Digital Twins, Data Assimilation, and Model Reduction for Surgical Planning and Vascular Diagnostics

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Integrating Machine Learning with Multiscale Modeling for Biomedical, Biological, and Behavioral Systems
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Outline

• Digital Twins paradigm for Hemodynamic Simulations

• Data Assimilation for Parameter Estimation

• Surgical Planning of Fontan Surgeries

• Non-invasive diagnostics of Coronary Artery Disease

• Machine learning methods for reconstructing anatomy and flow
Digital Twins Paradigm for Hemodynamics Simulations
Digital Twins Paradigm for Hemodynamics Simulations

Data

Pressure data from applanation tonometry

Flow/velocity data from phase contrast MR

Flow/velocity data from doppler ultrasound

Computational model

Sequence of wall motion surfaces segmented from time-resolved MR or CT data

Data
Traditional CFD

• Solve “**Newton’s Law for a fluid**”, unknowns are velocity and pressure

\[
\rho \left( \frac{\partial \vec{u}}{\partial t} + \vec{u} \cdot \nabla \vec{u} \right) = -\nabla p + \nu \Delta \vec{u}
\]

- **Acceleration**
- **Pressure**
- **Viscosity**

\[
\nabla \cdot \vec{u} = 0
\]

**Continuity Equation**

• “**Boundary conditions**”
  are on Q and/or P

• **Mesh independence**


http://bloodflow.engin.umich.edu/
CFD for Biofluids

• We simply almost never have enough data

• Instead we “plug in” reduced-order models of the circulation at inlets and outlets

• These models prescribe a property, not a waveform!

Windkessel Model

Vignon-Clementel, Figueroa et al. CMAME. 2006
CFD for Biofluids

- **Reduced-order models** can handle problems without enough data

- **Avoid** prescribing inconsistencies in non-simultaneous data

- Allow to correctly reproduce **pressure** (hardly ever reported!!) (operator that gives you pressure for a given flow)

- Most appropriate tool for **surgical planning**, in which we aim to study ‘virtual’ alternatives for which there is no data either
Image Segmentation and Mapping of Stiffness Parameters

Xiao, Humphrey, Figueroa, JCP, 2013
Full-body Scale Arterial Fluid-structure Interactions in Humans

Xiao, Humphrey, Figueroa, JCP, 2013

http://bloodflow.engin.umich.edu/
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Key applications

- CV Disease Research
- Surgical Planning
- Medical Device Evaluation
- Non-invasive Diagnostics

http://bloodflow.engin.umich.edu/
Method: Data Assimilation for Parameter Estimation
Data-driven Estimation

Goal:
Minimize discrepancy between model observations and real measurements

\[
\min_{X} J(X)
\]

\[
J(X) = \int_{0}^{T} (Z - H(X))^\top (W)^{-1} (Z - H(X)) dt + (X(0) - X_0)^\top (P)^{-1} (X(0) - X_0)
\]

- "Variational" approach
  - Gradient-based minimization
  - Adjoint method

- "Sequential" approach

\[
\dot{\hat{X}} = A(\hat{X}) + K(Z - H(\hat{X}))
\]
Augmented State

• Augmented state

\[
\chi = \begin{pmatrix} X \\ \theta \end{pmatrix} \quad \text{parameters}
\]

\[
\dot{\chi} = A(\chi)
\]

\[
\chi(0) = \chi_0 + \zeta^\chi \quad \text{Includes uncertainty in the parameters}
\]

• Observation operator

\[
Z = H(X) + \zeta^z \quad \text{measurement error}
\]

- Includes uncertainty in the parameters
- Simulated wall boundary
- Segmented data
- Distance to a sequence of wall motion surfaces (interpolated linearly in time)

\[
Z - H(X_n) = D(X_n) = \alpha_k \text{dist}(x + u, S_k) + (1 - \alpha_k) \text{dist}(x + u, S_{k+1})
\]
Sequential Approaches

• Classical Kalman filter gives optimal estimates for linear models

• “Unscented” Kalman filter\(^1\) is an effective extension to nonlinear models

• Reduced-order unscented Kalman filter\(^2\) (ROUKF) enables estimation of an uncertain subset of augmented model states (i.e. the model parameters)

• A set of \((p+1)\) “sigma points” (also called particles) samples the estimation-error probability distribution at each time step (\(p\) is the # of parameters)

• In practice, this means running \((p+1)\) concurrent simulations

2. Moireau et al., ESAIM: Control, Optimisation and Calculus of Variations, 2010
Integration of Data Assimilation Libraries with Flow Solvers

**Verdandi**  
*generic library for data assimilation*

\[
\begin{align*}
\hat{X}_{n+1}^+, \hat{\theta}_{n+1}^+ & \quad \text{Advance one time step} \\
\hat{X}_{n+1}^-, \hat{\theta}_{n+1}^- & \quad \text{Advance one time step} \\
\hat{X}_{n+1}^+, \hat{\theta}_{n+1}^+ & \quad \text{Compute a posteriori estimate} \\
\end{align*}
\]

\[
\begin{align*}
\hat{X}_{n+1}^+ & = A_{n+1}(\hat{X}_n^+; \hat{\theta}_n^+) \\
\hat{X}_{n+1}^- & = E_o(\hat{X}_{n+1}^-) \\
\hat{\theta}_{n+1}^- & = E_o(\hat{\theta}_n^-) \\
\Gamma_{n+1}^{(i)} & = Z_{n+1} - H(\hat{X}_{n+1}^i) \\
\Gamma_{n+1}^{(1)} & = 0 \\
\Gamma_{n+1}^{(2)} & = 0 \\
\Gamma_{n+1}^{(p+1)} & = 0 \\
\end{align*}
\]

\[
\begin{align*}
L_{n+1}^X & = [\hat{X}_{n+1}^i]D_o[I^o]^T \\
L_{n+1}^\theta & = [\hat{\theta}_{n+1}^i]D_o[I^o]^T \\
L_{n+1}^Z & = [\Gamma_{n+1}^{(1)}]D_o[I^o]^T \\
U_{n+1} & = 1 + (L_{n+1}^Z)^T W_{n+1}^{-1} L_{n+1}^Z \\
\hat{X}_{n+1}^+ & = \hat{X}_{n+1}^- + L_{n+1}^X U_{n+1}^{-1}(L_{n+1}^Z)^T W_{n+1}^{-1} E_o(\Gamma_{n+1}^{(1)}) \\
\hat{\theta}_{n+1}^+ & = \hat{\theta}_{n+1}^- - L_{n+1}^\theta U_{n+1}^{-1}(L_{n+1}^Z)^T W_{n+1}^{-1} E_o(\Gamma_{n+1}^{(1)}) \\
\end{align*}
\]

Xiao, Arthurs, Moireau, Schaeffter, Figueroa, in preparation

http://bloodflow.engin.umich.edu/
Full patient-specific aorta (real data)

Estimation of Windkessel Parameters (27 parameters)
Full patient-specific aorta (real data)

Lesson: all parameters are identifiable: estimates on $C$, $R_1$ and $R_2$ remain constant after several cycles
Full patient-specific aorta (real data)

Estimation of Windkessel Parameters (27 parameters)
Application: Surgical Planning of Fontan Surgeries
Fontan surgery for Hypoplastic Left Ventricle patients

• Cavo-pulmonary anastomosis (Fontan surgery) for patients with congenital heart defects in which the heart has a single working ventricle

• Split of hepatic flow between lungs critically important
Pulmonary AVMs

• Lack of hepatic angiogenesis inhibitors results in unchecked vascular proliferation in the pulmonary circulation.

• The right to left shunting of the PAVMs:
  1. Reduces hemodynamic resistance
  2. Reduces $O_2$ delivery to affected lung

Pulmonary AVMs

- Relatively common problem

Lack of hepatic venous return results in PAVMs in ~ 50% of patients with interrupted IVC & CVPA

Srivastava et al., Circulation, 1995
Pulmonary AVMs

• Evidence that rerouting of hepatic flow reverts PAVMs

Cavopulmonary pathway modification in patients with heterotaxy and newly diagnosed or persistent pulmonary arteriovenous malformations after a modified Fontan operation

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California, and Division of Cardiothoracic Surgery, Pediatric Cardiology, Lucile Packard Children’s Hospital at Stanford, Stanford University School of Medicine, Stanford, California
Patient history

- 19 yo female Fontan subject with severe right lung PAVM
- 82% $O_2$ saturation
- Dextrocardia
- Interrupted inferior vena cava (IVC)
- Leftward hepatic vein (HV) to pulmonary artery conduit
- Most systemic venous return through the azygous vein (AZV).
- Suspicion that all HVF was directed to the LPA, leading to PAVM in the RPA
Anatomical and hemodynamic data

CO = 6 L/min (PCMRI & Fick)
LPA flow via mass conservation
RPA : LPA split was 2.1 : 1
Digital Twin workflow for surgical planning

• A two-step process

1. Create the Digital Twin of the preoperative state (data verification)

   ![Diagram of data verification process]

   - Data on Flow
   - Verified Baseline Solution (Pre-operative)
   - Data on Pressure
   - Anatomical data

2. Explore different surgical or interventional alternatives (surgical planning)

   ![Diagram of surgical planning process]

   - Verified Baseline Solution (Pre-operative)
   - Option 1
   - Option 2
   - Option 3
Step 1: Digital Twin of the preoperative state

- Flow (SVC)
- Flow (INV)
- WK (LPA)
- Flow (AZ)
- WK (RPA)
- Flow (Shunt)

Pressure [mmHg]

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
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<tbody>
<tr>
<td>9</td>
<td>Red</td>
</tr>
<tr>
<td>11</td>
<td>Orange</td>
</tr>
<tr>
<td>50</td>
<td>Red</td>
</tr>
</tbody>
</table>

Velocity [cm/s]

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Blue</td>
</tr>
<tr>
<td>50</td>
<td>Red</td>
</tr>
</tbody>
</table>

(simulations run under rigid wall assumption)
Step 2: Surgical Planning

Option 1: Hepatic-to-Azygos

Pre  
Post

Option 2: Fontan-to-Innominate

Pre  
Post

Van Bakel et al., JCTR 2017
Step 2: Surgical Planning

Hepatic-to-Azygos

- 1 mL bolus into AZV
- 80:20 RPA:LPA split

Fontan-to-Innominate

- 1 mL bolus into FN
- 70:30 RPA:LPA split

Van Bakel et al., JCTR 2017
Step 2: Surgical Planning

- Sensitivity of bolus injection timing analyzed

- Fontan-to-azygos showed much higher variability
- Fontan-to-innominate was the recommended option
Step 2: Surgical Planning

- Post-operative angiogram shows more balanced RPA:LPA flow
- At follow-up, the patient’s systemic oxygen saturation has increased from 82% to 91%
- Overall symptoms improved
However, at long-term follow-up...

Dr. Palmer: Understanding the physiologic response
   Improve our goal functions
   Improve the model through reinforced learning
Application: Non-invasive diagnostics of Coronary Artery Disease
Coronary Artery Disease

- Plaque build-up in coronary arteries feeding the heart muscle
- Significantly increases likelihood of MI
- Most common CV disease in the US: 12 million+ diagnoses/yr
- CAD-related deaths > 20% total annual US mortality
- Total 1st year treatment in US: $5.54 billion
- 10 year cumulative cost: $126.6 billion
Diagnosis of CAD

Individual Presents with Chest Pain

Stress Test
CT Angiography
Quantitative Coronary Angiography (QCA)
FFR-Guidewire

Prior to Catheterization Lab
External during Cath Lab
FFR Data after Stenosis Assessment in Cath lab

http://bloodflow.engin.umich.edu/
CAD Diagnosis: Fractional Flow Reserve

- Invasive functional assessment: Ratio of **maximal blood flow** in a stenotic artery to normal maximal flow [Pijls]
  - Measure pressure in aorta and distal coronary artery via catheter
  - Drug-induced hyperemia

\[
FFR = \frac{\text{Distal Coronary Pressure (Pd)}}{\text{Proximal Coronary Pressure (Pa)}}
\]

- **FFR < 0.8 → ischemia → revascularization procedure**

https://www.radcliffecardiology.com/intervention/fractional-flow-reserve-ffr-0
CAD diagnosis: FFR

Benefits

- Quantitative measurement
- Accounts for variations in vessel geometry, collateral flow
- Better clinical outcomes than angiography alone

Drawbacks

- Increased risk to patient
- Costly
- Experimental variability

1 Year Adverse Events [Fearon 2012]

<table>
<thead>
<tr>
<th>Event</th>
<th>Angio-guided</th>
<th>FFR-guided</th>
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<tbody>
<tr>
<td>Death</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>MI</td>
<td>8.7%</td>
<td>3%</td>
</tr>
<tr>
<td>Repeat revasc</td>
<td>35%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Death/MI</td>
<td>35%</td>
<td>11.1%</td>
</tr>
<tr>
<td>MACE</td>
<td>50%</td>
<td>13.2%</td>
</tr>
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</table>

Variability in FFR measurement [Petraco]

Probability of changing diagnostic decision

http://bloodflow.engin.umich.edu/
Method: Machine learning methods for reconstructing anatomy and flow
• HeartFlow: $\text{FFR}_{\text{CTA}}$ [Taylor, Min]

- **Vessel Segmentation**
  - Image segmentation algorithms extract 3D geometry from CTA data

- **CFD**
  - Make assumptions about boundary conditions
  - Solve for velocity and pressure fields in patient geometry (steady, hyperemic flow)

- **$\text{FFR-CTA}$**
  - Normalize mean pressure field by the average mean aortic hyperemic pressure
• Analysis conducted outside the cath lab environment (‘less time pressure’)

• Challenges with imaging artefacts in CTA: calcifications
FFR\textsubscript{CTA}: DeepLumen, extracting the anatomy

CT Data

Vessel Paths

r distance predictions

3D regression CNN

3D feature map: w * h * 2r (padded unfolded 3D ring)
FFR\textsubscript{CTA}: DeepLumen, extracting the anatomy

https://tinyurl.com/yy4ml7o6
FFR\textsubscript{CTA}: Physiology

- Lack of direct information on hemodynamics
- Flows done based on estimates of myocardial mass

[Diagram showing the process of FFR\textsubscript{CTA} with CT data submitted, Physiologic model, and HeartFlow Analysis delivered.]
Angio-based determination of FFR

- **Vessel Segmentation**
  - 2D biplane angiograms

- **3D Reconstruction**
  - Forward projection or backward projection

- **Flow Modeling**
  - Assimilate Flow Data
  - Physical modeling
Optimization of CNN for Automatic Vessel Segmentation

Train NN to ignore catheter
Optimization of CNN for Automatic Vessel Segmentation

\[ \text{IOU} = \frac{|Y \cap \hat{Y}|}{|Y \cup \hat{Y}|} \]

\[ \text{Dice} = \frac{2|Y \cap \hat{Y}|}{|Y| + |\hat{Y}|} \]

MIOU is the average of IOU for each class

<table>
<thead>
<tr>
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<th>Synthetic Data</th>
<th>Clinical Data</th>
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<tbody>
<tr>
<td>Training set size</td>
<td>2460</td>
<td>1854</td>
</tr>
<tr>
<td>Validation set size</td>
<td>304</td>
<td>206</td>
</tr>
<tr>
<td>MIOU score</td>
<td>0.975</td>
<td>0.917</td>
</tr>
<tr>
<td>Dice score</td>
<td>0.980</td>
<td>0.916</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.980</td>
<td>0.952</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.994</td>
<td>0.995</td>
</tr>
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</table>

http://bloodflow.engin.umich.edu/
3D Reconstruction

Forward projection
3D Reconstruction

Backward projection

Match pairs of points using epipolar lines, find closest point of intersection of matched pair in 3D space
Flow Modeling: Extracting Data on Velocity

- Coronary Angiography gives **dynamic data** on the movement of the contrast agent through the vessels

https://www.ahajournals.org/doi/full/10.1161/01.cir.93.5.879
Flow Modeling: Extracting Data on Velocity

- Physics-based Deep Learning for assimilating the flow data

Flow Modeling

- Different approaches possible, limited time for computations (~ 10 minutes!)
- Model reduction via Graph Theory

![Diagram of Flow Modeling](http://bloodflow.engin.umich.edu/)
Conclusions

• Multi-scale Modeling and ML methods for CV applications are subject to the constraints and needs of the clinical application:

• Surgical Planning:
  ✓ Can benefit from more data and longer time for analysis
  ✓ Understanding of the goal is not always clear
  ✓ Clearly benefits from data assimilation & from unbiased determination of anatomical DT

• Non-invasive Diagnostics:
  ✓ Subject to tight timelines (optimization extremely important)
  ✓ Automation extremely important (no direct input from human)
  ✓ Data mining for physiology currently main challenge
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