Machine Learning in Precision Medicine
Coronary Health Prediction
- Cardiac Events (Atherosclerosis)
- Heart Transplant (Vasculopathy)

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Precision Medicine
- One-size-fits-all vs. Personalized care
  - Diagnosis
  - Treatment
  - Outcome prediction
    all patient-specific (genetics, lifestyle, environment, …)
- Precision medicine ➔ routine personalized healthcare
- How to get there?
  - AI will help
- Biggest problem?
  - Training data (and patient variability)
Cardiovascular Precision Medicine

- Cardiology at forefront of quantitative analysis for decades
  - QCA – 1980’s

- Cardiovascular imaging is everywhere
  - Angiography, IVUS, MR, CT, SPECT, PET, OCT, …

- Image analysis for clinical care is still mainly qualitative

- Quantification needs to be omnipresent in routine clinical care for precision medicine to reach its potential

Prediction of Major Adverse Cardiac Events:

Atherosclerosis – Coronary IVUS
Atherosclerotic Coronary Disease … Thin-Cap Fibroatheromas (TCFA)

MACE Risk – Major Adverse Cardiac Events

- High-risk coronary plaque:
  - Thin-cap fibroatheroma (TCFA)
  - Plaque burden PB > 70%
  - Minimal luminal area MLA < 4 mm²

- MACE prevention:
  - Identify locations at risk to develop high-risk plaques
  - Intervene (balloon angioplasty, stenting, medication, …)
Angiographic Lumen

Intravascular Ultrasound

IVUS + Virtual Histology

- White = Dense Calcium
- Red = Necrotic Core
- Dark Green = Fibrous (Fibro-fatty)
- Light green = Fibro-lipidic
Can Future TCFA Locations be Predicted? Can MACE be Predicted?

What will happen here?

TCFA
NonTCFA

Predicting Plaque Development (NIH-funded in 1999)

TRAINING of classifier to predict changes in a single variable of temporal plaque change

PREDICTION of plaque changes and performance assessment using a trained classifier

(a) FOLLOW UP in a vessel not used for training
(b)
Years Later …

- Non-trivial patient recruiting
  - US not well positioned for that
- Complex medical image analysis development
  - 3D morphologic analysis difficult in IVUS data
    - More art than science
    - Inherently n-D, optimal methods with JEI capabilities (LOGISMOS+JEI)
  - Establishing baseline/follow-up correspondence, deriving vessel geometry
    - 2-view X-ray angio for vessel shape, data fusion with IVUS
    - Catheters twist, pullback speeds not constant, landmarks not always available
    - Computed biomarkers unstable, …
  - Obvious need for machine learning at many levels (& small datasets)

Study Cohort

- 61 patients with stable angina pectoris
- 2 studies comparing statin therapy for atherosclerosis progression
- Plaque types (truth)
IVUS Image Segmentation

- LOGISMOS approach for simultaneous dual-surface segmentation
- User-guided computer-aided refinement (Just-Enough Interaction)
- User interaction time reduced from hours to several minutes
Baseline $\rightarrow$ Follow-up Automated Registration

**Baseline**

- Location-specific features
  - VH-based features
  - IVUS-based features

**Follow-up**

- Temporal plaque change
  - TCFA
  - non-TCFA

**Systemic Information**

- Demographics
- Biomarkers

**Feature Selection**

**Optimal Feature Subset**

**Random Forest Classifier**

predict TCFA based on baseline features
Feature Set – and Feature Selection

<table>
<thead>
<tr>
<th>Basic Clinical Measures</th>
<th>Plaque composition: Plaque phenotype, DC/NC/FF/FT [CSA], DC/NC/FF/FT [%], max. confluent NC, max. NC abutting, Plaque morphology: Lumen/EEM/PM [CSA], PB, remodeling index, distance to ostium, mean plaque thickness, std. plaque thickness, eccentricity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Plaque grayscale intensity: mean, median, std., max, min, mode. Plaque intensity histogram: first, median, third quartiles.</td>
</tr>
<tr>
<td>First-Order Descriptors (F22–F30)</td>
<td></td>
</tr>
<tr>
<td>Plaque Textures (F31–F46)</td>
<td>Contrast, correlation, energy, homogeneity ( \theta = 0^\circ, 45^\circ, 90^\circ, 135^\circ ).</td>
</tr>
<tr>
<td>Layered Plaque Components (F47–F118)</td>
<td>DC/NC/FF/FT [%] in 10%–90% inner &amp; outer rings.</td>
</tr>
<tr>
<td>Spatial Contextual Features (F19–F236)</td>
<td>Average feature value of one adjacent distal and one adjacent proximal frames. Calculate for all F1–F118.</td>
</tr>
</tbody>
</table>

Systemic Demographics & Biomarkers (F237–F254)

| Age, gender, weight, BMI, family history, smoking history, current smoker, hypertension, diabetes, hyperlipidemia, previous MI, beta-blockers, ACE inhibitors, previous statin treatment, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides. |

DC: dense calcium; NC: necrotic core; FF: fibrofatty; FT: fibrotic tissue; BMI: body mass index; MI: myocardial infarction; ACE: angiotensin-converting enzyme; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

61 patients with stable angina pectoris, Charles University Prague
BL + 12M Follow-up IVUS-VH

From BL image data predicting MACE at 12M: TCFA or PB≥70% or MLA≤4mm²

A B C D E F

Plaque types at baseline
Predicted plaque types
Plaque types at follow-up — truth
Virtual histology at baseline
Plaque types at baseline
Predicted plaque types at follow up
True plaque types at follow up
Virtual histology at follow-up

A B C D E F

Plaque types

Virtual histology

A B C D E F

Prediction process

TCFA PB≥70% MLA≤4mm² Non-high-risk

A B

TCFA

85.9 92.7 79.6

AUC 0.87

# features 16

80 85 90 95 100

80.4 88.2 90
Deep Learning Replacing Random Forests
Courtesy Ling Zhang (U of Iowa → NIH → NVIDIA)

Baseline Follow-up Registration of Location and Orientation

Basic Idea – Pixel-Level Prediction

Convolutional Neural Network (AlexNet; GoogleNet)

Our ConvNet

<table>
<thead>
<tr>
<th>conv1</th>
<th>conv2</th>
<th>conv3</th>
<th>conv4</th>
<th>fc5</th>
</tr>
</thead>
<tbody>
<tr>
<td>3×3, 64, pad 1, stride 1, pool 3×3</td>
<td>3×3, 128, pad 1, stride 1, norm.</td>
<td>3×3, 256, pad 1, stride 1</td>
<td>3×3, 512, pad 1, stride 1, pool 3×3</td>
<td>256, dropout</td>
</tr>
</tbody>
</table>

DL Predicting Future Wall Morphology/Composition

- 7 follow-up classes at pixel-level
  - background, lumen, adventitia, dense calcium (DC), necrotic core (NC), fibrotic tissue (FT), fibro-fatty tissue (FF)

- Data:
  - Patients: 15 training, 5 validation, 10 testing
  - Image Patches: 90,000 training, 23,000 validation, 51×51 pixels

- Results:
  - **7-classes:**

<table>
<thead>
<tr>
<th>Background</th>
<th>Lumen</th>
<th>Adventitia</th>
<th>DC</th>
<th>NC</th>
<th>FT</th>
<th>FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>90%</td>
<td>89%</td>
<td>58%</td>
<td>47%</td>
<td>47%</td>
<td>17%</td>
</tr>
</tbody>
</table>

- **3-classes:** Background, Lumen, Wall (Adventitia+DC+NC+FT+FF)
  - Total Accuracy = **88%**.
DL Predicting Future Wall Morphology

- **Prediction Tasks:**
  1. Plaque volume increase vs. Not
  2. Lumen volume decrease vs. Not
  3. Plaque burden increase vs. Not

- **Results on 10 Testing Patients:**

<table>
<thead>
<tr>
<th></th>
<th>Accuracy (1.5mm segment-level)</th>
<th>Accuracy (patient-level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque volume increase vs. Not</td>
<td>61%</td>
<td>80%</td>
</tr>
<tr>
<td>Lumen volume decrease vs. Not</td>
<td>51%</td>
<td>60%</td>
</tr>
<tr>
<td>Plaque burden increase vs. Not</td>
<td>58%</td>
<td>70%</td>
</tr>
</tbody>
</table>

- **Deep Learning on VH-IVUS vs. SVM on 18 Demographic Features:**

<table>
<thead>
<tr>
<th></th>
<th>Accuracy (SVM)</th>
<th>Accuracy (Deep Learning)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque volume increase vs. Not</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Lumen volume decrease vs. Not</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Plaque burden increase vs. Not</td>
<td>90%</td>
<td>70%</td>
</tr>
</tbody>
</table>

- **DL Predicting Future Wall Morphology/Composition**

- Small dataset, single prior time point
  - DL may not be able to predict (using these data):
    - Follow-up plaque components at pixel-level
    - Plaque/lumen/plaque-burden changes at 1.5mm segment-level
  - DL can predict the changes at patient-level
    - Combining with demographics for improved performance
  - DL allows to predict follow-up plaque types at frame-level as in [1]

Prediction of Transplant (Cardiac Allograft) Failure:

Coronary OCT

Cardiac Allograft Vasculopathy (CAV) = Thickening of Coronary Wall

- Wall thickening after HTx:

(a) 1M
(b) 12M
(c) 36M
**Heart Transplantation**

- Post HTx treatment requires quite a drastic medication regimen
  - Immunotherapy
  - Statins
  - Donor-specific antibodies
  - ...
- If clinically-significant CAV develops ➞ re-transplantation
- Drugs exist (side-effects) that can stop CAV if administered early
  - Ineffective if administered late

- ➞ Patients at high risk of CAV must be identified early

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**Automated 3D Segmentation of Coronary Wall**

![Automated 3D Segmentation of Coronary Wall](image)

- Media
- Intima
DL-based Exclusion Regions
Automatic identification of unreliable image-info regions
(Previously manual, high effort)

Patches:
- 60° angular span
- 2.2 mm depth
  - 2.0 mm tissue penetration
  - 0.2 mm inside lumen
- 10° overlap of neighbors

Wall layers visible = measurable
Wall layers invisible = NOT measurable
**CNN Architecture**

Unwrap → Convolution → Subsampling → Convolution → Subsampling → Fully Connected MLP

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**Training, Results**

Data:
- 100 pullbacks (~438 frames/pullback)
- ~40,000 OCT image frames
- 80% training vs. 20% testing
- Leave-20%-out cross validation

Results:
- Accuracy: 81.2%
- Inter-observer variability: 83.2%

Compared with

*Original* → *Truth = Expert tracing* → *Automated Exclusion Area*
Baseline/Follow-up Registration

Lumen Segmentation

Alignment

Register

Rotational angle:
- Between frames interpolation
- Start/end extrapolation

Visualization of IT Changes
25% of HTx Patients
Substantial IT Thickening at 12M

Biomarkers, Clinical Information Collected

<table>
<thead>
<tr>
<th>Before HTx</th>
<th>Clinical demographics</th>
<th>Biomarkers and Clinical Exams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical demographics</td>
<td></td>
<td>High-sensitive cardiac troponin T (hs-TnT)</td>
</tr>
<tr>
<td>Age</td>
<td>Gender of donor</td>
<td>B-type natriuretic peptide (BNP)</td>
</tr>
<tr>
<td>Sex</td>
<td>Age, weight, height, BMI</td>
<td>Total, HDL, LDL cholesterol</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cause of death</td>
<td>Triacylglycerol (TAG)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>Body weight</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight, height, BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure etiology</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Information collected during 1, 6, and 12-month patient follow-ups.

<table>
<thead>
<tr>
<th>Medication</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor profile</td>
<td>Cyclosporin A</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Cold ischemia time</td>
<td>Beta blocker</td>
<td>Hemoglobin A1c</td>
</tr>
<tr>
<td>Gender of donor</td>
<td>Statin or lipid lowering therapy</td>
<td>Plasma Glucose</td>
</tr>
<tr>
<td>Age, weight, height, BMI</td>
<td>Other bradycardia &amp; glucose lowering medication</td>
<td>Cytomegalovirus (CMV) infection status</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td>C-reactive protein (CRP)</td>
</tr>
<tr>
<td>Follow-up at 1, 6, &amp; 12 months</td>
<td></td>
<td>Heart rate &amp; 24h Holter EKG indices</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td>LV ejection fraction, filling pressure</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td>Cellular rejection mild/severe</td>
</tr>
<tr>
<td>Mycophenolate mofetil (MMF)</td>
<td></td>
<td>Humoral rejection</td>
</tr>
<tr>
<td>Acetylsalicylic acid (ASA)</td>
<td></td>
<td>Donor Specific Antibodies (DSA)</td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
<td>MICA Antibodies</td>
</tr>
</tbody>
</table>

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**Prediction Tasks**

- Image acquisition (OCT, CTA) – IKEM, CKTCH, Utah
- Image analysis, CAV Prediction – University of Iowa (IIBI)

- Can CAV status at 3 years be predicted? If so – when?
  - 12 month after HTx?
    - 1M + 12M OCT & 1M + 6M + 12M biomarkers/EKG + donor info
  - 6 months after HTx?
    - 1M OCT & 1M + 6M biomarkers/EKG + donor info
  - 1M after HTx?
    - 1M OCT & 1M biomarkers/EKG + donor info

**Prediction of CAV – Deep Learning Approach**

![Deep Learning Diagram]

- **Coronary OCT**
  - 1M and 12M
  - Segmentation
  - Registration
- **Coronary CTA**
  - 36M
  - Segmentation
  - Quant. Indices
First 4 patients reached 36M → CTA Imaging
Progressor – Non-progressor Separability at 1M?

AI for Cardiovascular Precision Medicine

- Prerequisites to precision medicine in atherosclerosis and/or HTx
  - Highly accurate quantitative analysis of coronary morphology
  - Relevant biomarkers
  - Longitudinal data
  - Large-enough dataset with ground truth
  - All is challenging
    - Requires Engineering – Medicine collaboration
    - Frequently multi-center data acquisition
  - And it is costly
- The potential rewards are worth the effort!
Team Effort

- IIBI – U of Iowa
  - Andreas Wahle
  - Zhi Chen
  - Zhihui Guo
  - Ling Zhang
  - Honghai Zhang
  - Trudy Burns
- Loyola University
  - John Lopez

- IKEM + VFN Prague
  - Tomas Kovarnik
  - Michal Pazdenik
- CKTCH Brno
  - Helena Bedanova
  - Eva Ozabalova

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  - NIH NHLBI
  - NIH NIBIB
  - MZv Czech Republic
  - Volcano