Tutorials and Examples of UQ/SA in Cardiovascular Modeling

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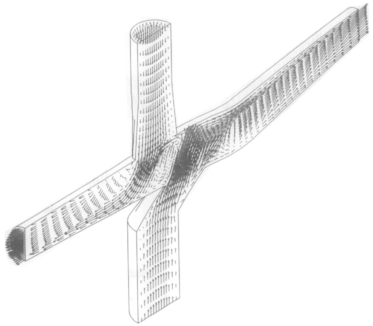
Presentation outline

- ✓ **I** - OLS and RVM Regression of interface 3D-0D pressure/flow and its use in reduced order modeling.
- ✓ **II** - Data assimilation in LPN circulation.
- ✓ **III** - Fancy spectral expansion for uncertainty propagation.

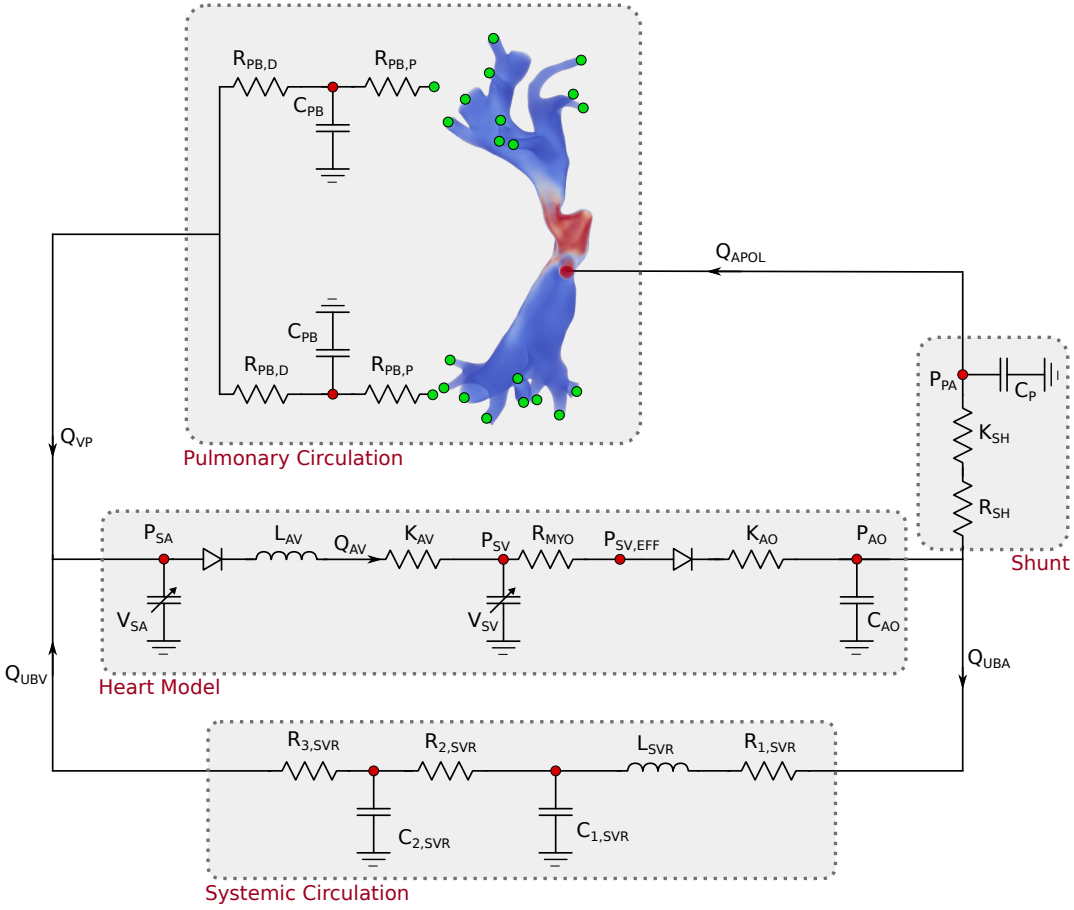
Geometric multi-scale modeling

- ✓ **CFD models** the total cavo-pulmonary connections appeared in the late 90's. Peripheral circulation is marginally accounted.
- ✓ **Modern** approaches:
  - Advanced FE for CFD, **FSI** problems.
  - Implicit **coupling** with circulation network.
  - **Stabilization** at coupled surfaces to prevent backflow divergence.



Dubini et al., 1996

Yang et al., 2012



Multiscale model layout for Single-Ventricle physiology

II - Reduced Models

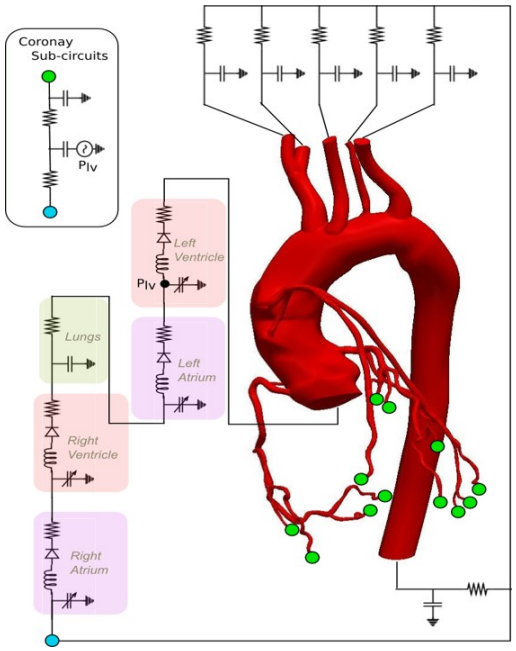
Condensation of multi-scale models

- ✓ **Model tuning**, i.e., selection of boundary conditions to match the physiology of a specific patient is of **paramount importance** in CV Simulation and is affected by multiple error/uncertainty sources.
- ✓ This step is typically performed using **optimization or estimation**, requiring **multiple** model evaluations.
- ✓ These operations become **computationally intractable** for multi-scale models, where a single model solution for a few heart cycles may require **several hours**.
- ✓ We aim to develop an **augmented lumped parameter model** providing similar results to the multi-scale model but requiring a **fraction of a second** to be solved.
- ✓ **Condensation approaches** used in our group:
  - Optimized **Resistive** surrogate.
  - Surrogate through **sparse** pressure-flow rate regression.

Resistive surrogate for coronary artery disease

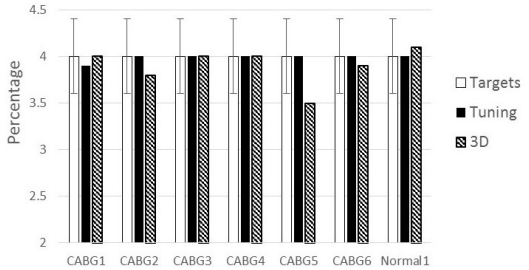
- ✓ Surrogate resistances are **proportional** to the outlet resistances to **preserve the flow split**.
- ✓ The **systemic** surrogate resistances and the **coronary** surrogate resistances are **iteratively refined** until multiscale and surrogate outputs differ less than 10%.

Multiscale layout for coronary simulations

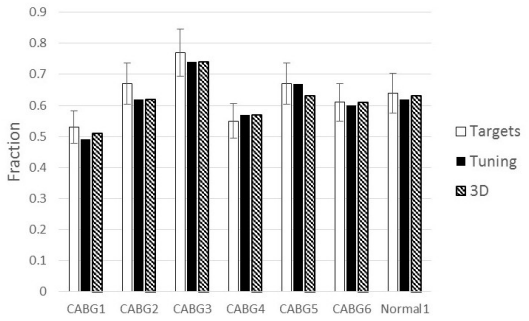


J. S. Tran et al., Computer & Fluids, 2016.

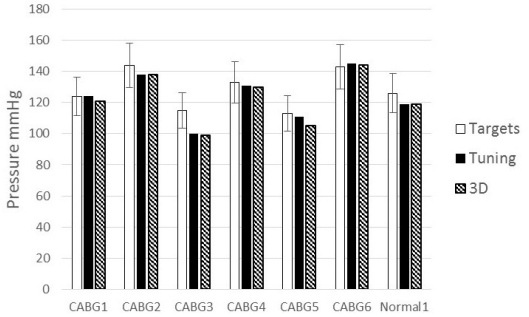
Aorta/coronary flow split



Ejection fraction



Maximum aortic pressure



Regression of 0D-3D interface pressure/flow rate

- ✓ Consider a region $\Omega \subset \mathbb{R}^3$ with boundary $\partial\Omega$ partitioned into **walls** $\boldsymbol{\Gamma}^w = \{\Gamma_j^w,\, j = 1, \ldots, n_w\}$ and **interfaces** $\boldsymbol{\Gamma} = \{\Gamma_j,\, j = 1, \ldots, n\}$.

- ✓ The average **pressure** p_i and **flow rate** q_i at the generic Γ_i are

$$p_i = \frac{1}{|\Gamma_i|} \int_{\Gamma_i} p \; d\,\Gamma_i, \quad q_i = \int_{\Gamma_i} (\mathbf{v} \cdot \mathbf{n}_i \,) \; d\,\Gamma_i$$

- ✓ We assume that the discrete 3D model can be **replaced** by

$$q_i(t) = f(\mathbf{p}, t, \boldsymbol{\gamma}) = \sum_{j=1}^{n_b} \alpha_{j,i}(t, \boldsymbol{\gamma})\, \phi_j(\mathbf{p}, t, \boldsymbol{\gamma}),\; i = 1, \ldots, n.$$

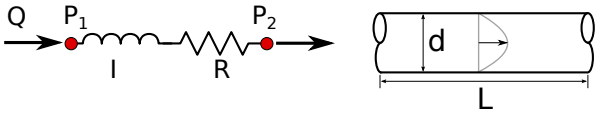
  where t represents **time**, $\boldsymbol{\alpha}_i = (\alpha_{1,i}, \ldots, \alpha_{n_b,i}) \in \mathbb{R}^{n_b}$ is a vector of **expansion coefficients**, ϕ_j is a set of **generic basis functions**, and $\boldsymbol{\gamma}$, a vector of **additional variables**.

- ✓ If we assume **rigid walls** and **negligible inertance** we can neglect dependence from t and $\boldsymbol{\gamma}$, this leads to

$$q_i = \sum_{j=1}^{n_b} \alpha_{j,i}\, \phi_j(\mathbf{p}),\; i = 1, \ldots, n.$$

Contribution of inertance

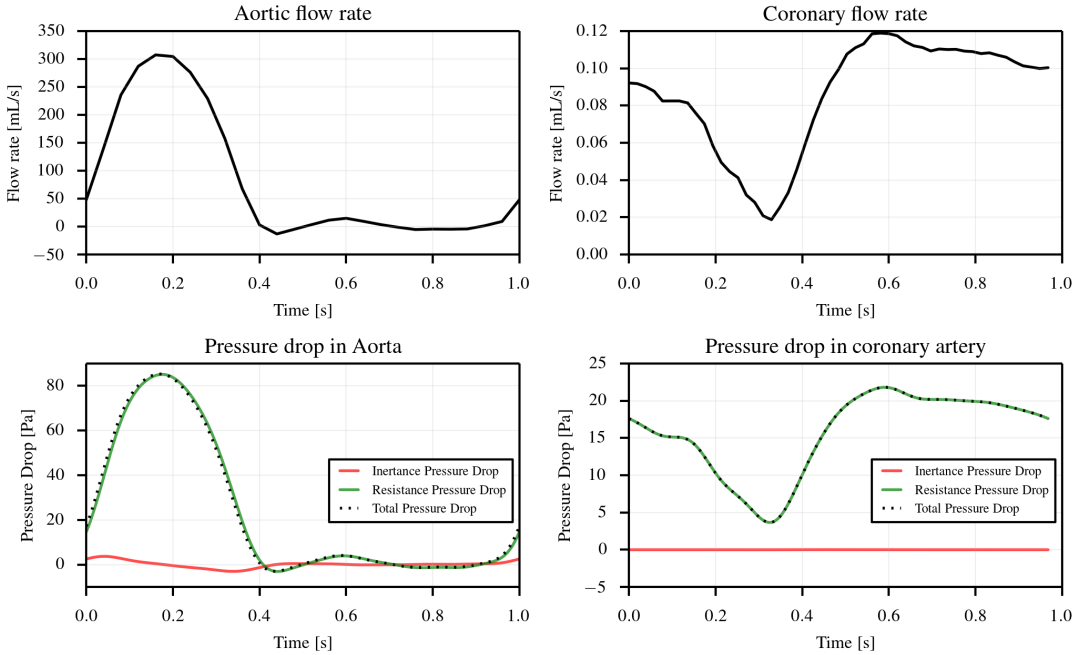
- ✓ Consider the relationship between pressure drop and flow rate in an **idealized rigid cylindrical vessel**.
- ✓ The contribution of inertance and resistance to the overall pressure drop **is separated** for an **aortic** and a **coronary** vessel.



$$(p_2 - p_1) = \Delta p = I\,\dot{q} + R\,q$$

$$= \left(\frac{\rho\,L}{\pi\,r^2}\right)\dot{q} + \left(\frac{8\,\nu\,L}{\pi\,r^4}\right)q$$

System	ρ [kg/m^3]	L [m]	ν [Pa·s]
Healthy adult aorta	1.060	0.664	4.0×10^{-3}
Healthy adult coronary	1.060	0.15	4.0×10^{-3}
System	**d [m]**	**I [Pa·s/m^3]**	**R [Pa·s^2/m^3]**
Healthy adult aorta	0.025	$1.43\times10^{+3}$	$2.77\times10^{+5}$
Healthy adult coronary	0.0034	$1.75\times10^{+4}$	$1.83\times10^{+8}$



OLS Estimator

- ✓ $\boldsymbol{\alpha}_i$ is determined by **minimization of the squared error**:

$$e_i = \sum_{j=1}^{m} [\mathbf{q}_i - \boldsymbol{\Phi}\,\boldsymbol{\alpha}_i]^2_{s_j} = (\mathbf{q}_i - \boldsymbol{\Phi}\,\boldsymbol{\alpha}_i)^T\,(\mathbf{q}_i - \boldsymbol{\Phi}\,\boldsymbol{\alpha}_i).$$

- ✓ The squared error e_i is proportional to the negative log-likelihood of the data for a **linear statistical model of the form**:

$$\mathbf{q}_i = \boldsymbol{\Phi}\,\boldsymbol{\alpha}_i + \boldsymbol{\epsilon}_i,$$

with **error** $\boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \sigma^2\, I)$, and **likelihood** $\ell_{\boldsymbol{\alpha}_i}(\mathbf{q}_i) = \mathcal{N}(\boldsymbol{\Phi}\,\boldsymbol{\alpha}_i, \sigma^2\, I)$.

- ✓ $\boldsymbol{\alpha}_{i,OLS}$ is **unbiased** and achieves **asymptotic efficiency** with covariance that attains the Cramér-Rao bound.

- ✓ Thus, the **inverse** of the Fisher information matrix at $\boldsymbol{\alpha}_i = \boldsymbol{\alpha}_{i,OLS}$ quantify the **second order statistics** of $\boldsymbol{\alpha}_{i,OLS}$.

$$\mathbf{C}_{\boldsymbol{\alpha}}^{-1} = \mathcal{I} = -\mathbb{E}\left[\frac{\partial^2\, log\, \ell_{\boldsymbol{\alpha}}(\mathbf{q})}{\partial \boldsymbol{\alpha}\, \partial \boldsymbol{\alpha}^T}\right] = \frac{1}{\sigma^2}\,\boldsymbol{\Phi}^T\,\boldsymbol{\Phi}.$$

RVM Estimator

- ✓ Relevance vector machines combine Bayesian estimation with **sparsity promoting hyper-priors**.

- ✓ Such hyperpriors are specified **over each coefficient** $\boldsymbol{\alpha}_i$ as independent, zero-mean, Gaussians with precisions $\boldsymbol{\beta} = (\beta_1, \beta_2, \ldots, \beta_{n_b})$:

$$P(\boldsymbol{\alpha}_i|\boldsymbol{\beta}) = \frac{1}{(2\,\pi)^{n_b/2}\,\prod_{k=1}^{n_b}\beta_k}\,\exp\left[-\frac{1}{2}\,\boldsymbol{\alpha}_i^T\mathbf{Z}\,\boldsymbol{\alpha}_i\right]$$

  with $\mathbf{Z}$ being a diagonal matrix with $Z_{j,j} = \beta_j$.

- ✓ The posterior $P(\boldsymbol{\alpha}_i|\mathbf{q}_i, \boldsymbol{\beta}, \sigma^2) \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ **is also Gaussian** with

$$\boldsymbol{\mu} = \sigma^{-2}\,\boldsymbol{\Sigma}\boldsymbol{\Phi}\mathbf{q}_i, \quad \boldsymbol{\Sigma} = (\boldsymbol{Z} + \sigma^{-2}\boldsymbol{\Phi}^T\boldsymbol{\Phi})^{-1}$$

- ✓ Values of β_j are determined by **iterative maximization of the marginal log-likelihood**

$$\mathcal{M}(\boldsymbol{\beta}) = log\,P(\mathbf{q}_i|\boldsymbol{\beta}, \sigma^2) = -\frac{1}{2}\left[N\,log(2\,\pi) + log|\mathbf{C}| + \mathbf{q}_i^T\mathbf{C}^{-1}\mathbf{q}_i\right],$$

  with $\mathbf{C} = \sigma^2\,\mathbf{I} + \boldsymbol{\Phi}\,\mathbf{Z}^{-1}\,\boldsymbol{\Phi}^T$.

Why RVM?

- ✓ So **why** we may want to use RVM instead of other algorithms for sparse regression?

- ✓ Let's compare, for example, **RVM** and **Orthogonal Matching Pursuit** (OMP):

  - In OMP a basis function can **only be added** to the model based on its correlation with the residual vector at the current iteration.

  - In RVM, basis functions can be **added** to or **removed** from the model or the associated representation coefficient **re-estimated**.

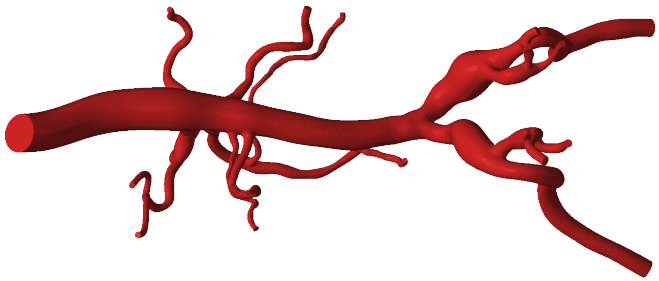
  - Simultaneous estimation of regression coefficients and noise intensity **cannot be performed with OMP** but **cross validation**-based approaches can be used at a higher computational cost.

  - RVM naturally deal with this problem by alternating estimations of the coefficient vector and its covariance with **re-estimation of the noise** intensity.

  - One of the main advantages of RVM over OMP is the ability of estimating the **full covariance matrix** of α_i, allowing to associate measures of confidence to the computed expansions.

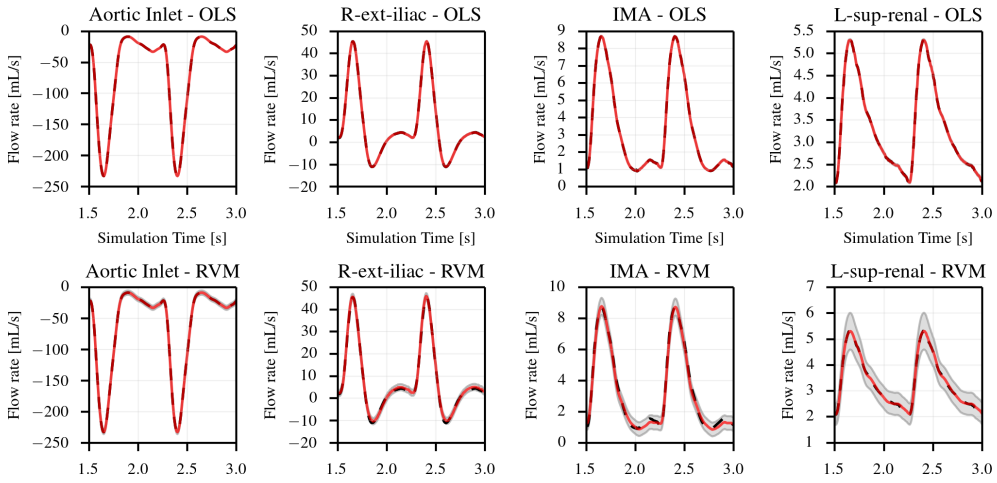
Regression results for aortic and coronary model

Abdominal Aorta Model - Open loop BC

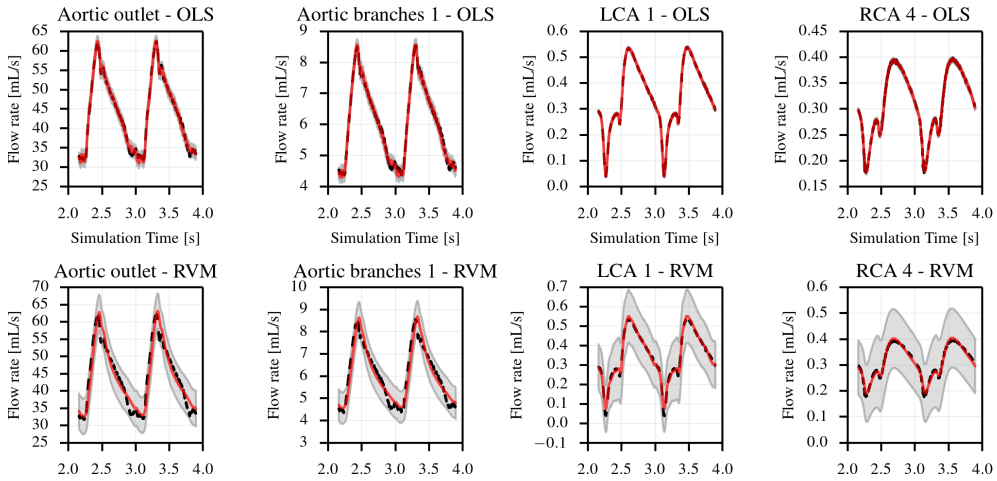


Coronary Model - Closed loop BC

Abdominal Aortic Model

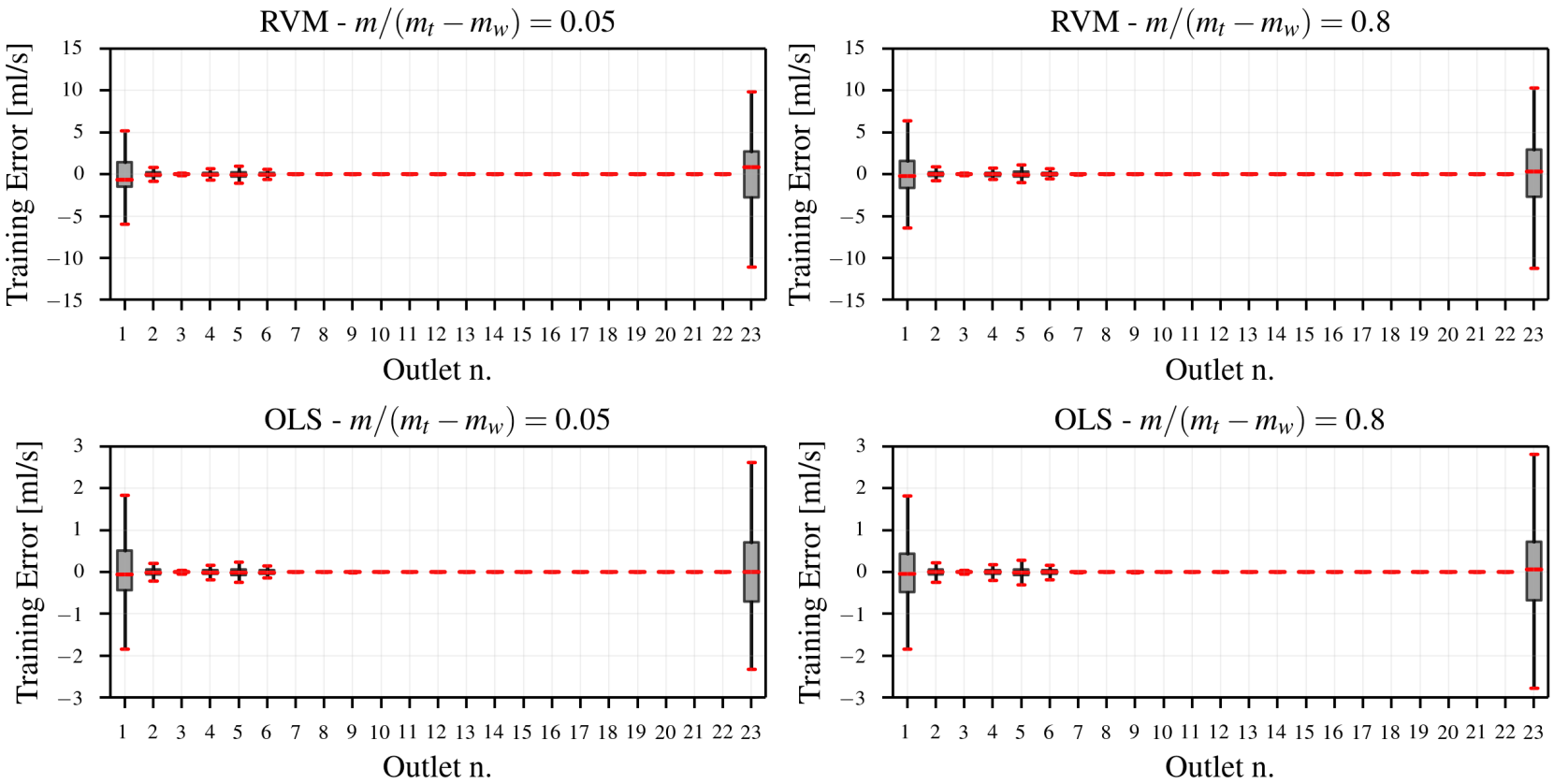


Coronary Circulation Model



Statistical model verification

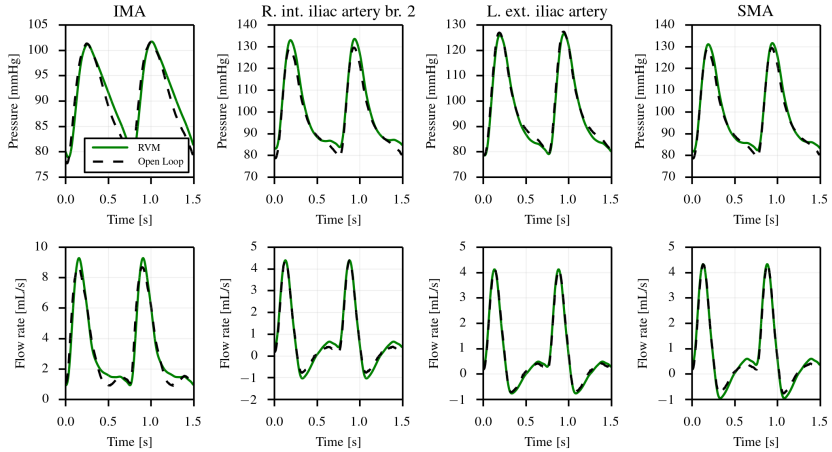
✓ We need to verify the error to be **zero-average Gaussians**, independent on all interfaces.



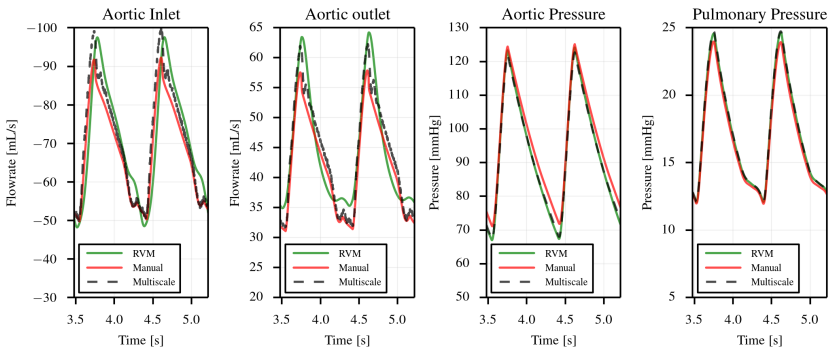
Inclusion in closed loop circulation models

- ✓ We **integrate** the regressor in the respective 0D network models.
- ✓ OLS regressors are **not stable and lead to divergence of RK4 iterations**.
- ✓ RMV regressors **are stable** and lead to LPN results that closely approximate the multiscale results.
- ✓ RMV results are compared to **optimally tuned** equivalent resistors surrogates.

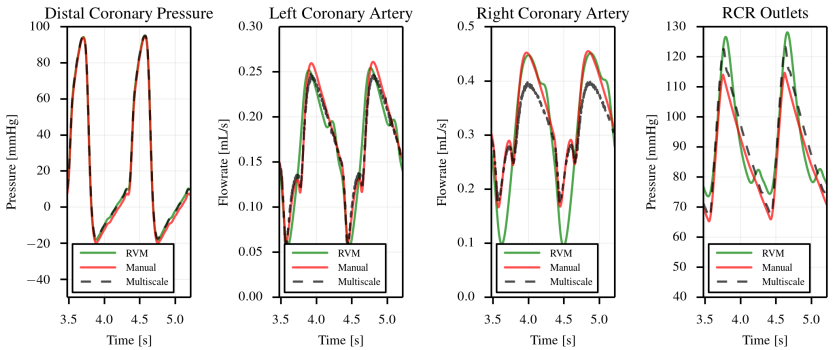
Aortic Model



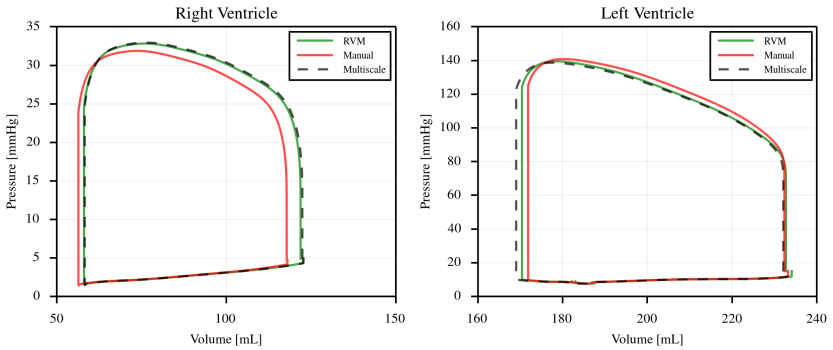
Coronary Model - Major Outlets



Coronary Model - Minor Outlets



Coronary Model - Ventricles

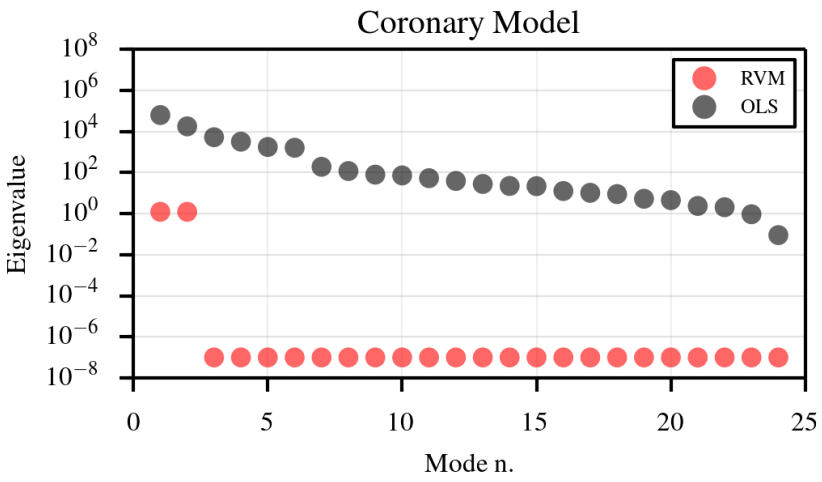


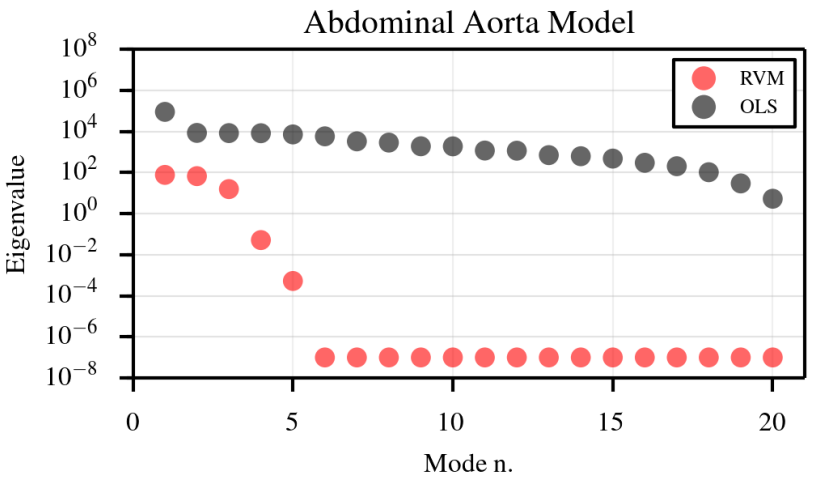
Amplification of pressure perturbations

- ✓ Stability considers how outlet flow rates are **amplified** by the surrogate as a result of pressure perturbations.
- ✓ Consider a **Gaussian pressure noise of uniform variance** σ^2 and flow rates at the interface written as a linear combination of outlet pressures:

$$q_i = \sum_{j=2}^{n+1} \alpha_{j,i}\, p_j = \hat{\boldsymbol{\alpha}}_i\, \boldsymbol{p}, \text{ and } \qquad \boldsymbol{q} = \boldsymbol{A}\,\boldsymbol{p}$$

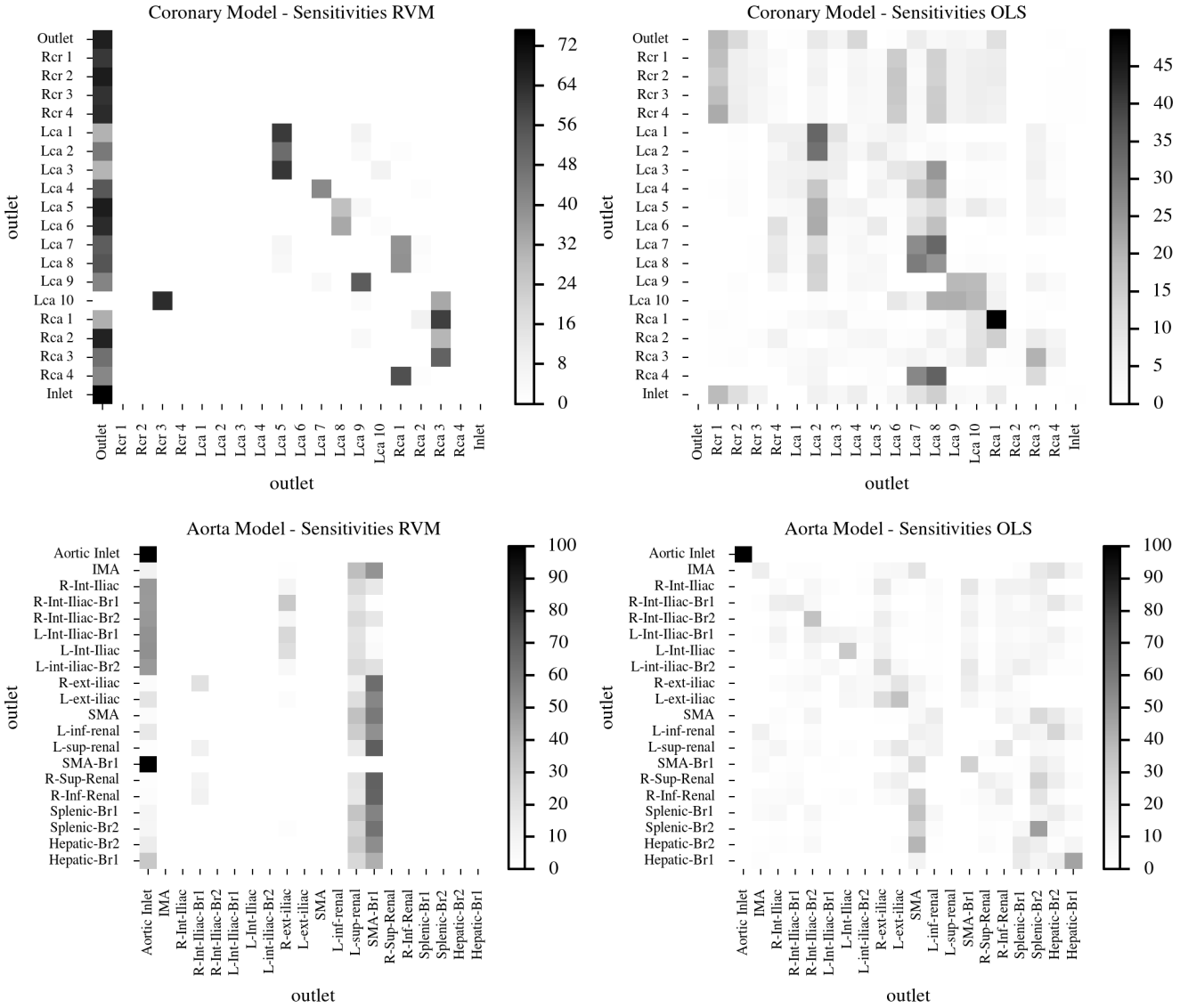
- ✓ A **pressure perturbation** $\boldsymbol{\delta}\mathbf{p} \sim \mathcal{N}(\mathbf{0}, \sigma^2\,\mathbf{I})$ will generate a **flow rate perturbation** $\boldsymbol{\delta}\mathbf{q} \sim \mathcal{N}(\mathbf{0}, \sigma^2\,\mathbf{A}\,\mathbf{A}^T)$.
- ✓ The eigenvalues of $\mathbf{A}\,\mathbf{A}^T$ thus represent the **noise amplification factors** through the linear transformation $\mathbf{A}$.





Direct sensitivities of interface flow rates

✓ Entries in each row **have sum equal to 100%** and quantify the effect of the outlet listed in the corresponding column.



III - Identifiability and Data Assimilation

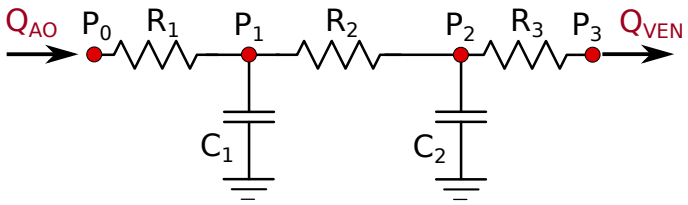
Data assimilation for lumped parameter circulation models

- ✓ Once a surrogate model is available the parameter estimation problem can be solved using a **lightweight lumped parameter model** that solves in **a fraction of a second**.
- ✓ **Features** of the lumped parameter models we consider:
  - **Non-linearity** due to heart contraction, unidirectional valves, non linear resistors (e.g., BT shunt).
  - **Only time statistics** are available for clinical measurements. For example, maximum/average/minimum pressure/velocity/volume.
- ✓ Optimization provides **only point estimates** for the model parameters and cannot handle target uncertainty.
- ✓ Filtering approaches can handle non linear models (e.g., extended/ensemble Kalman filters) but **require full time histories** for the measurements of interest (rarely available).
- ✓ We therefore use **adaptive MCMC** to sample from the joint posterior distribution of parameters.
- ✓ All good, but ... **are the parameters Identifiable?**

D. E. Schiavazzi et al., IJNMBE, 2016.

Part II: Estimation of LPN model parameters - Identifiability

RCRCR Peripheral Circulation Compartment



Selected scenarios

Scen.	Parameters	Data
SC1	**All** parameters	**All** data.
SC2	(**5**) R_{tot}, τ, C_1/C_2, R_1/R_2, R_3/R_2	(**5**) $P_{0,min}$, $P_{0,av}$, $P_{0,max}$, $P_{3,av}$, $P_{3,max}$
SC3	(**5**) R_{tot}, τ, C_1/C_2, R_1/R_2, R_3/R_2	(**3**) $P_{0,av}$, $P_{0,max}$, $P_{3,av}$
SC4	(**3**) R_{tot}, τ, C_1/C_2	(**5**) $P_{0,min}$, $P_{0,av}$, $P_{0,max}$, $P_{3,av}$, $P_{3,max}$

- ✓ **FIM** for model $\mathbf{G}(\mathbf{y})$ under diagonal Gaussian error covariance.

$$\mathcal{I}(\mathbf{y}) = \left[\frac{\partial \mathbf{G}(\mathbf{y})}{\partial \mathbf{y}}\right]^T \mathbf{C}_d^{-1} \left[\frac{\partial \mathbf{G}(\mathbf{y})}{\partial \mathbf{y}}\right]$$

- ✓ FIM Eigenvalues for **SC1**

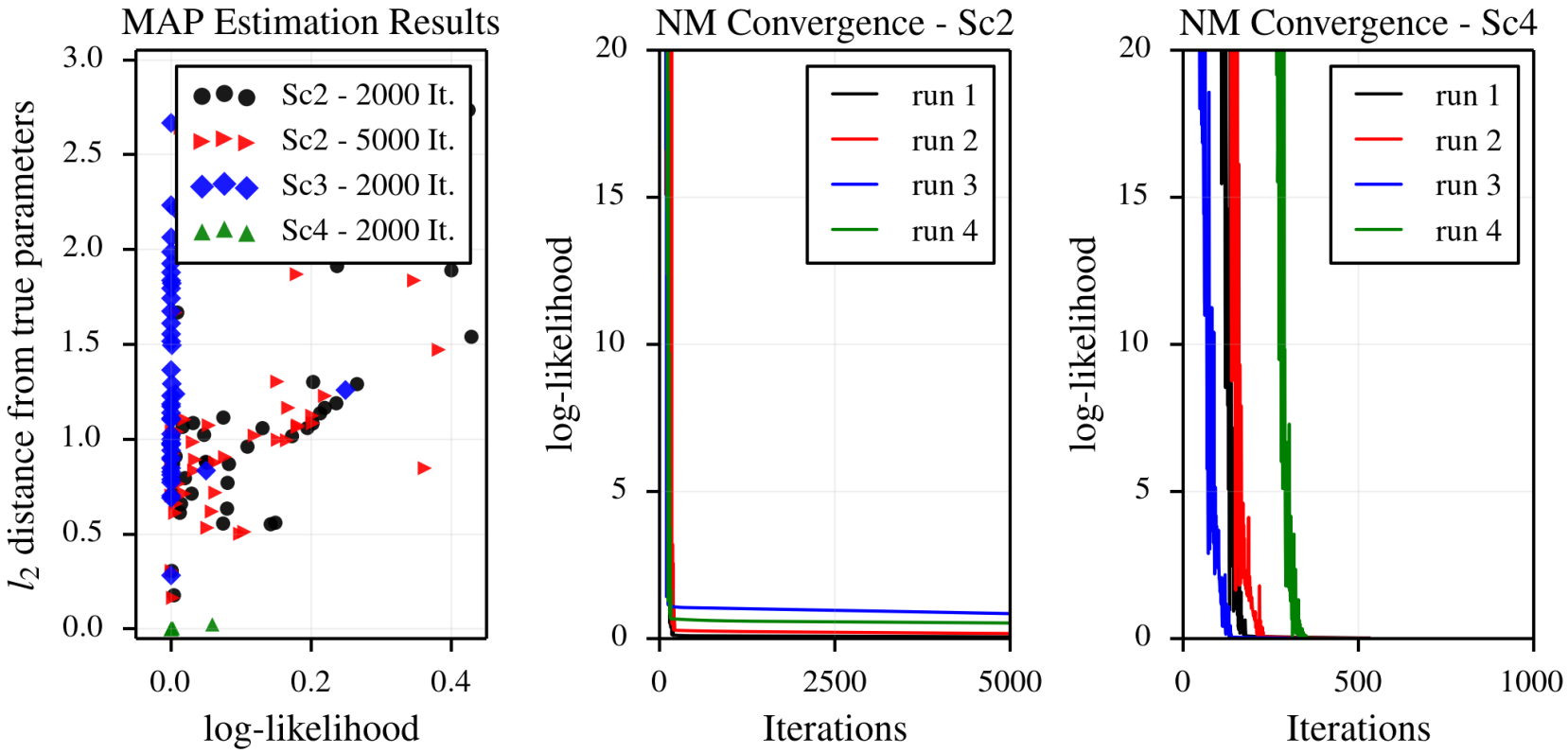
  $(\mathbf{0.000}, 2.052, \ldots, 189749.442)$

- ✓ FIM Null-Eigenvector

R_{tot}	0.0
τ	0.0
C_1/C_2	0.0
R_1/R_2	0.0
R_3/R_2	0.0
$P_{1,i}$	0.9806
$P_{2,i}$	-0.1962

Parameter estimation using optimization

✓ Can **optimization** be used to identify the LPN parameters?

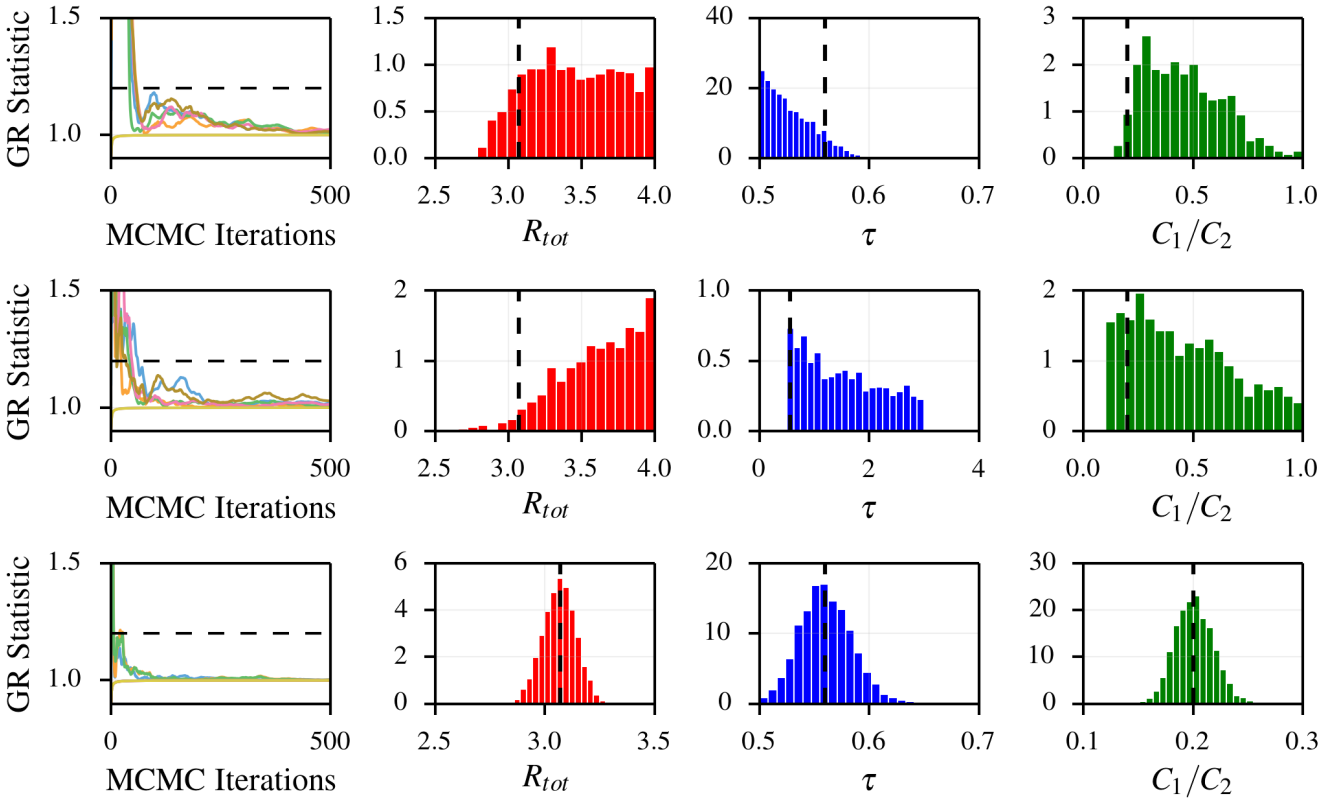


Bayesian LPN Parameter Learning

Benefits of Bayesian estimation:

- ✓ No **single point** estimate.
- ✓ **Prior** knowledge can be specified.
- ✓ Identifiability affects parameter **learning**.

$$\theta = 1 - \sqrt{\frac{\mathbb{V}\left[y_j|\mathbf{d}\right]}{\mathbb{V}\left[y_j\right]}}$$

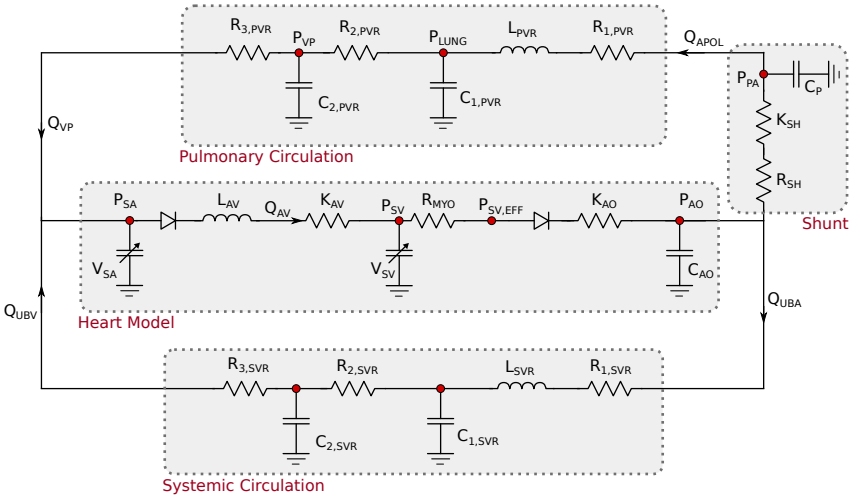


Bayesian estimation of RCRCR model parameters

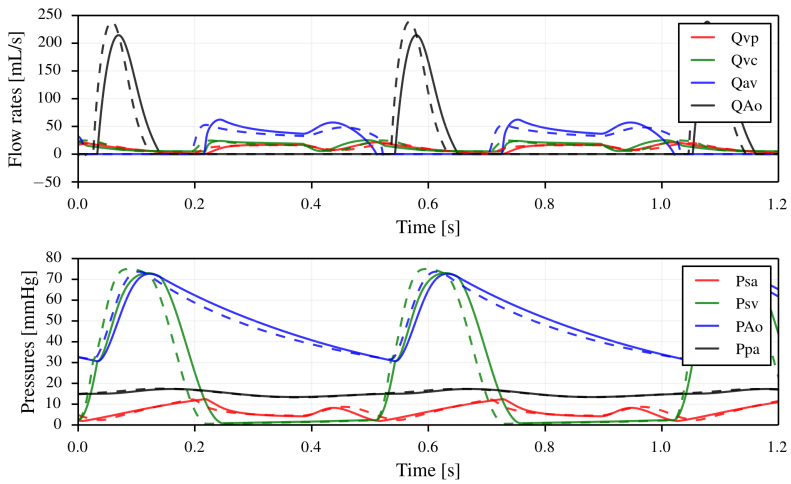
under Virtual Patient conditions

Parameter Estimation in Norwood circulation models

Norwood Circulation Model



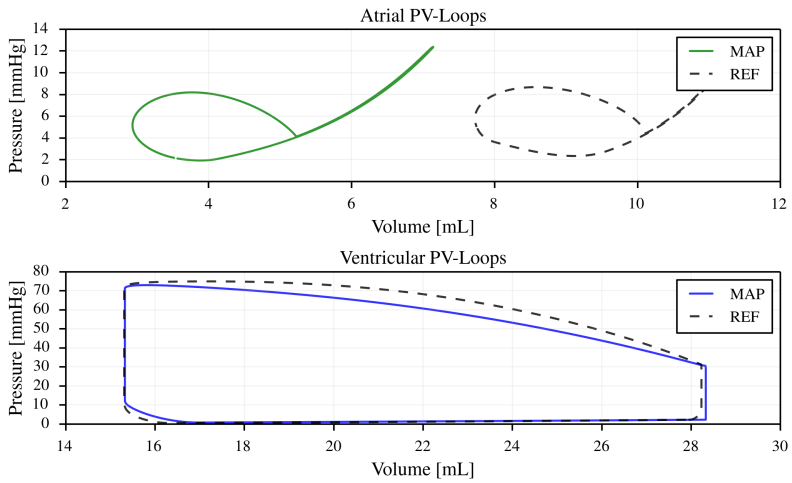
MAP Flow rates and Pressures



Clinical target matching

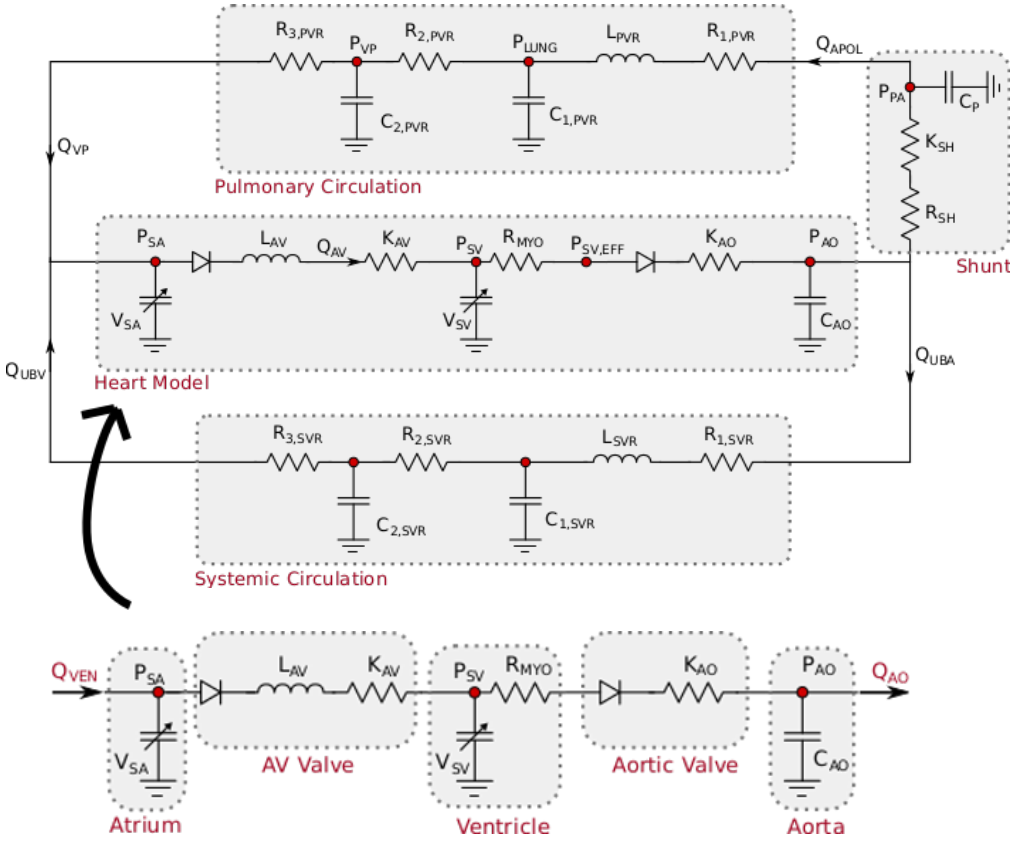
Target Quantity	Model Results	Target AV	Target SD	Weight
$P_{ao,av}$	49.568	48.855	2.442	0.5
$P_{ao,min}$	30.610	31.449	1.572	1.0
$P_{ao,max}$	72.625	73.625	3.681	1.0
$P_{sa,av}$	6.484	6.503	0.325	1.0
$P_{sv,max}$	72.972	74.933	3.746	1.0
$V_{sv,max}$	28.328	28.230	1.411	1.0
Q_p/Q_s	0.811	0.831	0.041	1.0
$P_{pa,av}$	15.034	15.126	0.756	1.0
CO	25.495	25.337	1.266	0.5
$Q_{VC,S}$	25.104	24.683	1.234	8.0
$Q_{VC,M}$	4.873	4.853	0.242	8.0
$Q_{VC,D}$	23.811	24.514	1.225	8.0
$Q_{VC,A}$	5.435	5.437	0.271	8.0
$Q_{PV,S}$	21.178	19.633	0.981	12.0
$Q_{PV,M}$	0.239	0.240	0.012	12.0
$Q_{PV,D}$	16.604	16.094	0.804	12.0
$Q_{PV,A}$	7.189	7.113	0.355	12.0
$P_{pa,min}$	13.376	13.405	0.670	1.0
$P_{pa,max}$	17.264	17.239	0.861	1.0
$P_{sv,0}$	2.280	2.251	0.830	1.0
$P_{sa,max}$	12.372	12.228	0.559	1.0

MAP Atrial and ventricular PV-loops



Multi-level Bayesian estimation of Heart model parameters

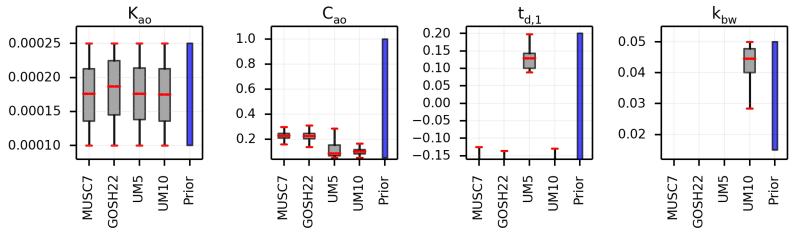
- ✓ Heart model contains **most** of the parameters and non linearities.
- ✓ Prescribed venous and aortic flow are **measured** through echo-Doppler/PC-MRI.
- ✓ **Multi-level estimation**: we **preliminary determine** the posteriors of the heart model parameters and **use this as prior** for full model parameter estimation.



D. E. Schiavazzi et al., IJNMBE, 2016.

MAP patient physiology and parameter learning

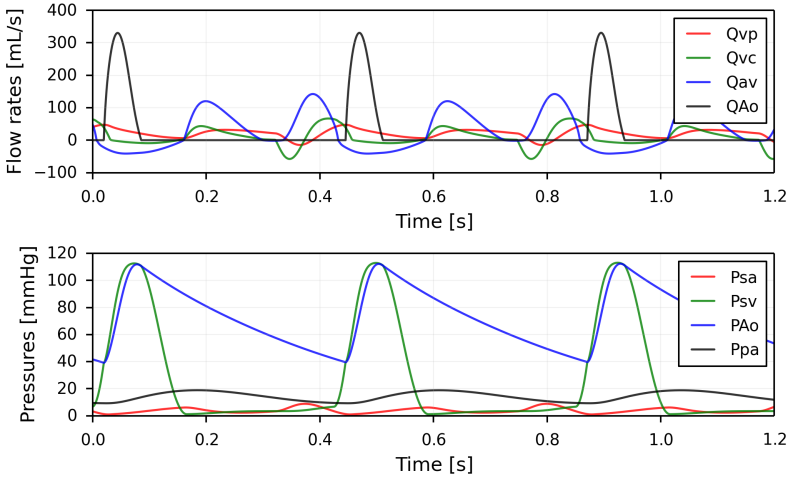
Additional parameter distributions - Norwood Model



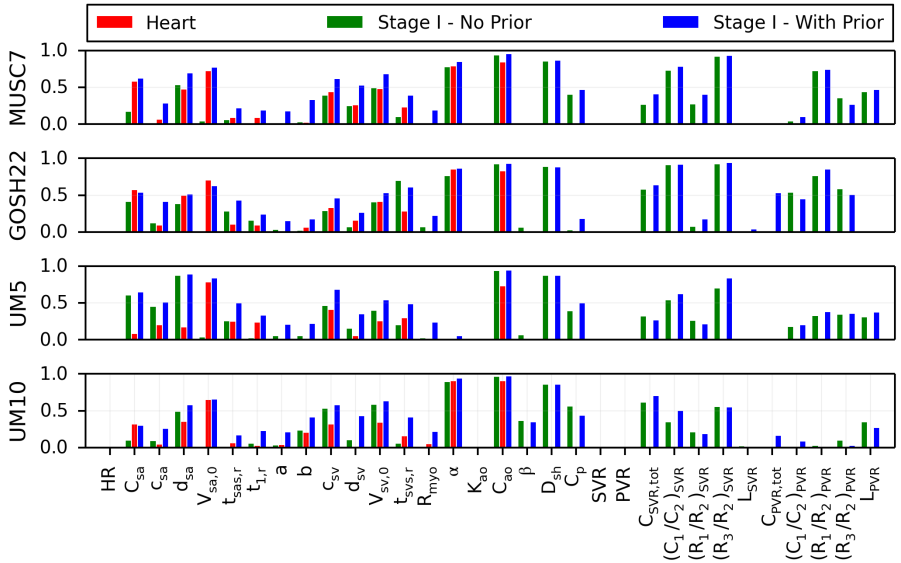
✓ **Parameter learning factor** estimated as:

$$\theta = 1 - \sqrt{\frac{\mathbb{V}[\mathbf{y}|\mathbf{d}]}{\mathbb{V}[\mathbf{y}]}}$$

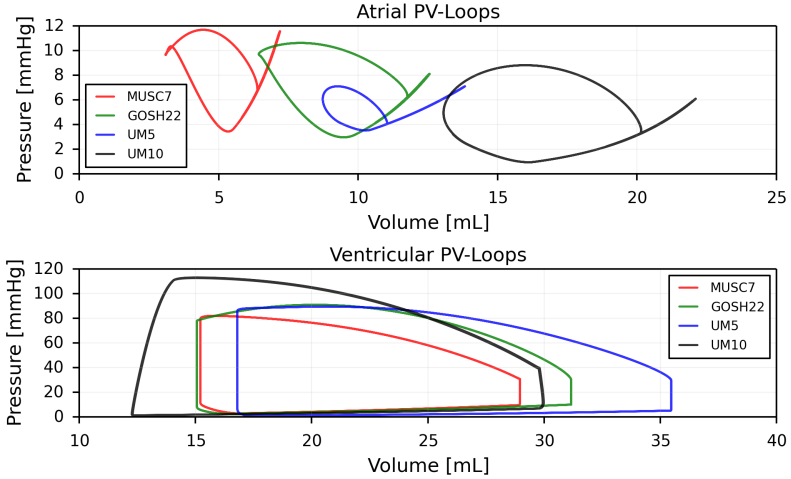
Pressures and flow rates for UM10



Parameter Learning factors



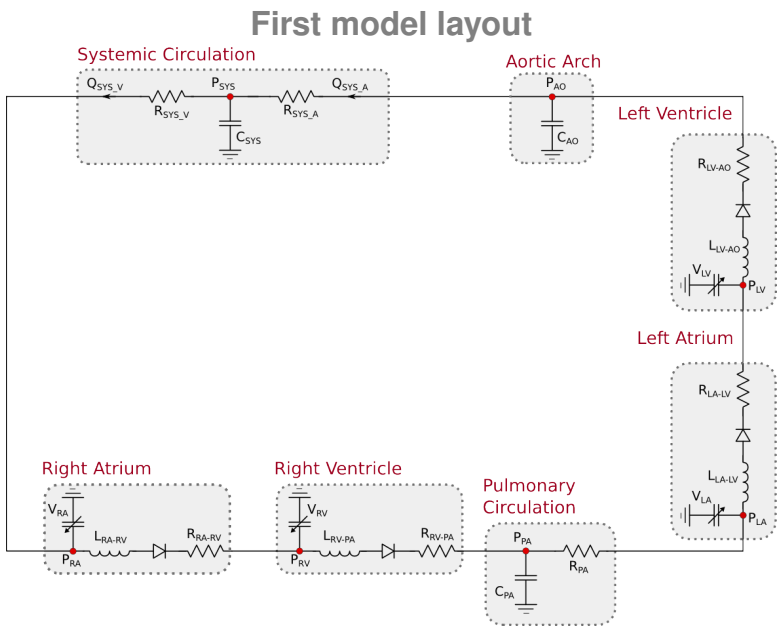
Atrial and Ventricular PV-loop for UM10

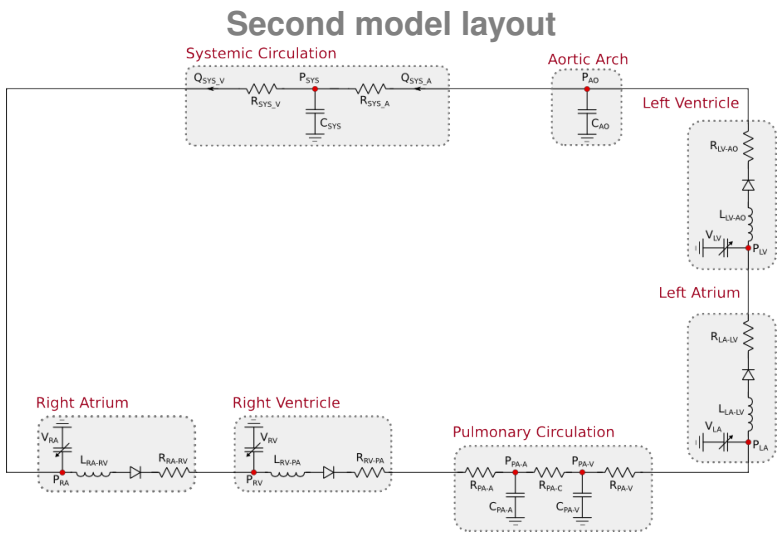


D. E. Schiavazzi et al., IJNMBE, 2016.

Estimating pulmonary pressures in diastolic heart failure

- ✓ Group II PH: **elevated pulmonary pressure** from **left heart dysfunction**.
- ✓ This type of dysfunction (left ventricular diastolic dysfunction) is **more difficult to diagnose** since it is not associated with a drop in ejection fraction and cardiac output.
- ✓ **Early diagnosis** of group II PH from minimally invasive clinical or sensor data, will help **preventing the occurrence and reduce the mortality** associated with this disease.
- ✓ Can integration of **physics-based modeling and lumped parameter circulation systems** and non-invasive data collection **improve the prediction of pulmonary pressures** (systolic, diastolic and wedge pressures) that are difficult to measure non-invasively.

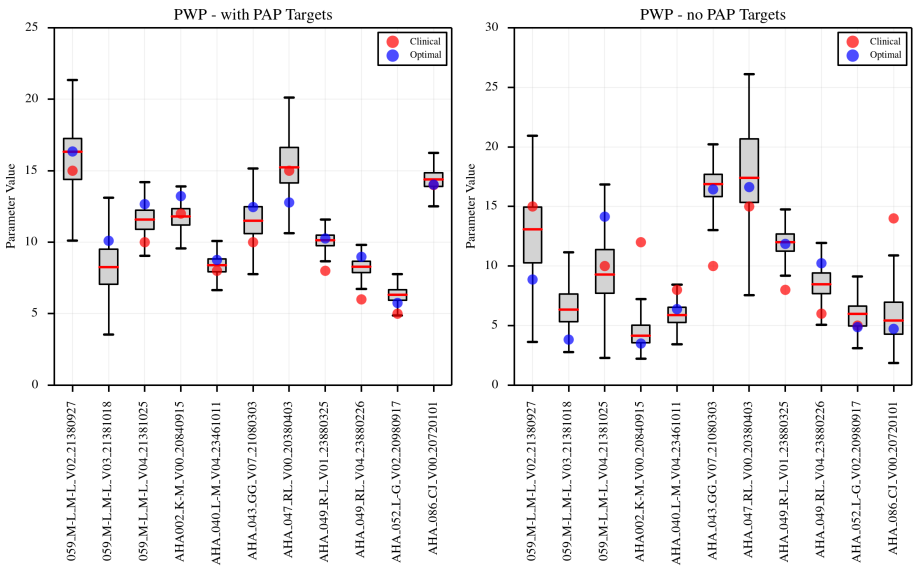


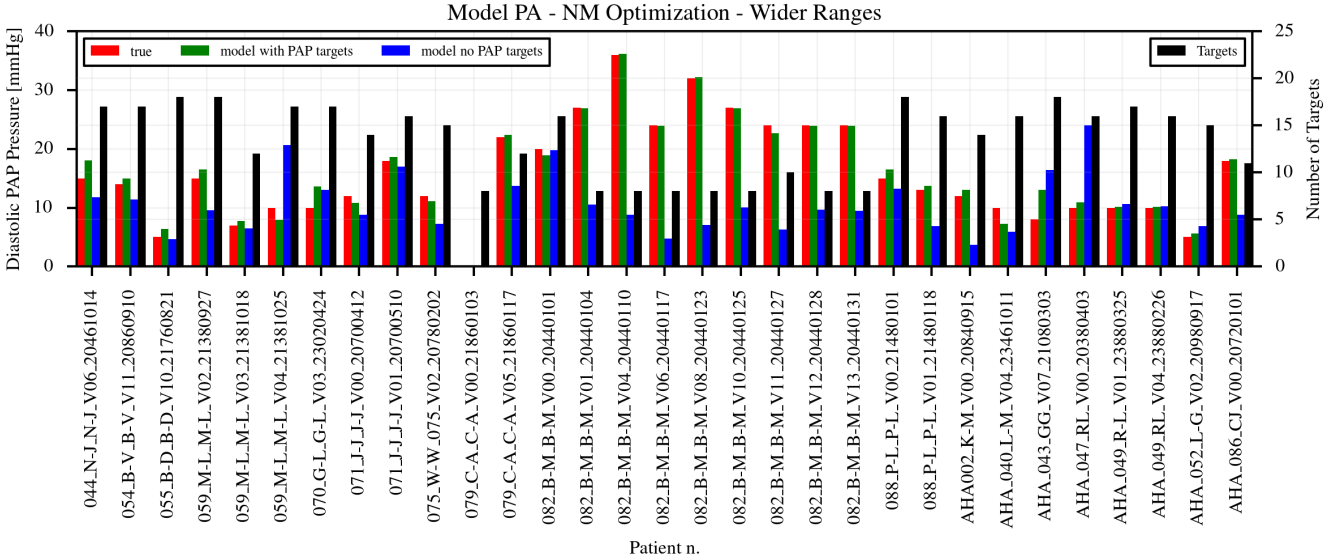


PAP errors in single visit prediction

- ✓ **Anonymized clinical targets** were obtained for several patients from a Google ATAP collaboration.
- ✓ Using Nelder-Mead optimization and adaptive MCMC estimation, the **diastolic, systolic and wedge pulmonary pressures where blindly estimated** for all visits and correlated with the total number of available targets.

Distributions of predicted PWP in heart failure patient



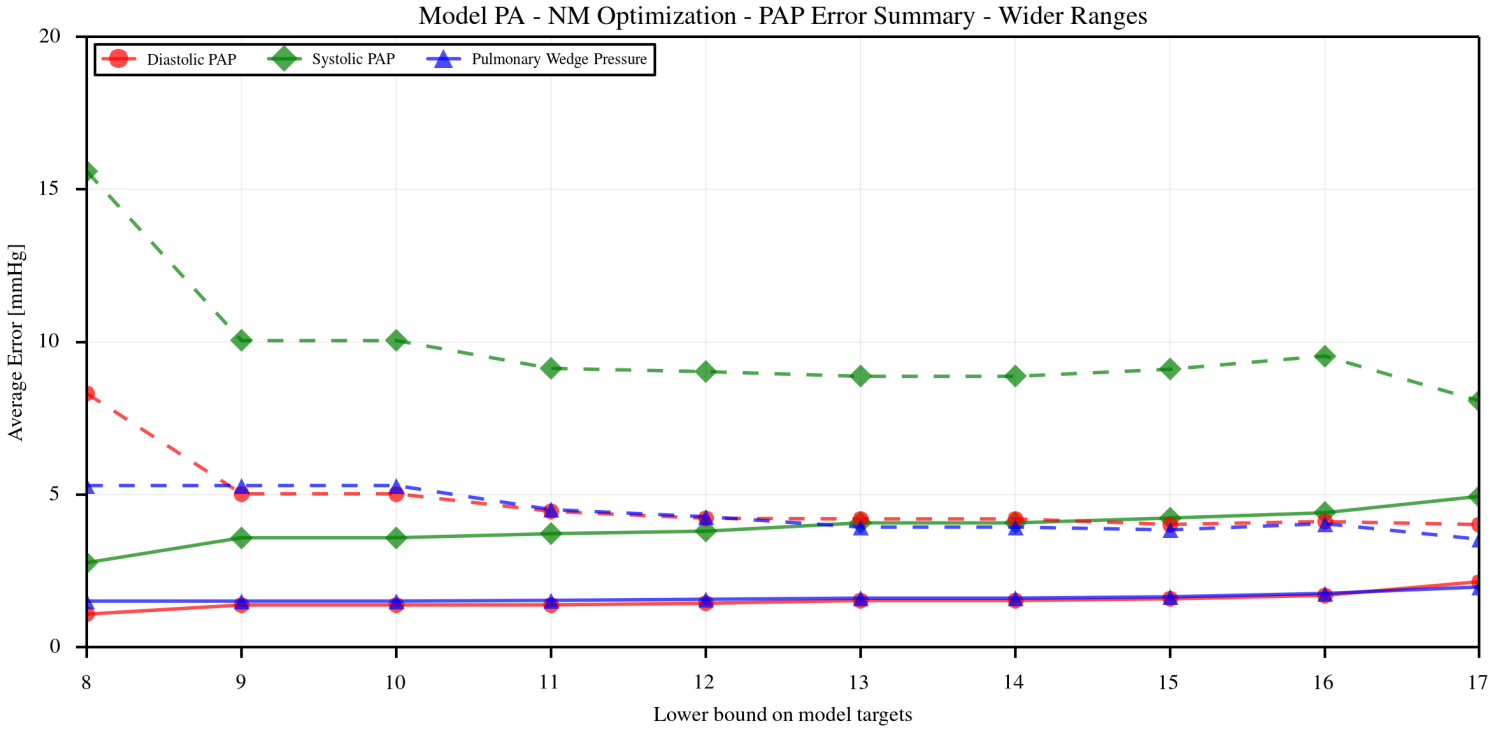


PAP errors in single visit prediction - MCMC

✓ MCMC estimation on the patients with more than 11 REDCap entries leads to improved average errors of about **7 mmHg for Systolic PAP**, **5 mmHg for Diastolic PAP** and **3 mmHg for PWP**.

REDCap Token	Units	Std	REDCap Token	Units	Std
heart_rate2	[mmHg]	3.0	mv_e_a_ratio	-	0.2
systolic_bp_2	[mmHg]	1.5	pv_at	[ms]	6.0
diastolic_bp_2	[mmHg]	1.5	pv_max_pg	[mmHg]	0.5
cardiac_output	[L/min]	0.2	ra_pressure	[mmHg]	0.5
systemic_vascular_resistan	[CGS]	50.0	ra_vol_a4c	[mL]	3.0
pulmonary_vascular_resista	[CGS]	5.0	la_vol_a4c	[mL]	3.0
cvp	[mmHg]	0.5	lv_esv	[mL]	10.0
right_ventricle_diastole	[mmHg]	1.0	lv_vol_a4c	[mL]	20.0
right_ventricle_systole	[mmHg]	1.0	lvef	-	2.0
rvedp	[mmHg]	1.0	pap_diastolic	[mmHg]	1.0
aov_mean_pg	[mmHg]	0.5	pap_systolic	[mmHg]	1.0
aov_peak_pg	[mmHg]	0.5	wedge_pressure	[mmHg]	1.0
mv_decel_time	[ms]	6.0			

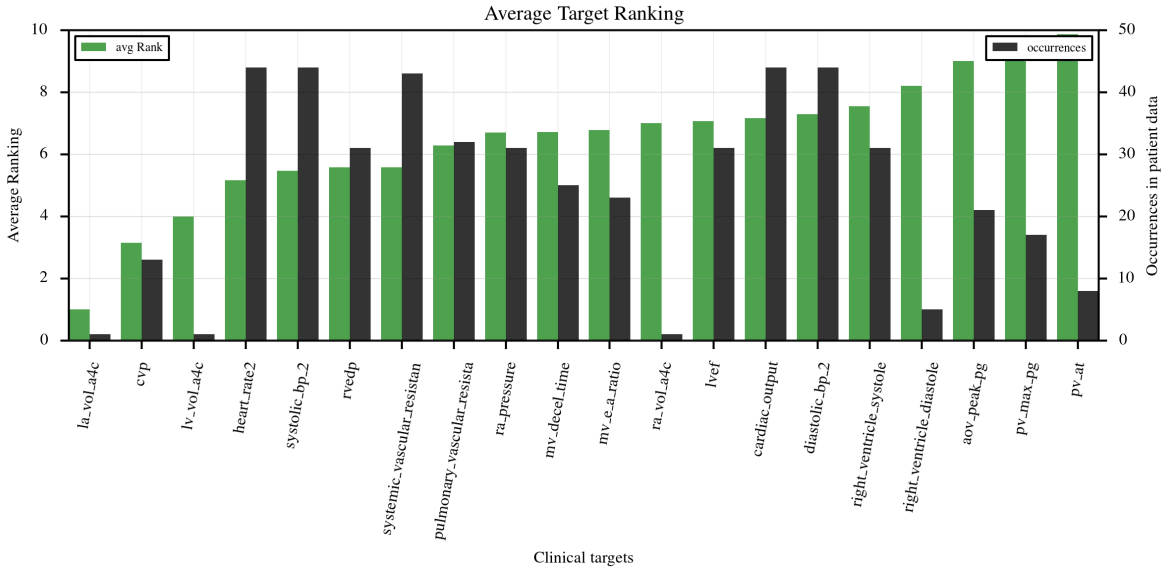
PAP errors vs. Number of included clinical targets



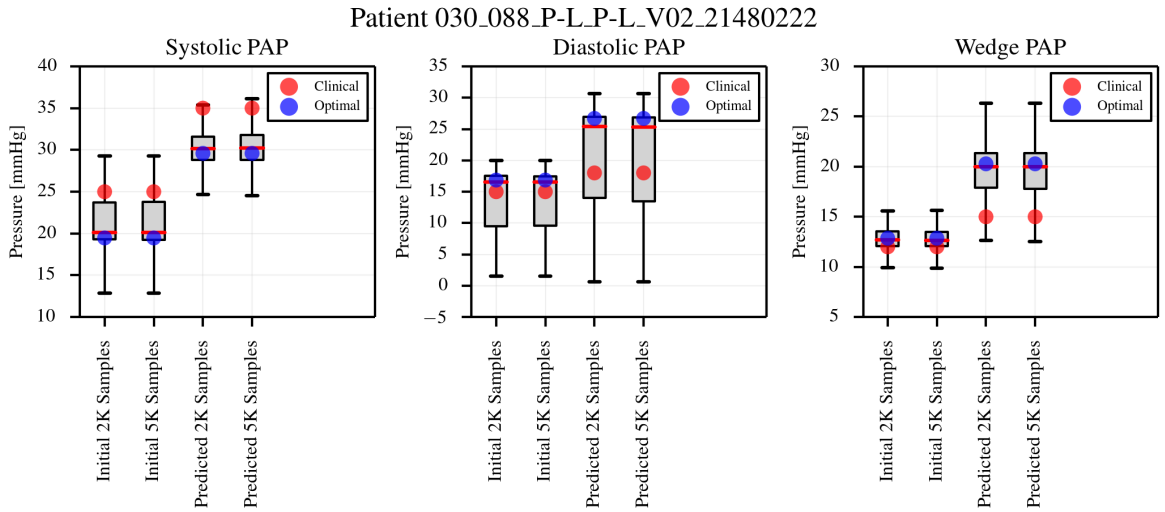
Follow-up visit prediction using Bayesian update

- ✓ Prediction of PAP follow-up trends using Bayesian update is successful in **46%** of the cases for **systolic** pulmonary pressure (24 patients), **58%** for **diastolic** pulmonary pressure (24 patients) and **80%** for **wedge** pulmonary pressure (10 patients).

Errors in PAP vs. Number of included clinical targets

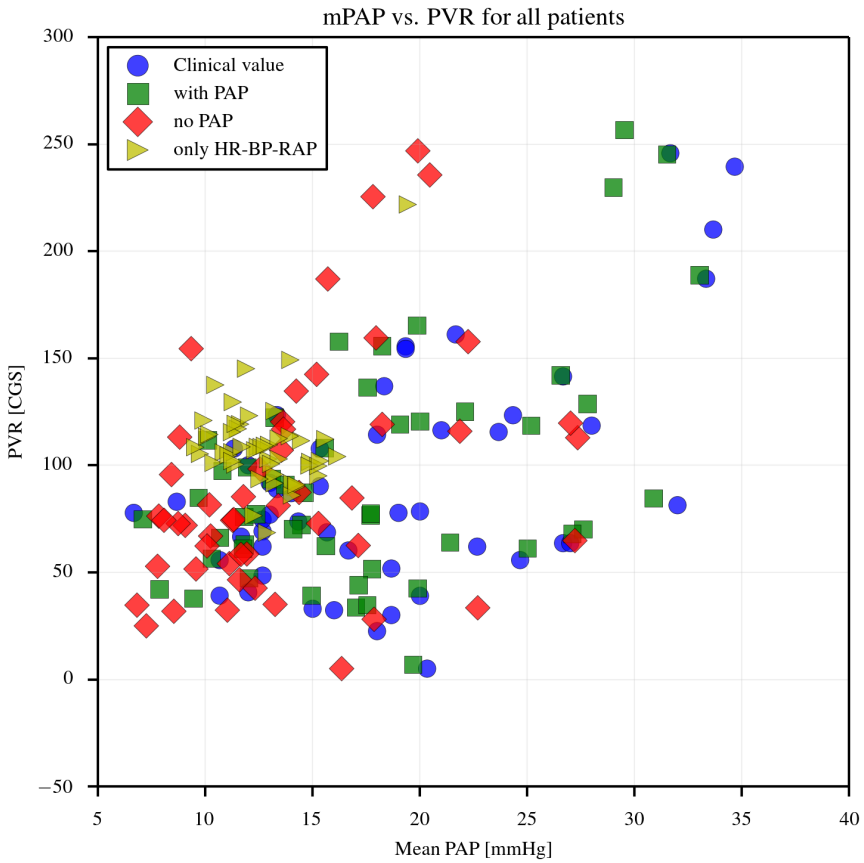


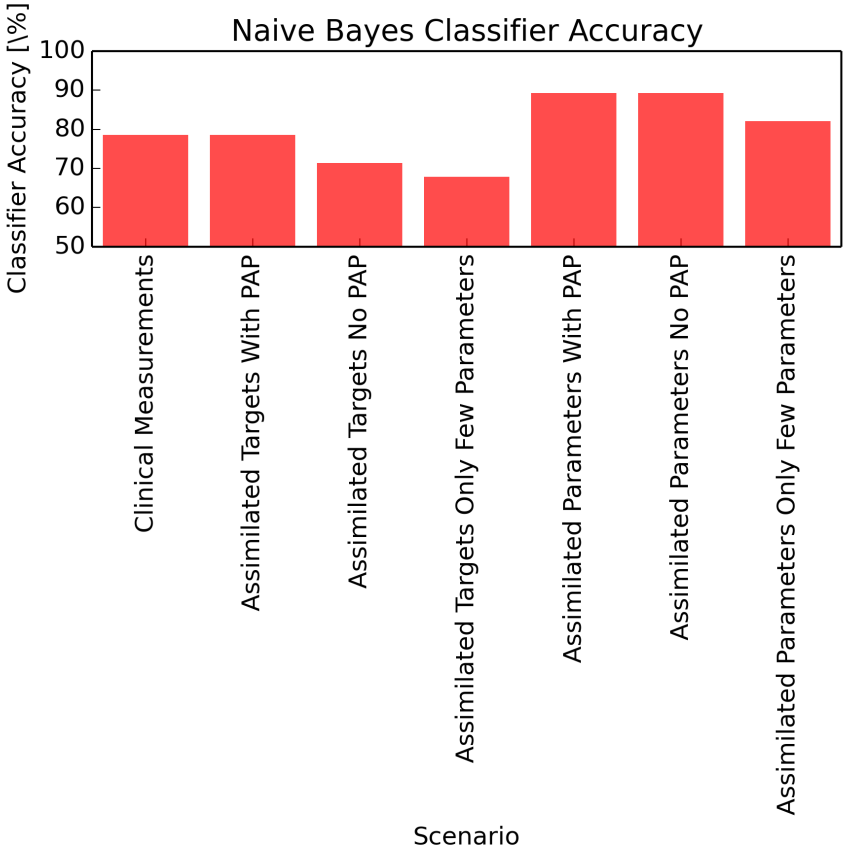
Errors in PAP vs. Number of included clinical targets



Heart Failure Detection

- ✓ Patients with pulmonary hypertension **were identified** in the cohort of 84 patients based on **mPAP vs. PVR**. The same quantities were predicted through models from a **smaller number of available targets** (with PAP, No PAP, only HR-BP-RAP).
- ✓ A **Naive Bayes classifier** is used to identify cases of pulmonary hypertension. Classification using assimilated parameters **gives good accuracy even if the the pulmonary pressures are not included**.

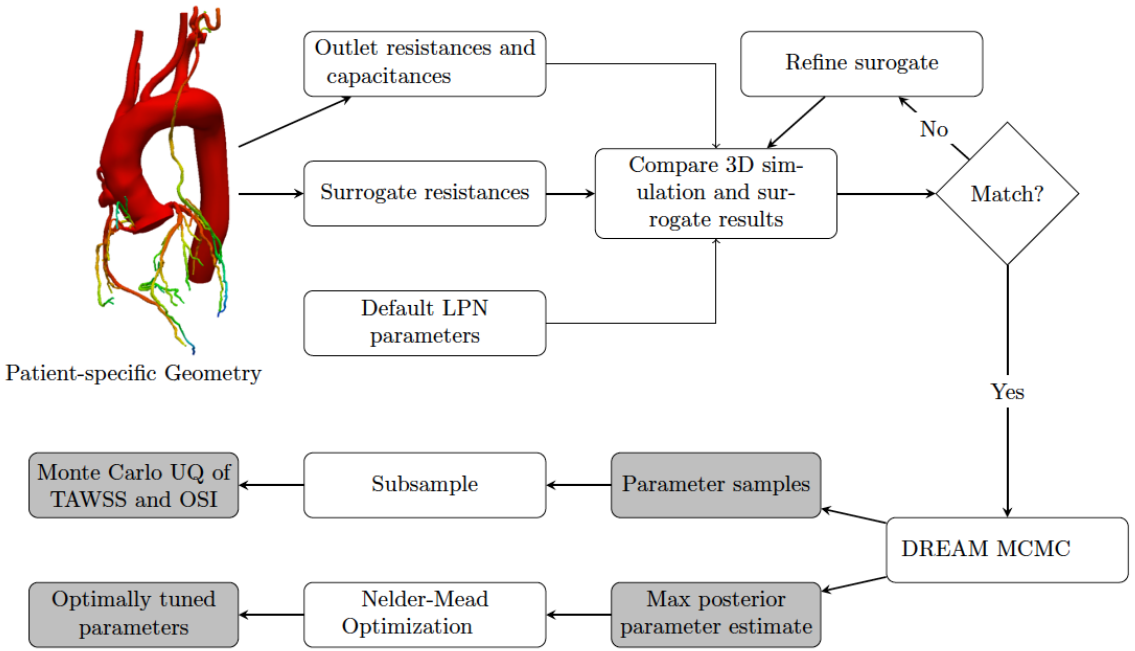




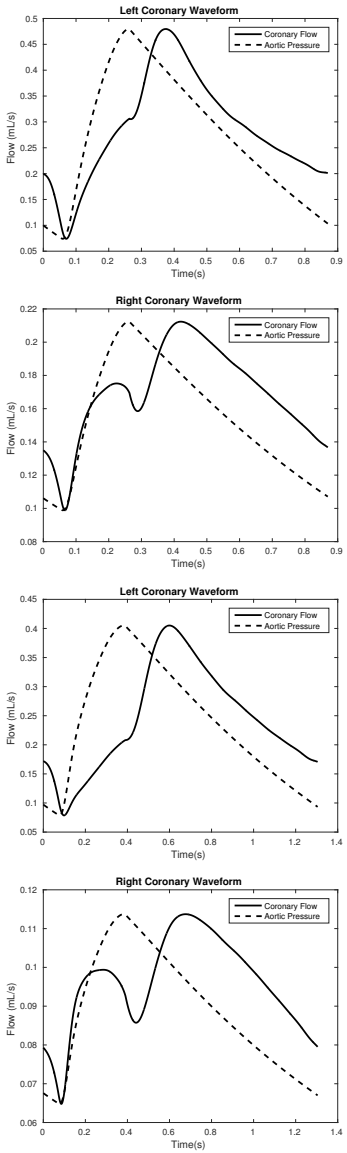
IV - Uncertainty Propagation

Data Assimilation and MCS in coronary artery disease

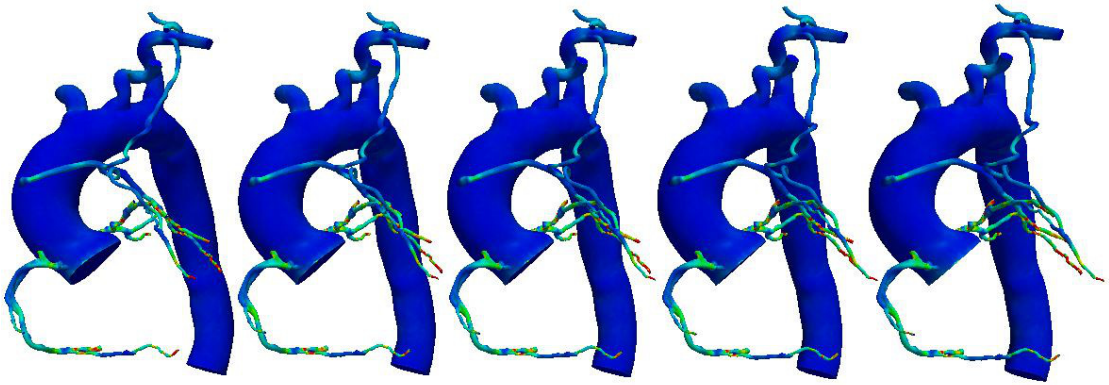
Workflow for UQ in coronary artery disease



Coronary flow waveforms



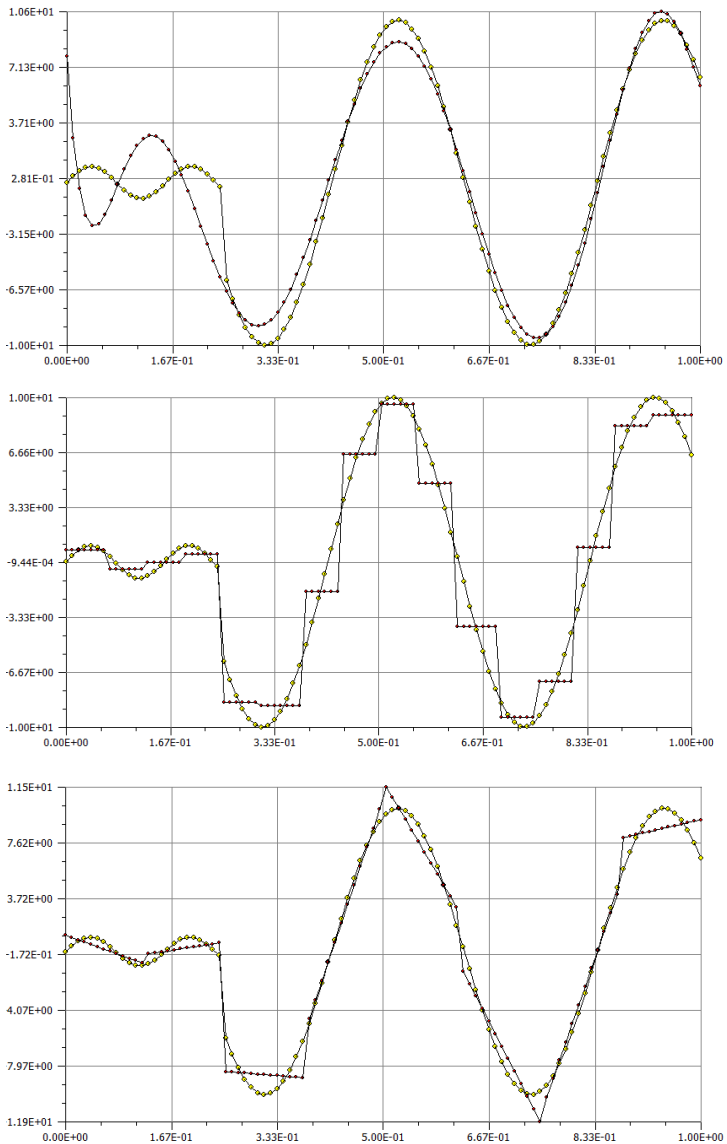
MCS convergence of TAWSS Standard Deviation (10 - 20 - 30 - 40 - 50 samples)



J. S. Tran et al., Computer & Fluids, 2016.

Why Alpert Multiwavelets?

- ✓ Multiresolution basis built on top of the **Legendre Polynomials**.
- ✓ It is still an **orthonormal** basis.
- ✓ Coefficients: **statistics** and feature **detection**.
- ✓ **Generalize** Wiener-Legendre and Wiener-Haar basis expansions.
- ✓ Has the ability to represent **discontinuous** responses.
- ✓ Piecewise smooth responses are **sparse** in the Alpert basis and coefficients are typically organized in compact subtrees.
- ✓ For **non-uniform random inputs**, however, the number of samples **may increase by transforming** the random inputs.



Alpert, 1993, Le Maître et al., 2004, Tryoen et al., 2012

Multiscaling orthogonality to arbitrary PDFs

- ✓ Probability space $(\Omega, \mathcal{F}, P)$ and random variable $y : \Omega \to \Sigma_y$.
- ✓ Input probability measure $\rho^k(y^{(j)})$, $j = 1, \ldots, n_q$ defined on the k-th partition $\Sigma_y^k \subset \Sigma_y$, **sampled at quadrature points**.
- ✓ Multiscaling family $\{\phi_i,\ i = 0, \ldots, m-1\}$ built **using the three-term recurrence**:

$$\phi_{-1} = 0,\ \phi_0 = 1,\ \phi_{i+1}(y) = (y - \alpha_i)\ \phi_i(y) - \beta_i\, \phi_{i-1}.\ i = 0, \ldots, m-1,$$

where:

$$\alpha_i = \frac{\langle \phi_i,\ y\, \phi_i \rangle_{\mathcal{H}^k}}{\langle \phi_i,\ \phi_i \rangle_{\mathcal{H}^k}}, \text{and } \beta_i = \frac{\langle \phi_i, \phi_i \rangle_{\mathcal{H}^k}}{\langle \phi_{i-1},\ \phi_{i-1} \rangle_{\mathcal{H}^k}}.$$

- ✓ Every inner product is evaluated using **numerical quadrature**:

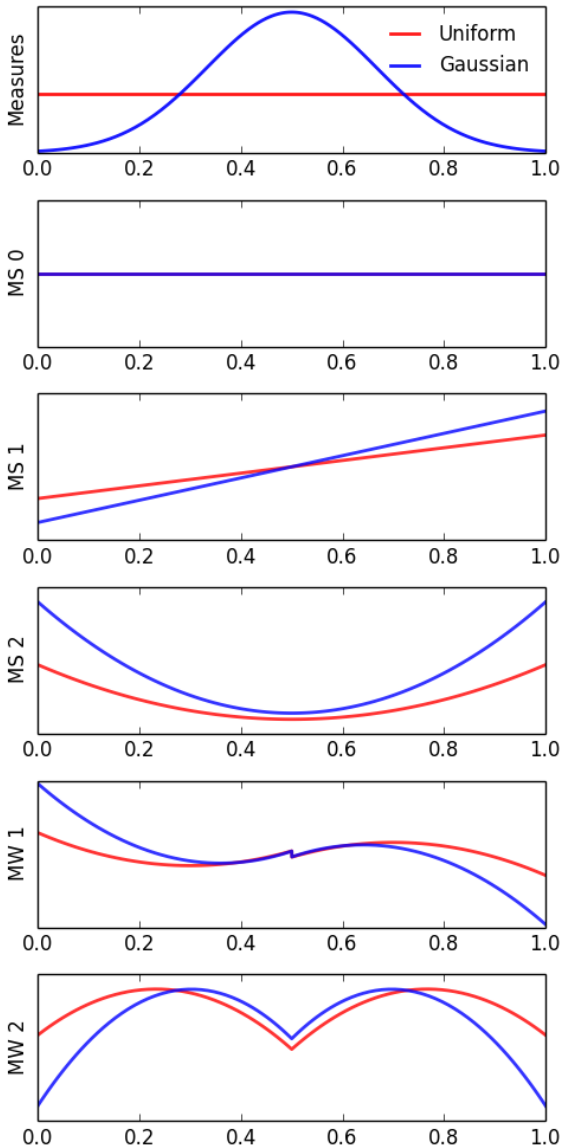
$$\langle f,\ g \rangle_{\mathcal{H}^k} = \int_{\Sigma_y^k} f(y)\, g(y)\, \rho^k(y)\, dy \approx \sum_{j=1}^{n_q} f(y^{(j)})\, g(y^{(j)})\, \rho^k(y^{(j)})\, w_j,$$

where w_j denotes the weights for the selected quadrature rule (**double** Clenshaw-Curtis quadrature in this study).

Construction of orthogonal multiwavelets

- ✓ $\mathbf{V}^k_{m,0}$ is the space of polynomials with order less than m in $[0,1]$, spanned by $\{\phi_i,\ i = 0, \ldots, m-1\}$.
- ✓ Construct a basis $\{\psi_i,\ i = 0, \ldots, m-1\}$ for $\mathbf{W}^k_{m,0}$ that **complements** $\mathbf{V}^k_{m,0}$ to the space of continuous polynomials of order less than m defined **separately on $[0, 1/2)$ and $[1/2, 1]$** , i.e., $\mathbf{W}^k_{m,0} \perp \mathbf{V}^k_{m,0}$, and $\mathbf{V}^k_{m,0} \oplus \mathbf{W}^k_{m,0} = \mathbf{V}^k_{m,1}$:

  1. **Build** $2m$ functions which span the space of polynomials of degree less than m on the interval $[-1, 0)$ and on $[0, 1]$.
  2. **Orthogonalize** m of them, first to $\{1, y, y^2, \ldots, y^{m-1}\}$, then to $\{y^m, y^{m+1}, \ldots, y^{2m-1}\}$.
  3. Implement **orthogonality** between ψ_i and ψ_j for $i \neq j$.
  4. **Rescale** to [0,1] and **normalize** to have $\langle \psi_i,\ \psi_j \rangle_{\mathcal{H}^k} = \delta_{i,j}$.



Alpert B. K., SIAM JMA, 1993.

Multi-resolution ANOVA for adaptivity

- ✓ Consider a **model** $u(y) : [0,1] \to \mathbb{R}$, whose response is **approximated** using:

$$u(y) \approx \sum_{i=0}^{m-1} \left[\alpha_i \, \phi_i(y) + \beta_i \, \psi_i(y)\right].$$

- ✓ As all $\{\phi_i(y), \psi_i(y),\ i = 0, \ldots, m-1\}$ except $\phi_0(y)$ have **zero average** over [0,1], the variance $\mathbb{V}[u(y)]$ can be decomposed as follows:

$$\mathbb{V}[u(y)] \approx \sum_{i=1}^{m-1} \alpha_i^2 + \sum_{i=1}^{m-1} \beta_i^2 = \mathbb{V}_{MS} + \mathbb{V}_{MW}$$

where the multiscaling and multiwavelet variances are identified. We use the relative importance of $\mathbb{V}_{MW}$ and $\mathbb{V}_{MS}$ to **determine whether we need to refine** $[0,1]$ into $[0,1/2)$ and $[1/2,1]$.

Monolithic approach in multiple dimensions

- ✓ For $d > 1$, **multi-index** $\mathbf{i} \in \mathcal{I} = \{(i_1, \ldots, i_d) : 0 \leq i_l < m_l, l = 1, \ldots, d\}$

$$\phi_{\mathbf{i}}(\mathbf{y}) = \phi_{i_1}(y_1) \ldots \phi_{i_d}(y_d), \quad \mathcal{S}_0^{\mathbf{m}} = \{\phi_{\mathbf{i}}(\mathbf{y}) : \mathbf{i} \in \mathcal{I}\}.$$

- ✓ **Permutations:** $\mathbf{q} \in \mathcal{Q} = \{(q_1, \ldots, q_d) : q_l \in \{0, 1\}, l = 1, \ldots, d\}$.

$$\psi_i^0 = \phi_i, \quad \psi_i^1 = \varphi_i, \quad \psi_{\mathbf{i}}^{\mathbf{q}}(\mathbf{y}) = \psi_{i_1}^{q_1}(y_1) \ldots \psi_{i_d}^{q_d}(y_d),$$

- ✓ The **orthogonal basis** set at $j = 0$ is

$$\mathcal{W}_0^{\mathbf{m}} = \{\psi_{\mathbf{i}}^{\mathbf{q}}(\mathbf{y}) : \mathbf{i} \in \mathcal{I}, \mathbf{q} \in \mathcal{Q} \backslash \{0\}\},$$

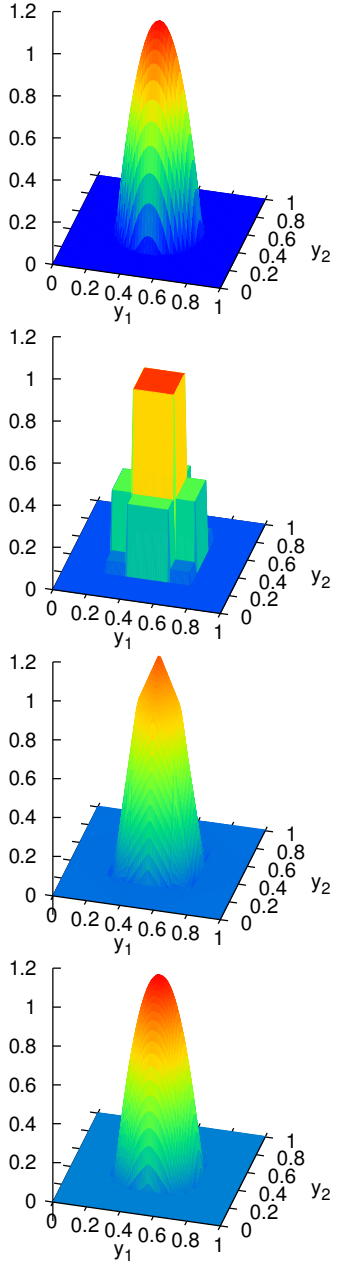
- ✓ At **higher resolutions**, $\mathbf{k} \in \mathcal{K} = \{(k_1, \ldots, k_d) : 0 \leq k_l \leq 2^j - 1, l = 1, \ldots, d\}$

$$\psi_{j,\mathbf{i},\mathbf{k}}^{\mathbf{q}}(\mathbf{y}) = 2^{jd/2} \psi_{i_1}^{q_1}(2^j y_1 - k_1) \ldots \psi_{i_d}^{q_d}(2^j y_d - k_d)$$

- ✓ **Expansion:** given $\mathbf{m} = (m_1, \ldots, m_d)$

$$u(\mathbf{y}) = \sum_{\mathbf{i} \in \mathcal{I}} \alpha_{0,\mathbf{i},\mathbf{0}} \, \psi_{0,\mathbf{i},\mathbf{0}}^{\mathbf{0}}(\mathbf{y}) + \sum_{j=0}^{\infty} \sum_{\mathbf{k} \in \mathcal{K}} \sum_{\mathbf{q} \in \mathcal{Q}} \sum_{\mathbf{i} \in \mathcal{I}} \alpha_{j,\mathbf{i},\mathbf{k}} \, \psi_{j,\mathbf{i},\mathbf{k}}^{\mathbf{q}}(\mathbf{y})$$

$$u(\mathbf{y}) = \sum_{i=1}^{\infty} \alpha_i \psi_i(\mathbf{y})$$



Binary Refinements and Multivariate Complexity

Monolithic multivariate expansion:

$$u(\mathbf{y}) = \sum_{\mathbf{i}\in\mathcal{I}} \alpha_{0,\mathbf{i},\mathbf{0}}\, \psi^{\mathbf{0}}_{0,\mathbf{i},\mathbf{0}}(\mathbf{y}) + \sum_{j=0}^{\infty} \sum_{\mathbf{k}\in\mathcal{K}} \sum_{\mathbf{q}\in\mathcal{Q}} \sum_{\mathbf{i}\in\mathcal{I}} \alpha_{j,\mathbf{i},\mathbf{k}}\, \psi^{\mathbf{q}}_{j,\mathbf{i},\mathbf{k}}(\mathbf{y})$$

- ✓ **Multi-element** approach:
  - ✓ Enables **parallel regression** on separate parameter space partitions.
  - ✓ **No refinement** needed at lower resolutions, but new elements.
- ✓ The hypercube partitions are stored using a **binary tree**:
  - ✓ Avoids need for **full tensor product** of multiwavelets basis (adaptive selection of interaction terms becomes possible).
  - ✓ Multiwavelet basis **do not need to be mixed up** along different axis.

D. E. Schiavazzi et al., CMAME, 2017.

Dependent inputs - change of measure

- ✓ In practical applications, random inputs are **often not independent**, e.g., M samples $\mathbf{y}^{(k)}$, $k = 1, \ldots, M$ generated from the joint distribution $\rho(\mathbf{y})$ **through MCMC**.

- ✓ Consider a **truncated multiwavelet expansion** of the stochastic response $u(\mathbf{y})$:

$$u(\mathbf{y}) \approx \sum_{\mathbf{i}=1}^{P} \alpha_i \psi_{\mathbf{i}}(\mathbf{y})$$

  with a multi-index order $\mathbf{i} = (i_1, i_2, \ldots, i_d)$, $\mathbf{i} : \mathbb{N}_{\geq 0} \to \mathbb{N}_{\geq 0}^d$.

- ✓ The family $\psi_{\mathbf{i}}(\mathbf{y})$ is orthogonal to the measure $\prod_{i=1}^d \rho_i(y_i) \neq \rho(\mathbf{y})$, i.e., the **product of the marginals**.

- ✓ The **moments** of $u(\mathbf{y})$ with order p are

$$\nu^p = \int_\Omega [u(\mathbf{y})]^p \, \rho(\mathbf{y}) \, d\mathbf{y}.$$

Soize and Ghanem, SIAM JSC, 2004.

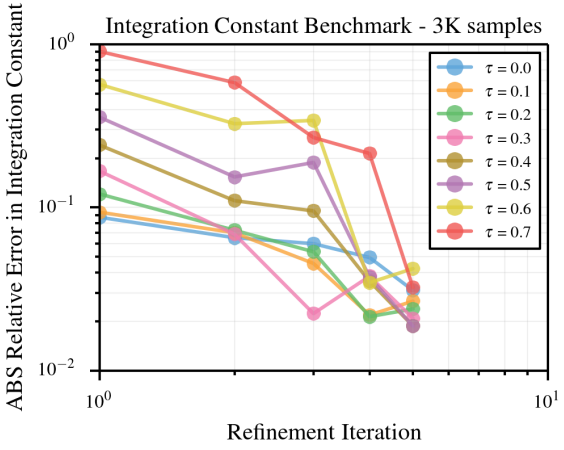
Dependent inputs from MCMC

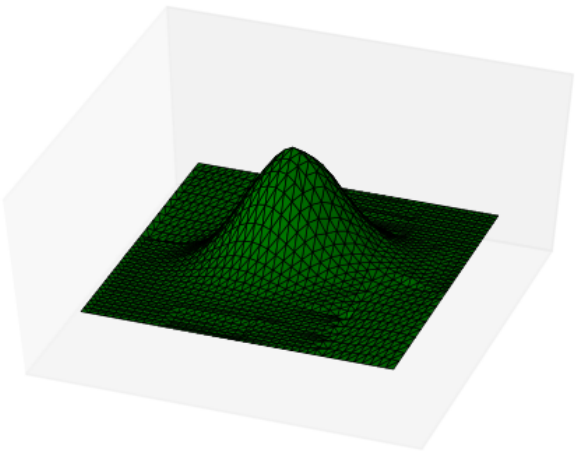
- ✓ By **multiplying and dividing** by the product of the marginals $\prod_{i=1}^{d} \rho_i(y_i)$ and *changing the measure*, we obtain:

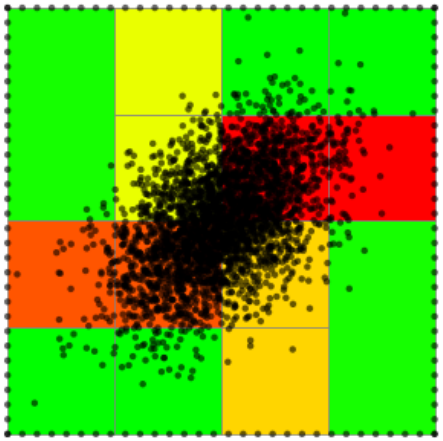
$$\nu_p = \int_\Omega \left[u(\mathbf{y})^p \frac{\rho(\mathbf{y})}{\prod_{i=1}^{d} \rho_i(y_i)} \right] \prod_{i=1}^{d} \rho_i(y_i)\, d\mathbf{y} = \int_\Omega f(\mathbf{y}) \prod_{i=1}^{d} \rho_i(y_i)\, d\mathbf{y}.$$

- ✓ Note also that regression of $f(\mathbf{y})$ from $\{u(\mathbf{y}^{(i)}) : i = 1, \ldots, M\}$ **requires the computation** of $\{\beta^{(k)} = \rho(\mathbf{y}^{(k)}) / \prod_{i=1}^{d} \rho_i(y_i^{(k)}),\ k = 1, \ldots, M\}$.

Numerical tests on multivariate Gaussian with various correlation coefficients

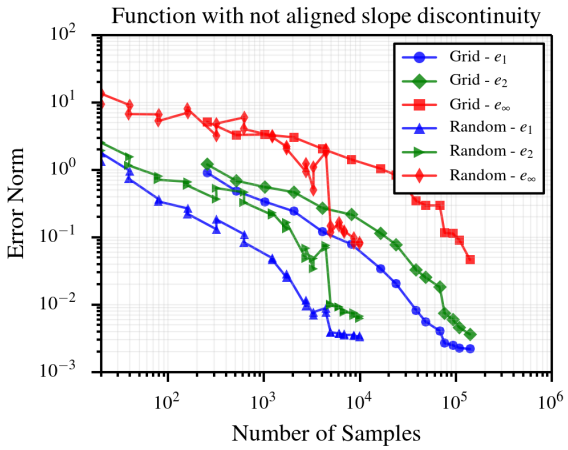


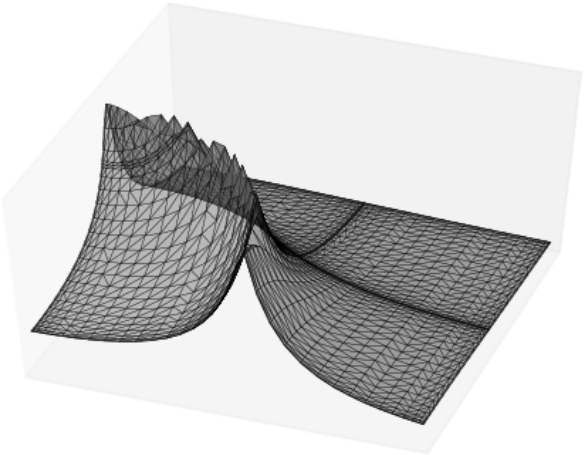


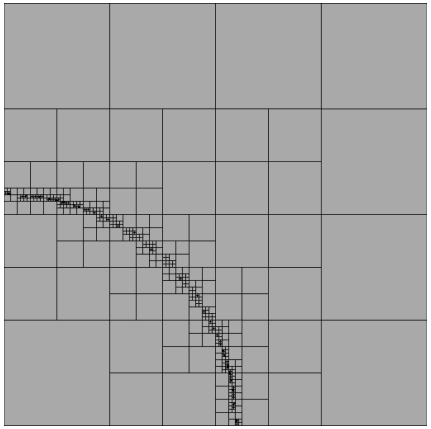


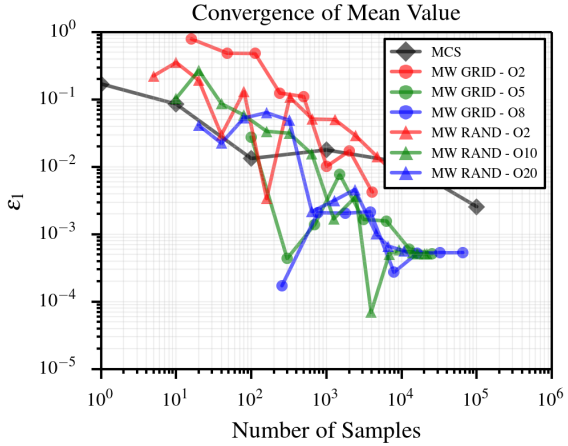
Soize and Ghanem, SIAM JSC, 2004.

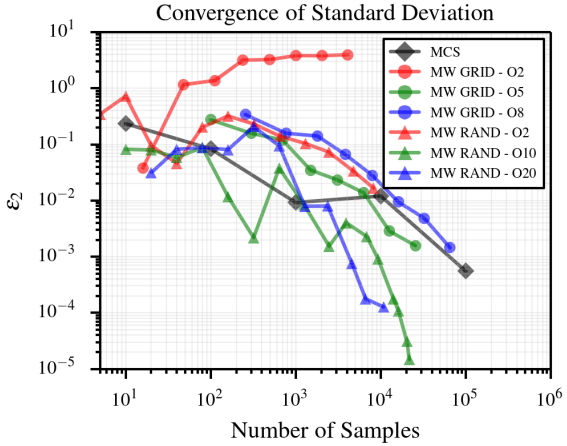
Validation on benchmark problems

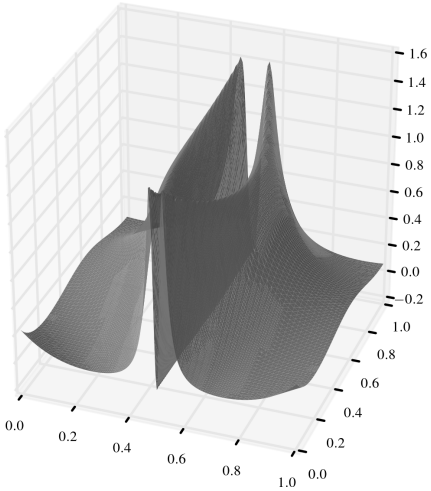






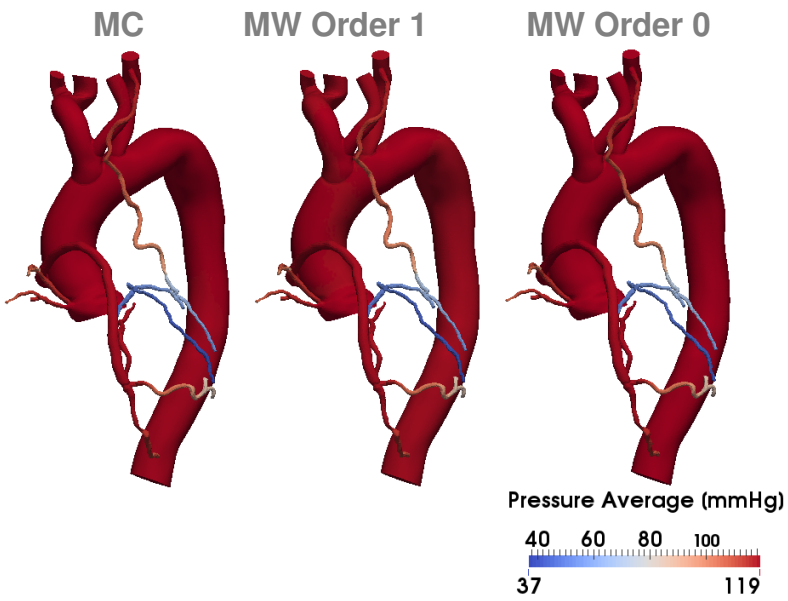


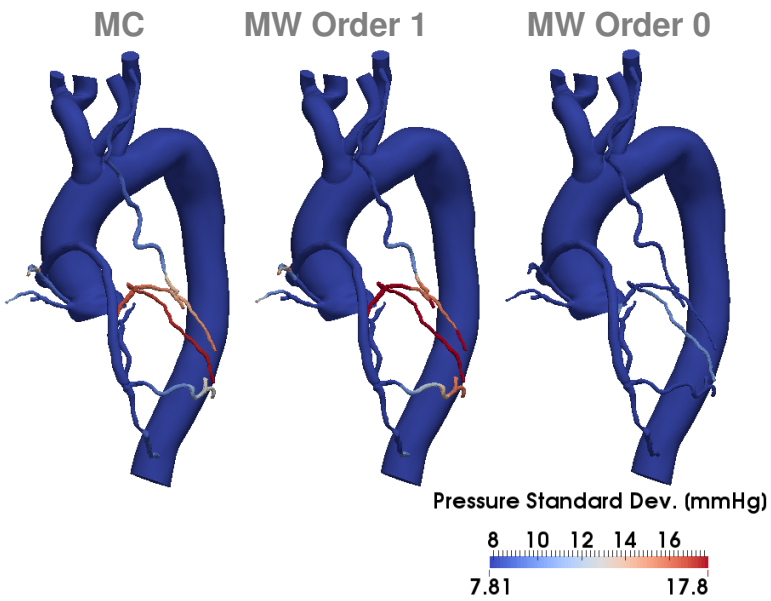




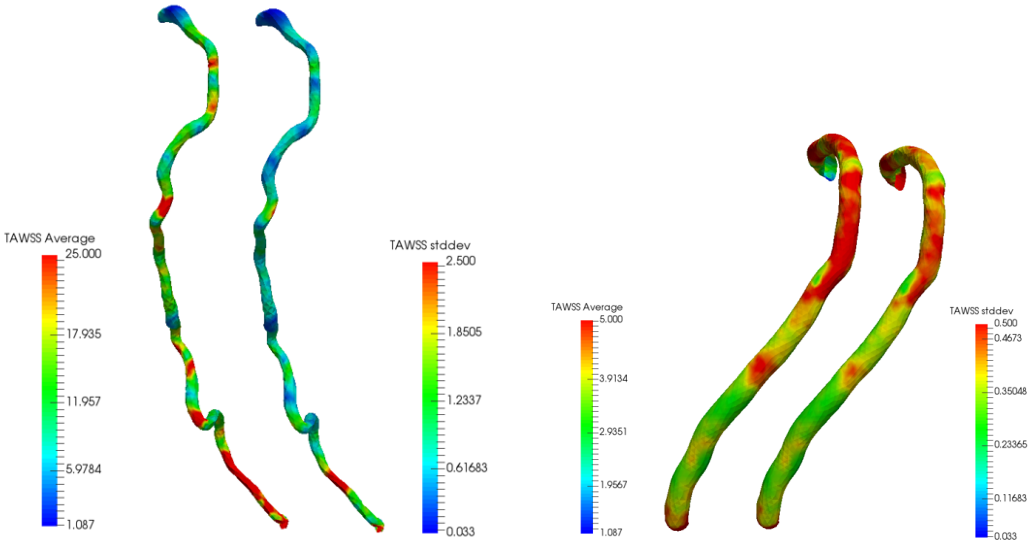
D. E. Schiavazzi et al., CMAME, 2017.

Validation on CV simulation





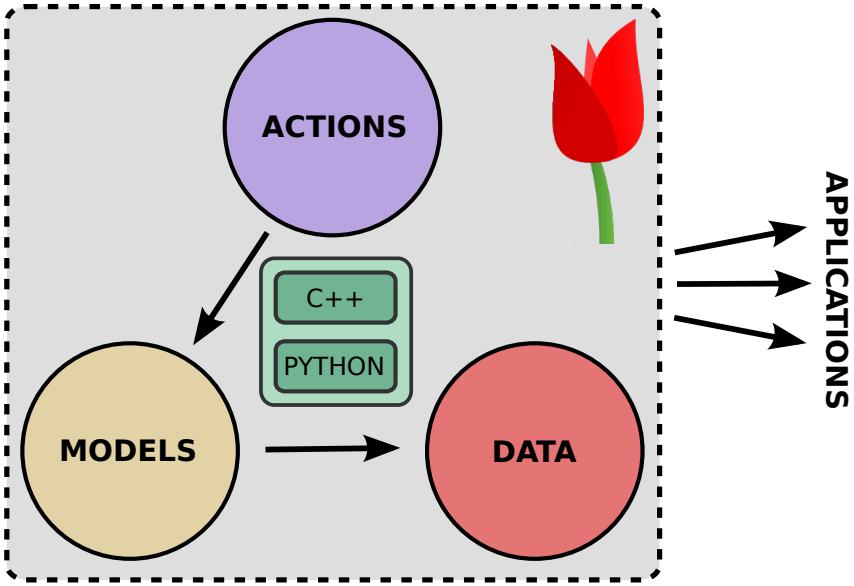
Applications to coronary artery disease **(sub-models)**



V - Software: tulip and SimVascular

tulip

tulip: a software library for sensor data assimilation and uncertainty analysis of computer models in physiology




```python
# Import UQ Library
import tulipUQ as uq
# Import Computational Model Library
import tulipCM as cm
# Import Data Library
import tulipDA as da
# Import Action Library
import tulipAC as ac


# Set Data Object
data = da.daData_multiple_Table()
data.readFromFile('data/dataFile.txt')

# Create Model
model = cm.cmModel()

# Assign Data Object To Model
model.setData(data)

# Set Action
action = ac.acAction(params)

# Set Model in Action
action.setModel(model)

# Compute
action.go()
```

NSF Funded Initiative:

PI - **Alison Marsden, Ph.D.**
Stanford University

PI - **Shawn Shadden**
UC Berkeley

PI - **Nathan Wilson**
OSMSC

Visit us at:
http://simvascular.github.io/

Features:

- ✓ **Complete opensource pipeline from image data to simulation results.**
- ✓ **Combined 2D and 3D segmentation tools.**
- ✓ **Solid modeling boolean operations.**
- ✓ **Meshing tools with adaptation.**
- ✓ **Readily available physiological boundary conditions (resistances, RCR, coronary).**
- ✓ **Multiscale modeling capabilities.**
- ✓ **Extensive online tutorial and help system.**

Conclusion and Ongoing Work

Conclusions:

- ✓ I hope I convinced you that Cardiovascular modeling is an **extremely rich, intrinsically uncertain application field**.
- ✓ Multiple model fidelities, model reduction, data assimilation and uncertainty propagation **need to be particularized** to this specific context.

Ongoing and future work:

- ✓ **Multilevel/Multifidelity approaches** for uncertainty propagation (**Casey Fleeter internship** Kindly supported by Sandia National Laboratory).
- ✓ **Bayesian model average** to design optimal circulatory layouts or vessel constitutive model selection.
- ✓ Uncertainty-aware **sub-model analysis** for coronary artery disease.
- ✓ **Improving parallel MCMC efficiency** on very large distributed datasets and for computationally expensive models.
- ✓ **Combining computational models with near-infrared spectroscopy** to detect peripheral vascular disease from optical measurements of hemoglobin concentration.
- ✓ **Development of tulip** and integration with SimVascular.

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Software:

- ✓ Simvascular (**simvascular.github.io**)
- ✓ Simtk.org portal