Computational Methods for Personalized Cardiovascular Medicine

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Personalized Medicine

"Providing the right treatment to the right patient, at the right dose at the right time"

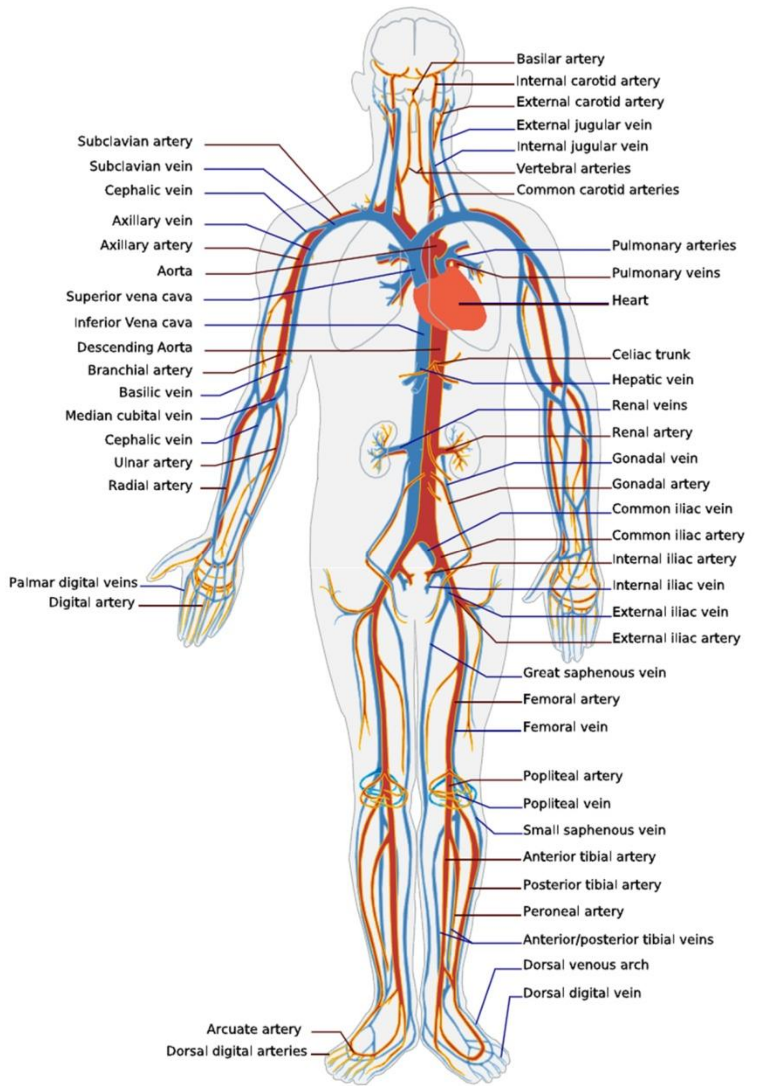
European Commission

- Factors causing disease have started to be understood as early as the 19th century, through developments made in chemistry and microscopy
- With the developments in medical imaging, genetics and artificial intelligence the diagnosis and treatment of pathologies have become more granular
- Ongoing developments in computational biology, medical imaging and regenerative medicine are setting the stage for truly personalized decision making and treatment
- However, there still is a long way before fully understanding why various pathologies initiate and evolve, and why there are considerable differences in how patients react to certain treatment plans

à nowadays clinicians still chose sub-optimal treatment plans or take sub-optimal decisions on a daily basis

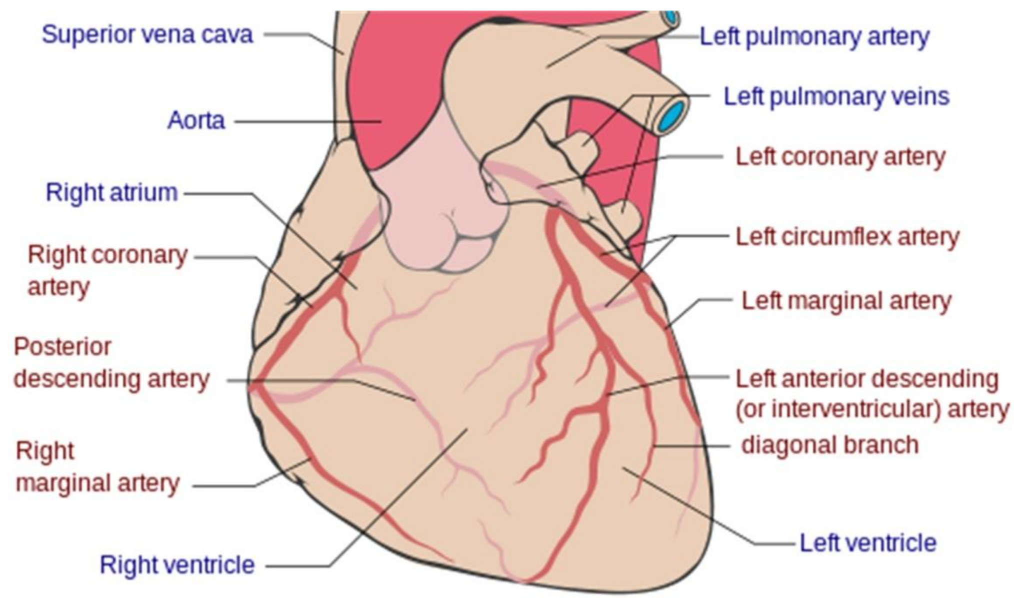
- The ultimate goal of personalized medicine is to identify apriori the subjects responding well to certain treatments and distinguish them from those who will not have any benefit and instead have to support costs and endure unpleasant side effects

The Cardiovascular System



Pathologies

- Atherosclerosis
- Aneurysm
- Congenital disorder
- Cardiac insufficiency



The Coronary Circulation – Coronary Artery Disease (CAD)

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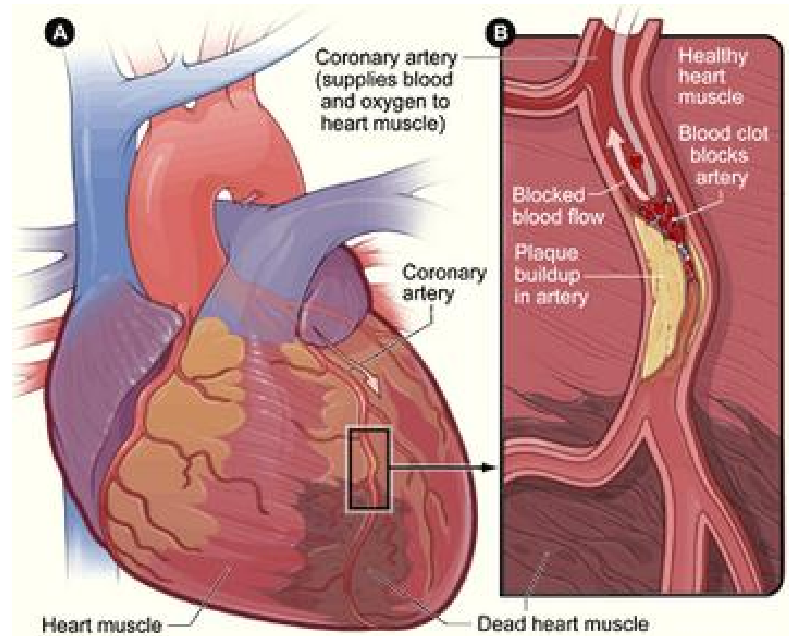
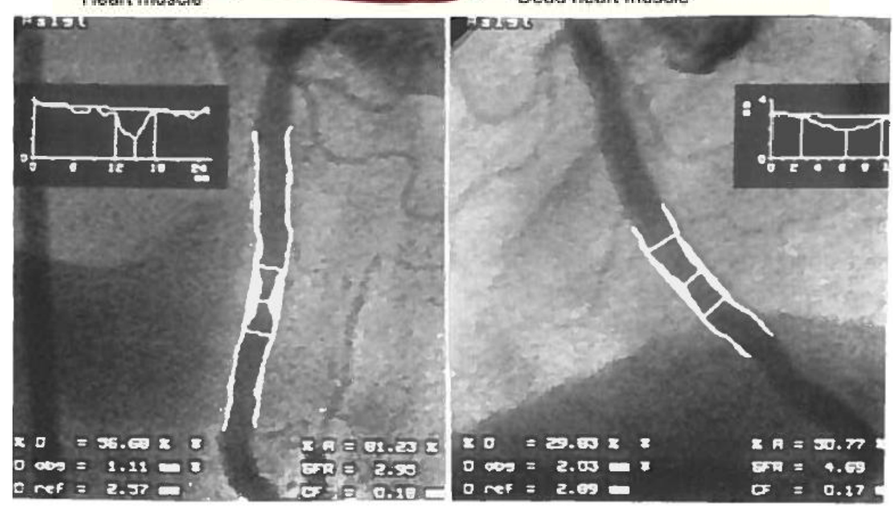
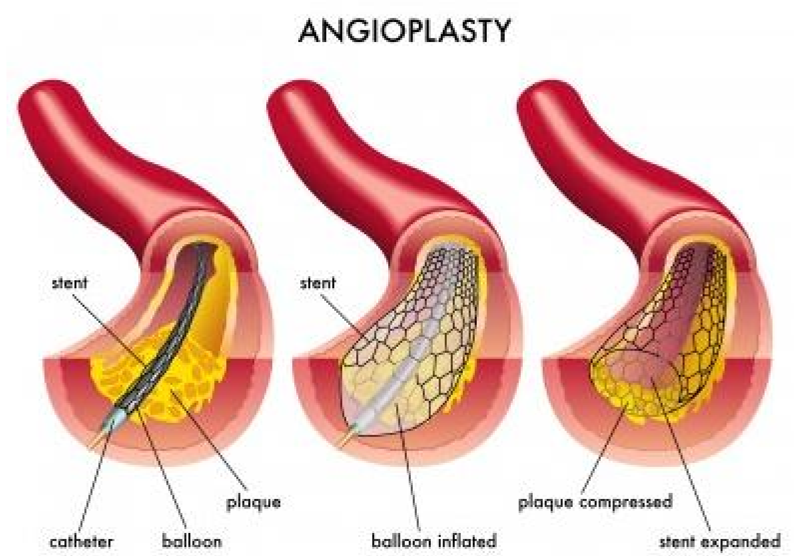
CAD:

- stable angina
- unstable angina
- myocardial infarction
- sudden coronary death

- Diagnosis: Anatomical (QCA à %DS > 50%)





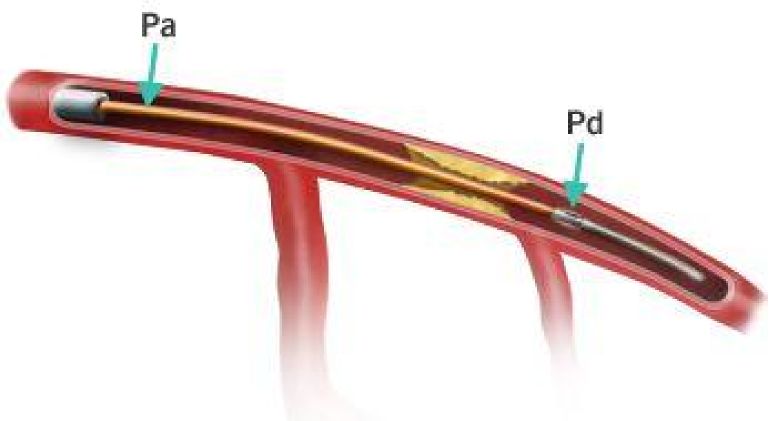


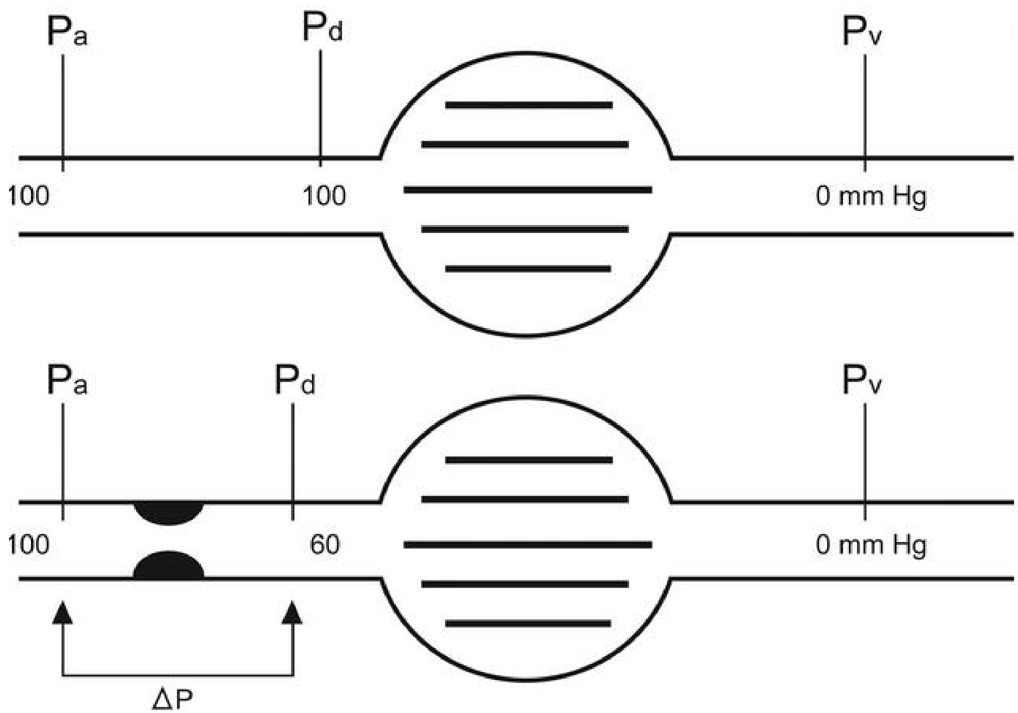
Functional Assessment of CAD – Fractional Flow Reserve

$$FFR = \frac{hyperemic\ flow\ in\ stenotic\ artery}{hyperemic\ flow\ in\ normal\ artery} = \frac{Q_{max}^{S}}{Q_{max}^{N}}$$

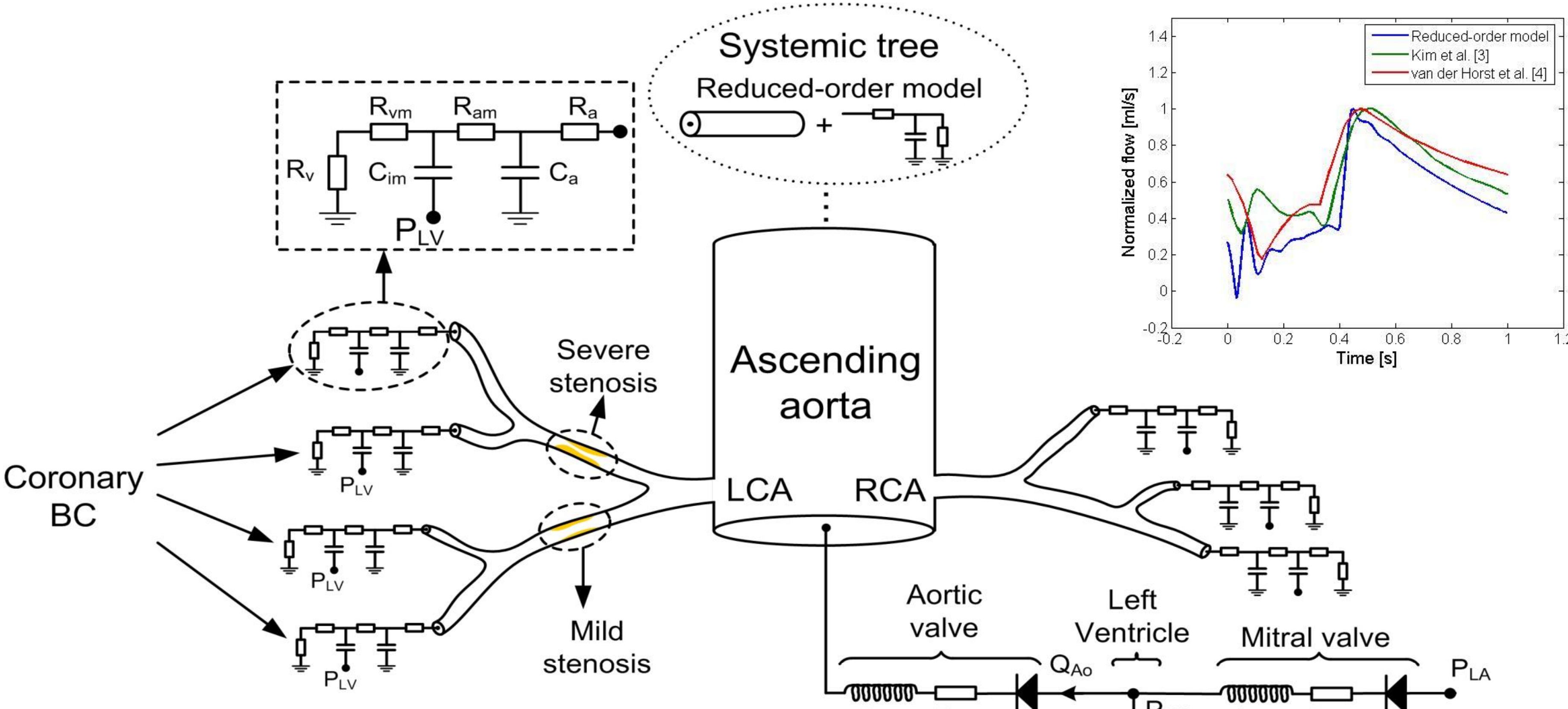
$$FFR = \frac{P_d - P_v}{P_a - P_v} @ \frac{P_d}{P_a}$$

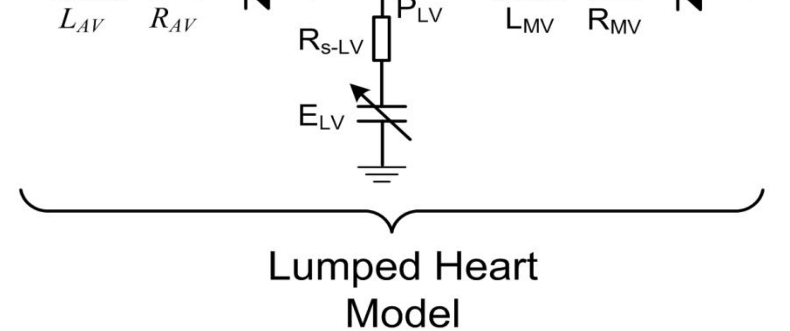
***FFR* < 0.8 à PCI / CABG**





Reduced-order hybrid CFD based blood flow model



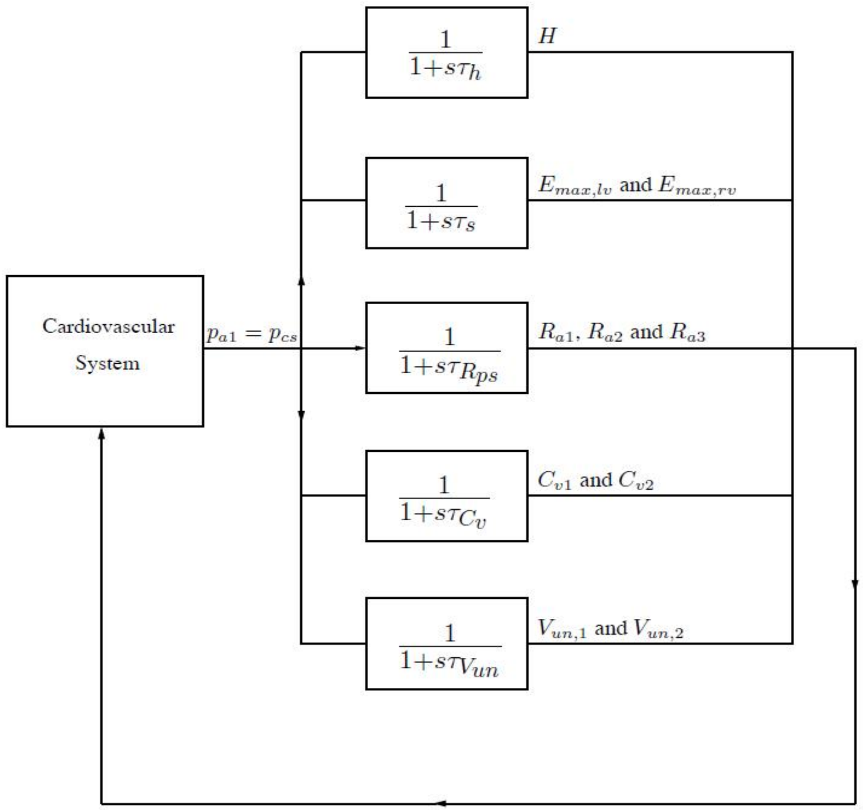


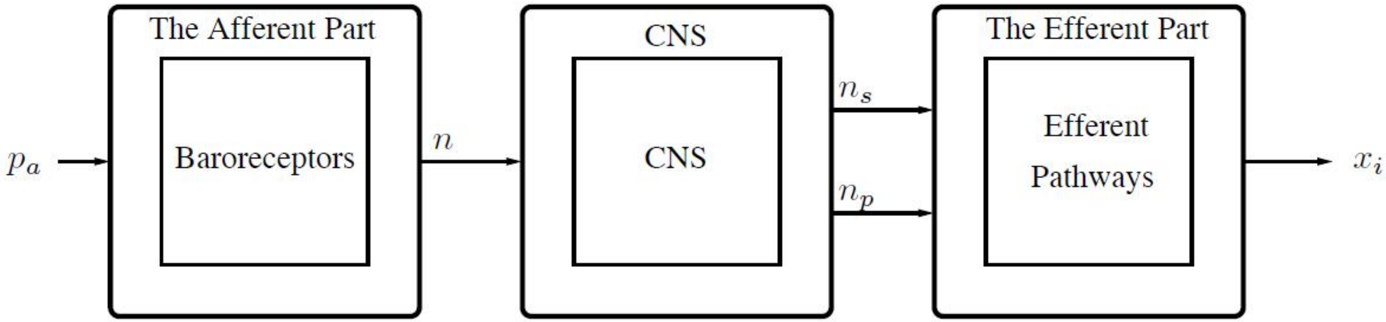
Model: System of partial differential equations which can only be solved numerically

Reduced-order hybrid CFD based blood flow model

The Baroreceptor model controls various parameters of the cardiovascular system:

- heart rate
- ventricular elastance
- peripheral resistance
- venous compliance
- venous unstressed volume





Modeling the coronary autoregulation

Principle:

- At rest the microvascular resistances are adapted so as to achieve the required level of coronary flow

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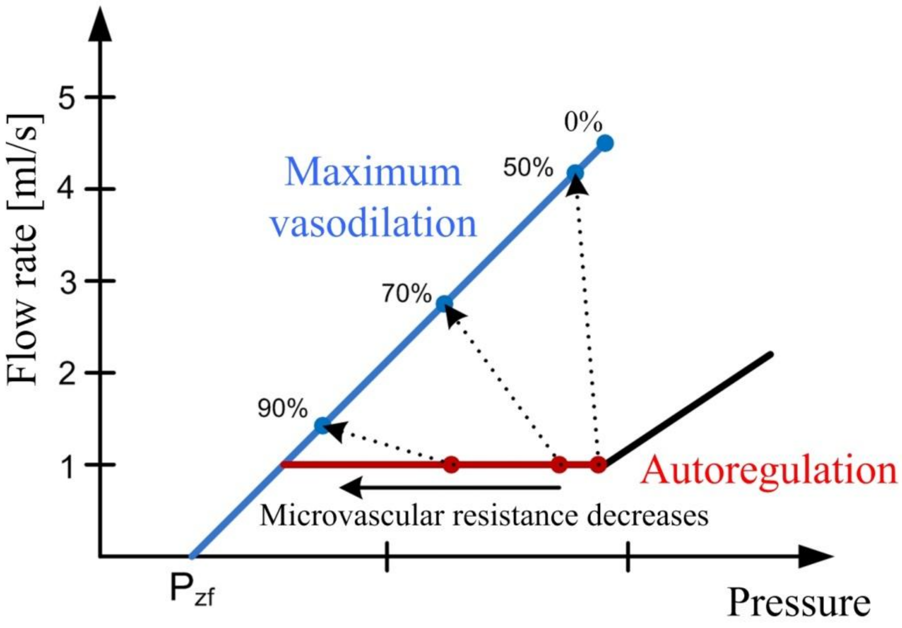
Coronary autoregulation – *autoregulation* (*nrBranch*).

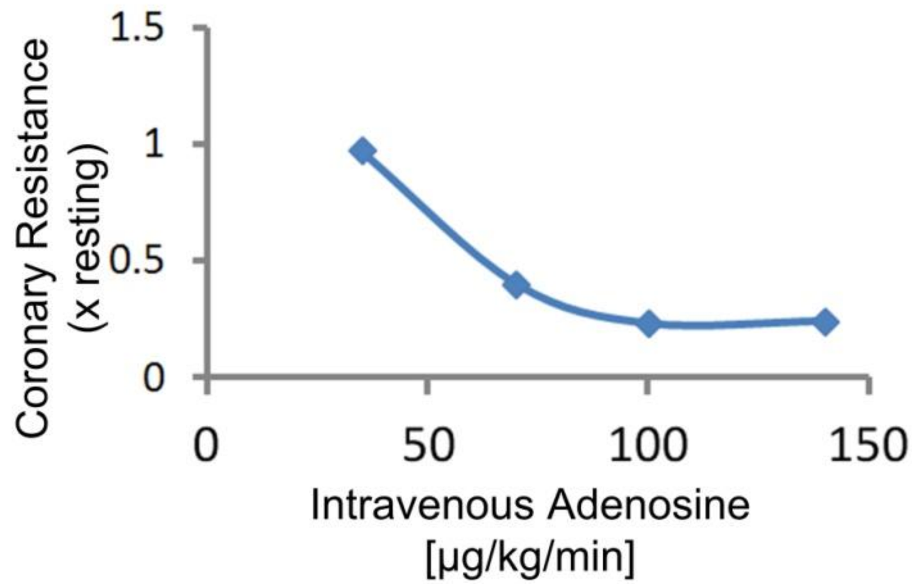
$i \leftarrow$ nrBranch
$(R_{t-current})_i = (R_{t-microv})_i - ((P_{in})_i - (P_{out})_i)_i / Q_i$
for each daughter branch j of branch i
    $\Phi_j \leftarrow (R_{t-microv})_i / (R_{t-microv})_j$
    $(R_{t-microv})_j \leftarrow (R_{t-current})_i / \Phi_j$
    Distribute resistance $(R_{t-microv})_j$ to corresponding terminal branches
    Compute equivalent resistances in subtree of branch j
    autoregulation(j)
end if
if current branch is terminal branch
    $(R_{t-microv})_i \leftarrow (R_{t-current})_i$
end if

Personalization of coronary hemodynamic computations

Principles:

- Rest state flow rate is proportional to anatomical markers (LV mass, vessel radius, etc.)
- Flow rate in each branch is proportional to the radius
- Microvasculature reacts predictably to hyperemia $Q_i = k \times r_i^n$

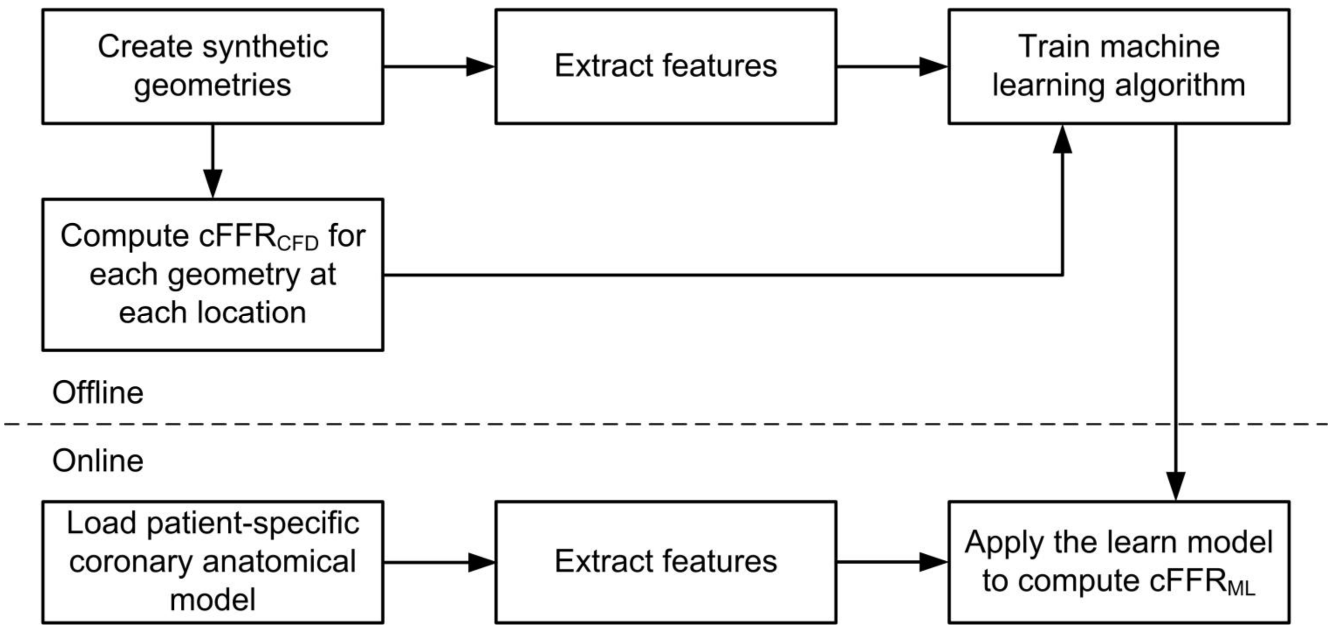




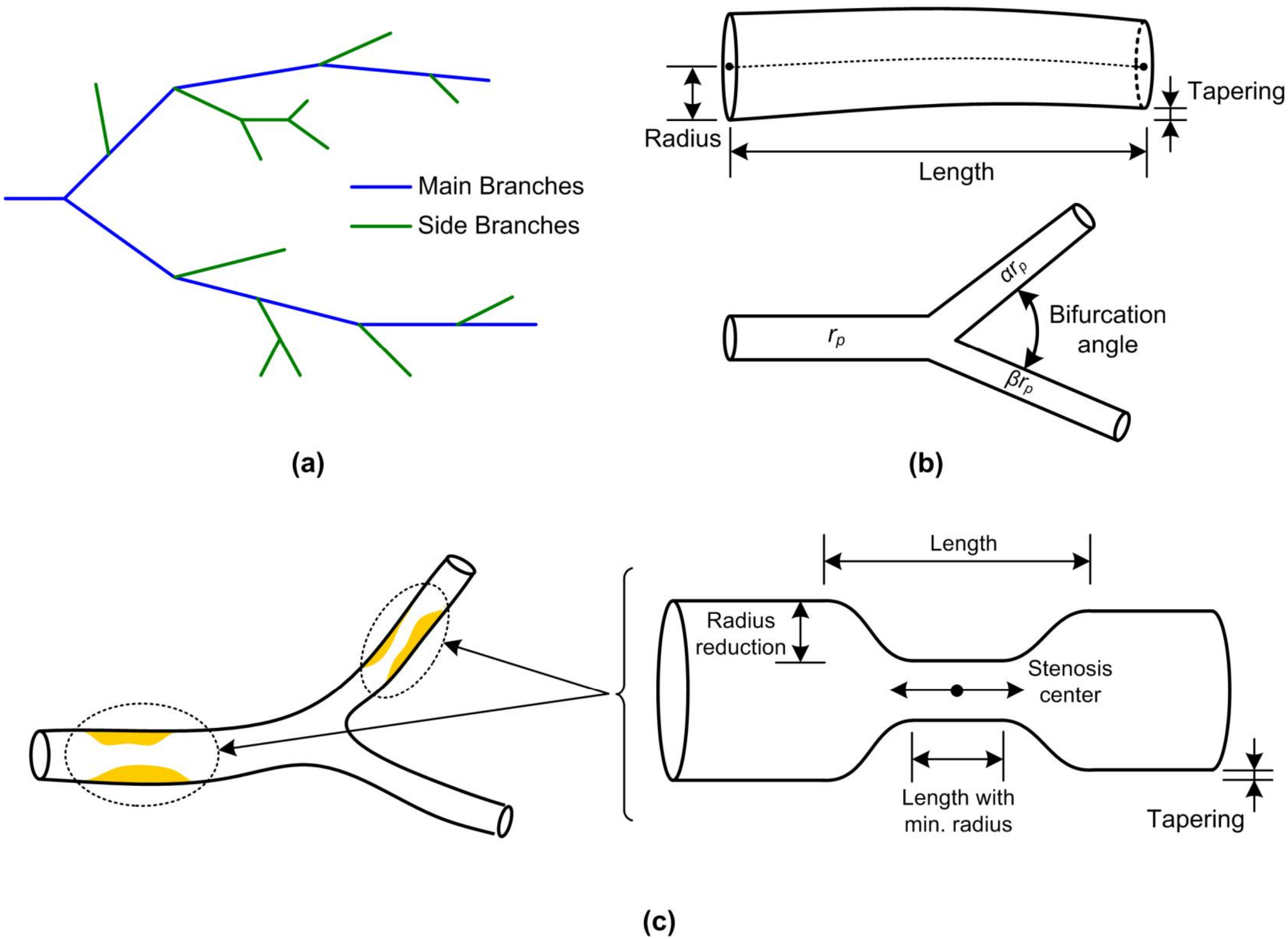
A machine-learning based approach for FFR computation

Principle:

- Run computational fluid dynamics model on a large synthetic dataset and determine ground truth FFR values
- Train deep neural network to learn the mapping between input data and FFR
- Apply trained deep neural network on patient-specific dataset to derive patient-specific FFR values



Synthetic data generation



Machine learning based FFR – Results

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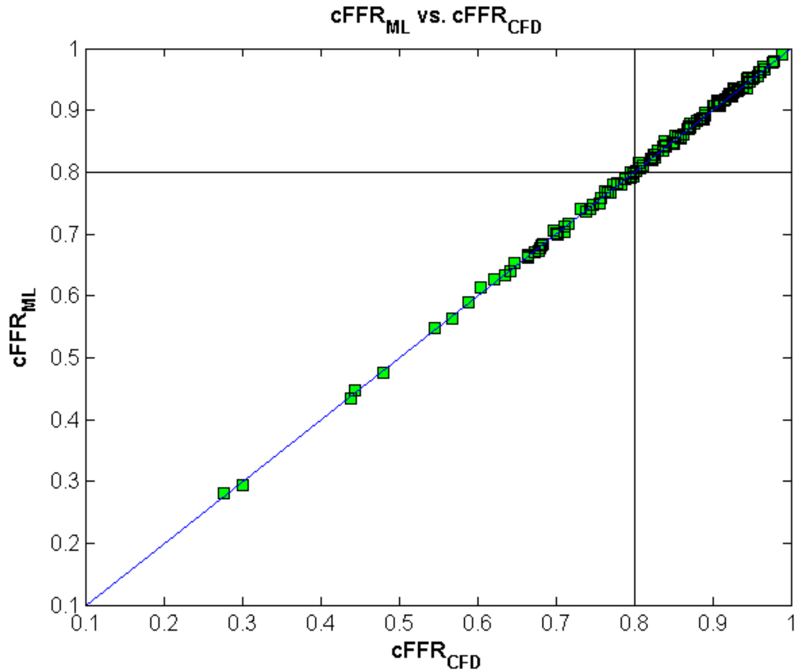
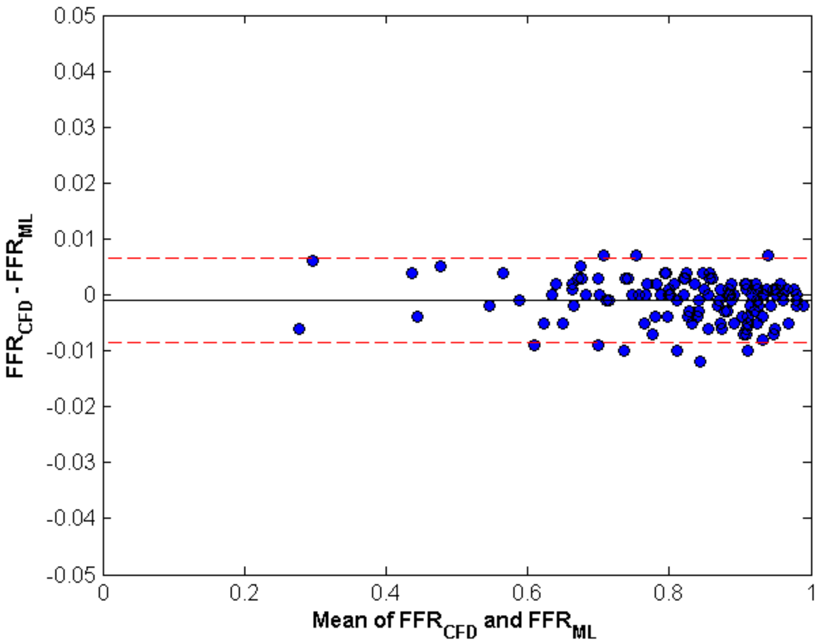
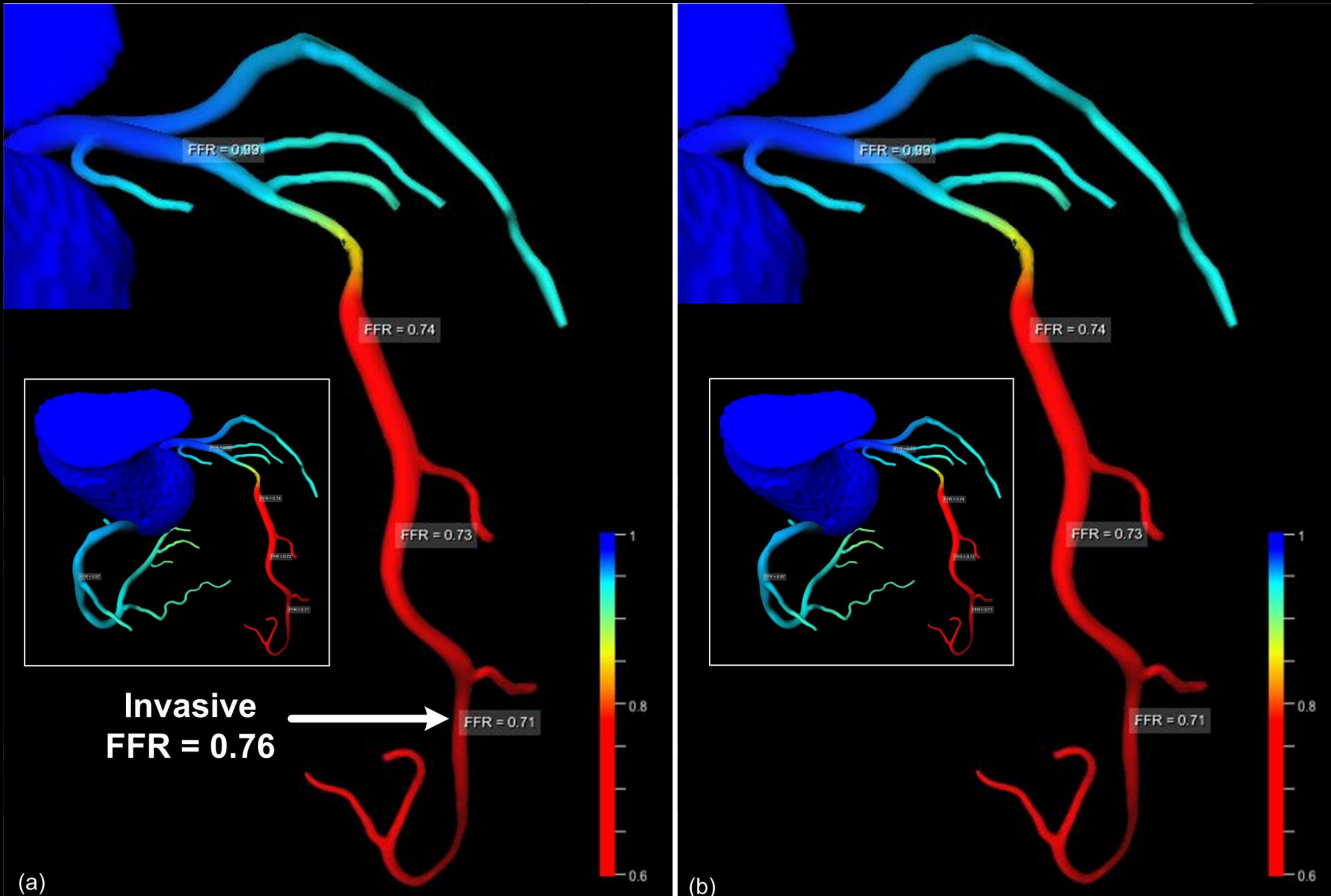
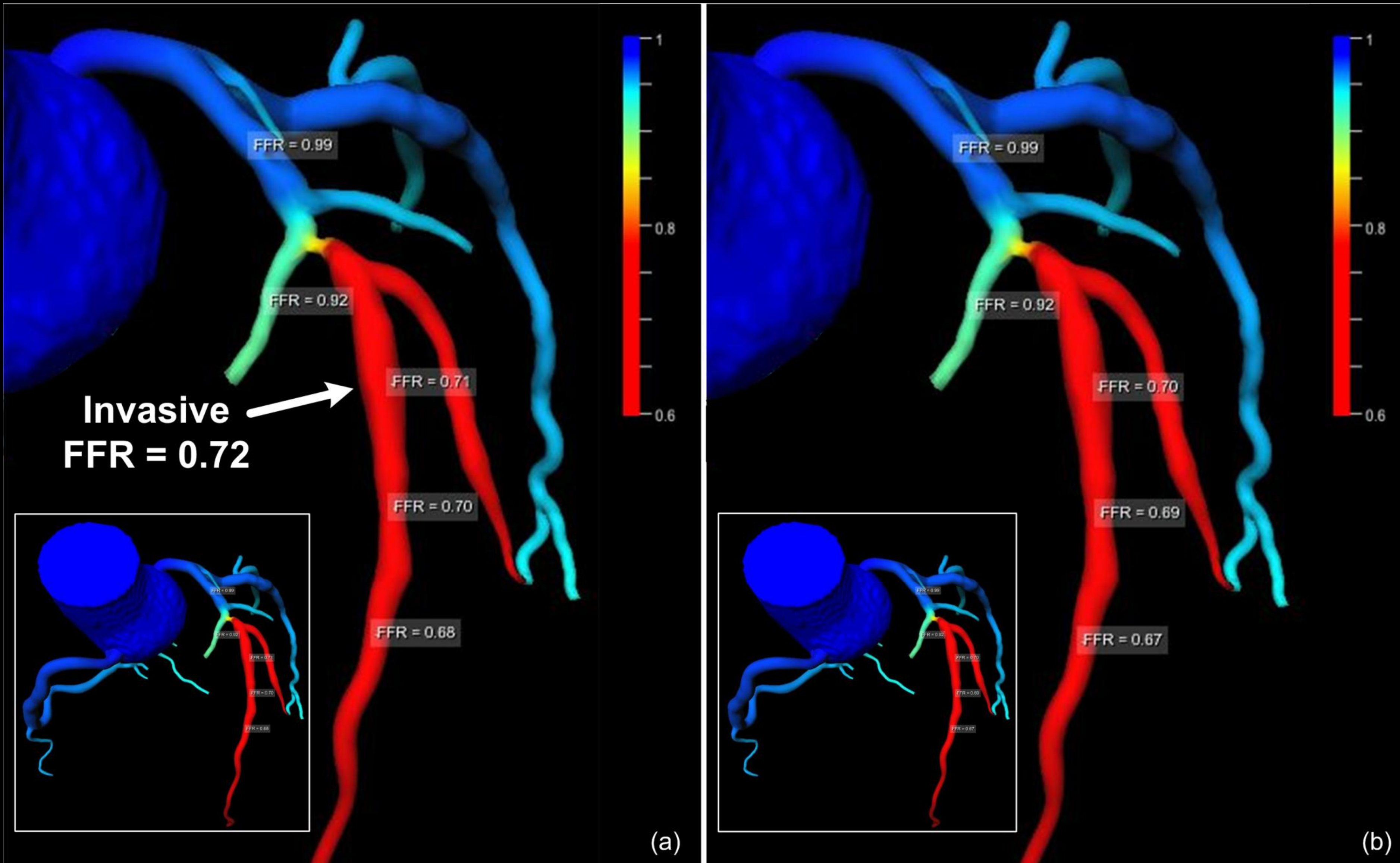
- CFD and ML based are statistically not discernible
  - Correlation: 0.9994, $p < 0.001$
  - mean difference: -0.00081 ± 0.0039
- Average execution time: 196.3 ± 78.5 sec. for the CFD model à 2.4 ± 0.44 seconds for the ML model

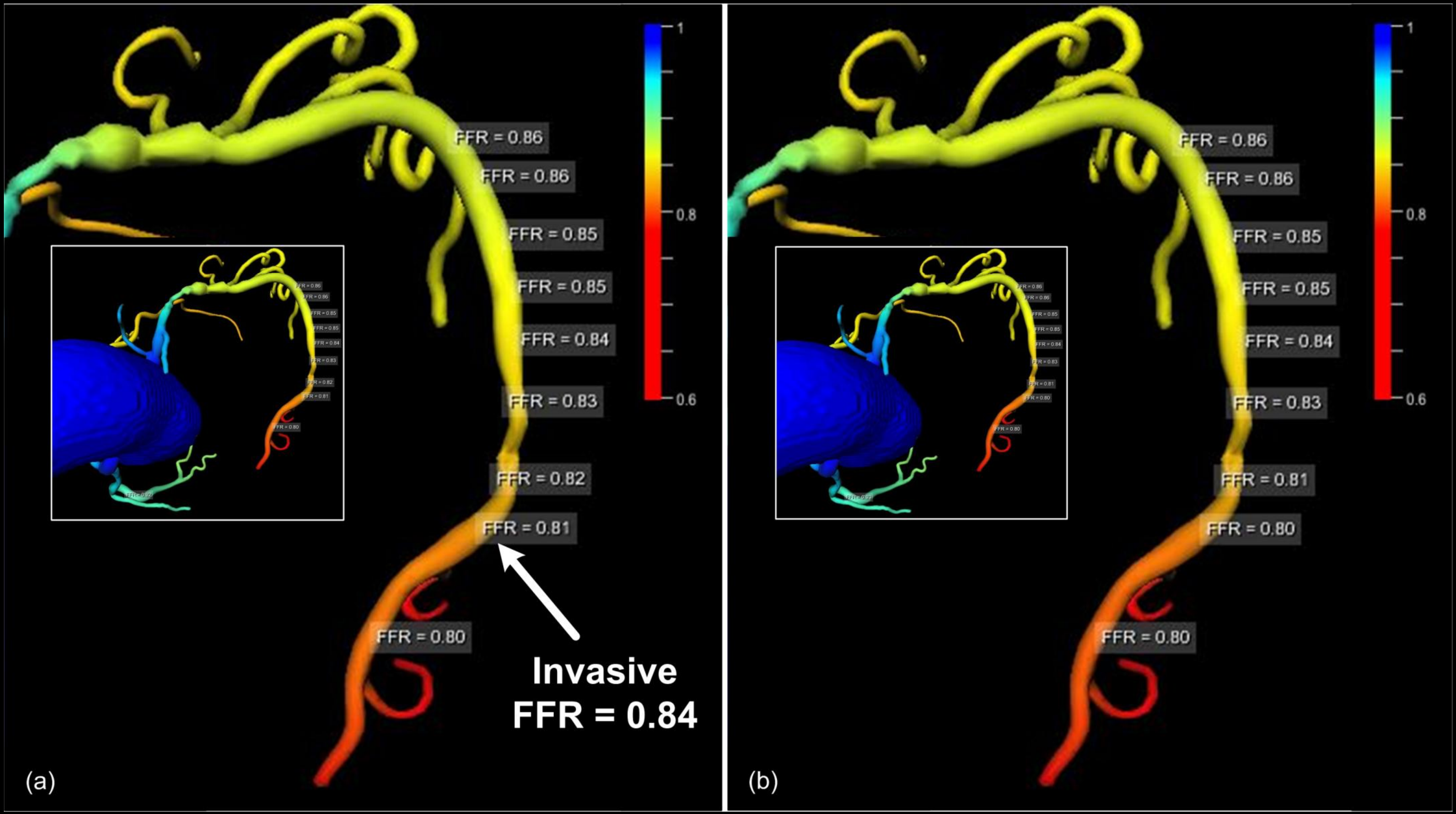






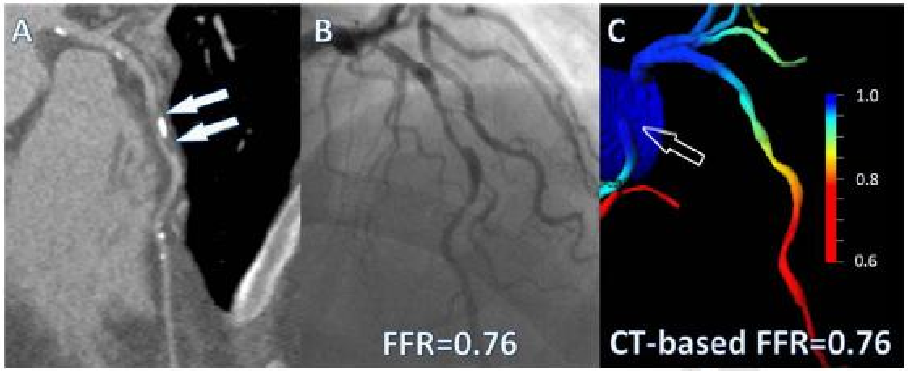
FFR = 0.99
FFR = 0.74
FFR = 0.73
FFR = 0.71
Invasive
FFR = 0.76
1
0.8
0.6
(a)
FFR = 0.99
FFR = 0.74
FFR = 0.73
FFR = 0.71
1
0.8
0.6
(b)


FFR = 0.99
FFR = 0.92
FFR = 0.71
FFR = 0.70
FFR = 0.68
Invasive
FFR = 0.72
1
0.8
0.6
(a)
FFR = 0.99
FFR = 0.92
FFR = 0.70
FFR = 0.69
FFR = 0.67
1
0.8
0.6
(b)

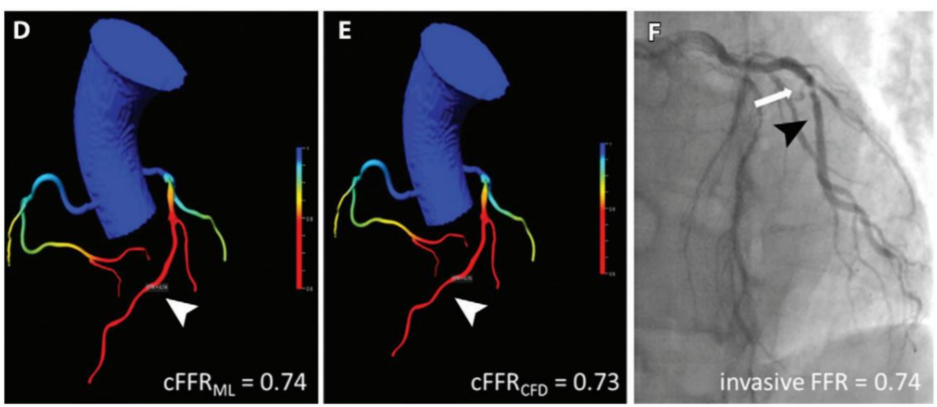


FFR = 0.86
FFR = 0.86
FFR = 0.85
FFR = 0.85
FFR = 0.84
FFR = 0.83
FFR = 0.82
FFR = 0.81
FFR = 0.80
Invasive
FFR = 0.84
1
0.8
0.6
(a)
FFR = 0.86
FFR = 0.86
FFR = 0.85
FFR = 0.85
FFR = 0.84
FFR = 0.83
FFR = 0.81
FFR = 0.80
FFR = 0.80
1
0.8
0.6
(b)

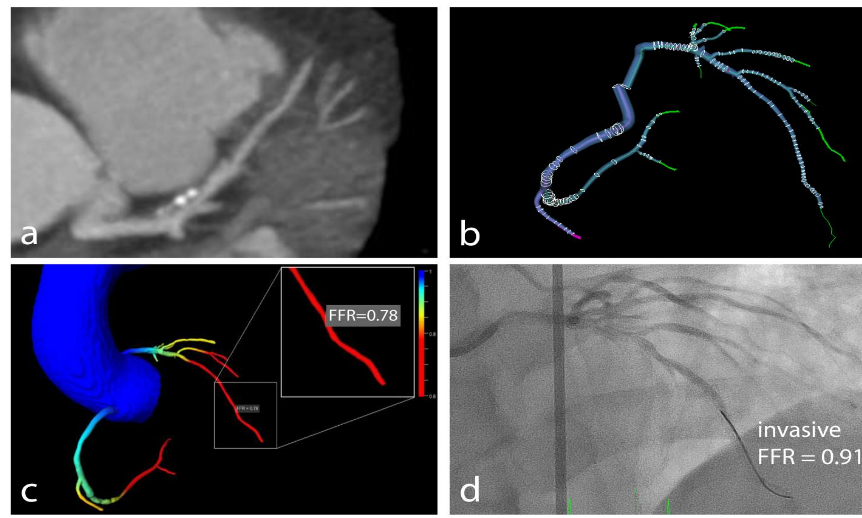
Non-invasive FFR computation – Publications



Coenen, A. et al., *Fractional Flow Reserve Computed from Noninvasive CT Angiography Data: Diagnostic Performance of an On-Site Clinician-operated Computational Fluid Dynamics Algorithm*, Radiology, 2015.



Renker, M. et al., *Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve*, The American Journal of Cardiology, 2014.



Tesche, C. et al., *Coronary CT Angiography–derived Fractional Flow Reserve: Machine Learning Algorithm versus Computational Fluid Dynamics Modeling*, Radiology, 2018.

A Hierarchical Parameter Estimation Framework for Tuning Boundary Conditions in Hemodynamic Computations

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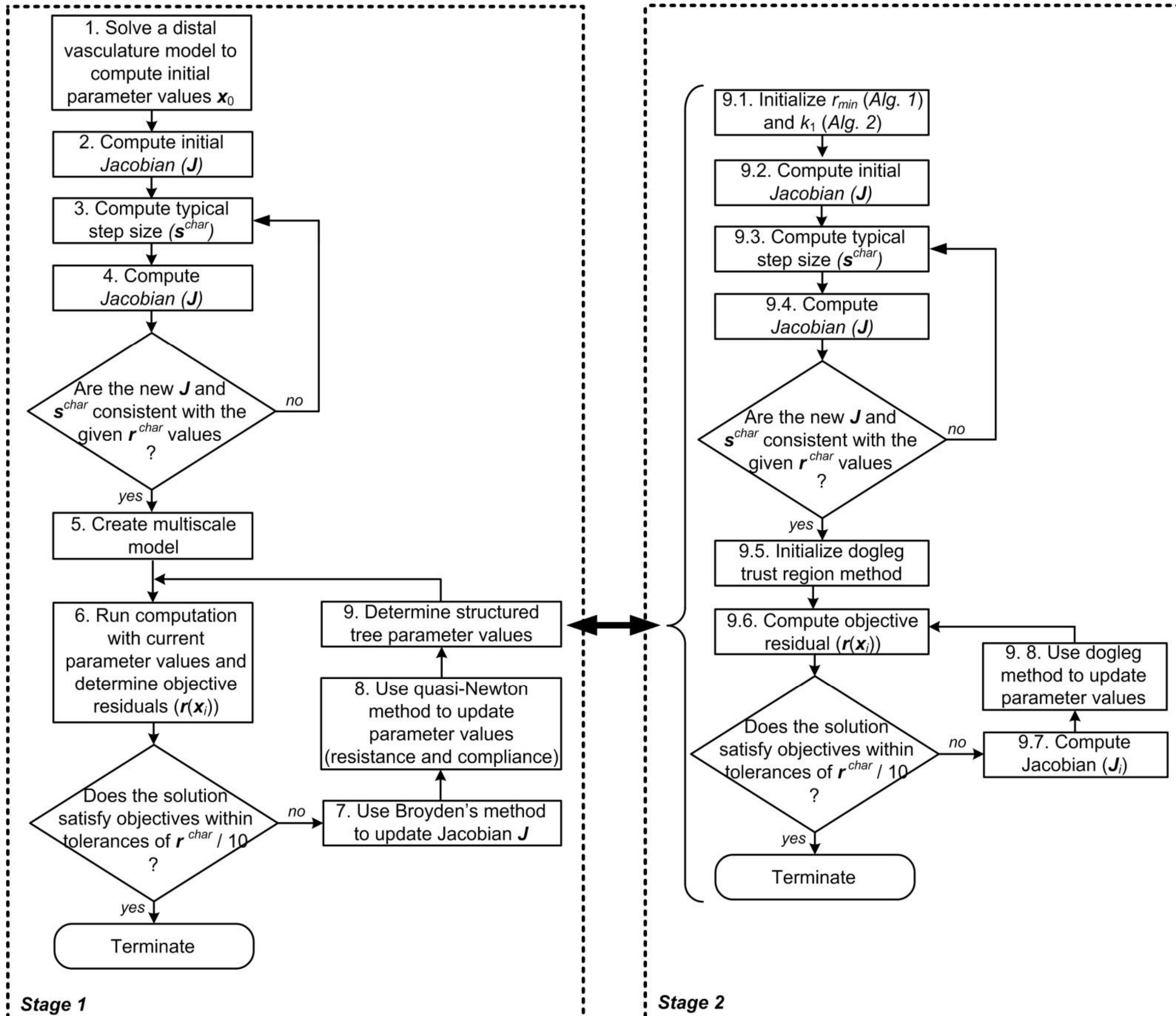
- A calibration problem is formulated at each of the two stages in the hierarchical framework
- Common hemodynamic properties, like resistance and compliance, are estimated at the first stage
- The second stage estimates the parameters of the structured trees so as to match the values of the hemodynamic properties determined at the first stage



A Hierarchical Parameter Estimation Framework for Tuning Boundary Conditions in Hemodynamic Computations

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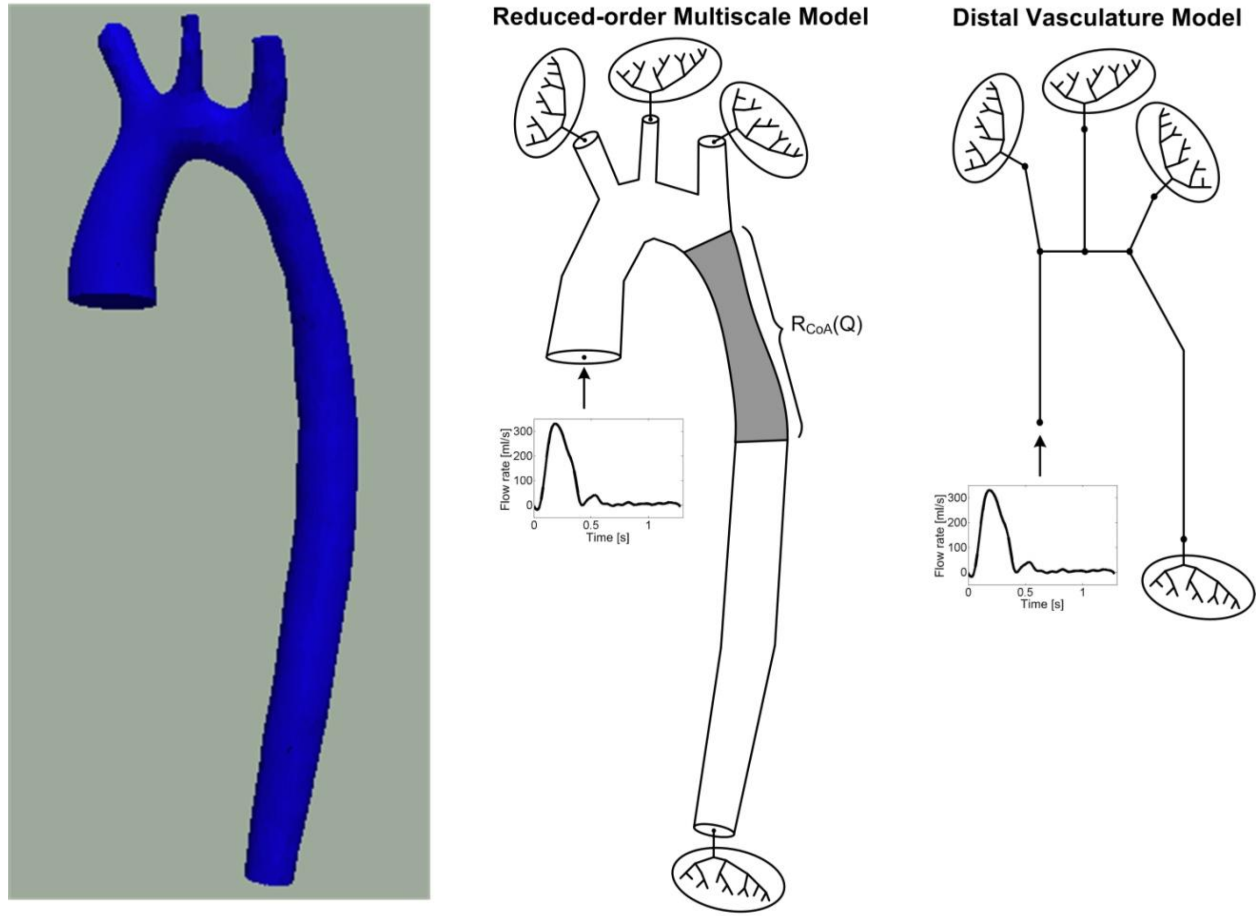
- The parameter estimation framework solves a system of nonlinear equations, formulated based on a set of objectives for the pressures and flow rates:

$$\mathbf{r}\begin{pmatrix} R_{t-BC} \\ R_{t-LCC} \\ R_{t-LS} \\ R_{t-DAo} \\ C_{SupraAo} \\ C_{DAo} \end{pmatrix} = \begin{Bmatrix} (P_{\max})_{comp} - (P_{\max})_{target} \\ (P_{\min})_{comp} - (P_{\min})_{target} \\ (\Phi_{LCC})_{comp} - (\Phi_{LCC})_{target} \\ (\Phi_{LS})_{comp} - (\Phi_{LS})_{target} \\ (\Phi_{DAo})_{comp} - (\Phi_{DAo})_{target} \\ (Q_{DAo-\max})_{comp} - (Q_{DAo-\max})_{target} \end{Bmatrix} = \begin{Bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{Bmatrix}$$



(a) (b) (c)

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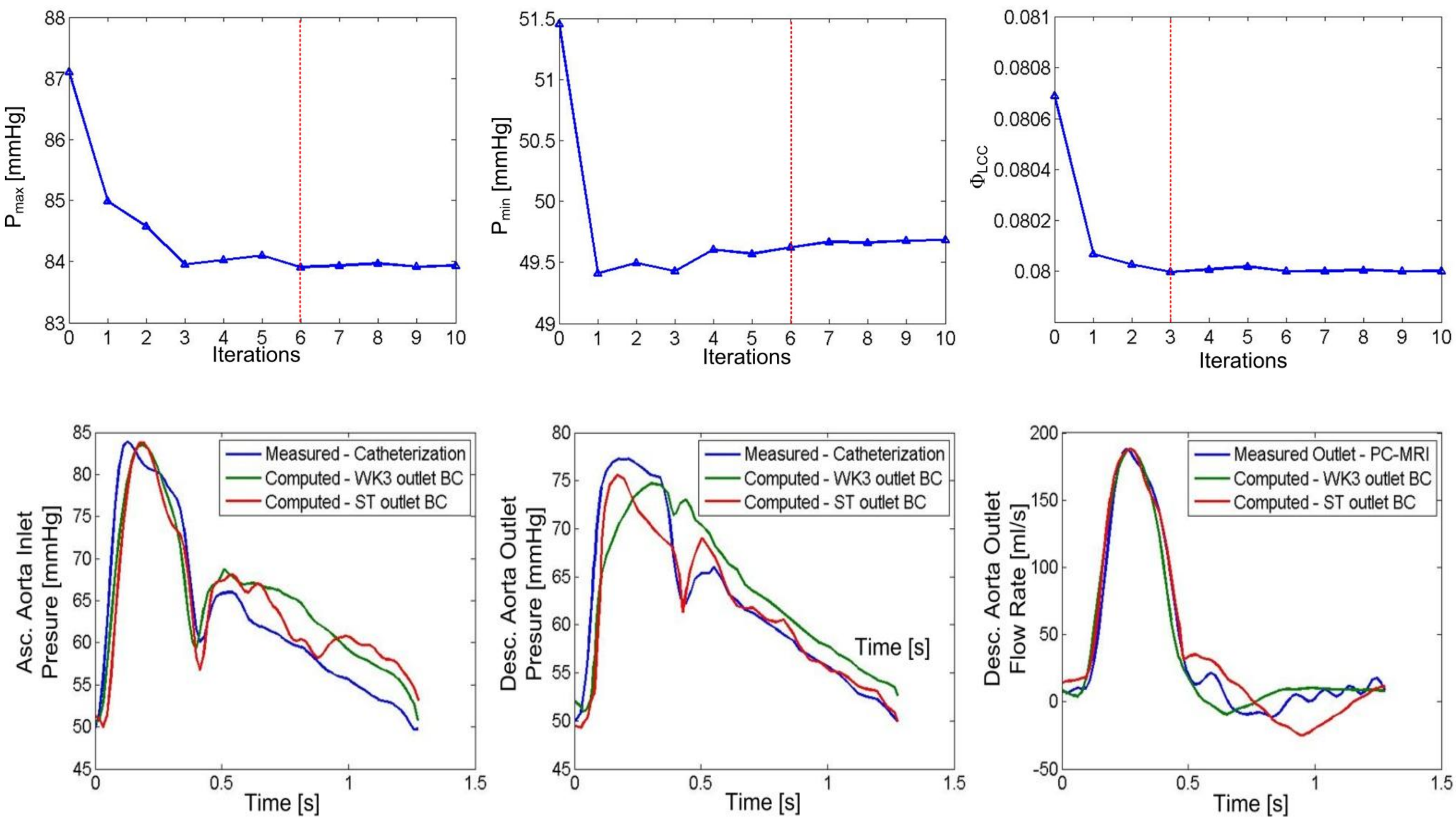
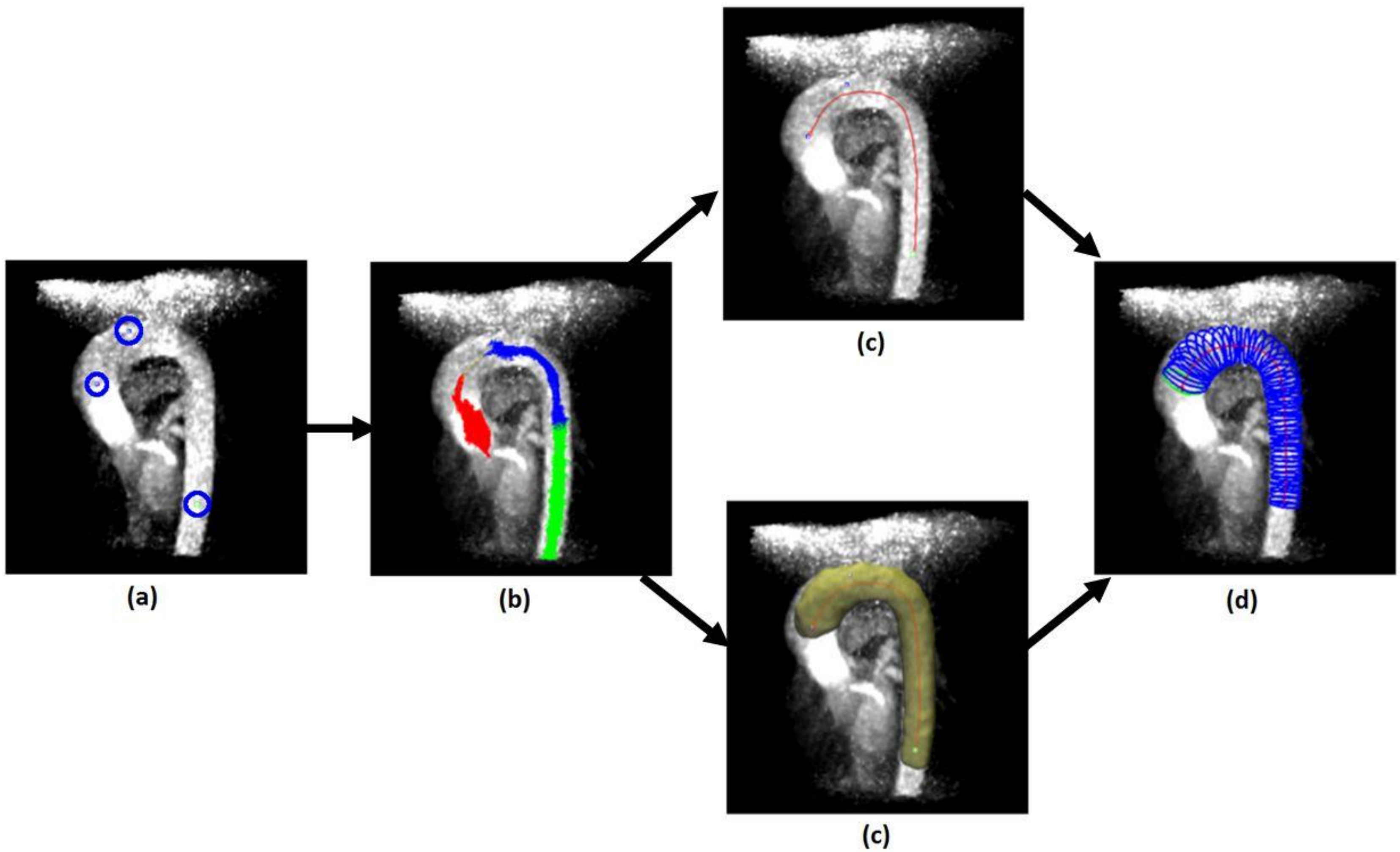
A Hierarchical Parameter Estimation Framework for Tuning Boundary Conditions in Hemodynamic Computations



Non-invasive assessment of patient-specific aortic hemodynamics from 4D flow MRI data



Non-invasive assessment of patient-specific aortic hemodynamics from 4D flow MRI data

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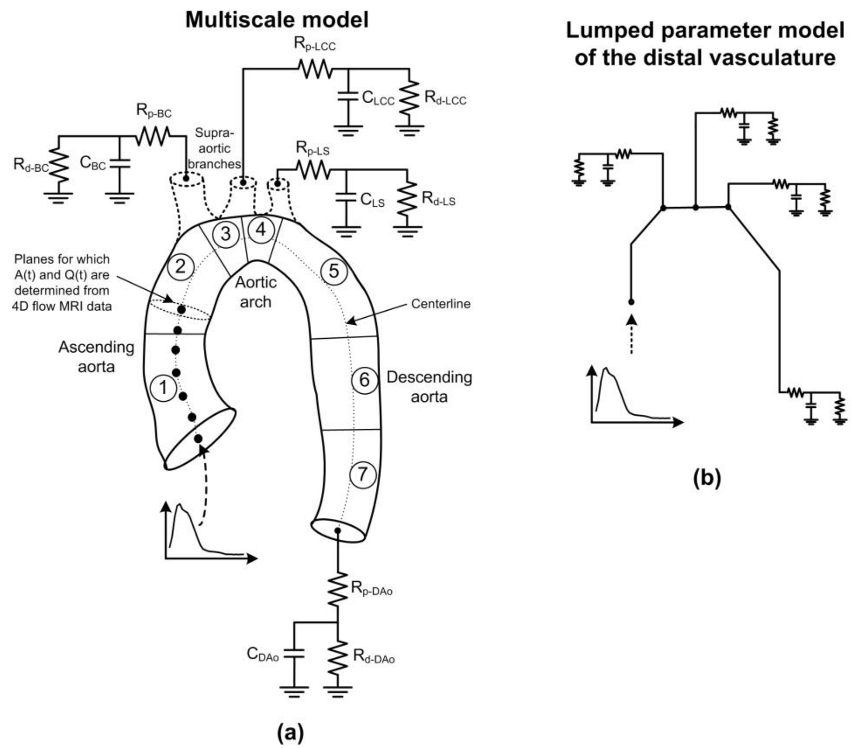
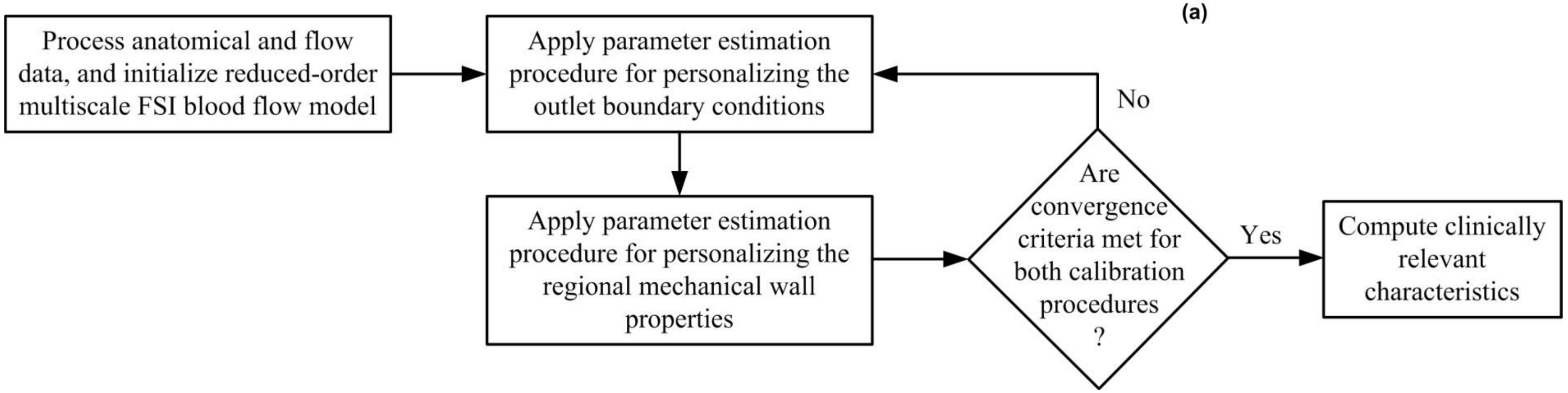
- A framework based on a reduced-order multiscale fluid-structure interaction blood flow model, and on two calibration procedures is introduced:
    - Windkessel parameters of the outlet boundary conditions are personalized by solving a system of nonlinear equations
    - The regional mechanical wall properties of the aorta are personalized by employing a non-linear least squares minimization method





Non-invasive assessment of patient-specific aortic hemodynamics from 4D flow MRI data

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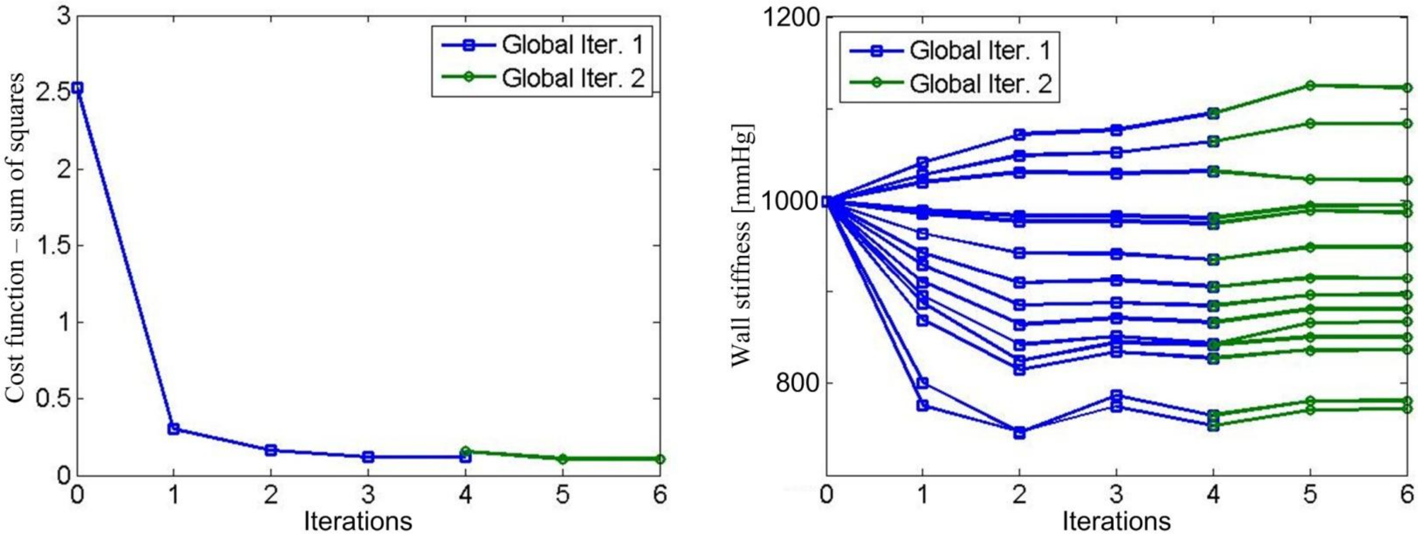
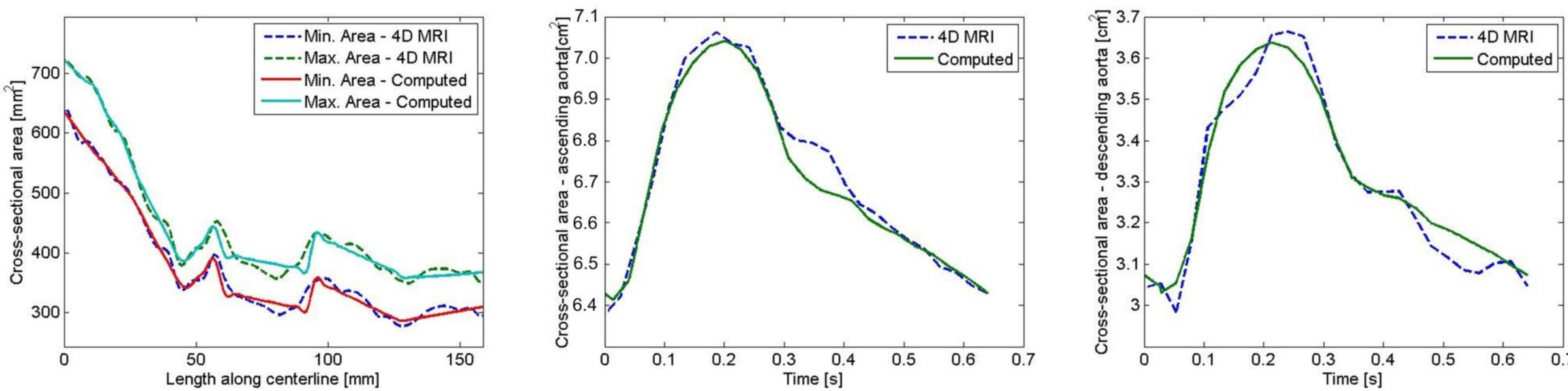


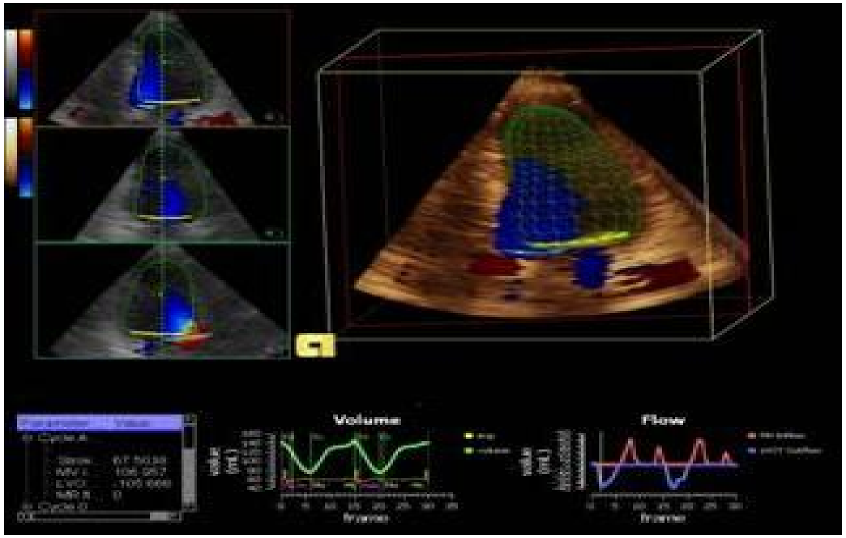
(a) (b)

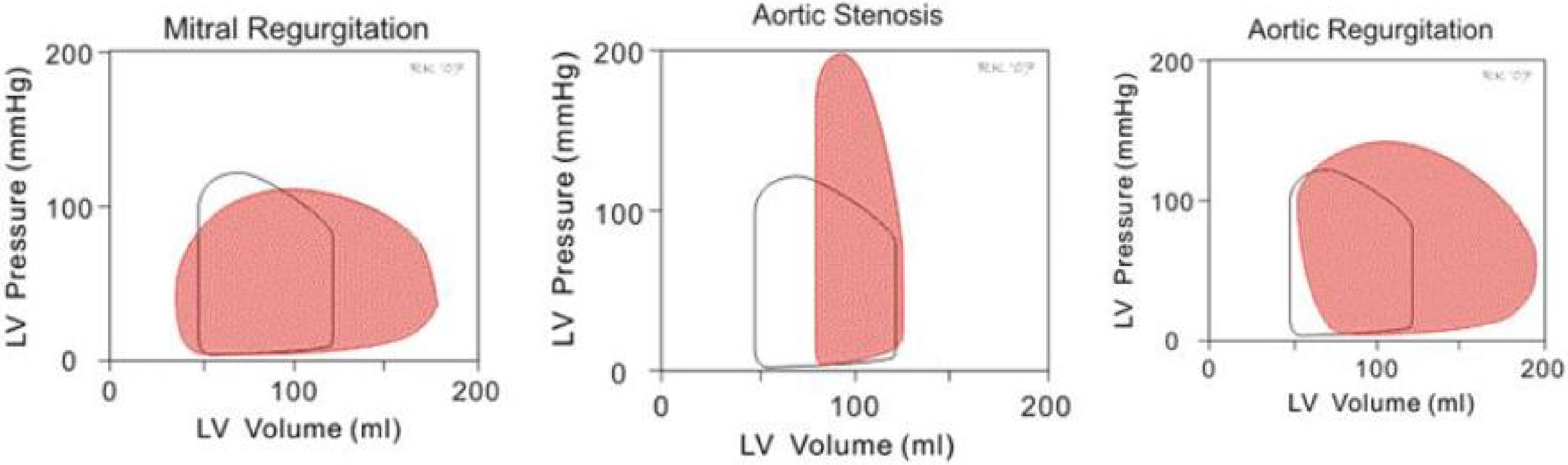


(a) (b) (c)

Model Based Non-invasive Estimation of PV Loop from Echocardiography

- The left ventricular pressure-volume (PV) loop represents an efficient tool for understanding and characterizing cardiac function
- Various heart diseases impact the LV PV loop in different ways:
    - Mitral regurgitation
    - Aortic stenosis
    - Aortic regurgitation

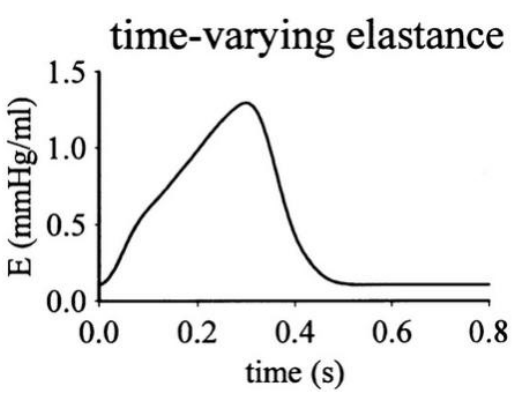


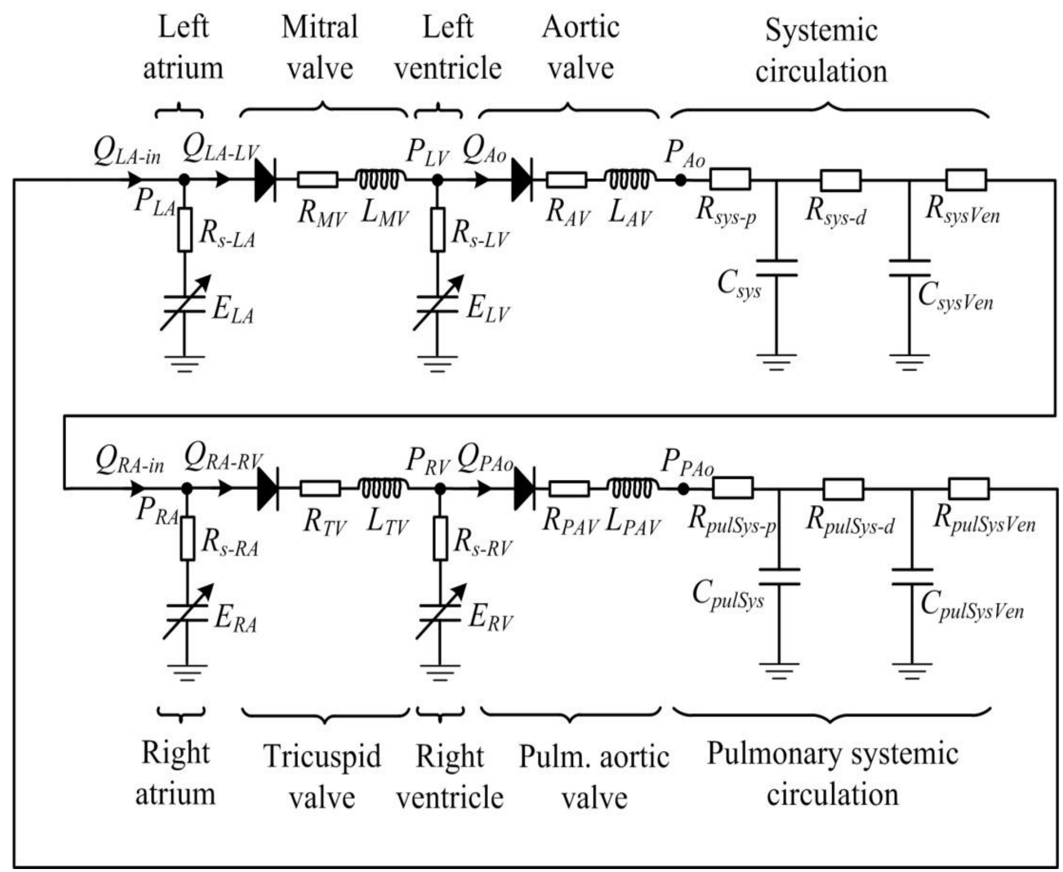


Model Based Non-invasive Estimation of PV Loop from Echocardiography

- The parameter estimation problem is formulated as a numerical optimization problem
- Objectives: match patient-specific systolic pressure, diastolic pressure and ejection fraction

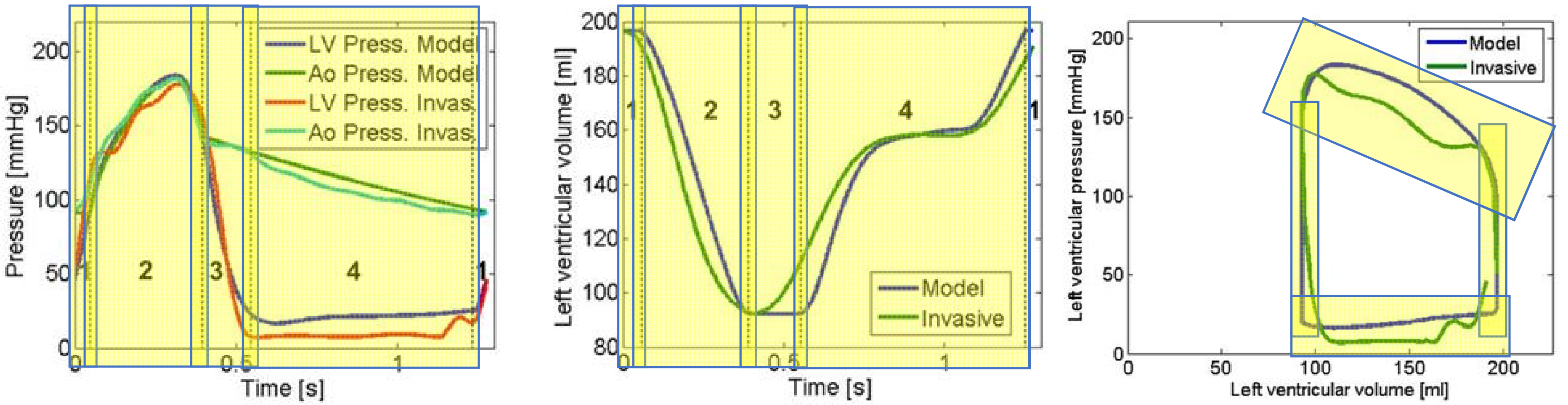
$$\rho\begin{pmatrix} E_{max-LV} \\ V_{0-LV} \\ C_{sys} \end{pmatrix} = \begin{cases} (SBP)_{comp} - (SBP)_{ref} \\ (DBP)_{comp} - (DBP)_{ref} \\ (EF)_{comp} - (EF)_{ref} \end{cases} = \begin{cases} 0 \\ 0 \\ 0 \end{cases}$$





Model Based Non-invasive Estimation of PV Loop from Echocardiography

- The four phases of the cardiac cycle can be clearly identified in the computed results:
  - Isovolumetric contraction (1)
  - Ventricular ejection (2)
  - Isovolumetric relaxation phase (3)
  - Ventricular filling phase (4)
- There is a close agreement between the model based and the invasive time-varying LV and aortic pressures, time-varying LV volumes, and PV loops



GPU-based high performance computing

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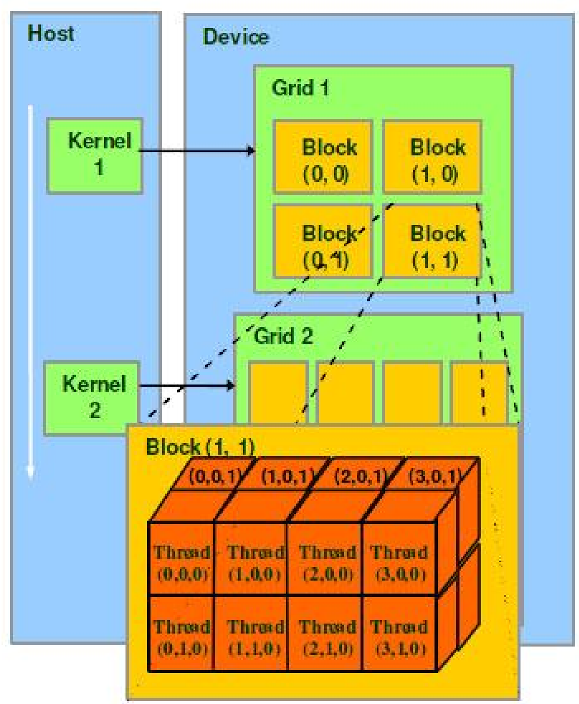
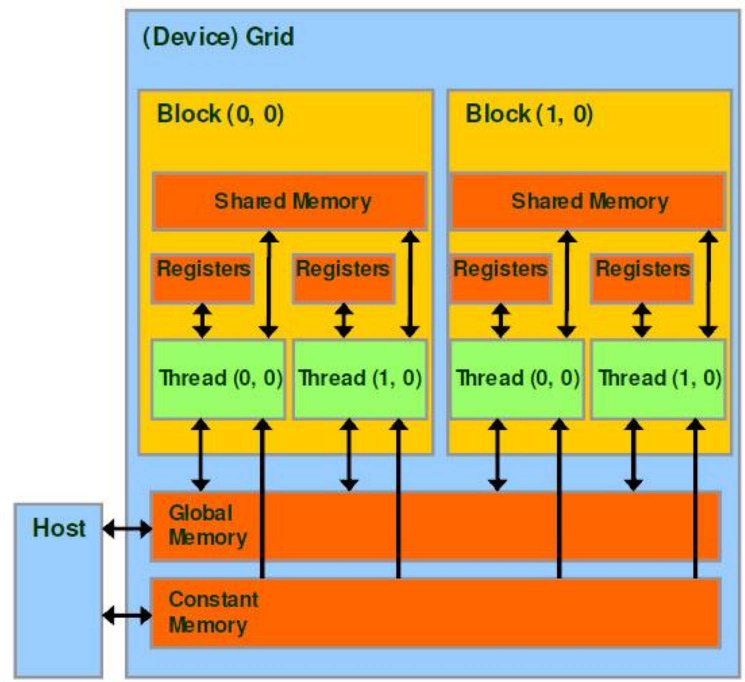
Resource allocation

GPU:

Execution Configuration and Memory Model





Optimized Three-Dimensional Stencil Computation on Fermi and Kepler GPUs

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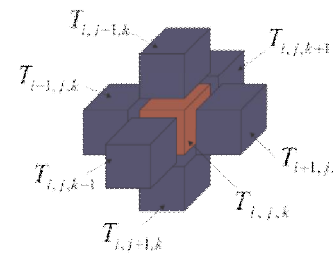
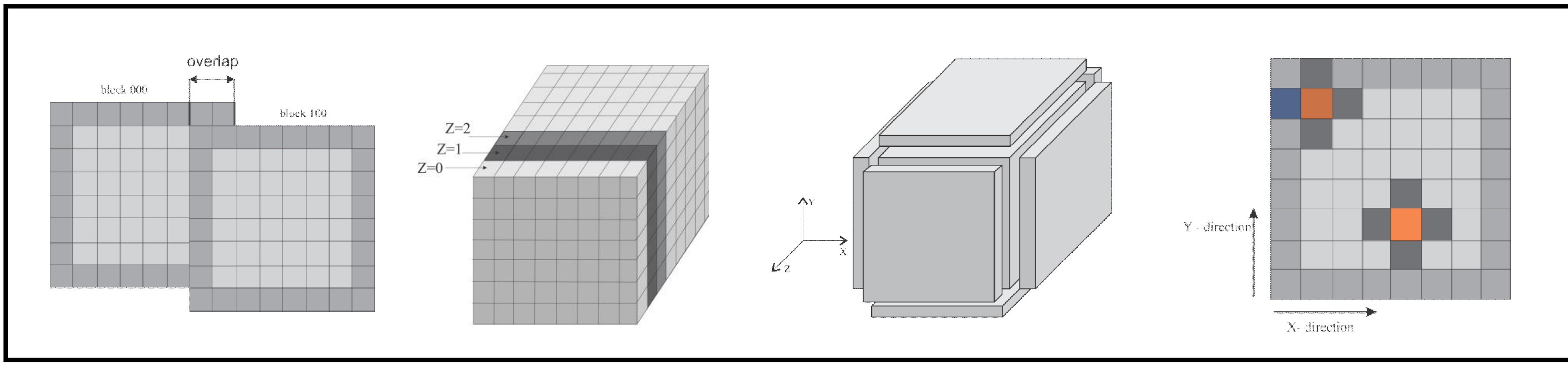
- Stencil based algorithms are used intensively in scientific computations
- Graphics Processing Units (GPU) based implementations of stencil computations speed-up the execution significantly compared to conventional CPU only systems





Method	GTX480	GTX 660M	GTX 680
3DBase	1.7	3.45	0.62
3DShMOverL	3.5	6.17	1.13
3DShMNoOverL	1.8	3.78	0.73
2DBase	1.2	3.09	0.63
2DReg	0.9	2.47	0.58
2DShM	1.2	2.87	0.59
2DShMReg	1.09	2.32	0.48

Method	Execution time [ms]	Reg. per thread	Divergent branches	Shared memory per block [bytes]	Total number of 64 bit global load instr.	Total number of 64 bit global store instr.
3DBase	0.62	25	12016	-	14002632	2000376
3DShMOverL	1.13	19	20811	4096	4741632	2000376
3DShMNoOverL	0.73	21	12694	8000	3524851	2000376
2DBase	0.63	25	94	-	14002632	2000376
2DReg	0.58	25	94	-	10033632	2000376
2DShM	0.59	25	94	800	6953688	2000376
2DShMReg	0.48	25	94	640	2984688	2000376

My Health My Data (MHMD)

- Call: H2020 ICT-18-2016
- Issues of data subjects' privacy and data security represent a crucial challenge in the biomedical sector
- *My Health My Data* aims at changing the existing scenario by introducing a distributed, peer-to-peer architecture, based on Blockchain and Personal Data Accounts
- Goal is to determine new mechanisms of trust and of direct, value-based relationships between people, hospitals, research centers and businesses

- UTBV Role:
  - Development of analytics solutions on top of the architecture (e.g. risk models based on blood flow modeling)
  - Development of homomorphic encryption solutions based on PHE and AI

Information Technology: The Future of Cancer Treatment (ITFoC)

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- Call: FLAG-ERA JTC 2016
- Every patient is unique: no individual tumor has ever been observed before, or will ever be observed again, due to the enormous genetic/epigenetic heterogeneity between and within tumors and patients, causing each patient (and even cells within the same tumor) to react differently to drugs
- To be able to provide *the right drug at the right dose for every patient*, ITFoC develops demonstrators, based on a deep molecular characterization of tumor and patient as input to virtual patient models of individual patients in silico

- UTBV Role:
  - Personalization of molecular models using novel parameter estimation frameworks, based on sensitivity analysis, uncertainty quantification, and model reduction
  - Employ AI based techniques for personalized assessment

Information Technology: The Future of Cancer Treatment (ITFoC)

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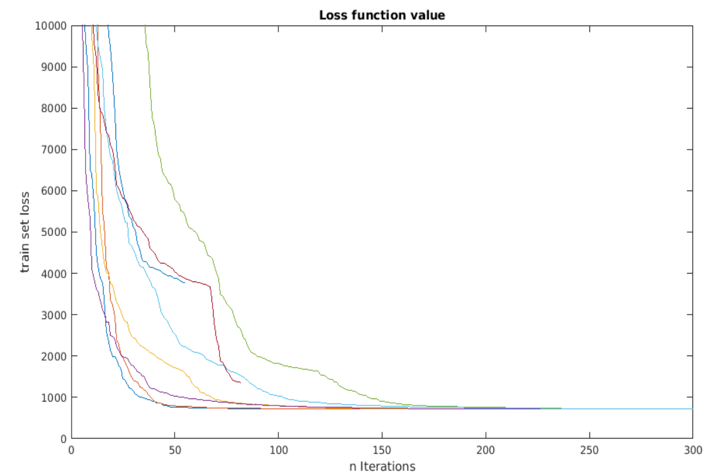
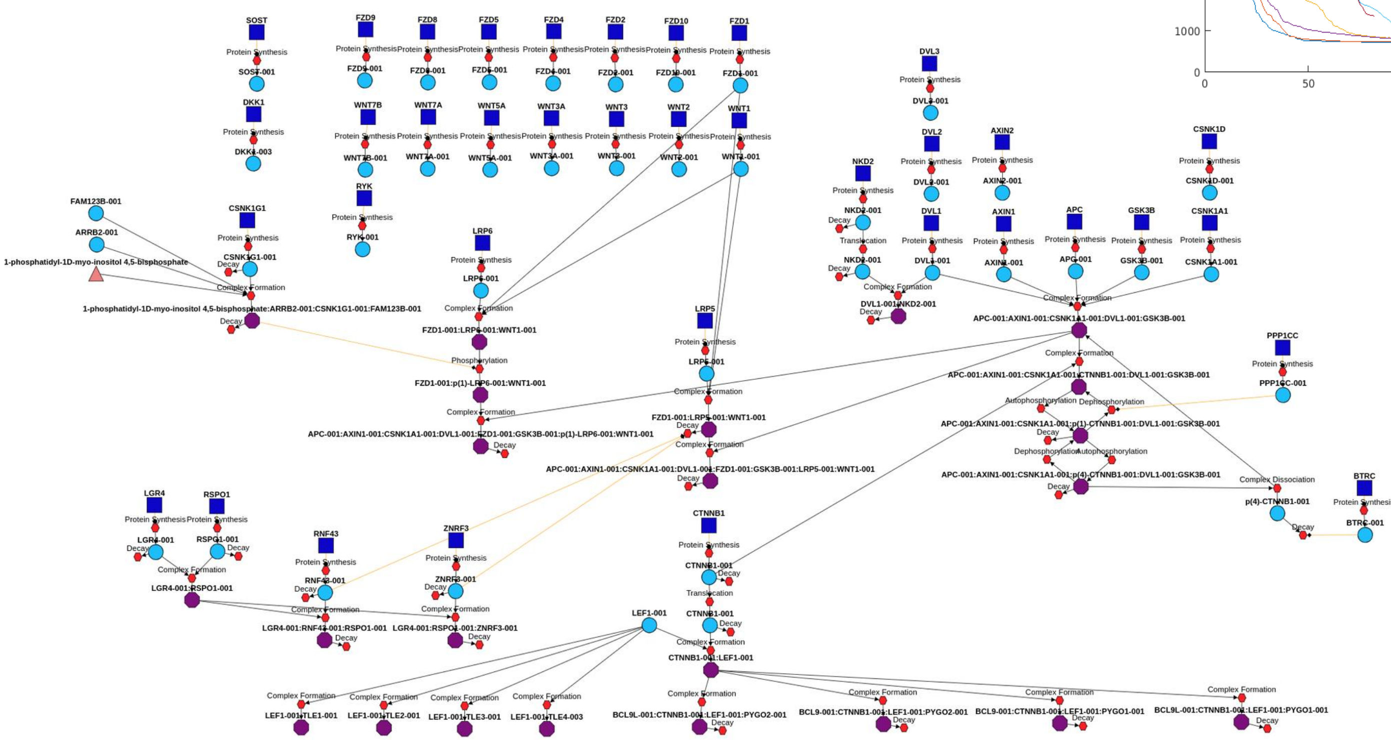
- State space models are considered, e.g. WNT model:

$$x \in \mathbb{R}^{421}$$

$$\theta \in \mathbb{R}^{1156}$$

$$u \in \mathbb{R}^{189}$$





Frictionless Energy Efficient Convergent Wearables for Healthcare and Lifestyle Applications (CONVERGENCE)

- Call: FLAG-ERA JTC 2016
- The wearable sensor platform proposed in CONVERGENCE is centered on energy efficient wearable proof-of-concepts at system level exploiting data analytics developed in a context driven approach (in contrast with more traditional research where the device level research and the data analytics are carried out on separate path, rarely converging)

- UTBV Role:
  - Development of a personalized hemodynamics model which uses as input information provided by a wearable system (e.g. heart rate, blood pressure, etc.)

Academic career

- PhD: 2010 – 2013
- PostDoc: 2014 – 2015
- Teaching:
  - Associated: 2009 - 2014
  - Lecturer: 2014 – 2017
  - Associate Prof.: 2017 - present
- Courses: Numerical Methods, Programmable Logic Controllers
- Coordinated several bachelor and master thesis, leading to the publication of ISI Proc. papers (IEEE EMBC, IEEE HPEC, IEEE ICSTCC, etc.)
- Actively involved in the coordination of two PhD theses focused on personalized medicine:
  - Lattice Boltzmann based Fluid-Structure Interaction Blood Flow Models
  - Deep Learning based Diagnosis of Breast Cancer Patients.

Summary of research and academic results

- Published 48 scientific papers:
  - 13 ISI journals
  - 20 ISI proceedings
  - 15 BDI proceedings
- Cumulated impact factor for ISI publications: 106.7
- Principal Investigator in 3 international grants
- Principal Investigator in 2 national grants
- Research team member in 9 international / national grants
- 18 international patent applications (EPO, WPO, USPTO)
- 87 citations in journals, conf. proceedings, and books
- h-index: 7 – ISI Web of Science, 13 – Google Scholar
- Published 4 books:
  - 1 with an international publisher (Springer)
  - 3 with a national publisher (Editura Universitatii Transilvania)
- Published 2 textbooks (Editura Universitatii Transilvania)

Future activities

Transilvania University of Brașov

- Apply system's theory approaches for personalized medicine:
  - Diagnosis and treatment planning of cardiovascular pathologies
  - Diagnosis and treatment planning of different types of cancer (breast, colon, etc.)
- Further strengthen the link between computational modeling and artificial intelligence based approaches à development of hybrid personalized precision medicine models
- Further enhance international collaborations with leading European research universities / centers: Max Planck Institute, EPFL, Barcelona Supercomputing Center, King's College London, NTNU, etc.
- Increase level of funding through EU research grants (H2020, ERA)
- Further expand the UTBV ATI team, and continuously strengthen and diversify the know-how in the group

THANK YOU!