant \Delta_N(\mu)$,
- **sharp**: $\dfrac{\Delta_N(\mu)}{\|e(\mu)\|_X} \leqslant \eta_{\max}(\mu)$,
- **efficient**: the computation of $\Delta_N(\mu)$ does not depend on $\mathcal{N}$.

Greedy algorithm

Algorithm 1: Greedy algorithm to construct the reduced basis.

Input: $\mu_0 \in D^\mu$, $\Xi_{\text{train}} \subset D^\mu$ and $\varepsilon_{\text{tol}} > 0$

$S \leftarrow [\mu_0]$;

while $\Delta_N^{\max} > \varepsilon_{tol}$ **do**

$\quad \mu^\star \leftarrow \arg\max_{\mu \in \Xi_{\text{train}}} \Delta_N(\mu)$ (and $\Delta_N^{\max} \leftarrow \max_{\mu \in \Xi_{\text{train}}} \Delta_N(\mu)$);

$\quad V_{N+1} \leftarrow \left\{ \xi = \boldsymbol{T}^{\text{fem}}(\mu^\star) \right\} \cup V_N$;

$\quad$ Append $\mu^\star$ to S;

$\quad N \leftarrow N + 1$;

end

Output: Sample S, reduced basis V_N

Performance study

	Finite element resolution $T^{\text{fem}}(\mu)$			Reduced model $T^{\text{rbm},N}(\mu), \Delta_N(\mu)$
	$\mathbb{P}_1$	$\mathbb{P}_2$ (np=1)	$\mathbb{P}_2$ (np=12)	
Problem size	$\mathcal{N} = 207\,845$	$\mathcal{N} = 1\,580\,932$		$N = 10$
t_{exec}	5.534 s	62.432 s	10.76 s	2.88×10^{-4} s
speed-up	11.69	1	5.80	$\mathbf{2.17 \times 10^5}$

Table 2: Times of execution, using mesh M3 for high fidelity simulations.

- The reduced model time corresponds to computation of both output and error bound.
- Online resolution **independant** of the high fidelity dimension $\mathcal{N}$.

Results over a sampling $\Xi_{\text{test}} \subset D^\mu$ of 100 parameters

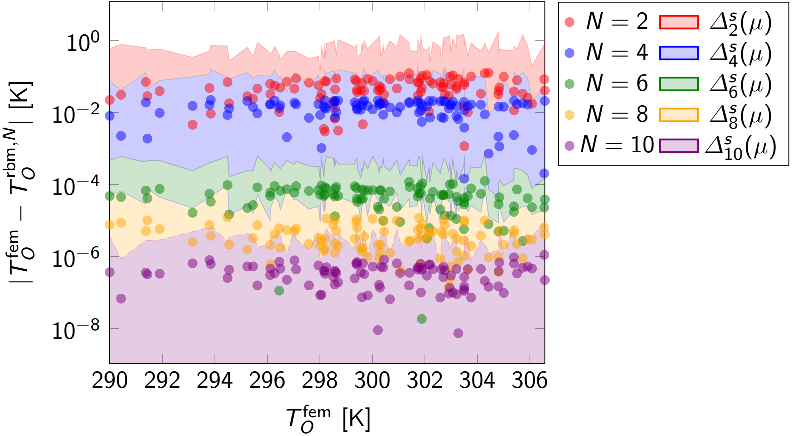


Figure 2: Error on RBM for various reduced basis sizes with error bound $\Delta_N(\mu)$.

Results over a sampling $\Xi_{\text{test}} \subset D^\mu$ of 100 parameters

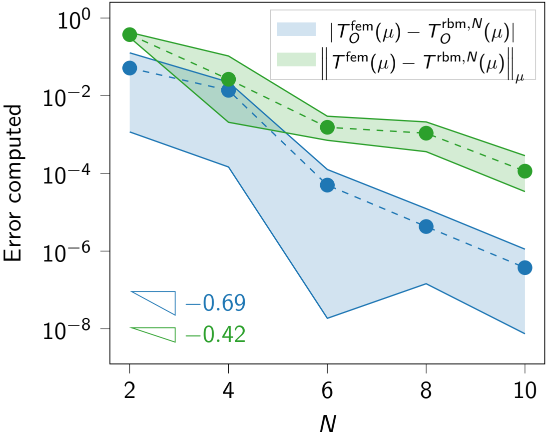


Figure 2: Convergence of the errors on the field and the output on point O.

Sensitivity analysis

Sobol indices

- $\mu = (\mu_1, \dots, \mu_n) \in D^\mu$,
- $\mu_i \sim X_i$ where $(X_i)_i$ is a family of **independent** random variables,
- Output $s_N(\mu) \sim Y = f(X_1, \dots, X_n)$,
- Distributions X_i selected from data available in the literature.

Sobol indices

- **First-order indices:** $S_j = \dfrac{\mathrm{Var}\left(\mathbb{E}\left[Y|X_j\right]\right)}{\mathrm{Var}(Y)}$ effect of one parameter on the output
- **Total-order indices:** $S_j^{\mathrm{tot}} = \dfrac{\mathrm{Var}\left(\mathbb{E}\left[Y|X_{(-j)}\right]\right)}{\mathrm{Var}(Y)}$ interaction of all parameters but one on the output

where $X_{(-j)} = (X_1, \dots, X_{j-1}, X_{j+1}, \dots, X_n)$.

Stochastic sensitivity analysis (SSA)

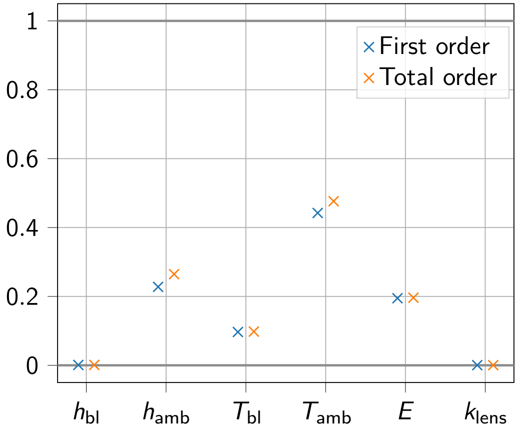
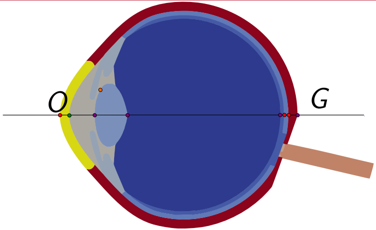


Figure 3: Sobol indices: temperature at point O



Temperature at the level of the **cornea**:

- **significantly** influenced by T_{amb}, h_{amb} (external factors) and E, T_{bl} (subject specific parameters) $\longrightarrow$ need for measurements/better model for these contributions
- **minimally** influenced by k_{lens}, h_{bl} $\longrightarrow$ can be fixed at baseline value
- **high order** interactions on T_{amb}, h_{amb}

Stochastic sensitivity analysis (SSA)

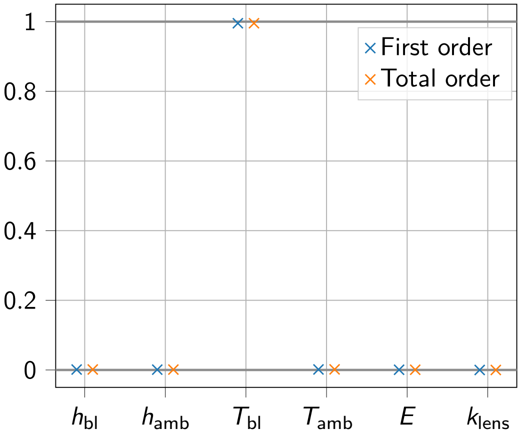
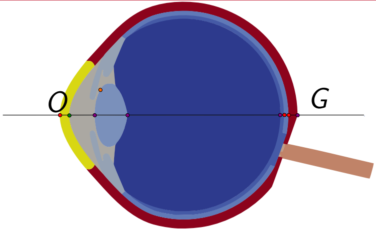


Figure 3: Sobol indices: temperature at point G



Temperature at the back of the eye:

- only influenced by the blood temperature

Conclusion and outlook

- **Heat transport model in the human eye:** FEM simulations, validation against experimental data, and model order reduction,
- **Reduced model** with a **certified error bound**,
- **Sensitivity analysis:** computation of Sobol indices thanks to MOR, highlight of the impact of some parameters on the output.

Thomas Saigre et al. "Model order reduction and sensitivity analysis for complex heat transfer simulations inside the human eyeball". submitted. Dec. 2023

Perspectives:

- **Model:** couple thermal effect with aqueous humor dynamics in the anterior chamber,
- **Non intrusive** methods with zoom in zone of interest for non linear of non affine problems (EIM, NIRB),
- **Application:** robust framework to simulate drug delivery in the eye.

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- **Reduced model** with a **certified error bound**,
- **Sensitivity analysis:** computation of Sobol indices thanks to MOR, highlight of the impact of some parameters on the output.

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Perspectives:

- **Model:** couple thermal effect with aqueous humor dynamics in the anterior chamber,
- **Non intrusive** methods with zoom in zone of interest for non linear of non affine problems (EIM, NIRB),
- **Application:** robust framework to simulate drug delivery in the eye.

Thank you for your attention!

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Error bound

Variational formulation of the problem:

Given $\mu \in D^\mu$, find $u(\mu) \in X^{\mathcal{N}}$ such that $a(u(\mu), v; \mu) = \ell(v; \mu) \quad \forall v \in X^{\mathcal{N}}$

The error $e(\mu) = \boldsymbol{T}^{\text{fem}}(\mu) - \boldsymbol{T}^{\text{rbm},N}(\mu)$ satisfies

$$a(e(\mu), v; \mu) = \ell(v; \mu) - a(\boldsymbol{T}^{\text{rbm},N}(\mu), v; \mu) \quad \forall v \in X^{\mathcal{N}}$$

We set the *residual* $r(\mu)$ as $r(v, \mu) := \ell(v; \mu) - a(\boldsymbol{T}^{\text{rbm},N}(\mu), v; \mu) \quad \forall v \in X^{\mathcal{N}}$

$$\boxed{\Delta_N(\mu) := \frac{\|r(\mu)\|_{X'}}{\alpha_{\text{lb}}(\mu)}}$$

whre $\alpha_{\text{lb}}(\mu)$ is a lower bound of the coercivity constant of $a(\cdot, \cdot; \mu)$.

Distributions