

The Emerging Discipline of Computational Medicine

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What is *Computational Medicine*?

In *Computational Medicine*, we:

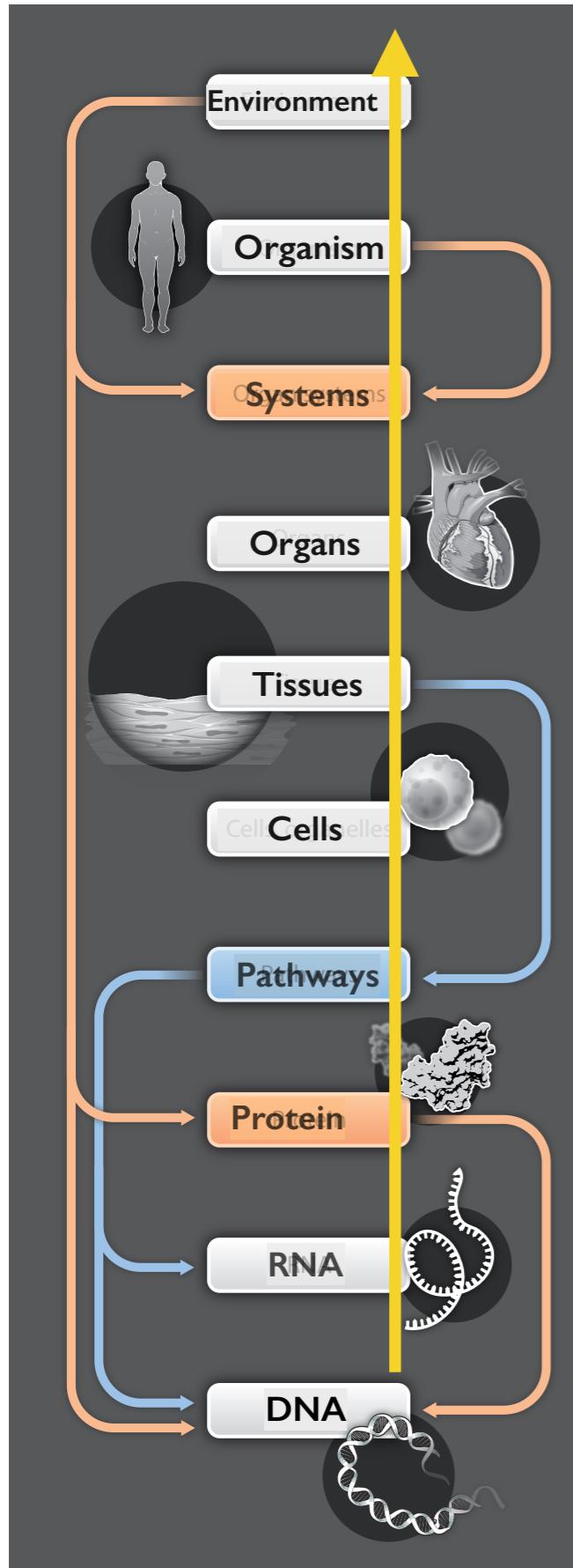
- Develop mechanistic computational models of disease
- Personalize them using patient data
- Apply them to deliver precision medicine tailored to the needs of the individual

Research Areas in the ICM

Computational:

- Molecular Medicine
- Physiological Medicine
- Anatomical Medicine
- Healthcare

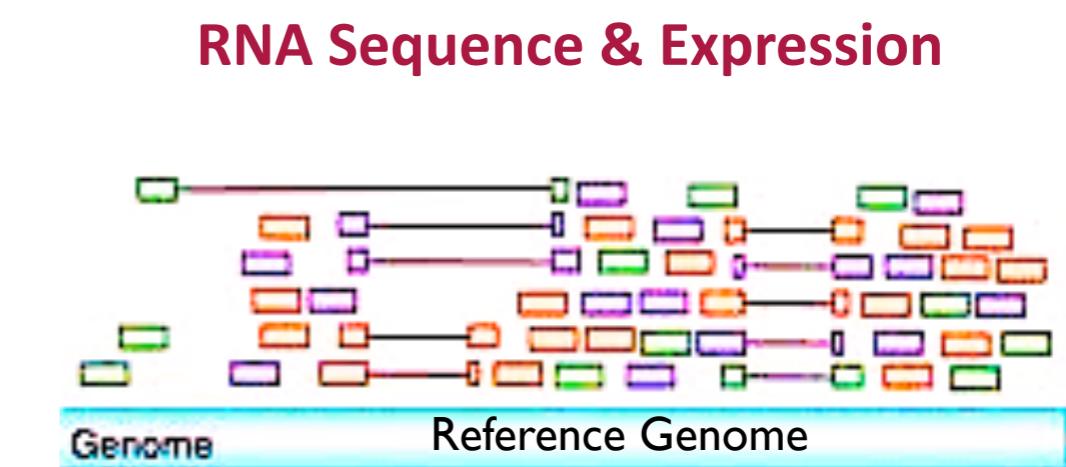
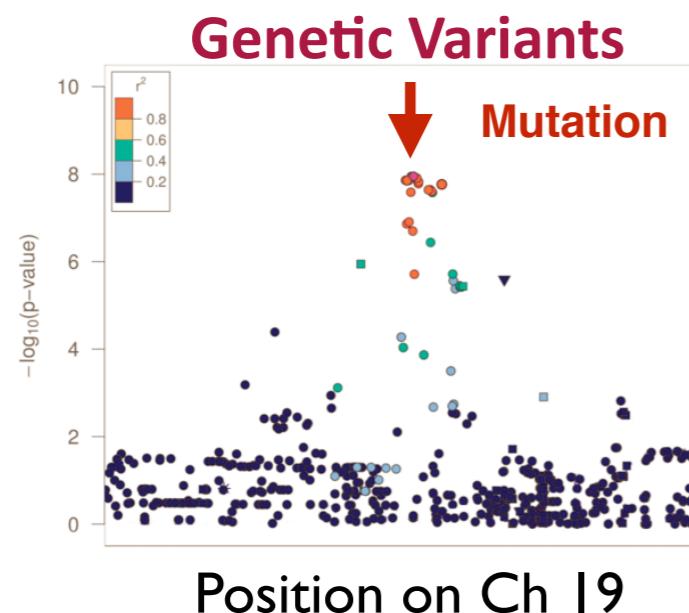
Why are Models Needed?



- Complexity at each biological level
- **Feed-forward & feed-back coupling** between levels
- Function does not reside at one level
- Physician's “mental models” no longer suffice
- Models are necessary to navigate the complex landscape of disease

- Data
- Computation

\$1K Personal Genome, Illumina HiSeq X Ten
 30x coverage, 600 GBases/day, .3 TBs/ day



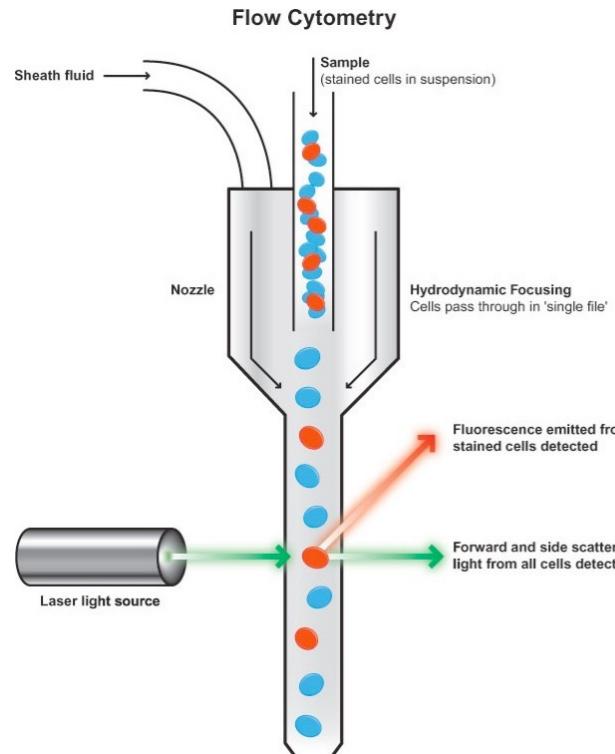
DNA Methyl (acetyl)-ation
 (MethylC-Seq,...)

RNA Structure
 (SHAPE-Seq)

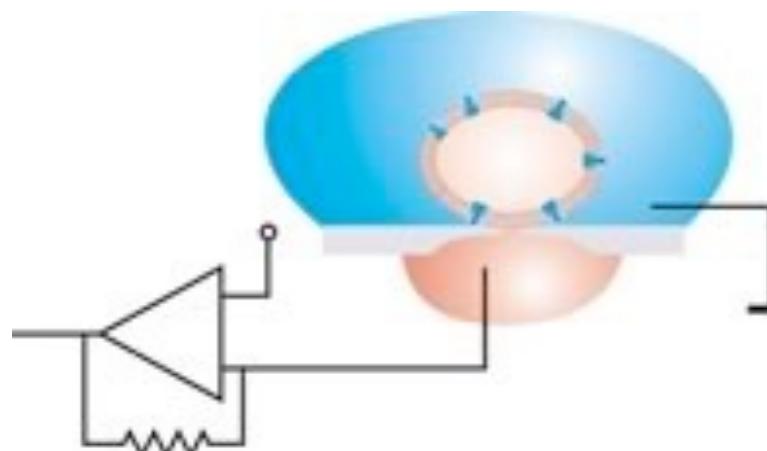
Regulation of Gene Expression
 (ChIP-, FAIRE-Seq, ...)

Protein & Metabolite Expression
 (HPLC, Mass Spec)

Protein Networks
 (Yeast 2-Hybrid, FRET)

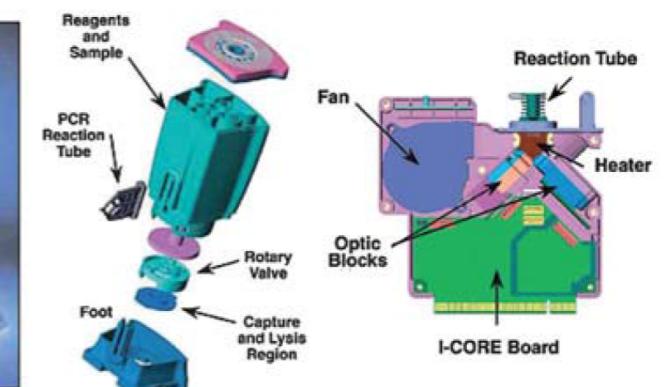


High Throughput Flow Cytometry:
mRNA/protein expression, signaling proteins

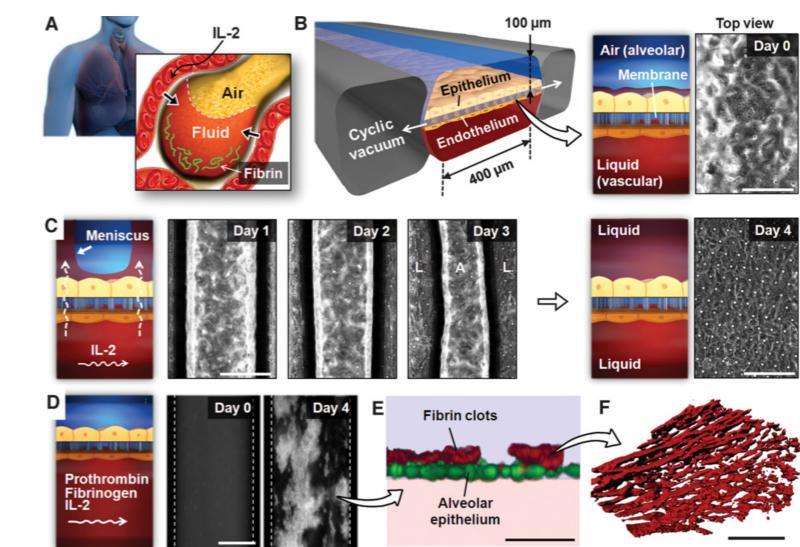


High Throughput Patch Clamp:
electrophysiology

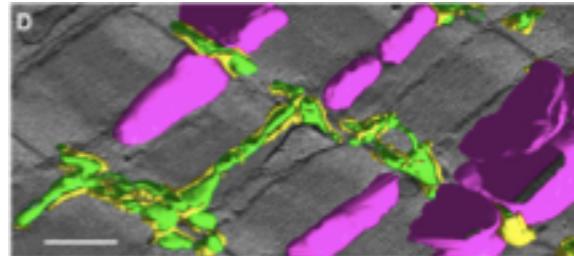
Point of Care Microfluidics:
Infectious diseases, blood gases, ...



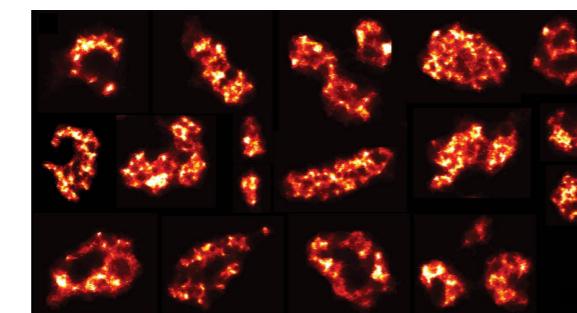
Organ on a Chip



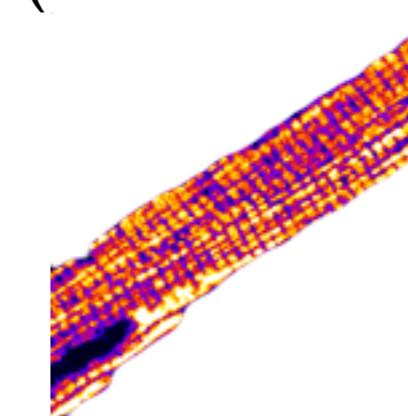
EM Tomography (nm's)



fPALM, STORM (10's nm)

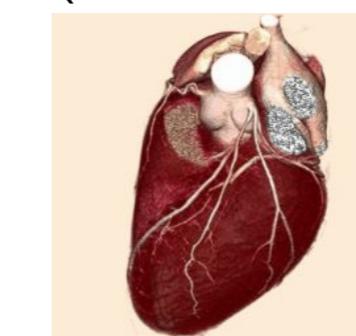


Single-/multi-photon
(100's nm to um's)



Structure

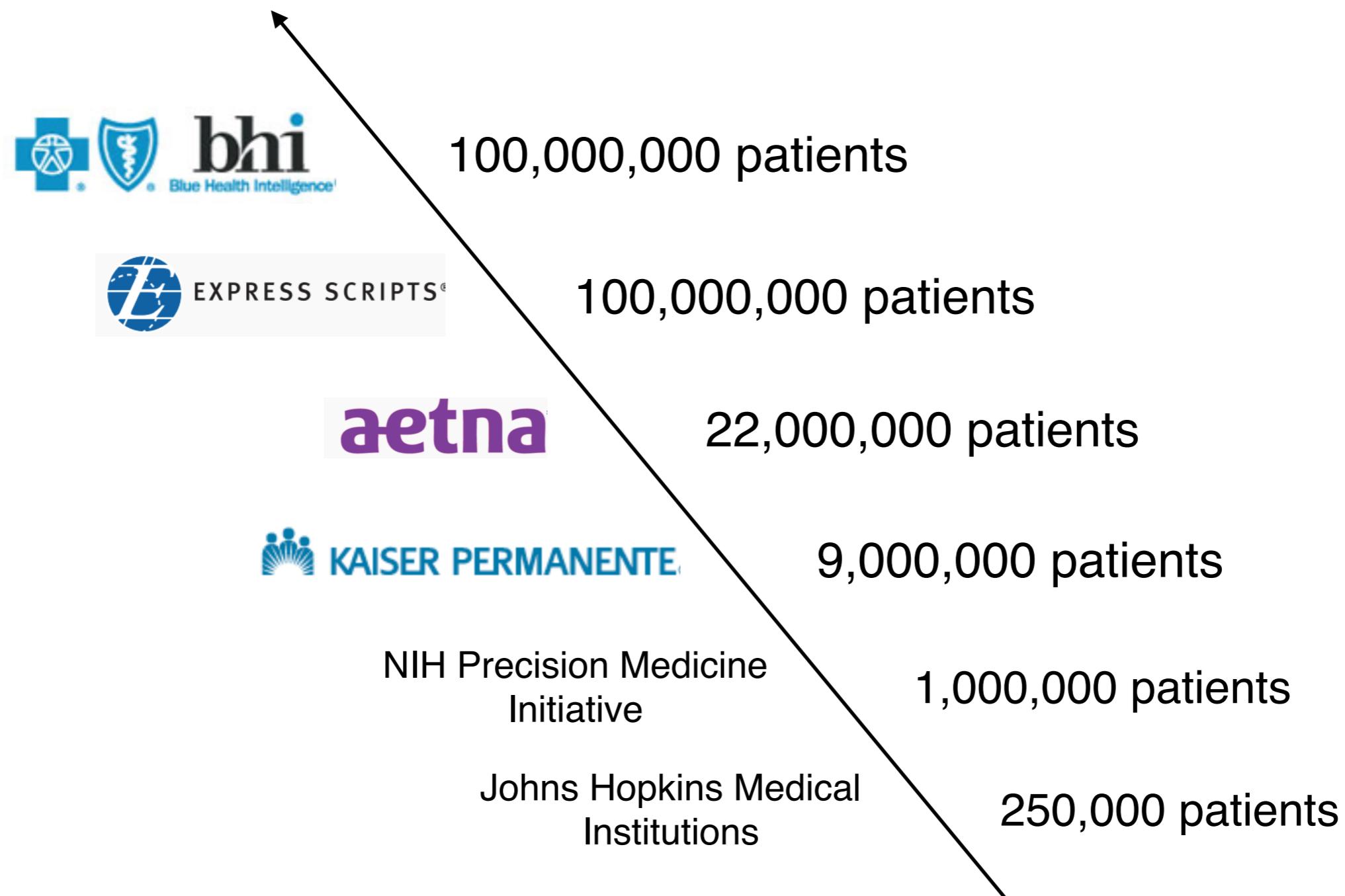
Multi-Detector CT
(100's um's)

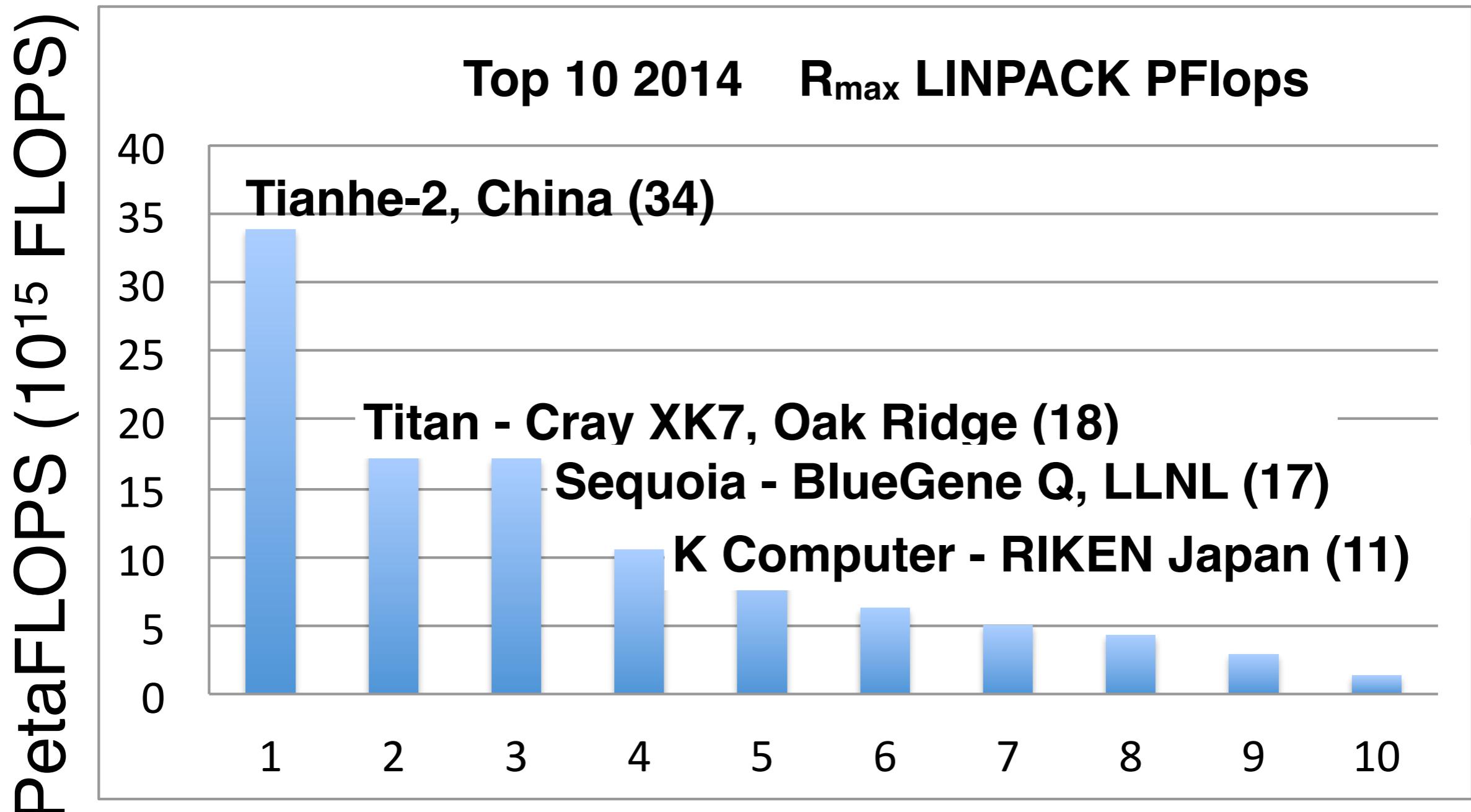


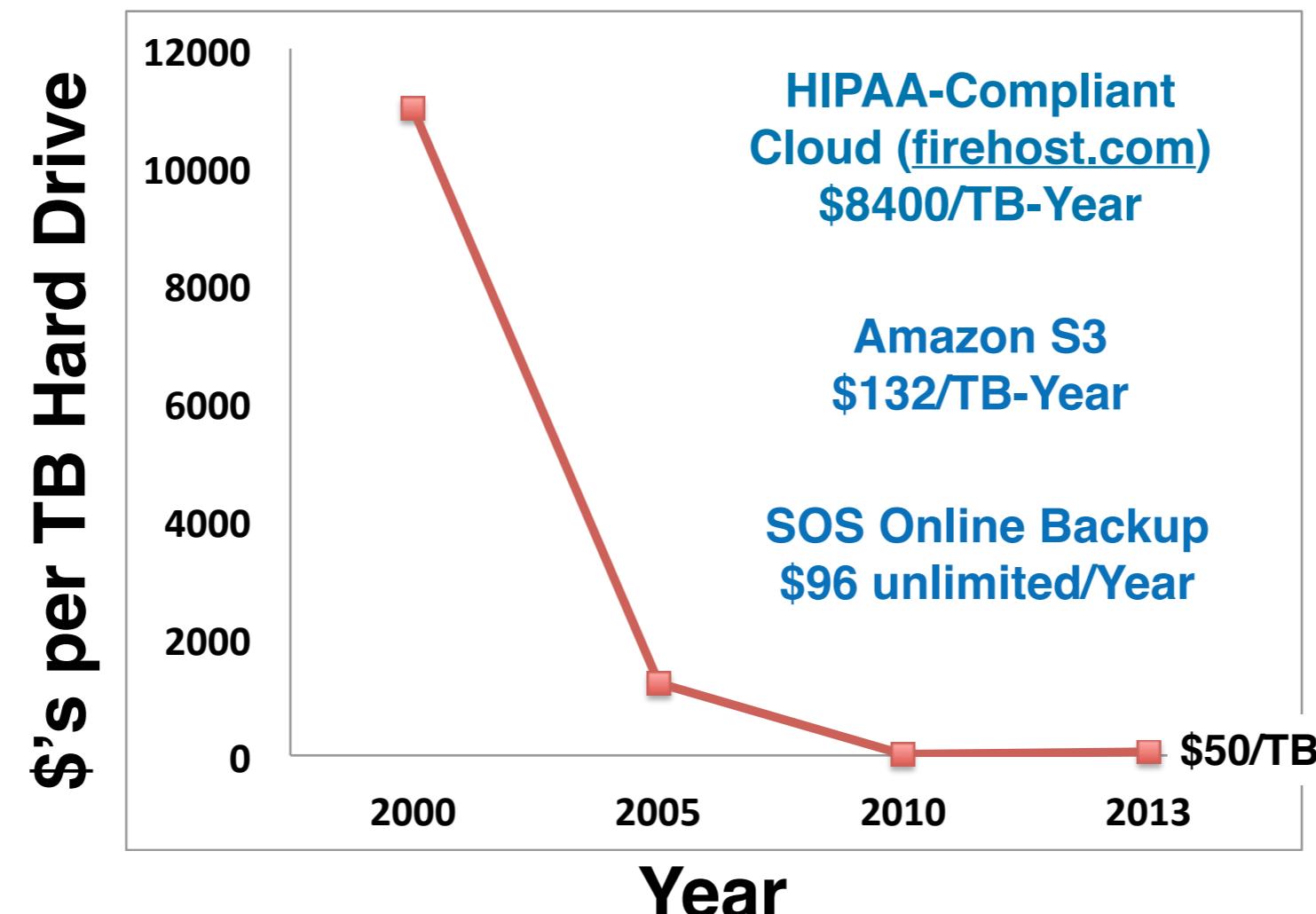
300 um³ voxels, 175 mSec

Enabling Technologies

The Electronic Medical Record



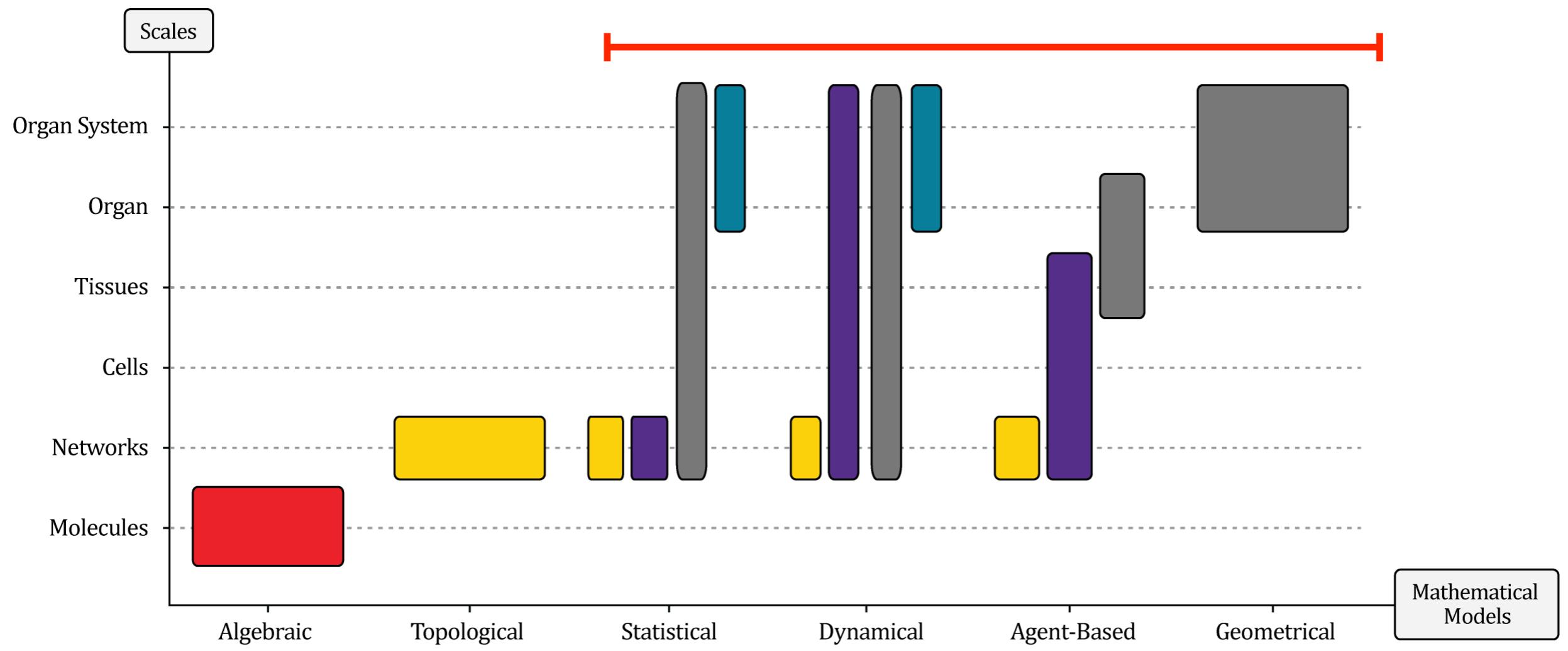




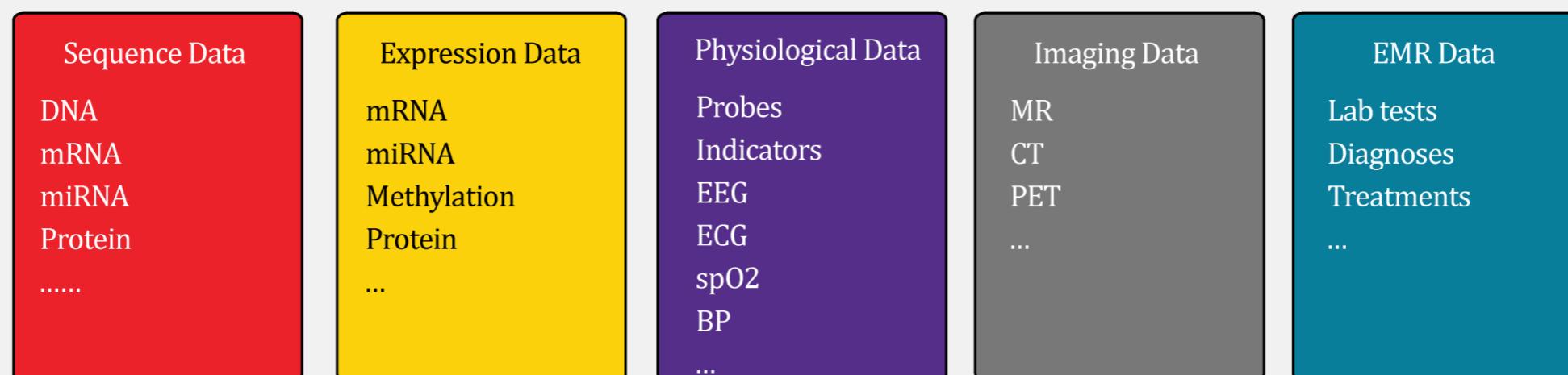
Translating Models to Clinical Care

Where are we?

Types of Models



Data Modalities



Definitions:

Patient state $\underline{X}_i \in \mathbb{R}^p$, p is feature space dimension

$$\underline{X}_i = \begin{bmatrix} \text{genome} \\ \text{transcriptome} \\ \text{proteome} \\ \text{physiome} \\ \text{Images} \\ \text{EMR} \end{bmatrix}$$

Normal, disease class
 $\{C_{\text{normal}}, C_{\text{disease}}\}$
 T_i is class label for i^{th} patient

Training data set $S = \{ (\underline{X}_1, T_1), (\underline{X}_2, T_2), \dots, (\underline{X}_N, T_N) \}$

Classifier $F()$:

Learn $F(\underline{X}_i) \rightarrow T_i$ from S with as few errors as possible

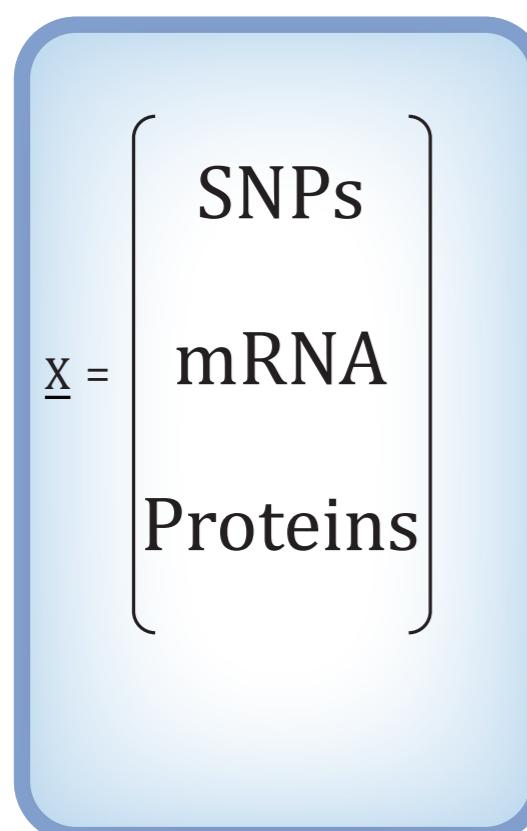
Validate by testing $F()$ on new data

Computational Molecular Medicine

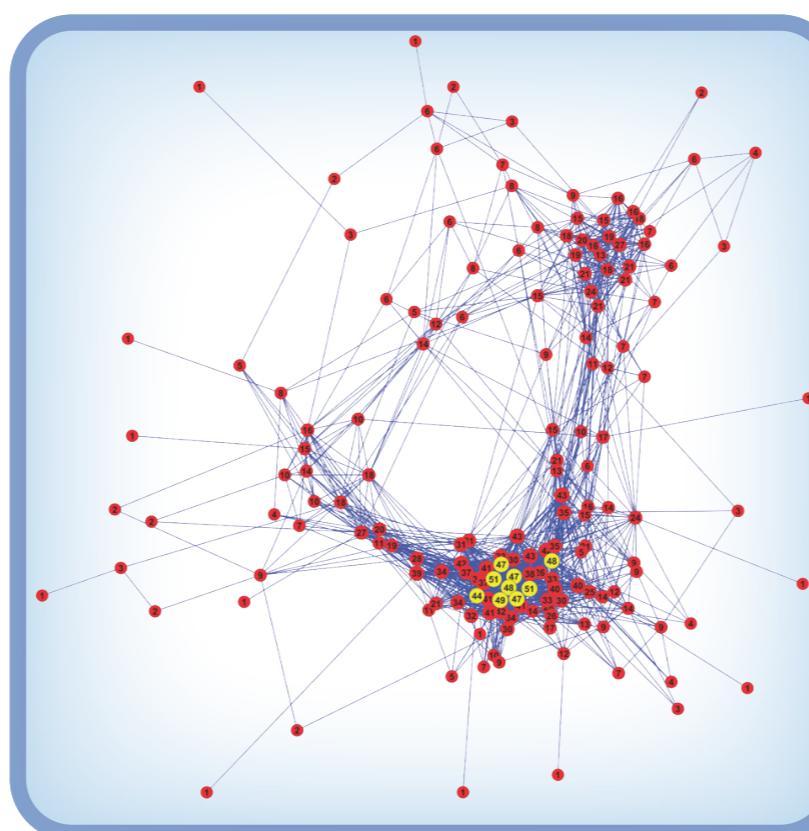
Learning Network Phenotypes

The Fundamental Challenge to Machine Learning in Biology

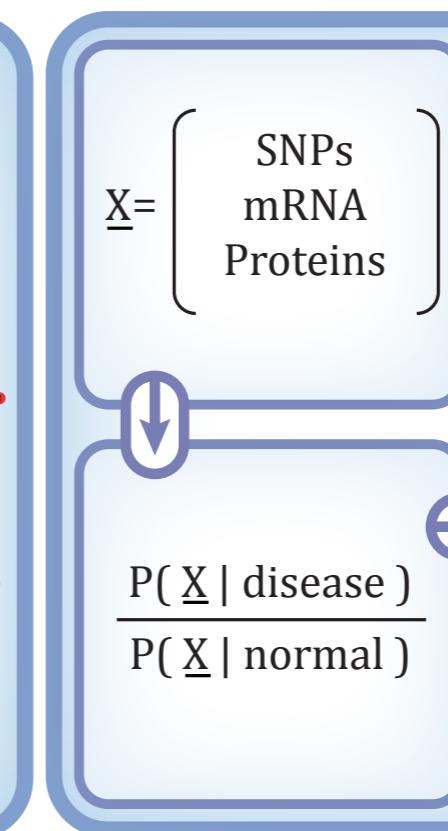
The “Small N, Large p Problem”



Parts and Measurements
Phenotype $\underline{X} \in \mathbb{R}^p$



Relationships



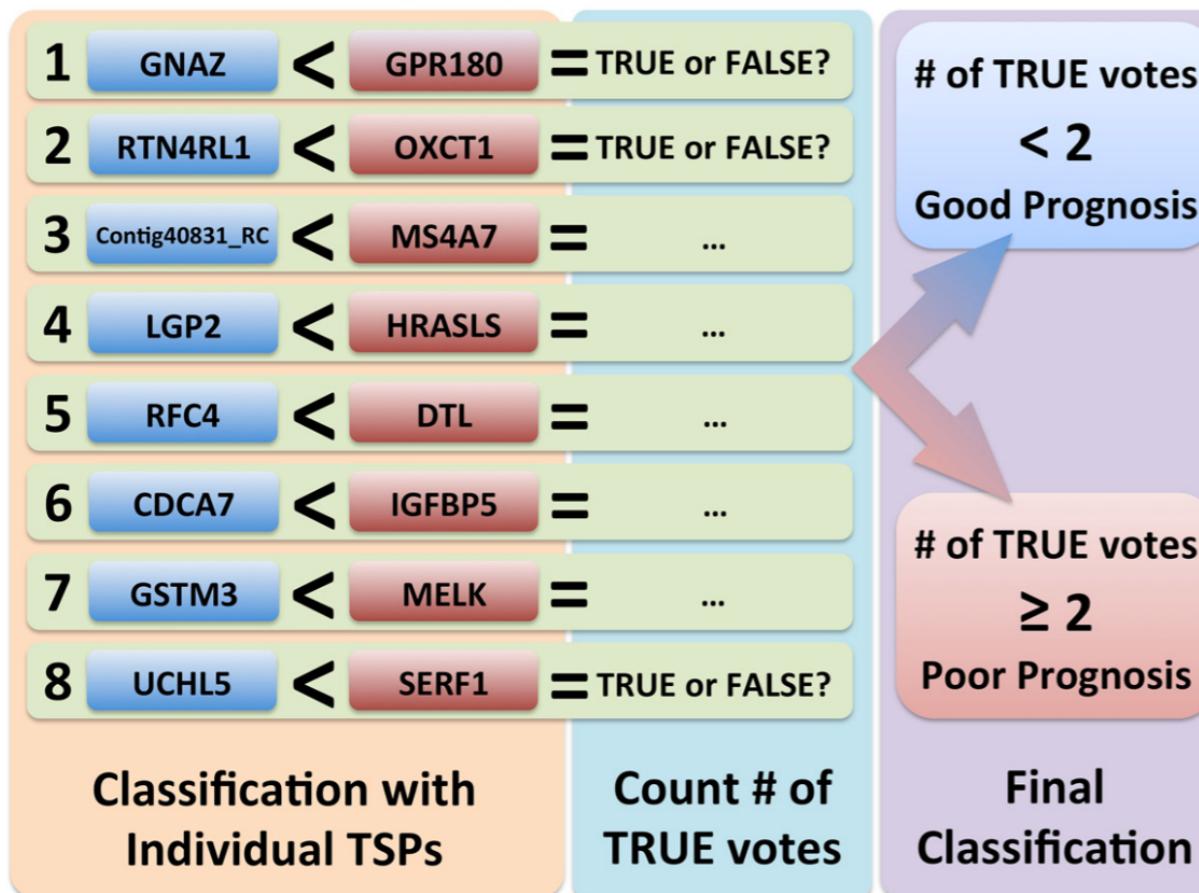
Statistical Disease Model



Computational Molecular Medicine

Simple 0,1-Parameter Classifiers

K K-TSP Classifier



Pharmacogenomics

AZD0530 Pancreatic Cancer
 100% Sensitive, 83% Specific

Tipifarnib Acute Myeloid Leukemia
 100% Sensitive, 92% Specific

uRNA Diagnostic

Gastric Cancer
 95% Sensitive, 90% Specific

mRNA Diagnostic

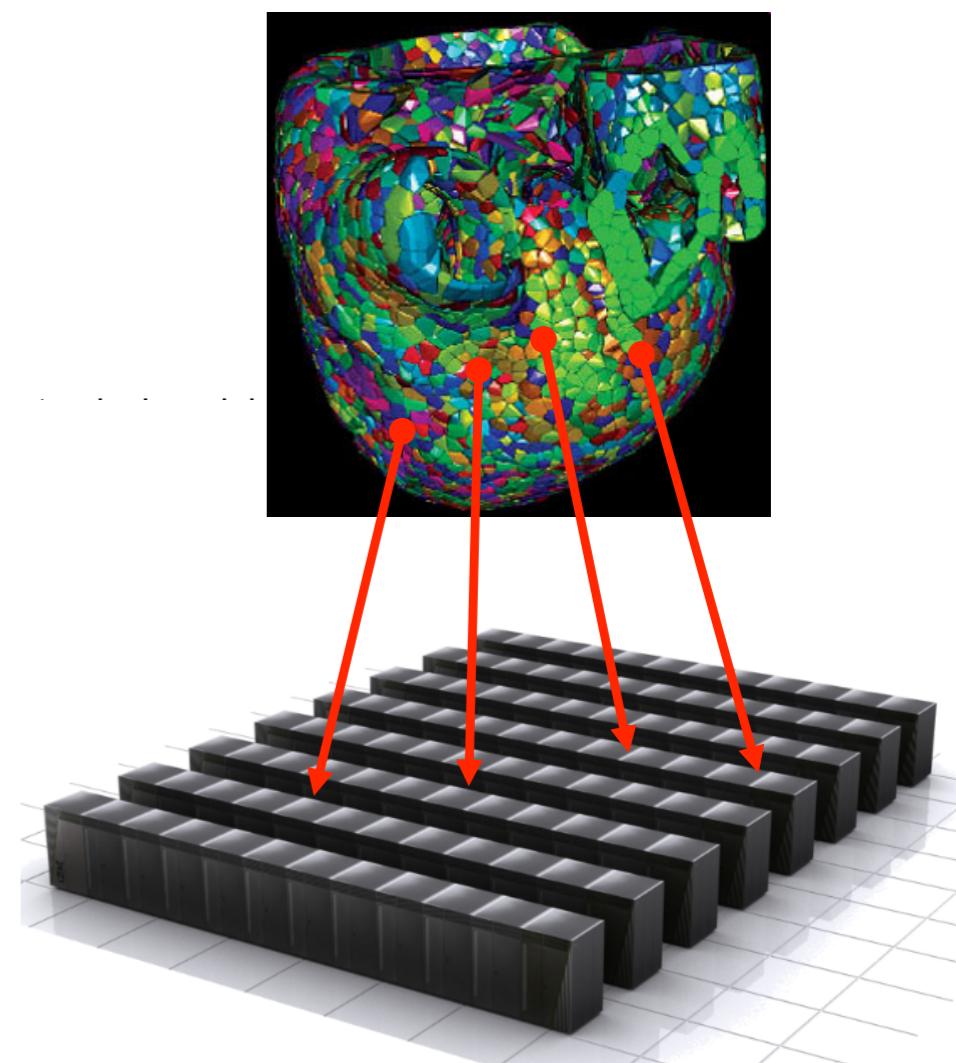
Dementia Alzheimer's Type
 88% Sensitive, 89% Specific

Protein Diagnostic

Inflammatory Bowel Disease
 89% Sensitive, 81% Specific

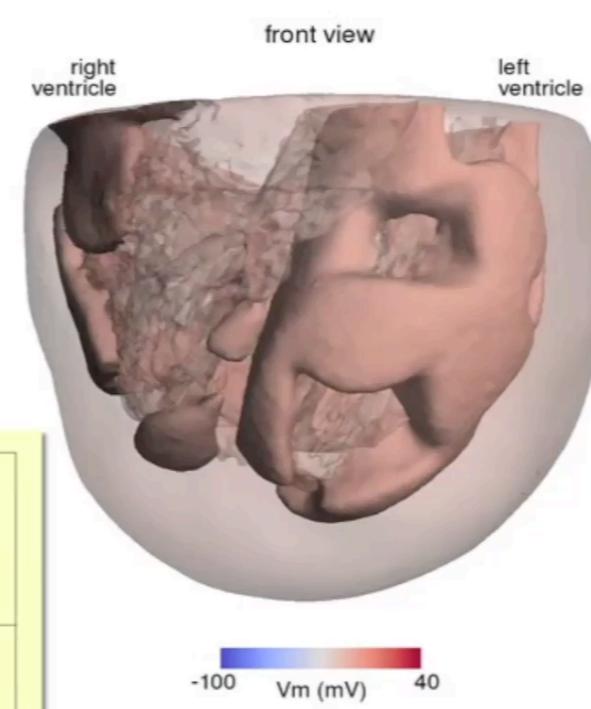
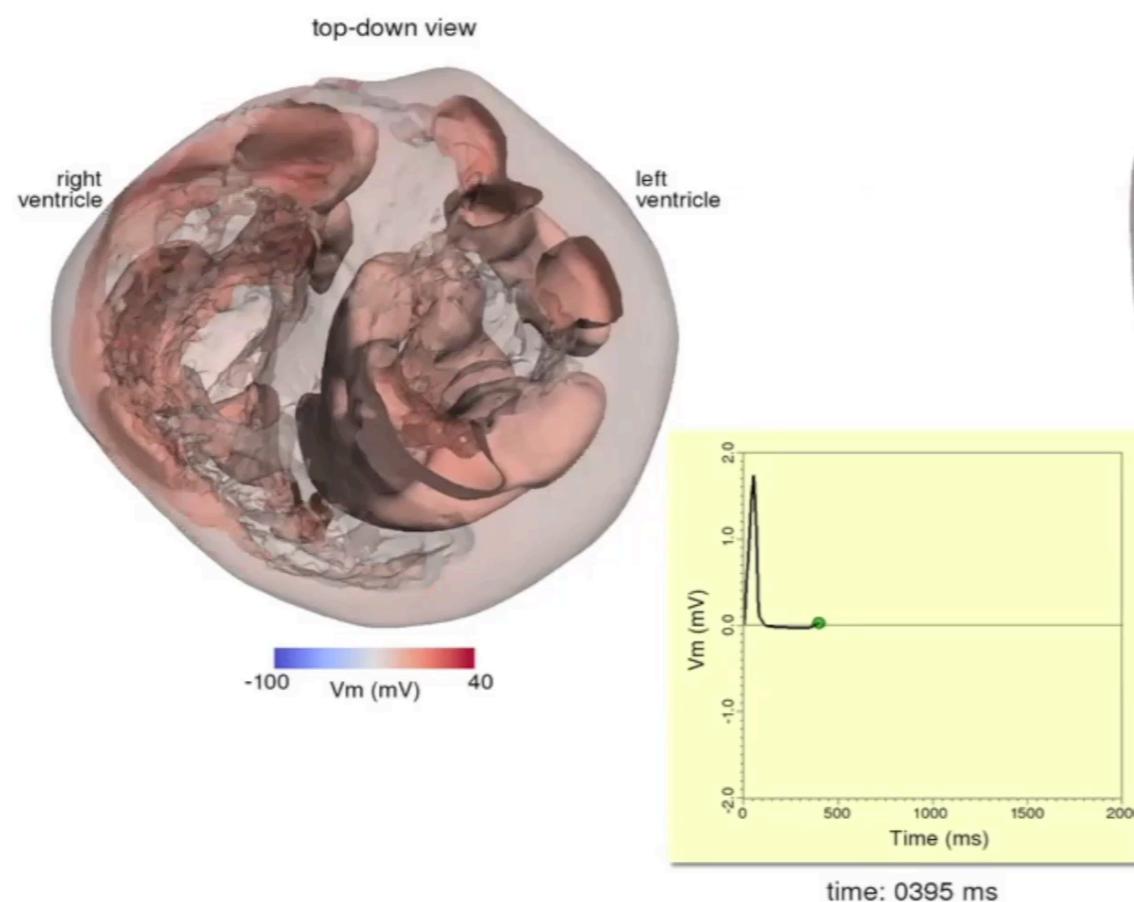
IBM Cardioid Human Heart Model

Anatomical Human
Heart Model



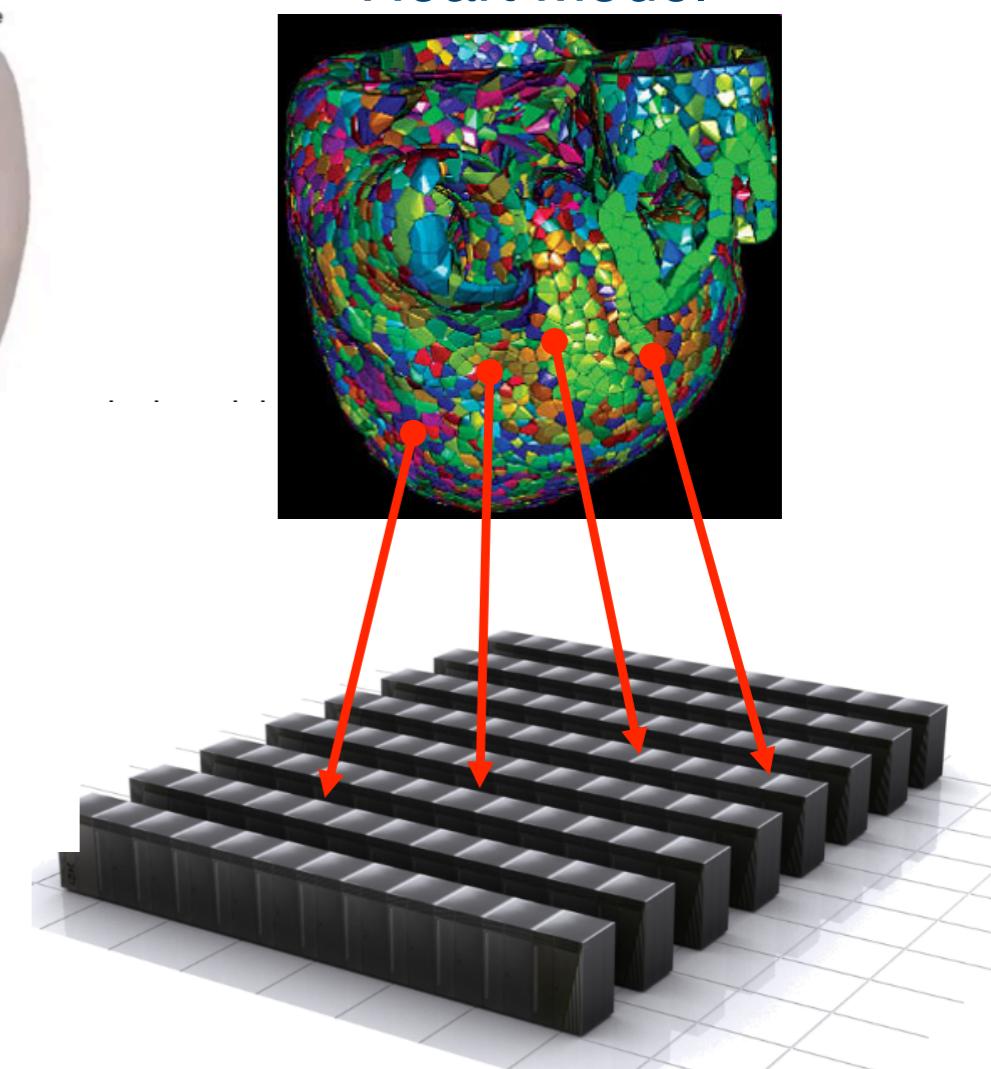
96 Racks of BlueGene Q Sequoia

IBM Cardioid Human Heart Model



Simulate electrical conduction in human heart near real time!

Anatomical Human Heart Model



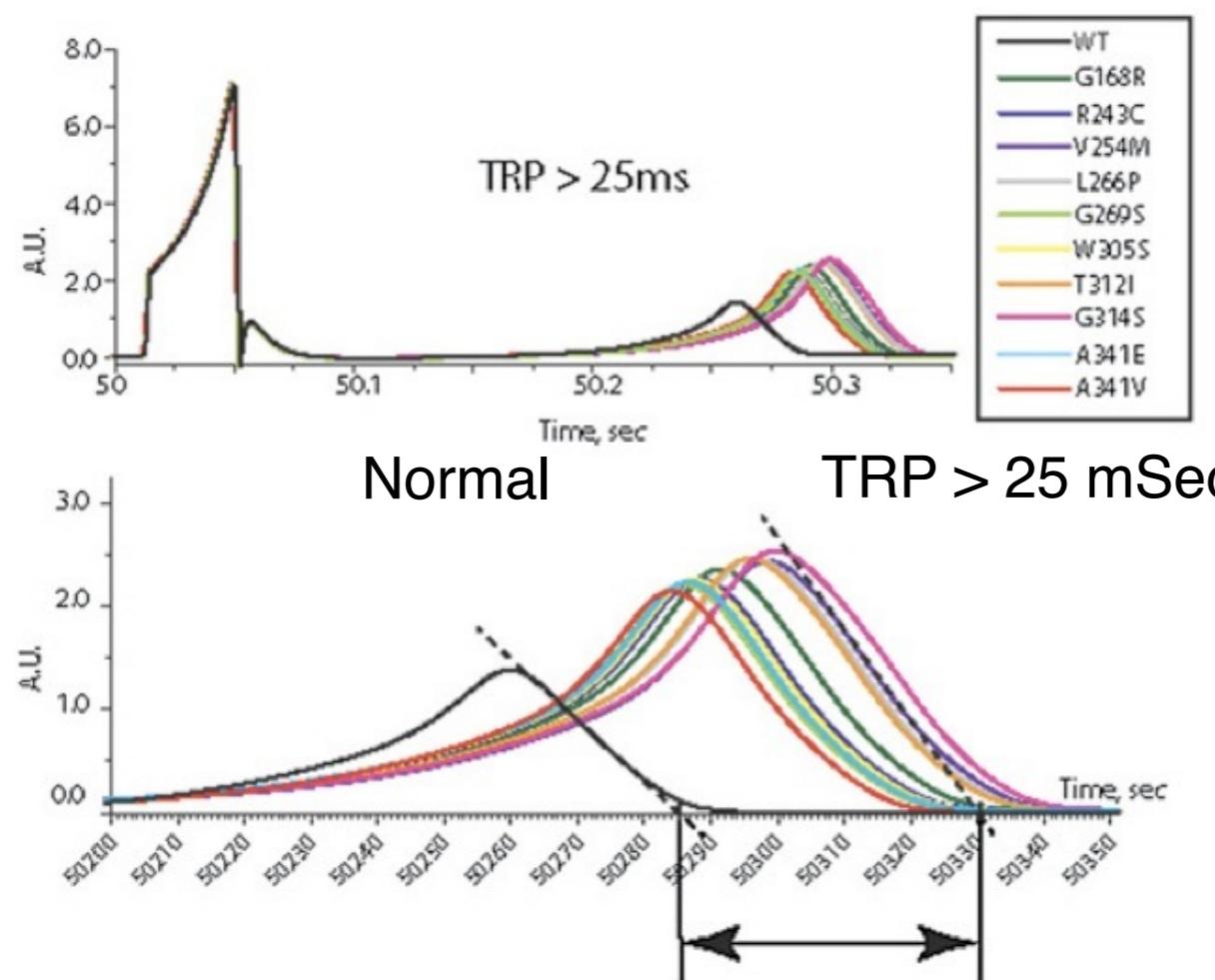
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Computational Physiological Medicine

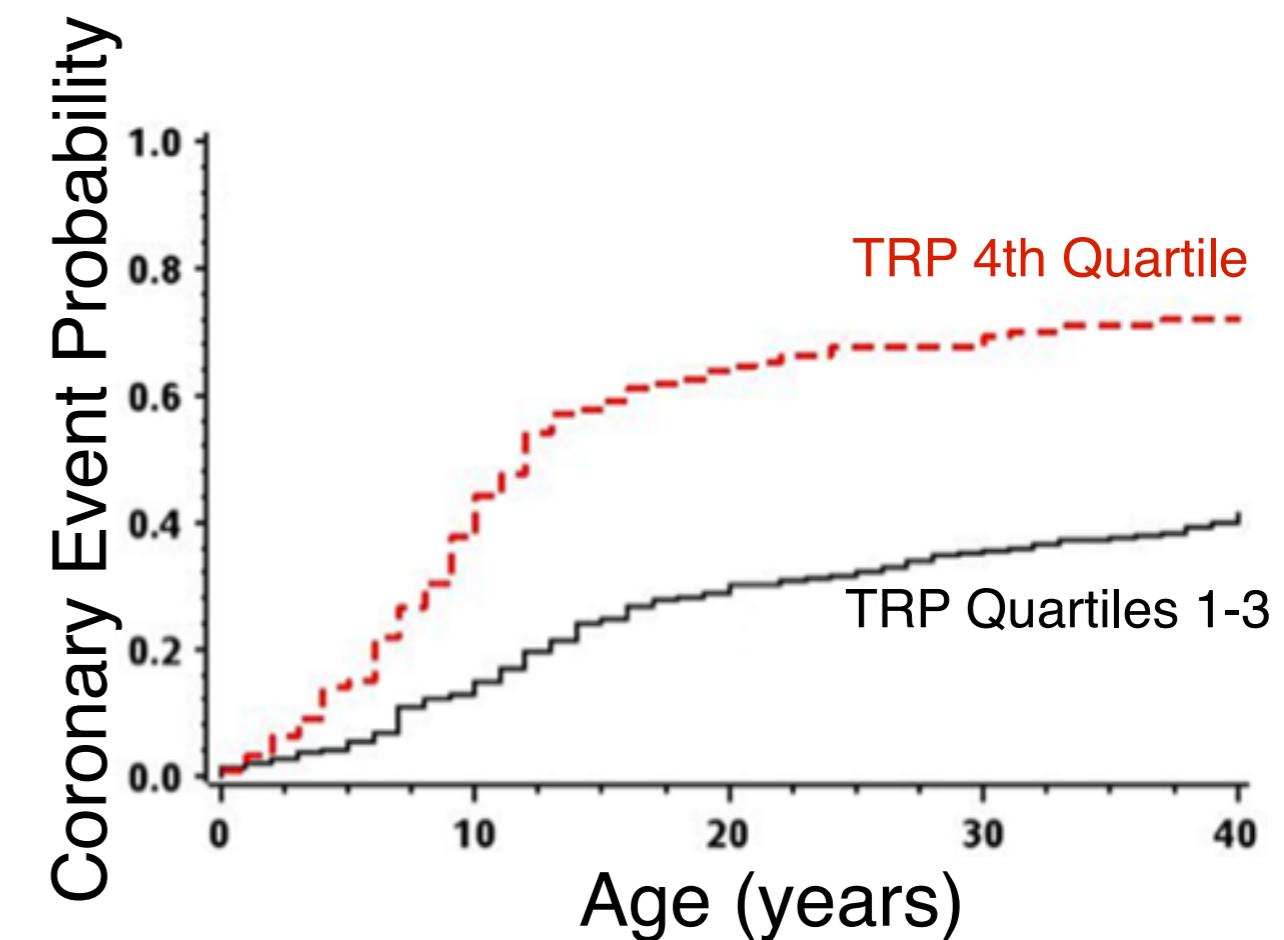
Computational Biomarker for Coronary Events

Long QT Syndrome

Model Transmural Conduction & Repolarization Prolongation (TRP)



Events vs Age and TRP

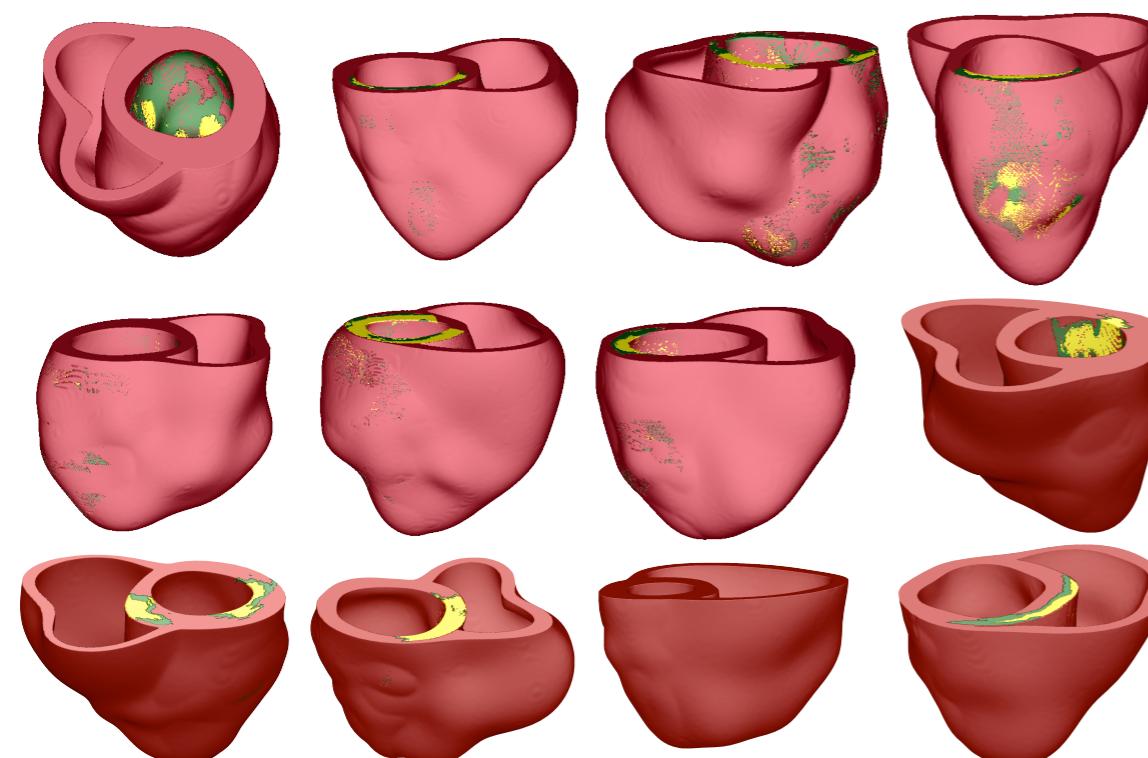


Model revealed mutations \Rightarrow largest TRP

Computational Physiological Medicine

Personalized cardiac ablation therapy

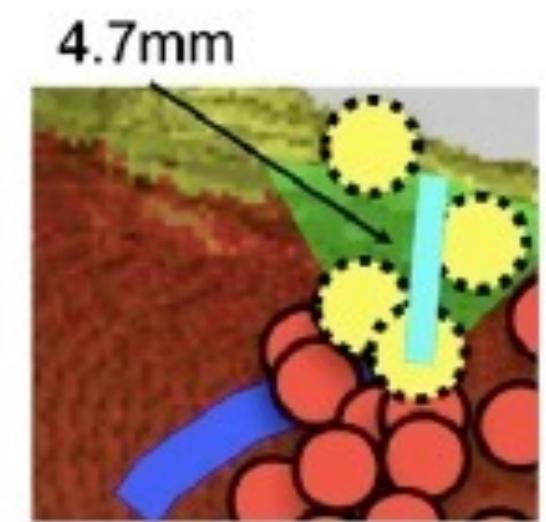
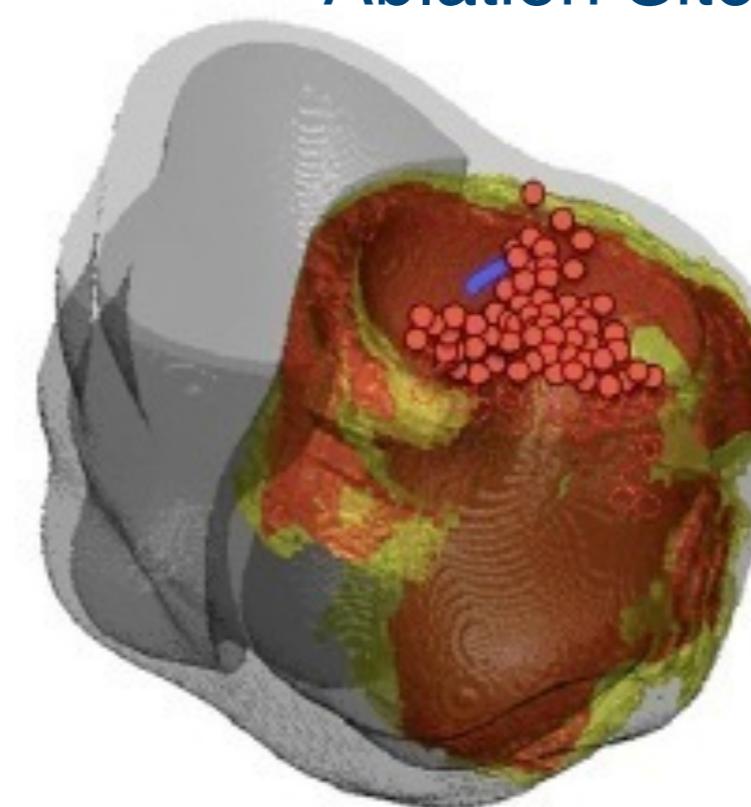
MRI-Based Anatomical Models of 12 Patient Hearts



 Normal

 Scar

Simulations Reveal Optimal Ablation Site per Patient



 Predicted Ablation Zone (PAZ)

 Surgical ablation outside PAZ

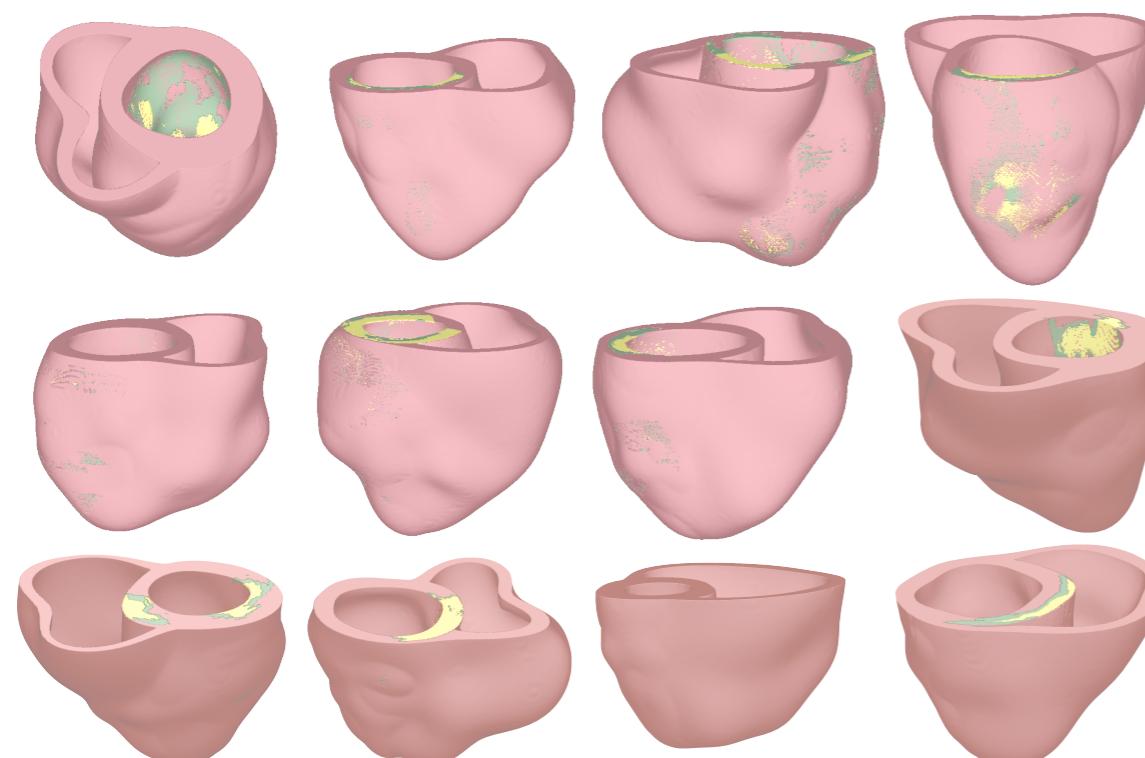
 Optimal Ablation Zone

 Surgical ablation inside PAZ

Computational Physiological Medicine

Personalized cardiac ablation therapy

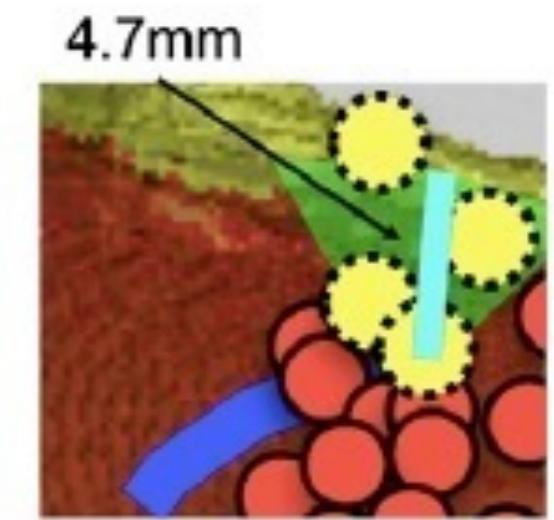
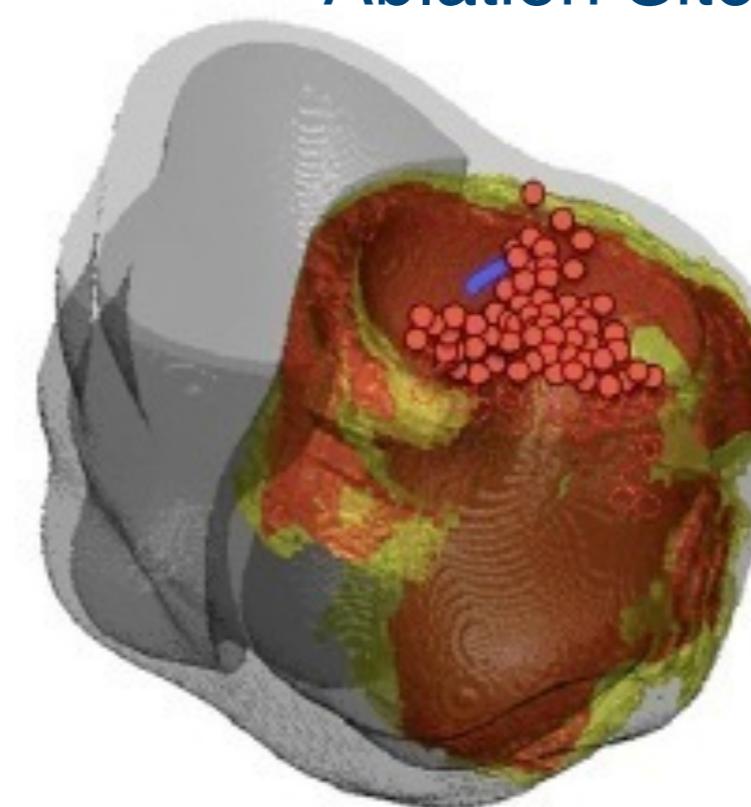
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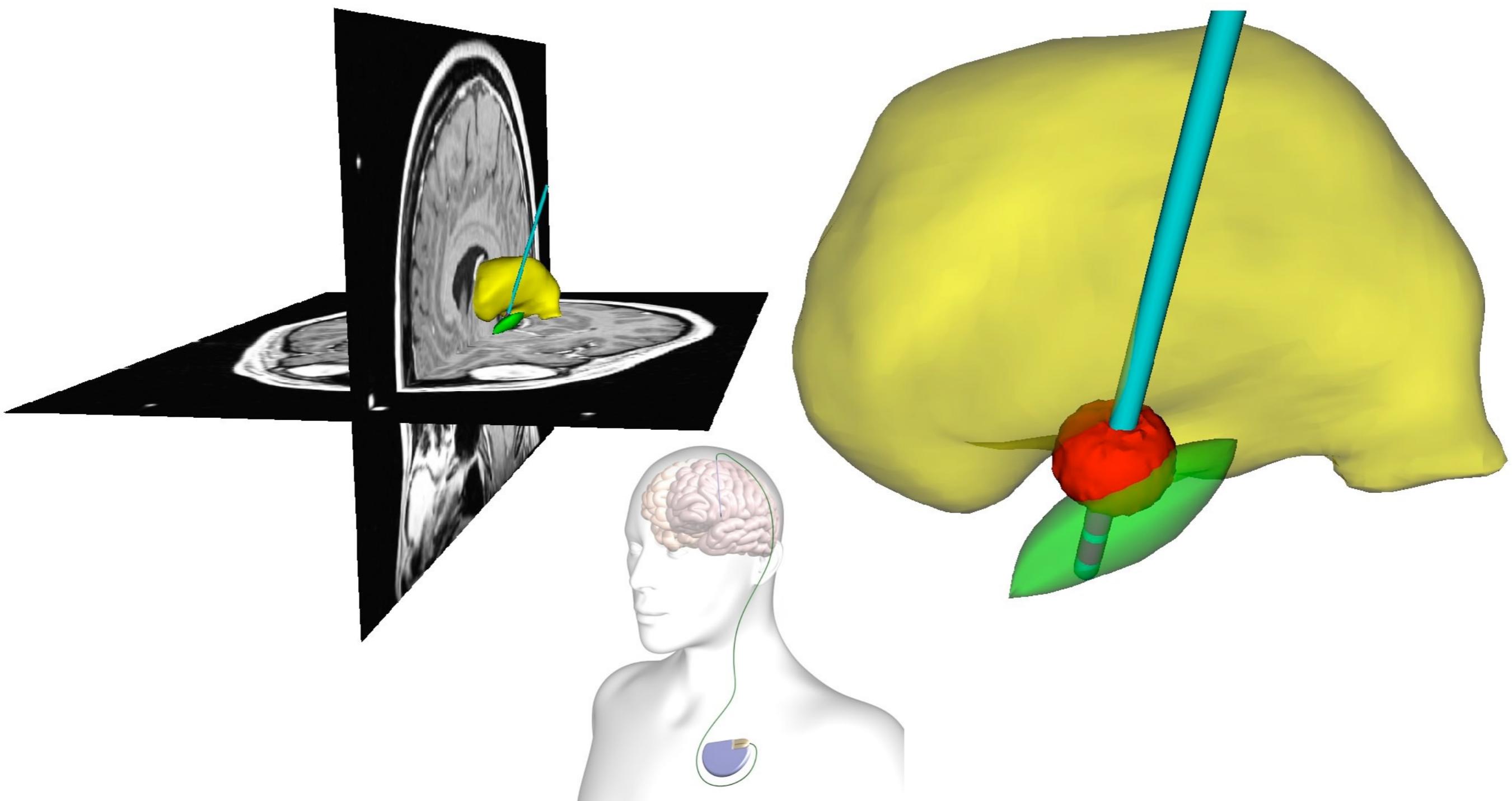
Scar

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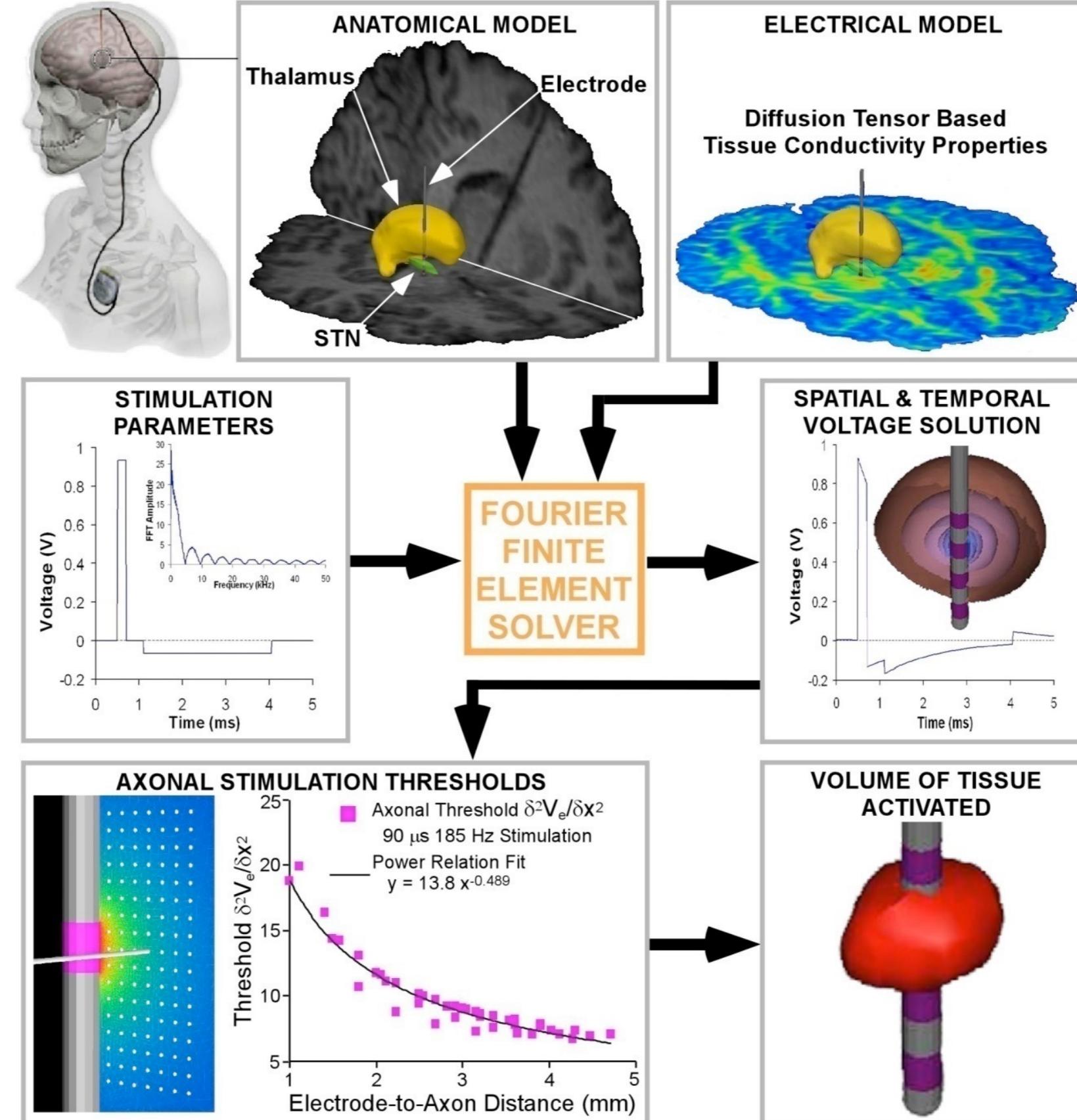
-  Predicted Ablation Zone (PAZ)
-  Surgical ablation outside PAZ
-  Optimal Ablation Zone
-  Surgical ablation inside PAZ

Deep Brain Stimulation



Computational Physiological Medicine

Fine-Tuning Deep Brain Stimulation



Computational Physiological Medicine

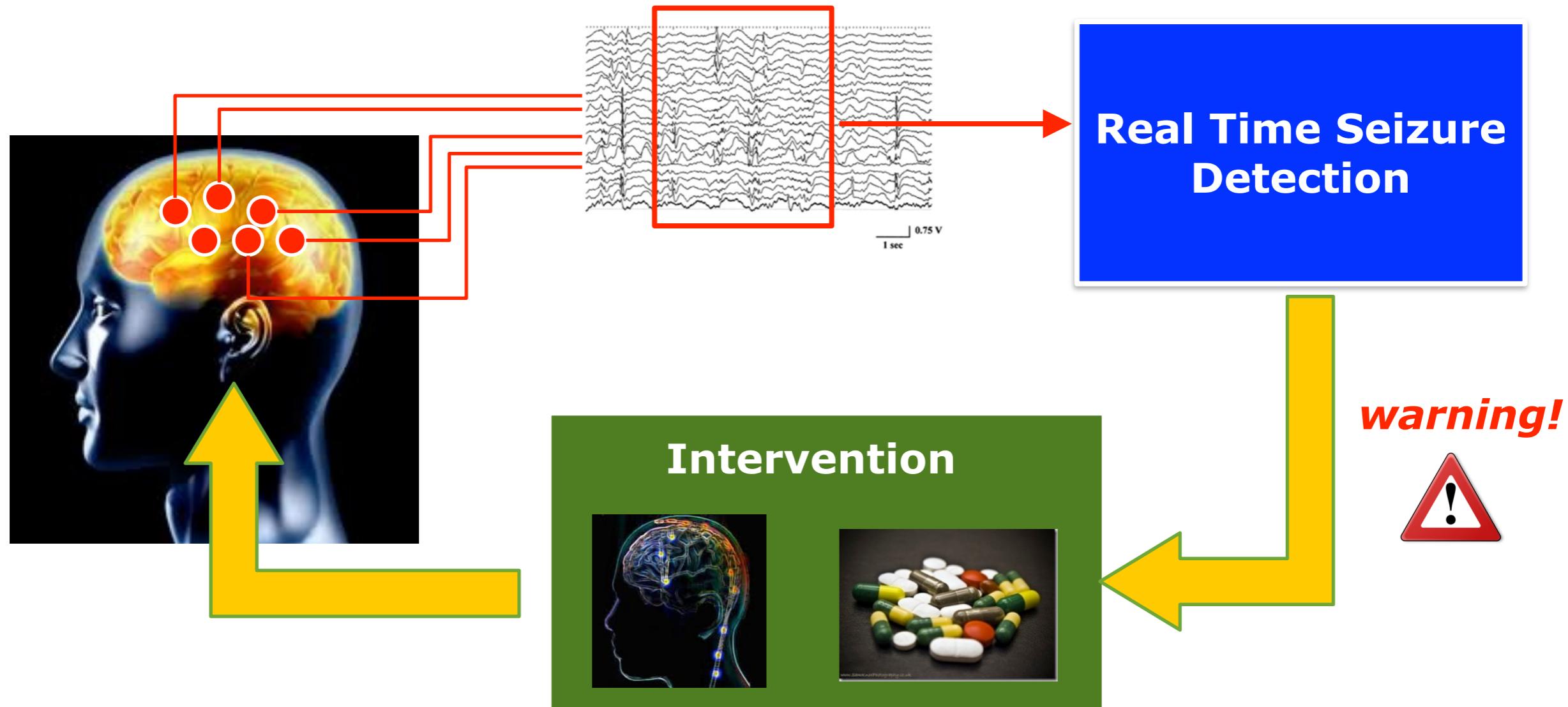
Models in Devices

 intelect[®]
medical, inc.

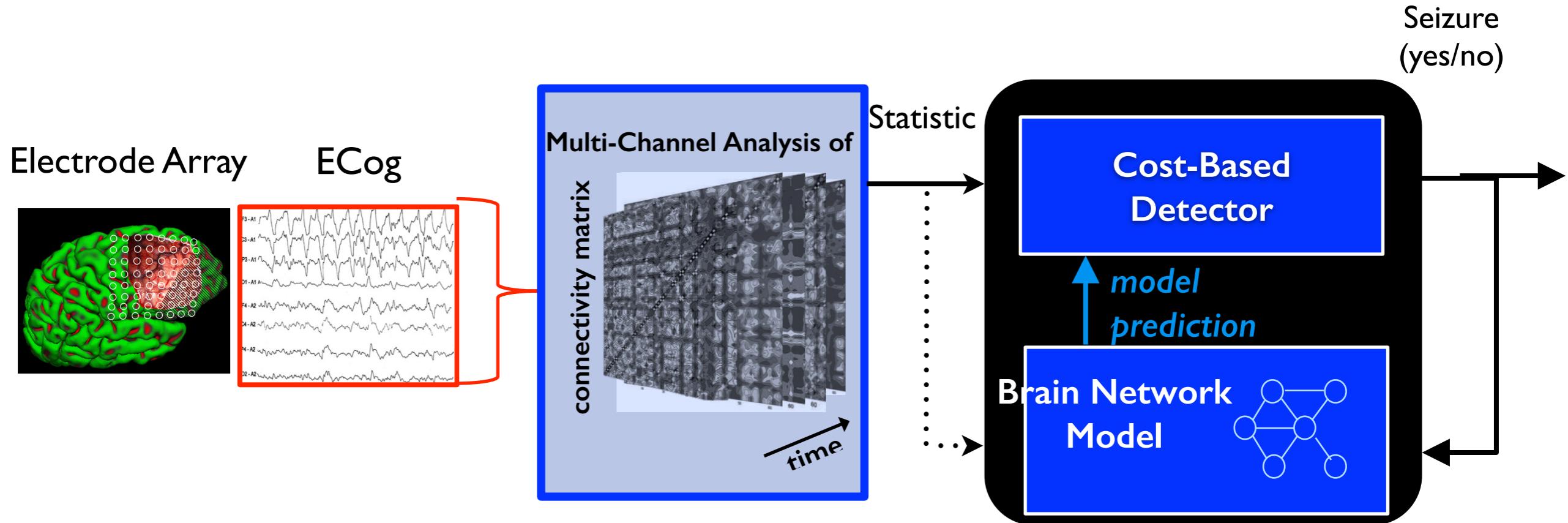
GUIDE™ | DBS



www.intelectmedical.com



**Need to intervene immediately
prior to or at seizure onset.**

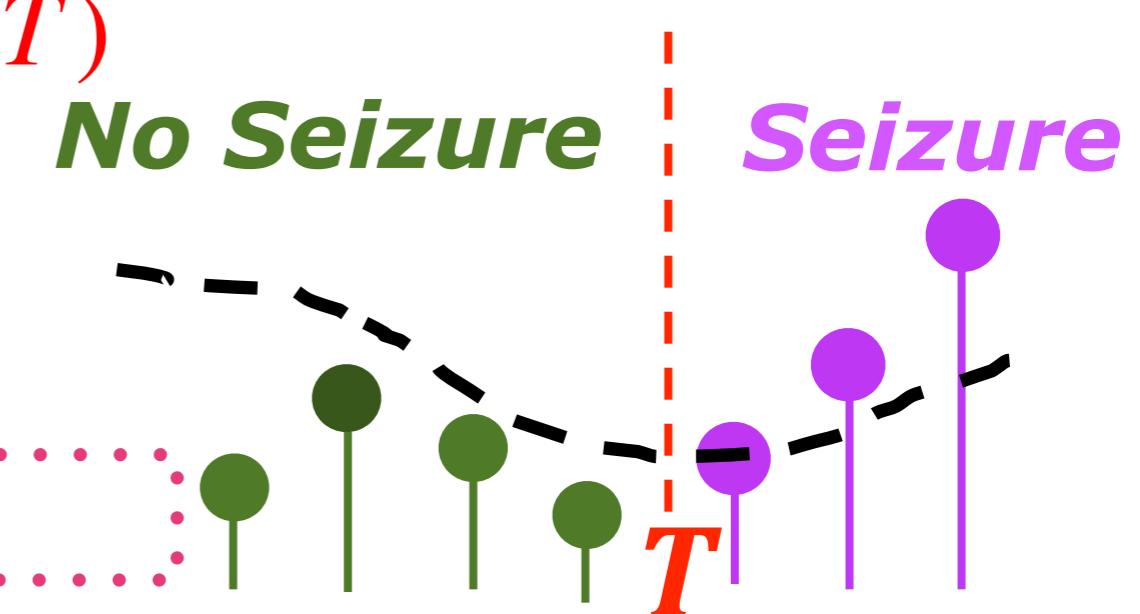


$$T_S^* = \arg \min_{T_S} d(|T - T_S|) + \Pr(T_S < T)$$

Detection Delay

Prob. False Alarm

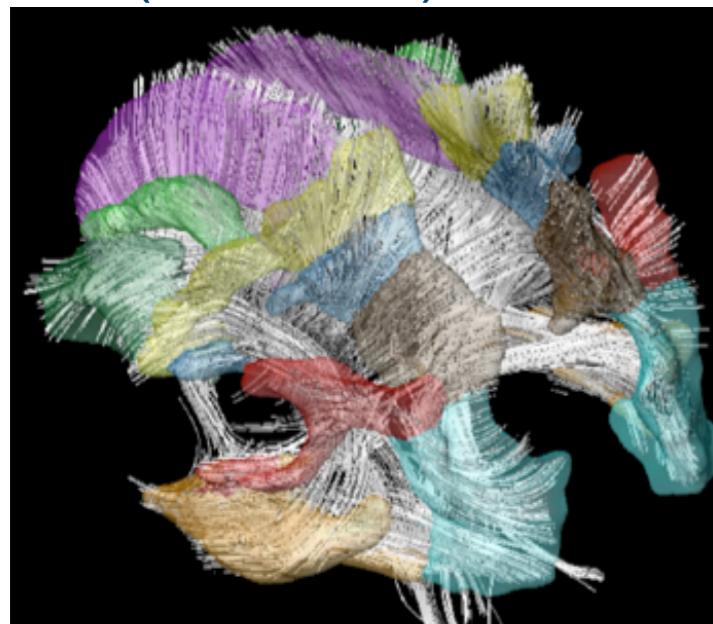
Reduces Detection Delay by 50%



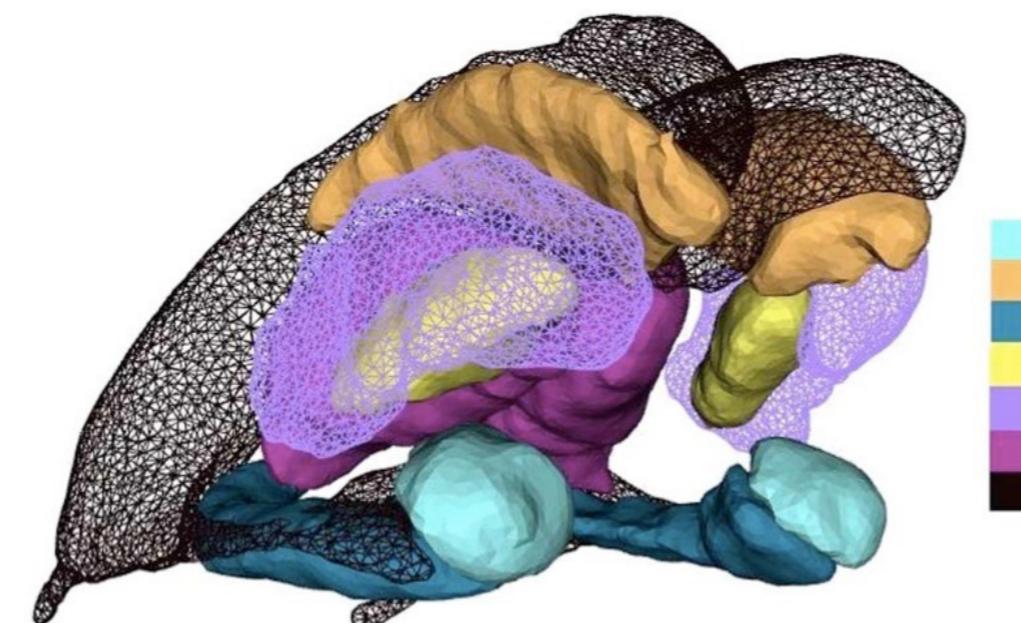
Computational Anatomical Medicine

Modeling Anatomy via Atlases & Transformations

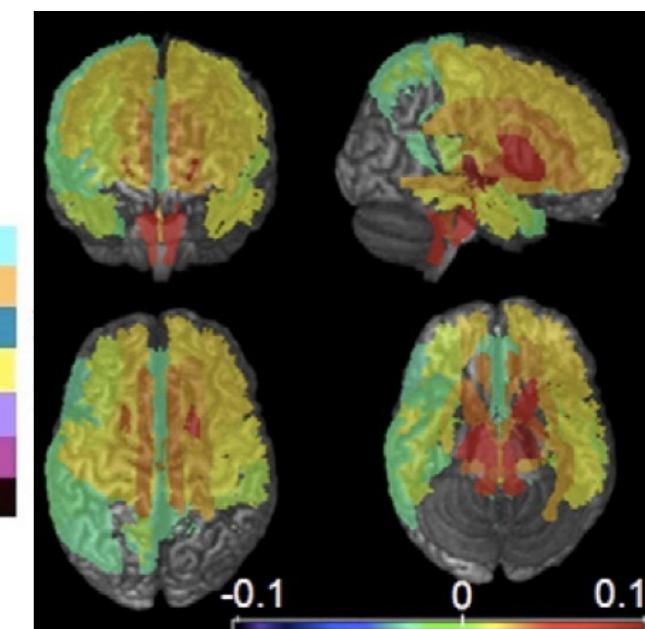
Human White Matter
(fiber tract) Atlas¹



Sub-Cortical Volume Atlas²



Human Neonatal
Brain Atlas³



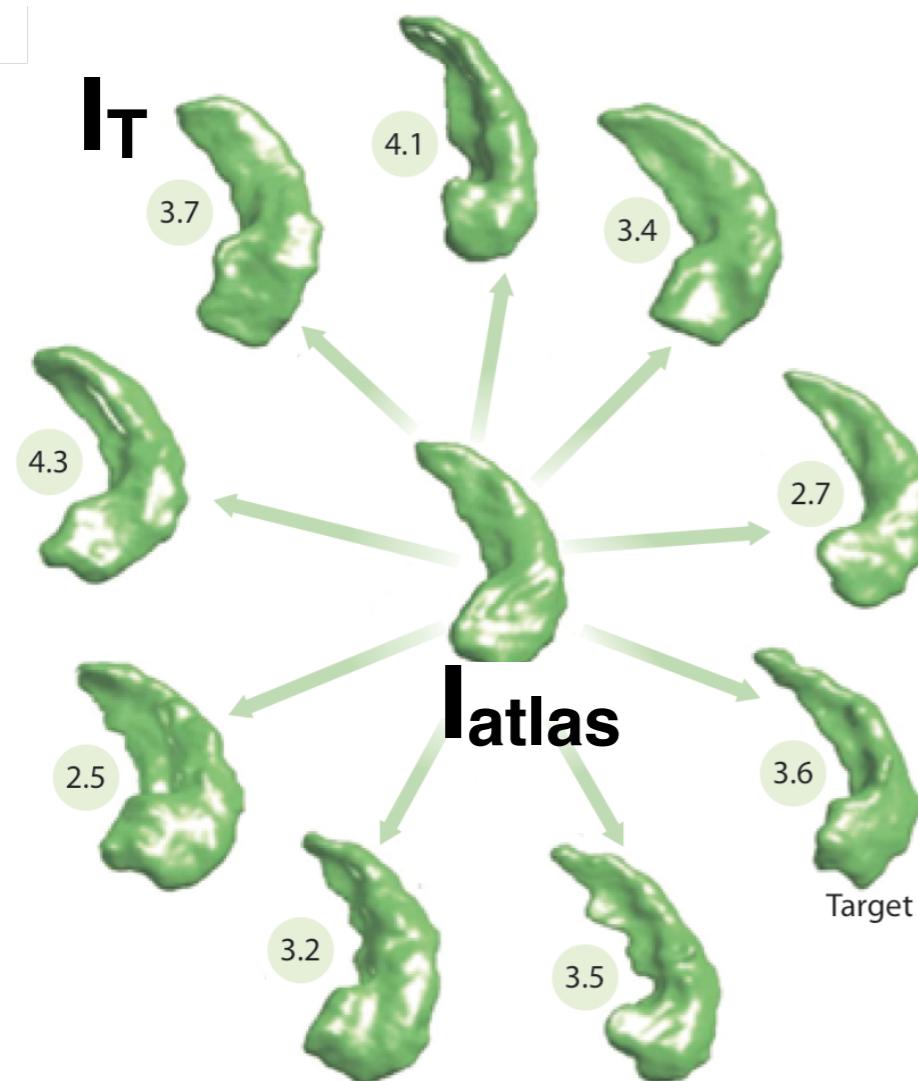
¹Oishi et al (2008) *Neuroimage* 44(3): 447

²Qiu et al (2010) *IEEE TIP* 19(6): 1539

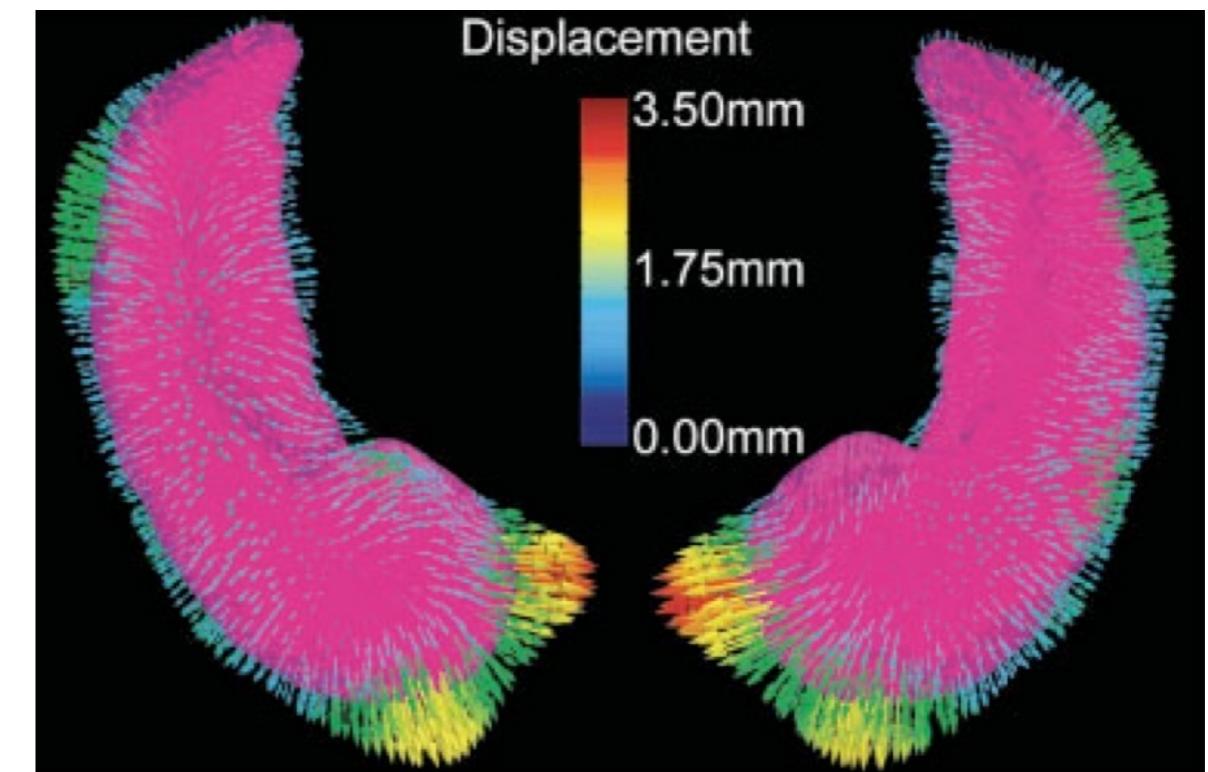
³Oishi et al (2011) *Neuroimage* 56(1): 8

Computational Anatomical Medicine

Modeling anatomic shape and its variations

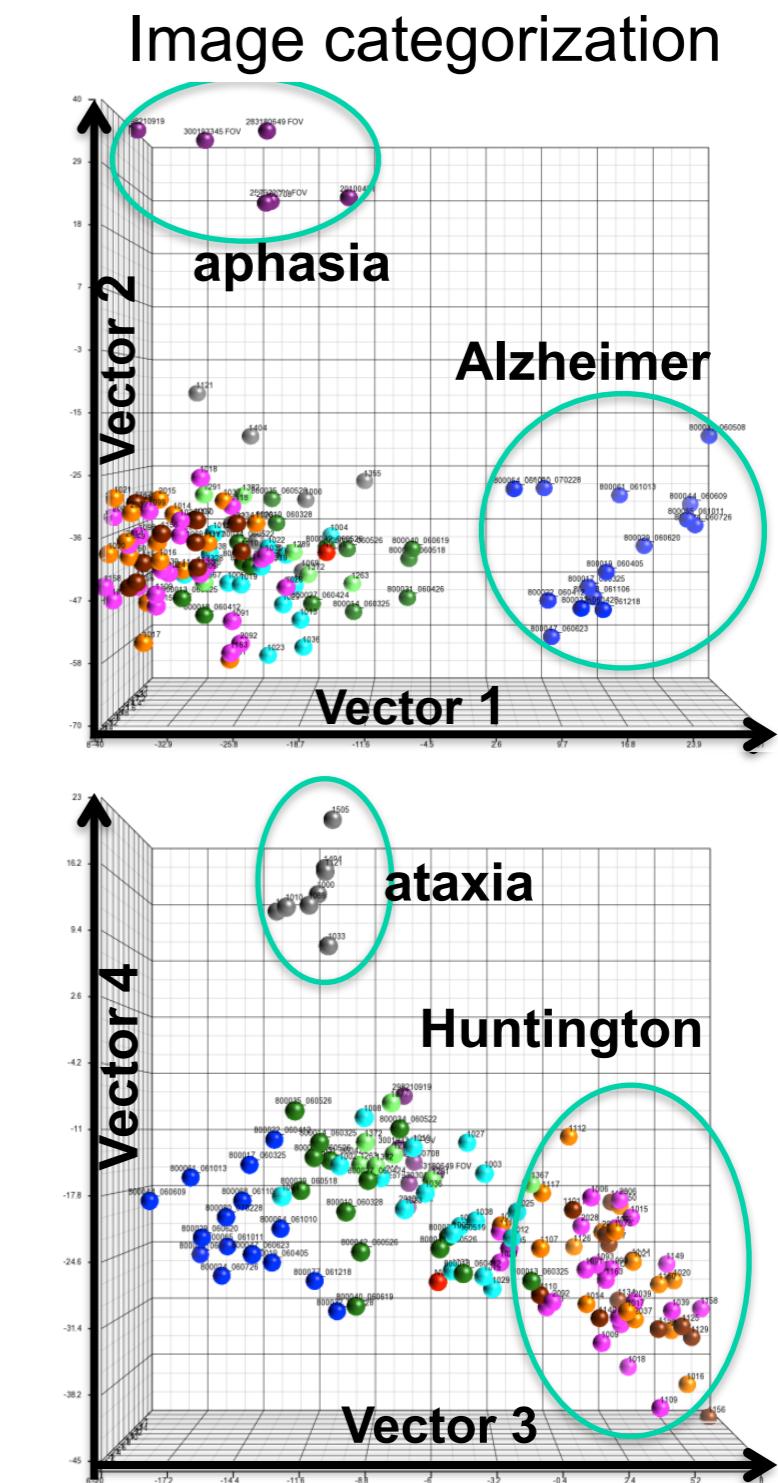
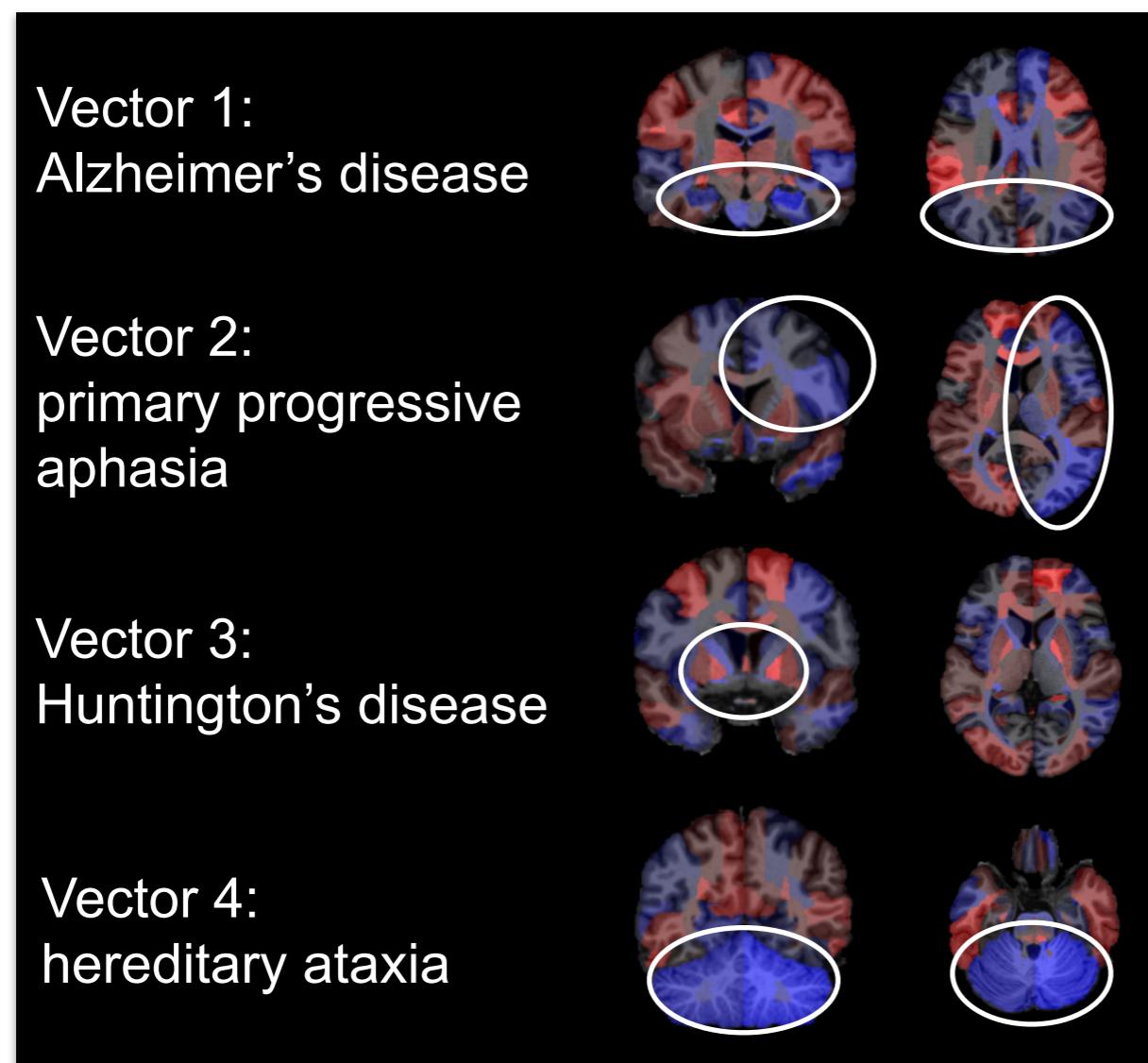
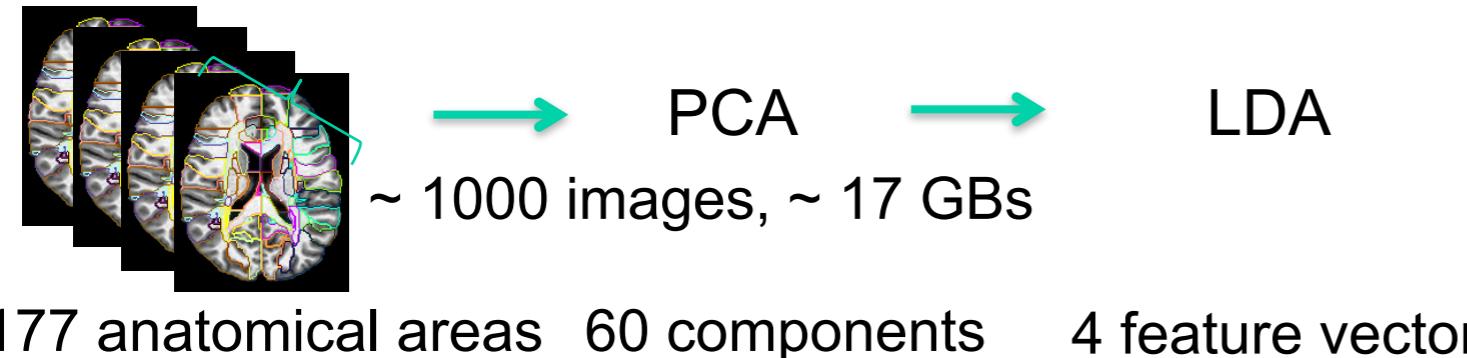


Hippocampal Shape
Alzheimer's = purple, Normal = arrows



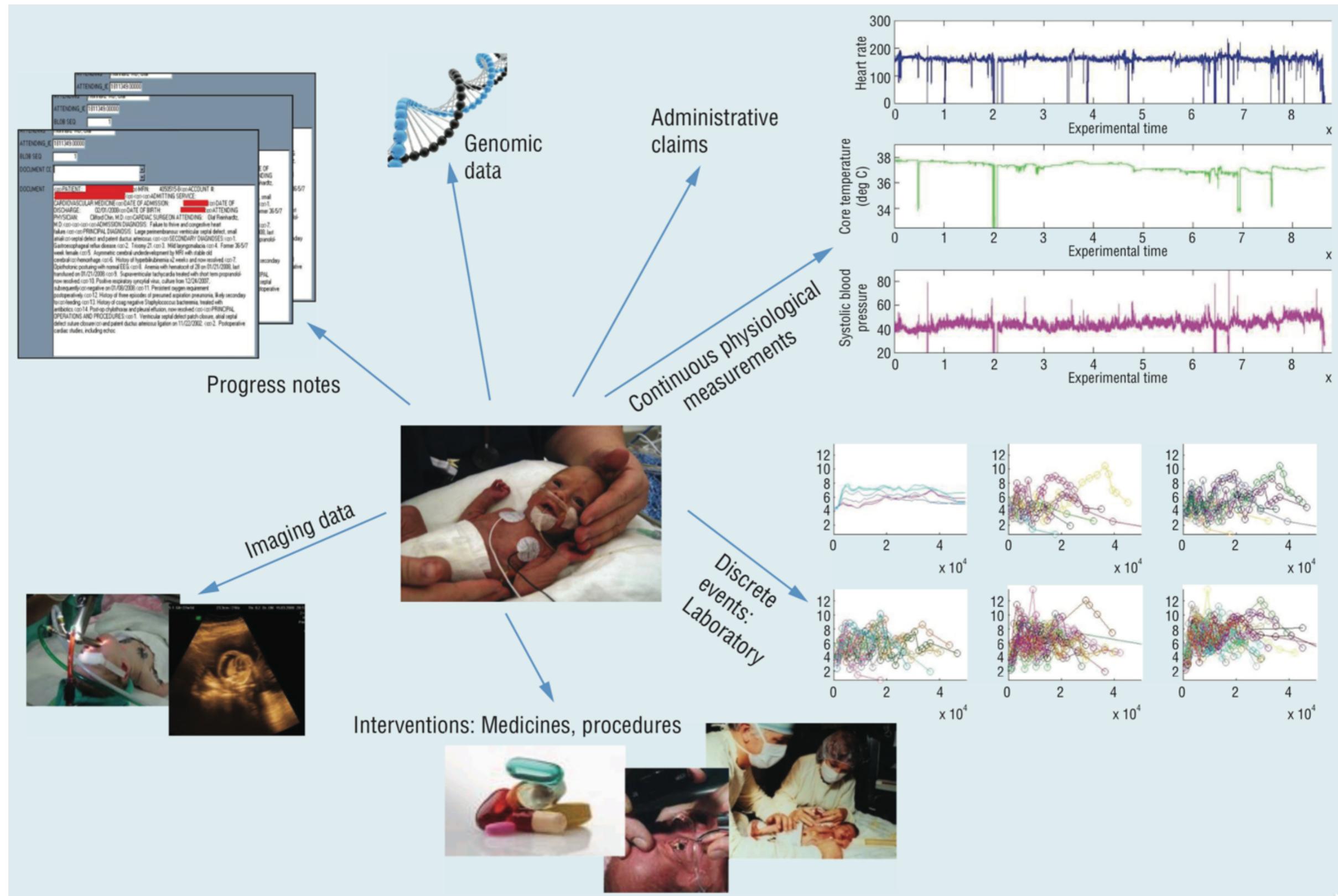
Computational Anatomical Medicine

Non-Invasive Detection of Brain Diseases



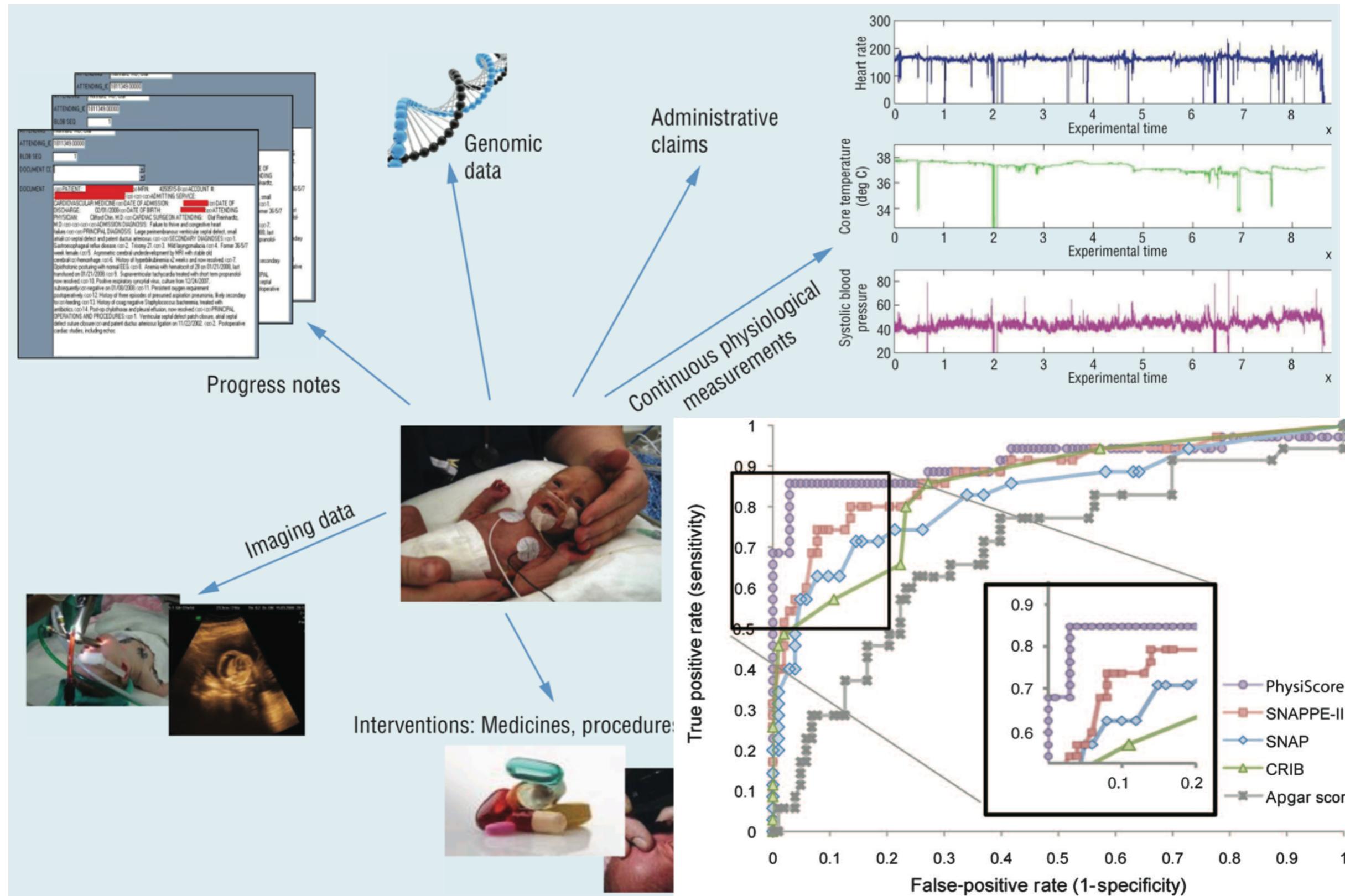
Computational Healthcare

Learning From Big Data



Computational Healthcare

Learning From Big Data



Computational Healthcare

Spread of Infectious Disease and PH Policy

The US National Large Scale Agent Model



300 Million Agents H1N1
Origin southern CA US

Constraining Data

Historical Records (H1N1 2009)
Google Alerts
Program for Monitoring Emerging Diseases
HealthMap
World Health Organization
CDC
OpenFlight Airport Database
National Healthcare Safety Network
OpenFlights Airports Database
NAVTEQ Traffic Patterns
Historical Records (e.g., H1N1 2009)
age, immune & disease state, travel,
attend school, hospital employee, fear

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 - practice
 - training
 - outcomes
 - cost

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- Personalized, mechanistic disease models will enable
 - collapse of “big data” to models
 - the “Patient Model Record” versus “Patient Electronic Record”

- Medicine is becoming a computational science and the consequences will be profound
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- Personalized, mechanistic disease models will enable
 - collapse of “big data” to models
 - the “Patient Model Record” versus “Patient Electronic Record”
- Regulatory challenges - FDA review and approval of models?

School of Engineering

Ardekani



Bader



Charon



Mac Gabhann



Geman



Karchin



Miller



Mittal



Ratnanather



Sarma



Trayanova



Vidal



Vogelstein



Younes



Saria



School of Medicine

Anderson



Barta



Epstein



Winslow

