The Emerging Discipline of Computational Medicine

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Whiting School of Engineering

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

Winslow, R. L., Trayanova, N., Geman, D. and Miller, M. I. (2012). Computational Medicine: Translating Models to Clinical Care. *Sci. Transl. Med*. 4(158): p.158rv11

INSTITUTE for COMPUTATIONAL MEDICINE

Research Areas in the ICM

Computational:

- Molecular Medicine
- Physiological Medicine
- Anatomical Medicine
- Healthcare

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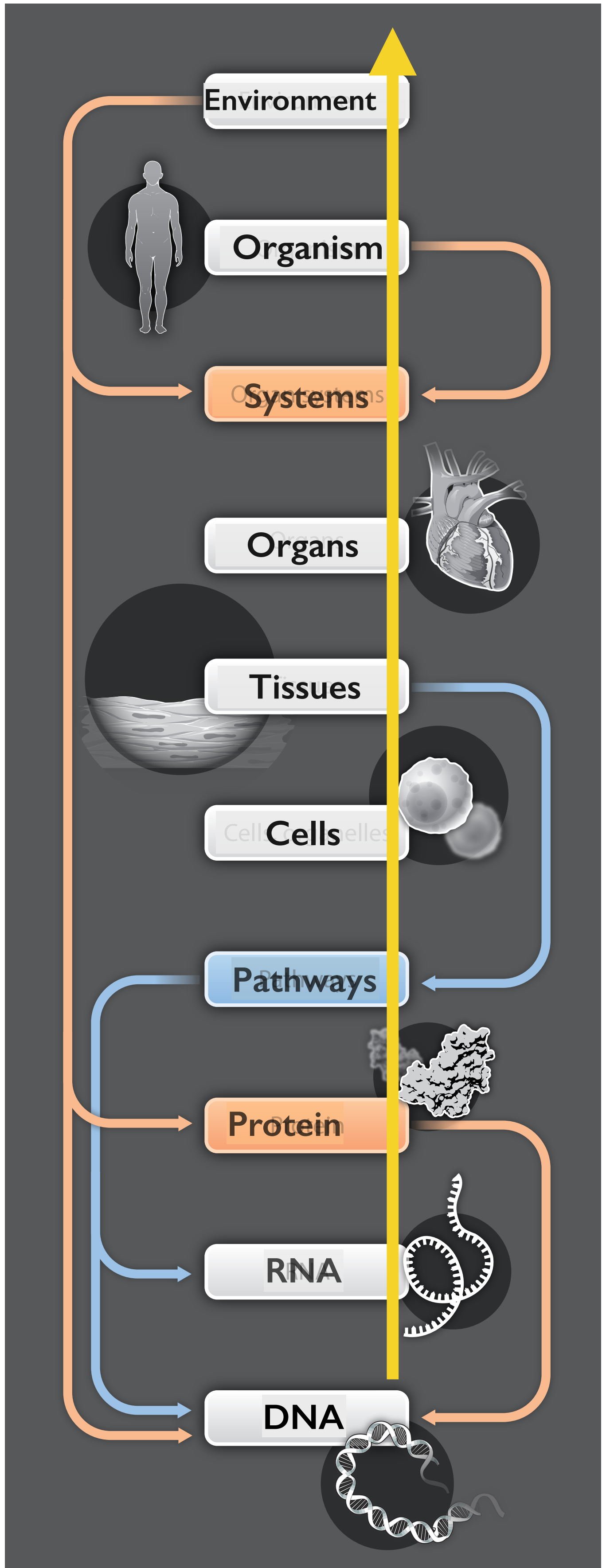
Why are Models Needed?



- 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

Denis Noble, "The Music of Life"

Enabling Technologies

- Data
- Computation

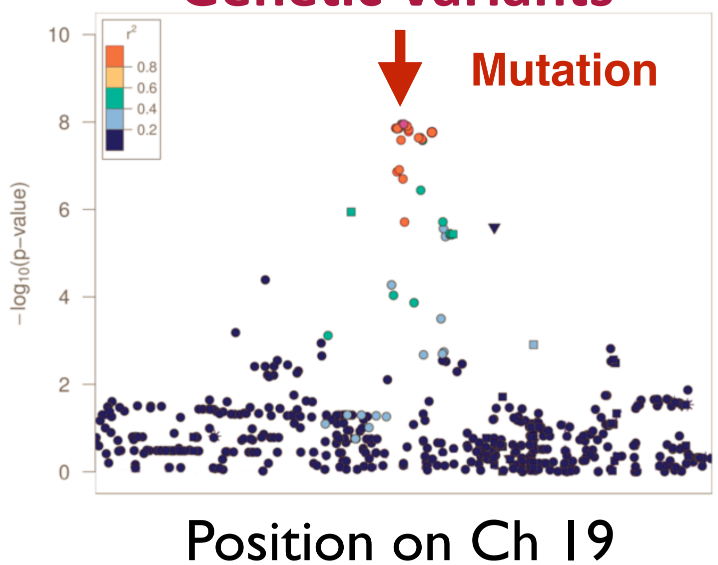
Enabling Technologies

"Seqs" & "Omes"

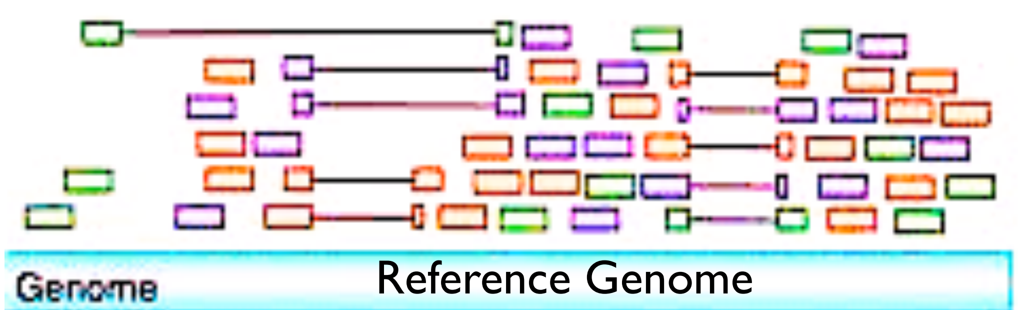
$1K Personal Genome, Illumina HiSeq X Ten

30x coverage, 600 GBases/day, .3 TBs/ day

Genetic Variants



RNA Sequence & Expression



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

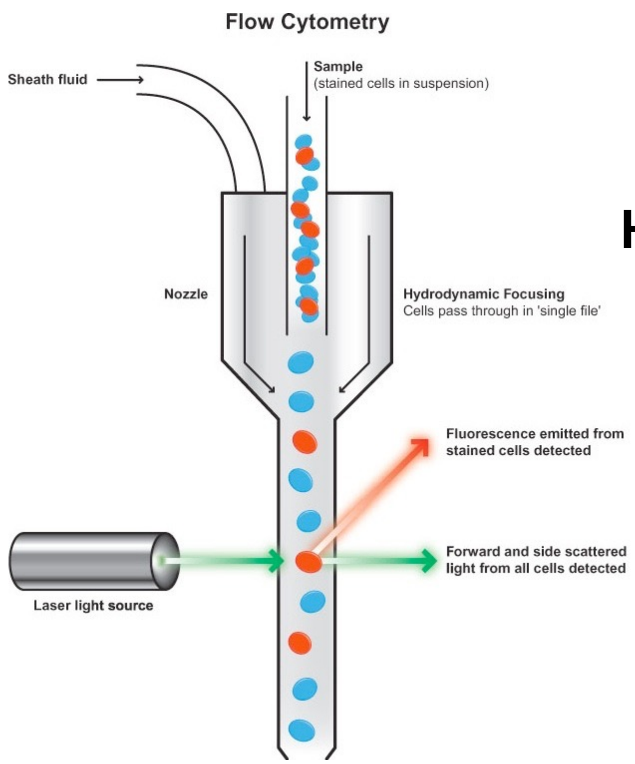
RNA Structure
(SHAPE-Seq)

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

Protein & Metabolite Expression
(HPLC, Mass Spec)

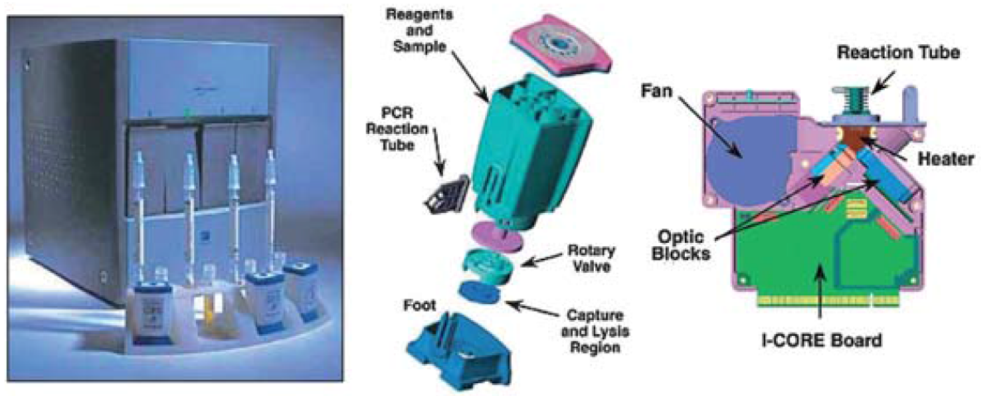
Protein Networks
(Yeast 2-Hybrid, FRET)

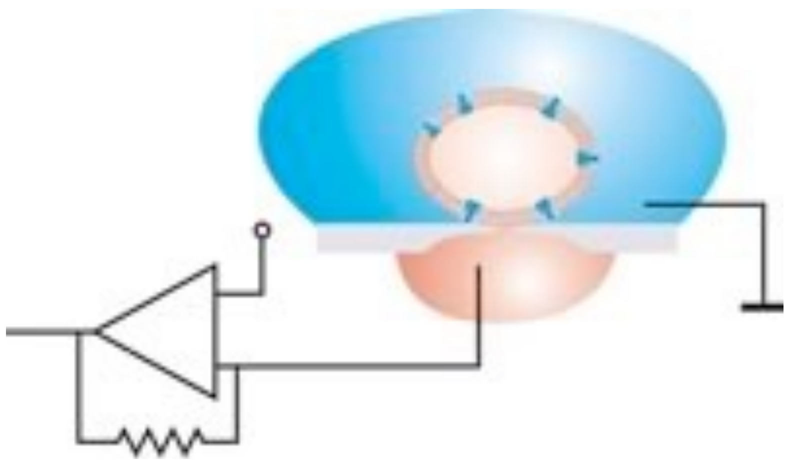
Enabling Technologies
Lab-on-Chip



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

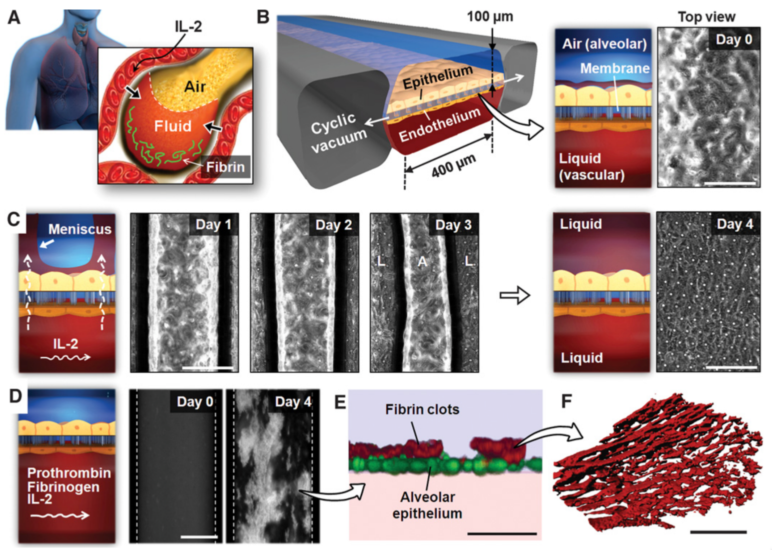
Point of Care Microfluidics:
Infectious diseases, blood gases, …





High Throughput Patch Clamp:
electrophysiology

Organ on a Chip



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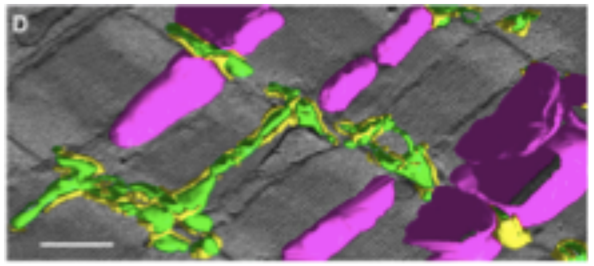
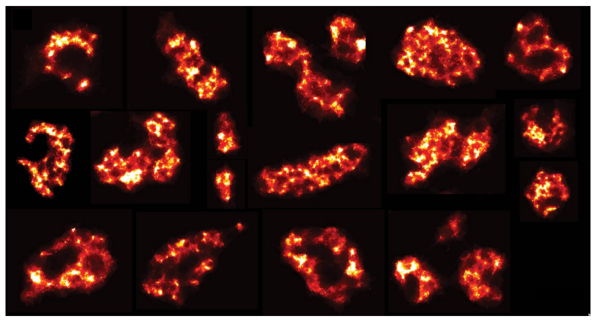
Enabling Technologies

Imaging

EM Tomography (nm's)

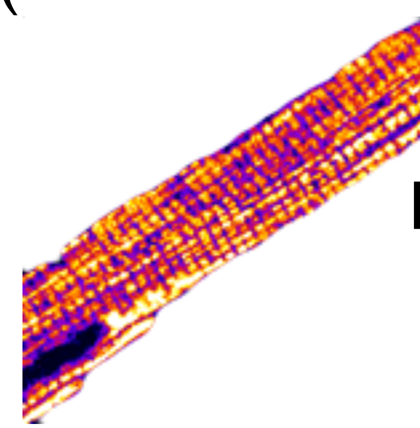


fPALM, STORM (10's nm)

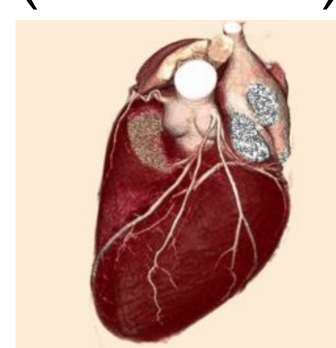


Structure

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



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



300 um^3 voxels, 175 mSec

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Enabling Technologies
The Electronic Medical Record

bhi Blue Health Intelligence — 100,000,000 patients

EXPRESS SCRIPTS — 100,000,000 patients

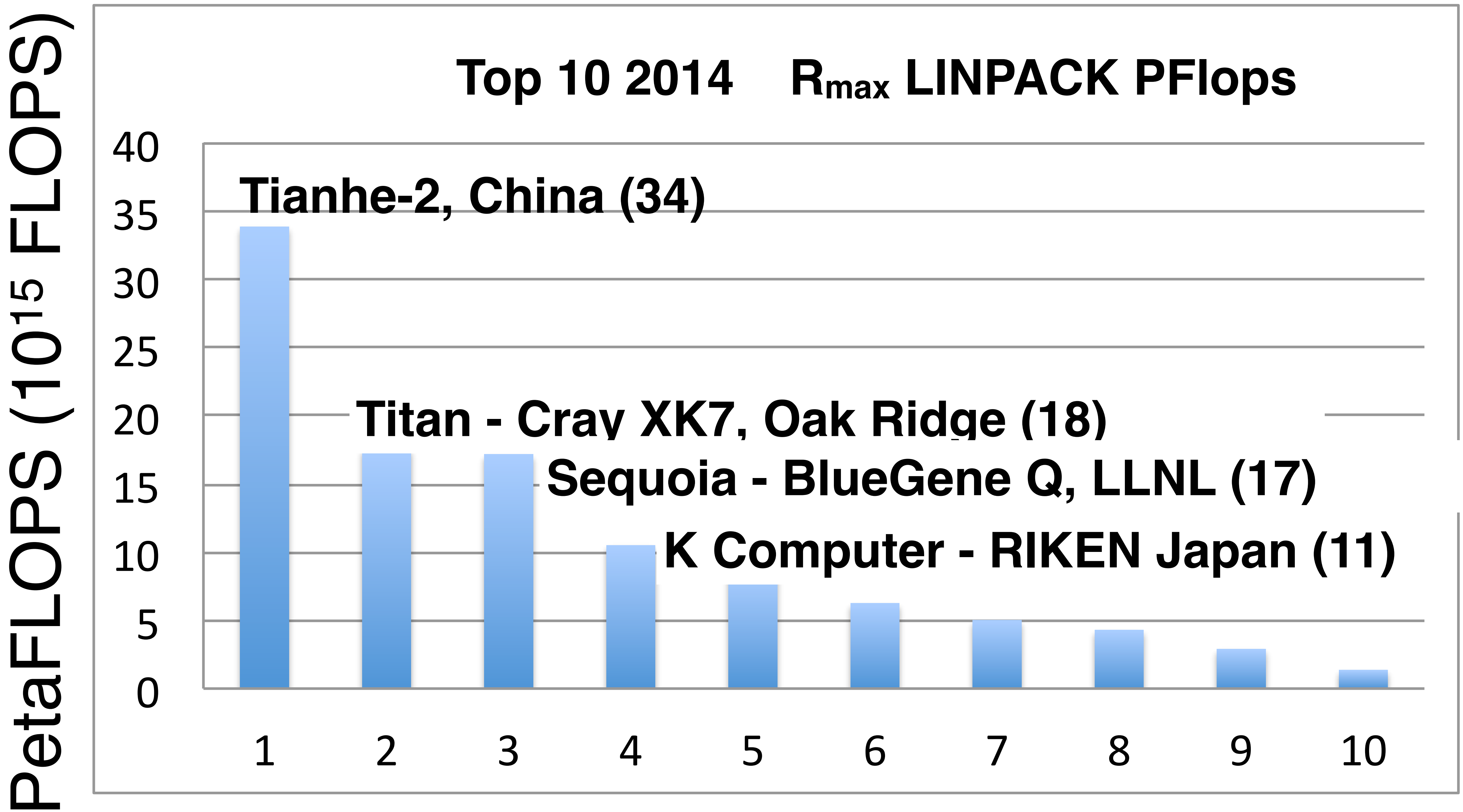
aetna — 22,000,000 patients

KAISER PERMANENTE — 9,000,000 patients

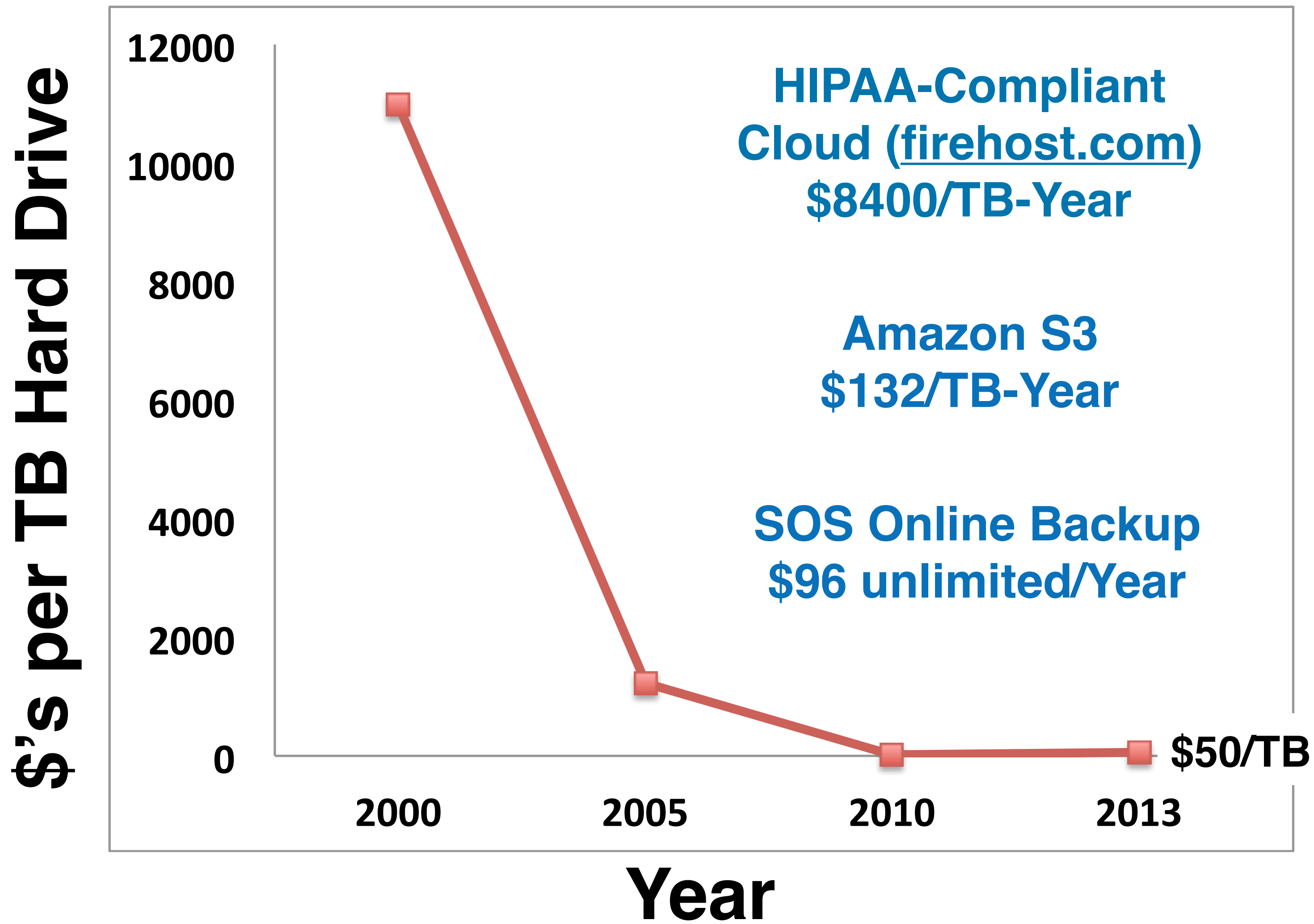
NIH Precision Medicine Initiative — 1,000,000 patients

Johns Hopkins Medical Institutions — 250,000 patients

Enabling Technologies
High Performance Computing

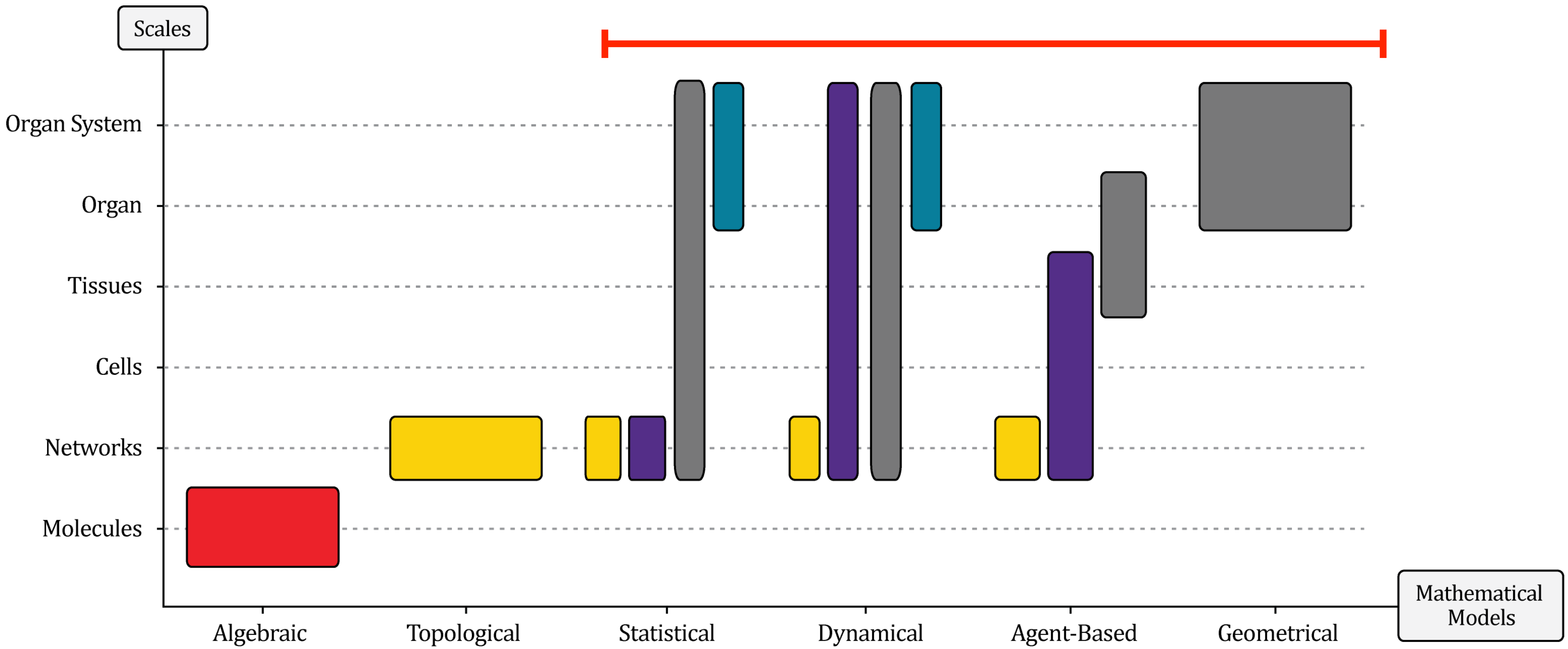


Enabling Technologies
Storage



Where are we?

Types of Models



Data Modalities

Sequence Data
DNA
mRNA
miRNA
Protein
......

Expression Data
mRNA
miRNA
Methylation
Protein
...

Physiological Data
Probes
Indicators
EEG
ECG
spO2
BP
...

Imaging Data
MR
CT
PET
...

EMR Data
Lab tests
Diagnoses
Treatments
...

Definitions:

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

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

Normal, disease class

$\{C_{normal}, C_{disease}\}$

T_i is class label for i^{th} patient

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

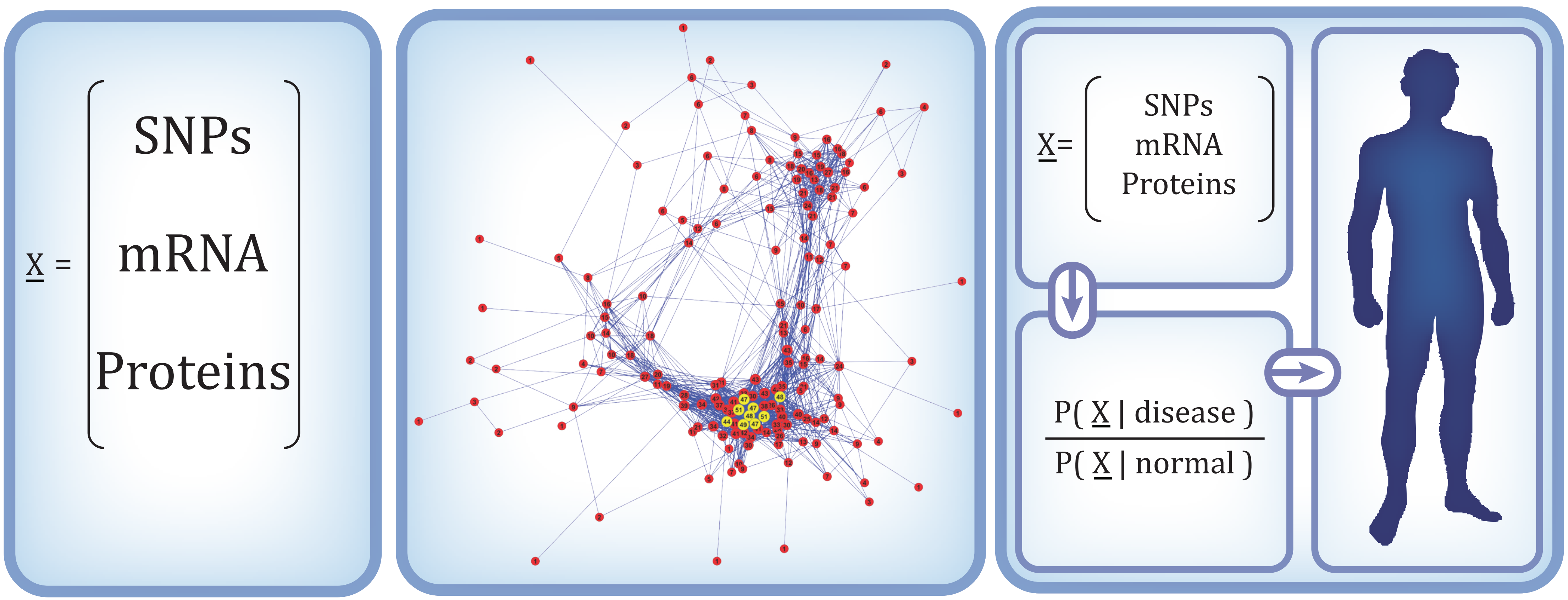
Classifier F( ):

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

Validate by testing F( ) on new data

The Fundamental Challenge to Machine Learning in Biology

The "Small N, Large p Problem"



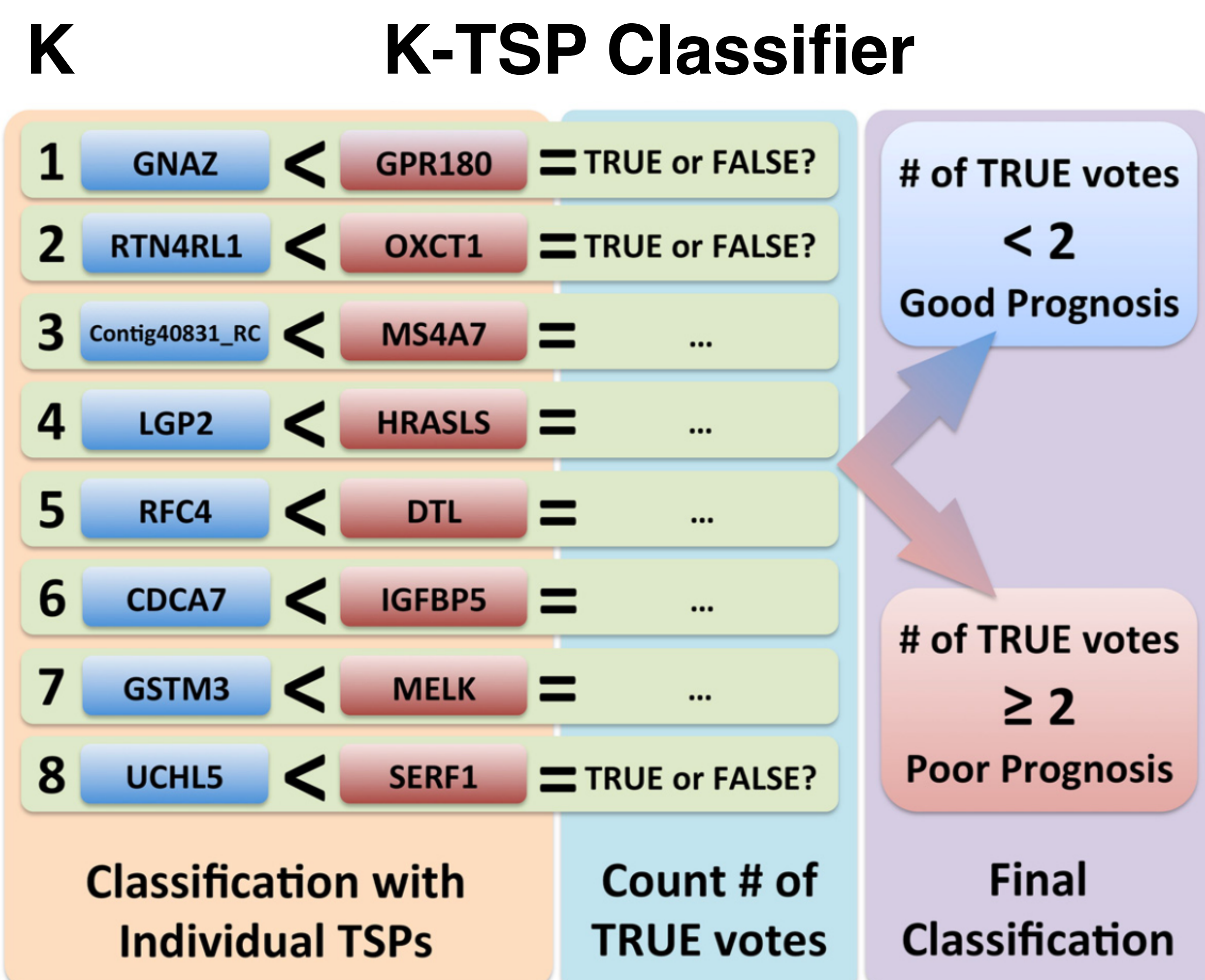
Parts and Measurements
Phenotype $\underline{X} \in R^p$

Relationships

Statistical Disease Model

Computational Molecular Medicine

Simple 0,1-Parameter Classifiers



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

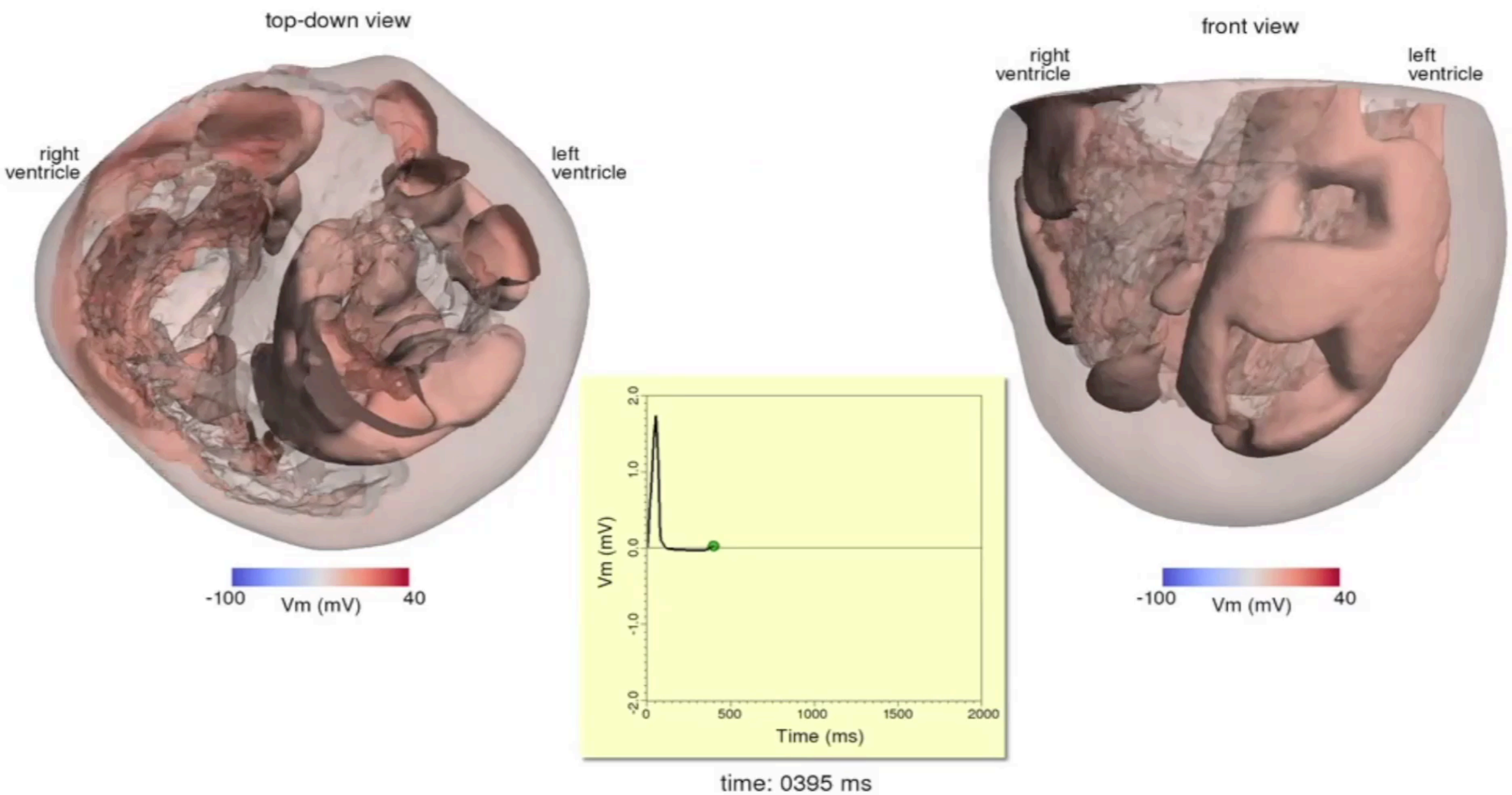
Dementia Alzheimer's Type
88% Sensitive, 89% Specific

Protein Diagnostic

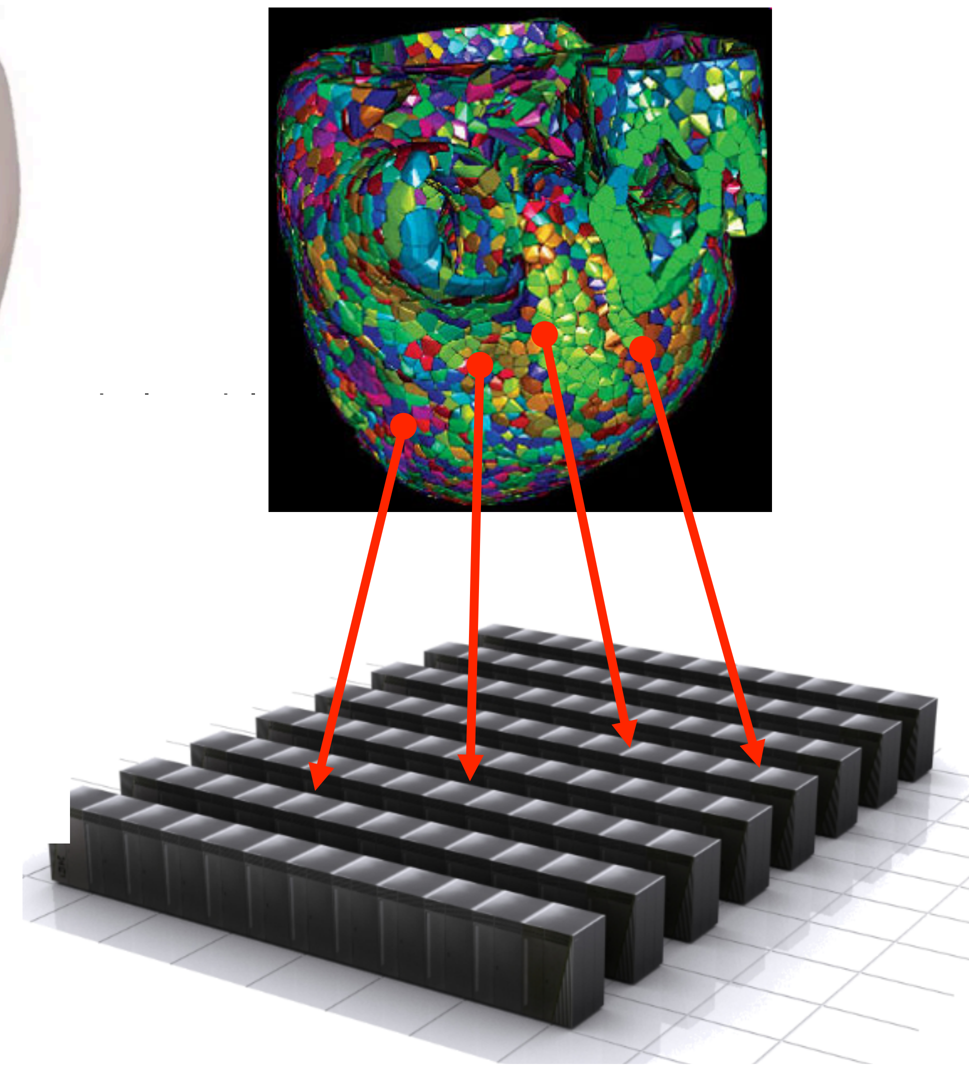
Inflammatory Bowel Disease
89% Sensitive, 81% Specific

Geman et al (2004). *Stat. Appl. Genet. Mol. Biol.* 3(1): 19

IBM Cardioid Human Heart Model



Anatomical Human Heart Model



96 Racks of BlueGene Q Sequoia

Simulate electrical conduction in human heart near real time!

Functional Genomics & Systems Biology Group
Center for Computational Biology, IBM TJ Watson &
Lawrence-Livermore National Laboratory

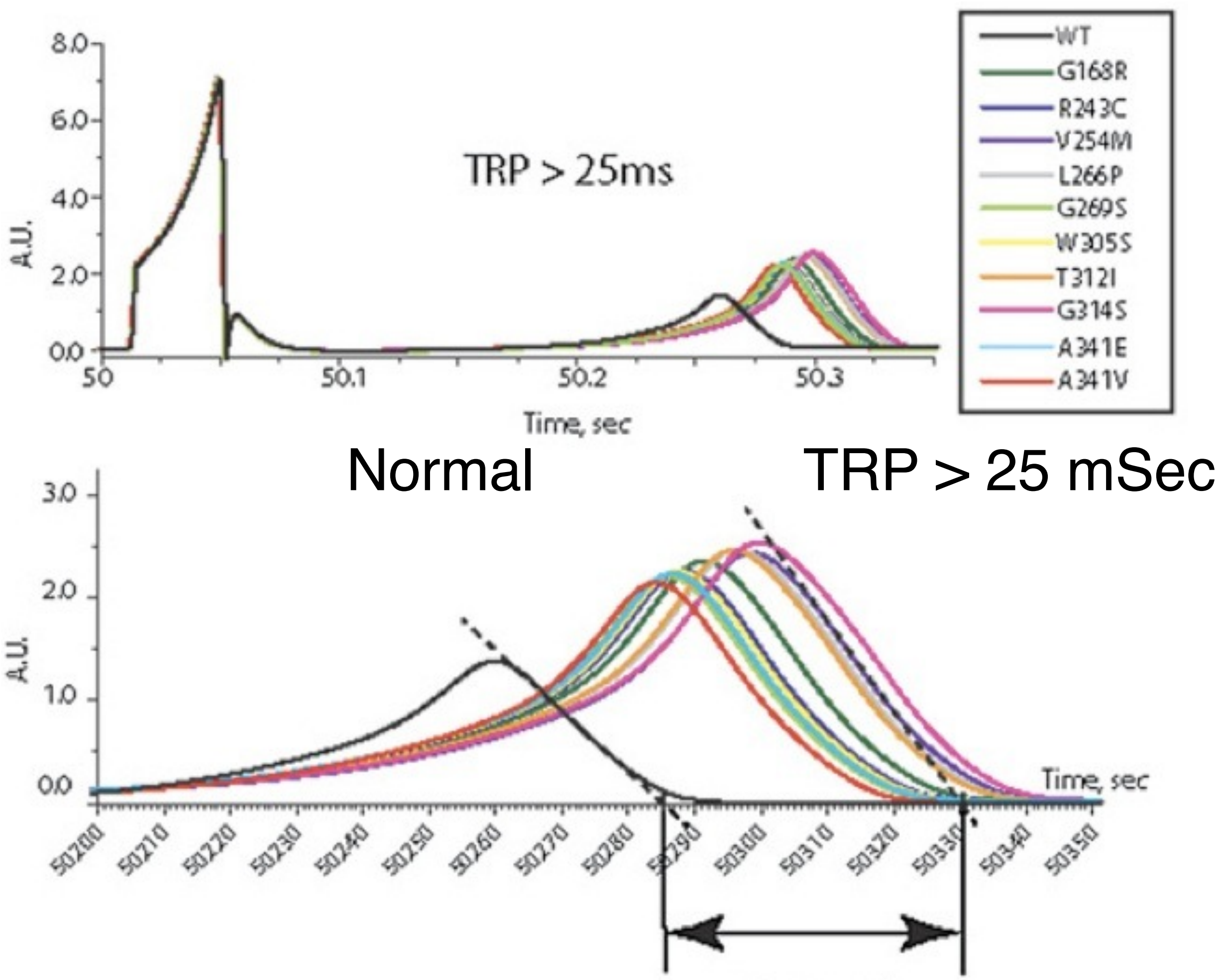
Reumann et al (2008) Large-scale cardiac modeling on the Blue Gene Supercomputer, IEEE EMBS Conf Proc 2008: 577

Computational Physiological Medicine

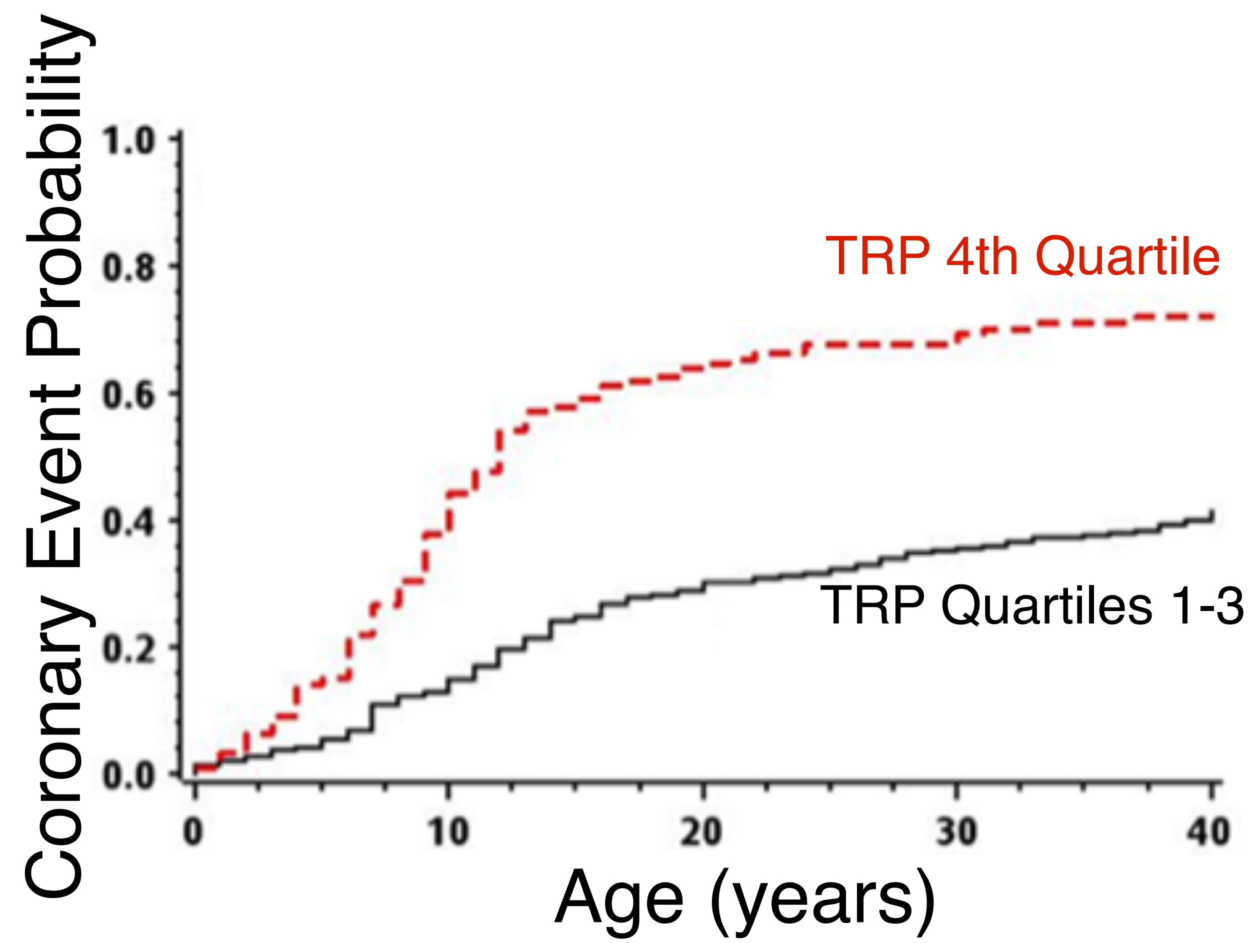
Computational Biomarker for Coronary Events

Long QT Syndrome

Model Transmural Conduction & Repolarization Prolongation (TRP)



Events vs Age and TRP



Model revealed mutations ⇒ largest TRP

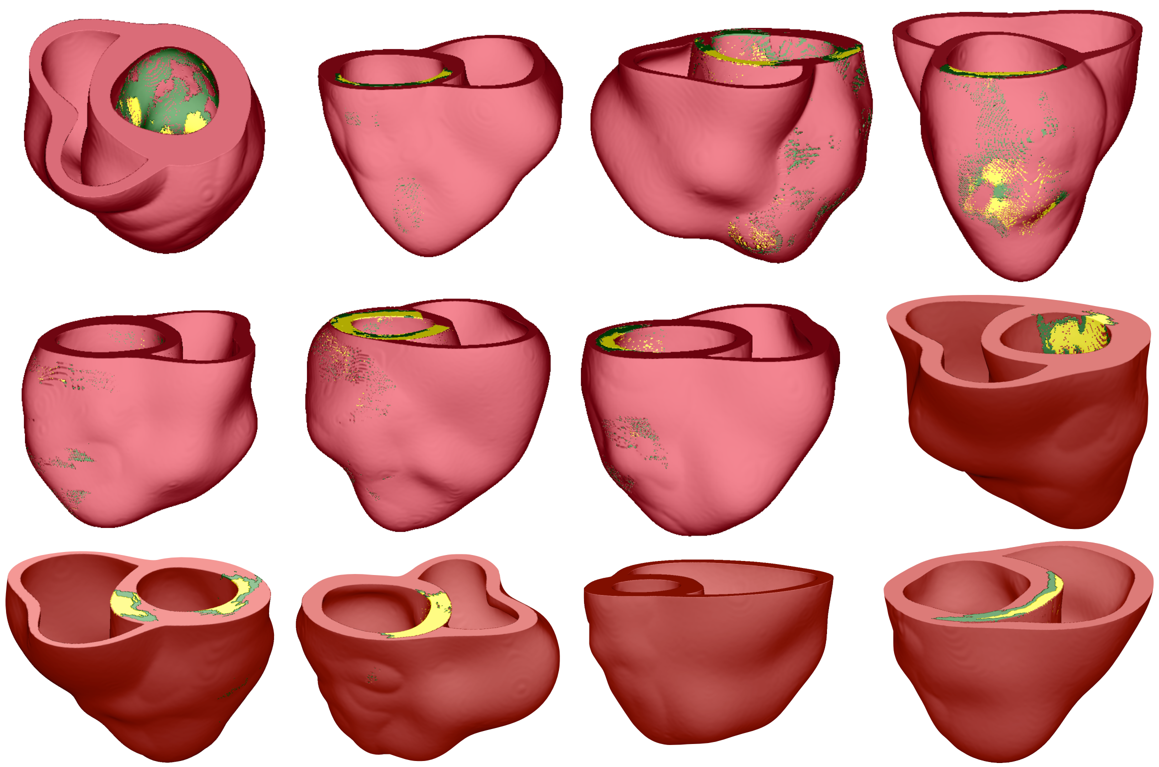
Functional Genomics & Systems Biology Group
Center for Computational Biology, IBM TJ Watson

Hoefen et al (2012) In Silico Cardiac Risk Assessment in Patients with Long QT Syndrome: *JACC* 60(21): 2182

Computational Physiological Medicine

Personalized cardiac ablation therapy

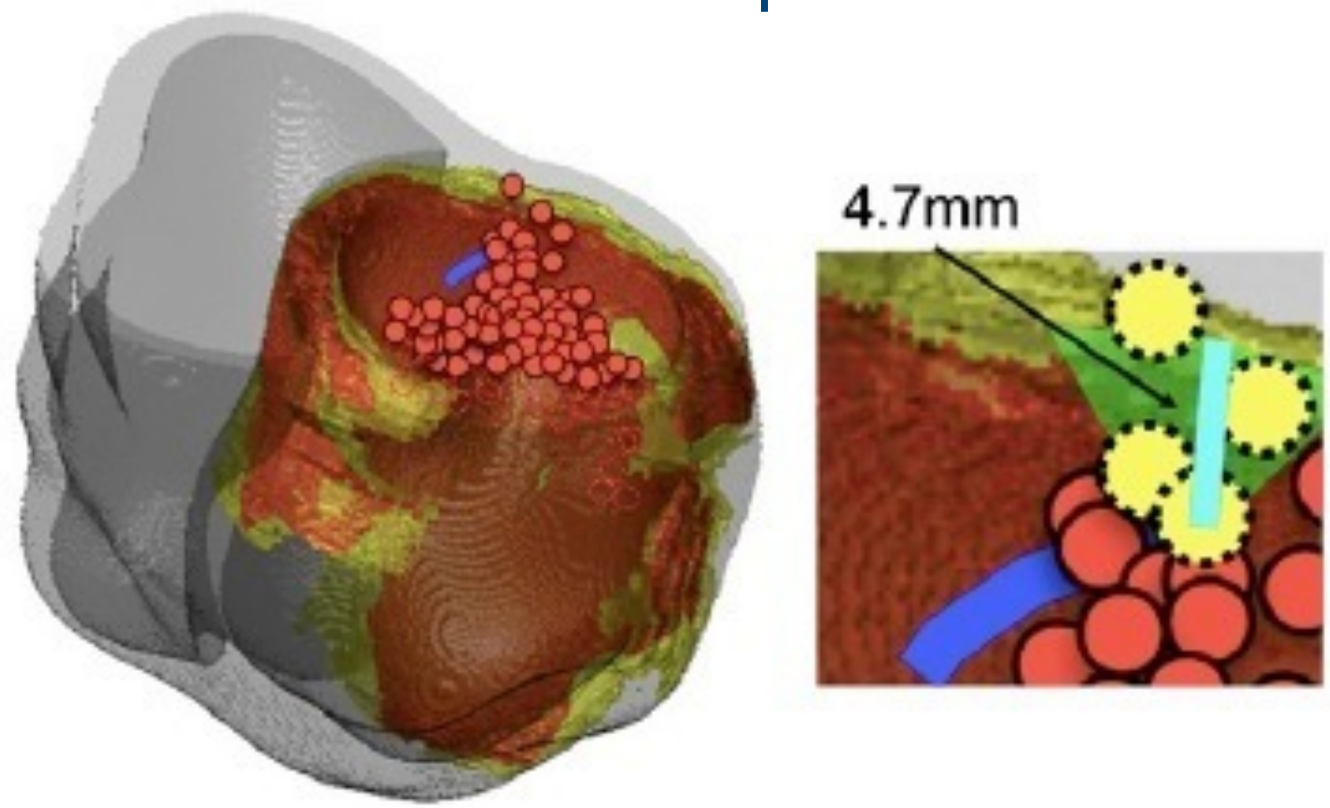
MRI-Based Anatomical Models of 12 Patient Hearts



Normal

Scar

Simulations Reveal Optimal Ablation Site per Patient



Predicted Ablation Zone (PAZ)

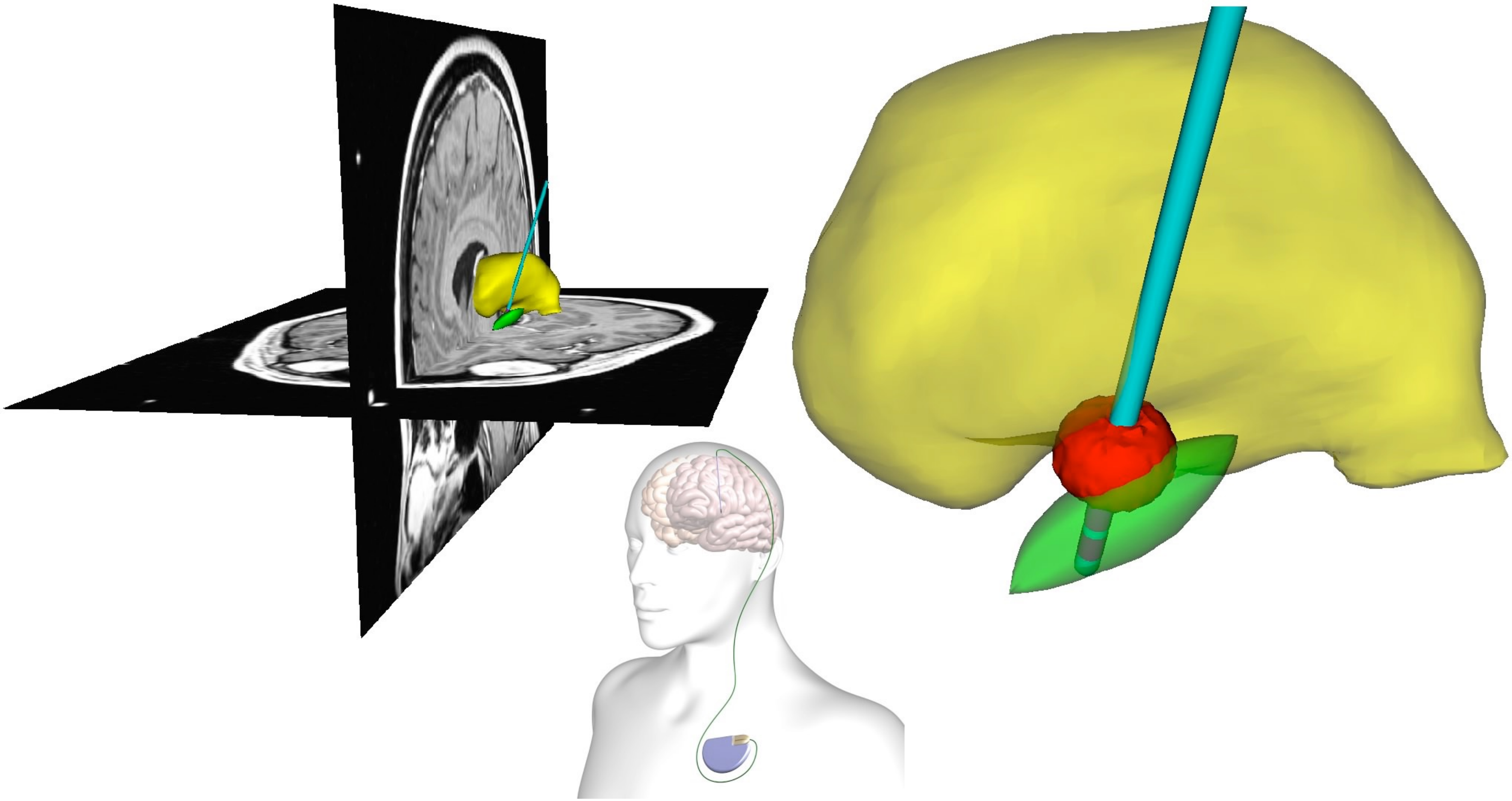
Surgical ablation outside PAZ

Optimal Ablation Zone

Surgical ablation inside PAZ

Ashikaga et al (2013) Feasibility of image-based simulation to estimate ablation target in human ventricular arrhythmia, *Heart Rhythm*, in press

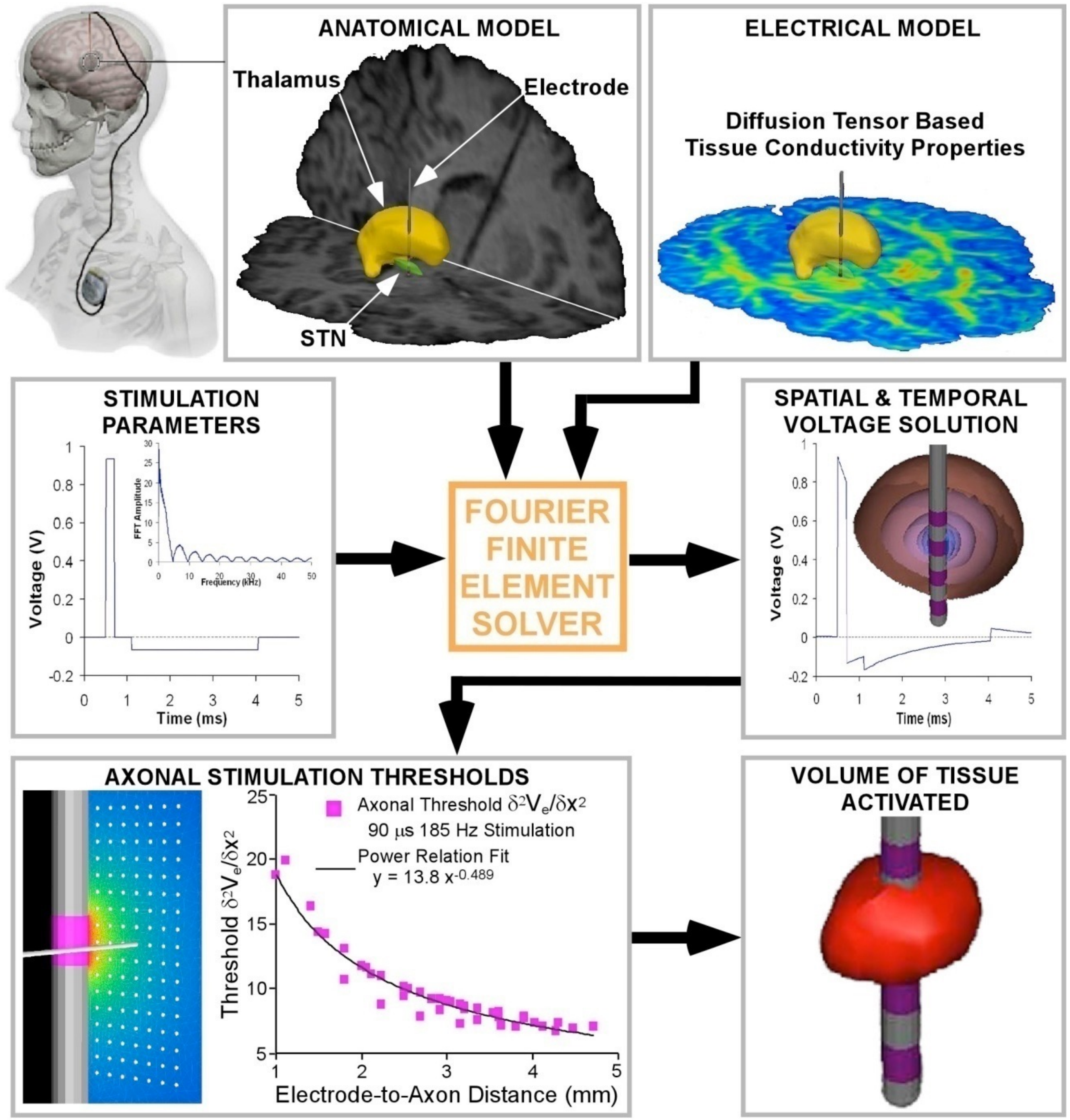
Deep Brain Stimulation



Frankemolle et al (2010) Brain 133(3): 746

Computational Physiological Medicine

Fine-Tuning Deep Brain Stimulation



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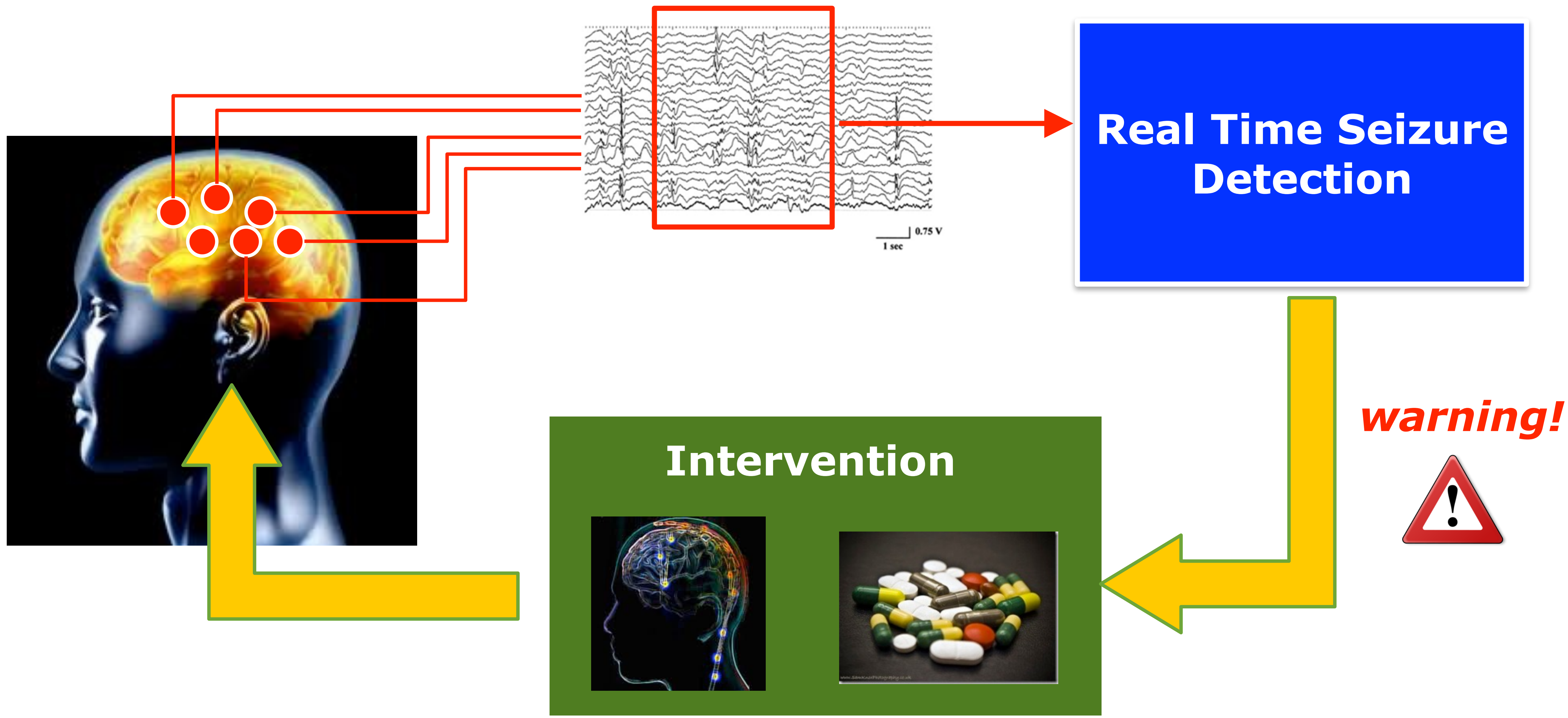
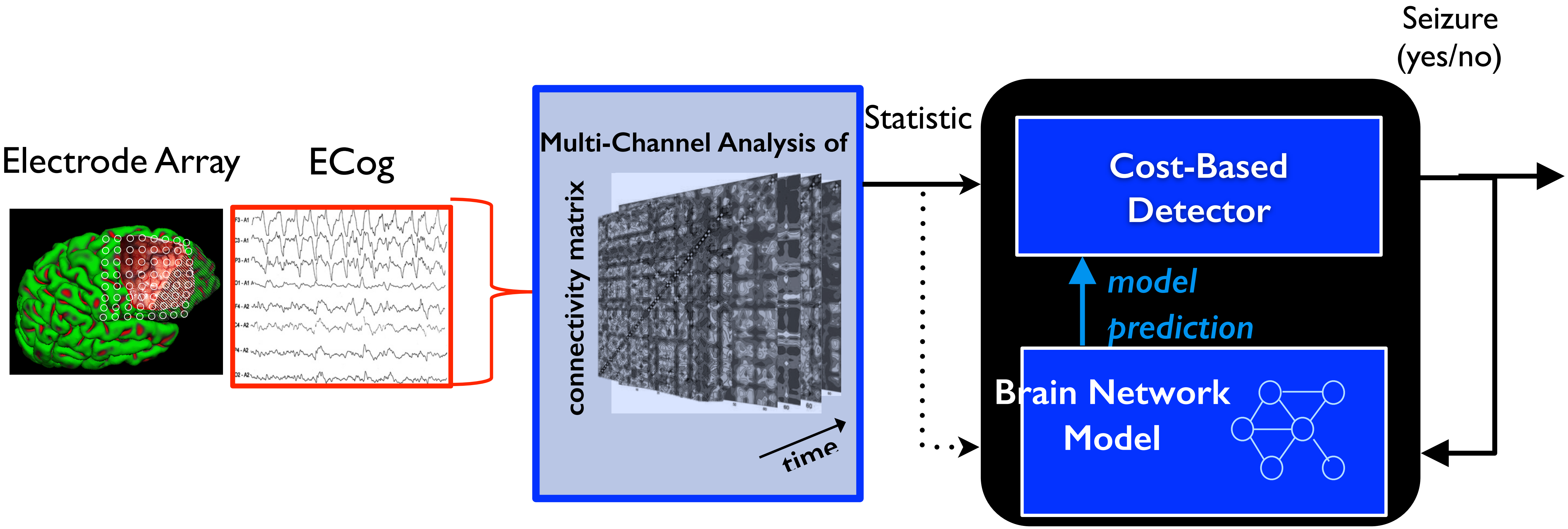
Computational Physiological Medicine

Models in Devices



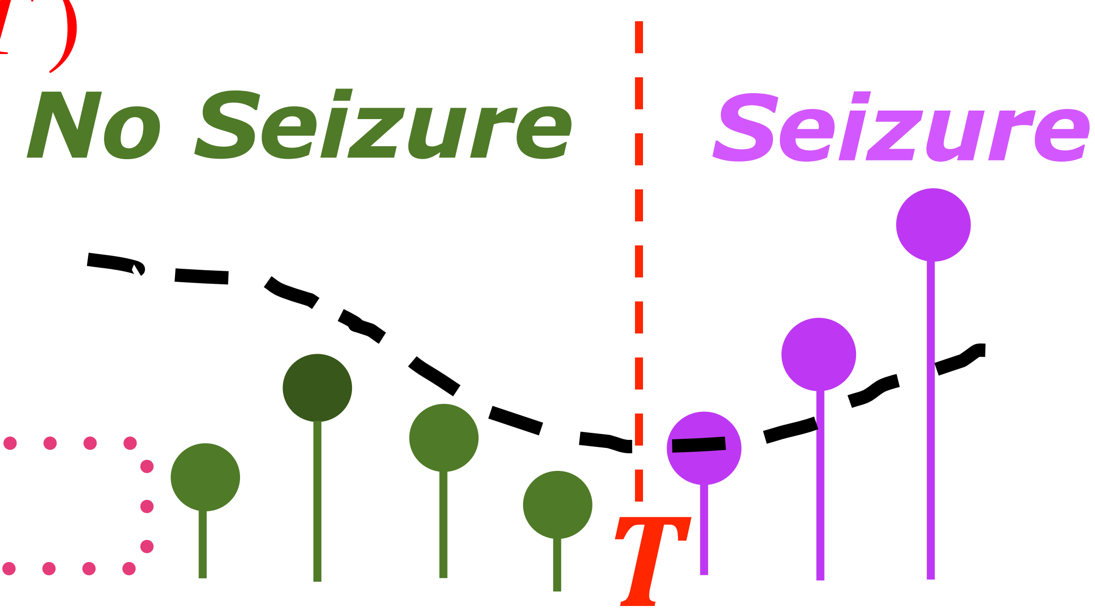
Need to intervene immediately prior to or at seizure onset.

Computational Physiological Medicine
Models in Devices



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

Detection Delay **Prob. False Alarm**



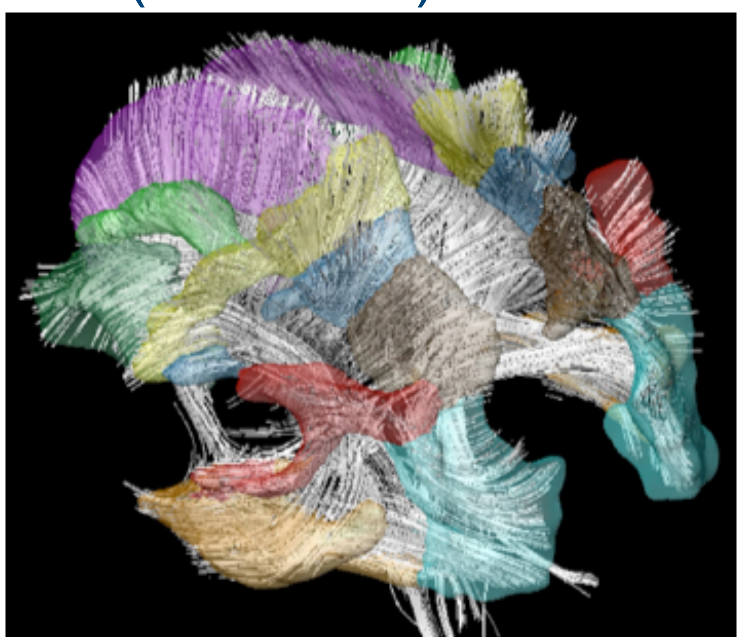
Reduces Detection Delay by 50%

Santaniello et al(2011) Epilepsy & Behavior, 22, pp 49–60.

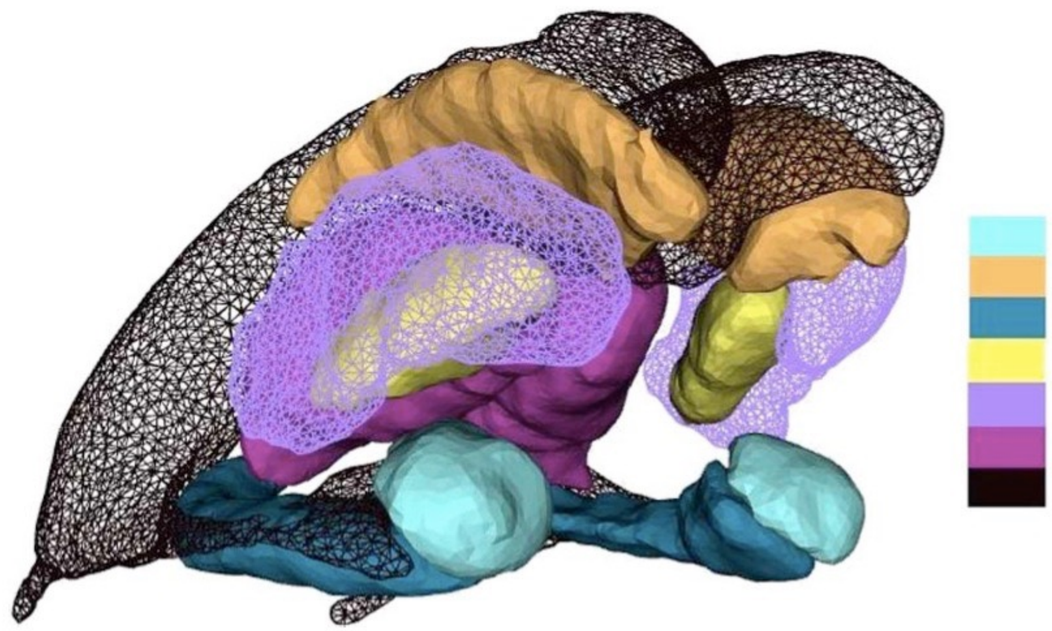
Computational Anatomical Medicine

Modeling Anatomy via Atlases & Transformations

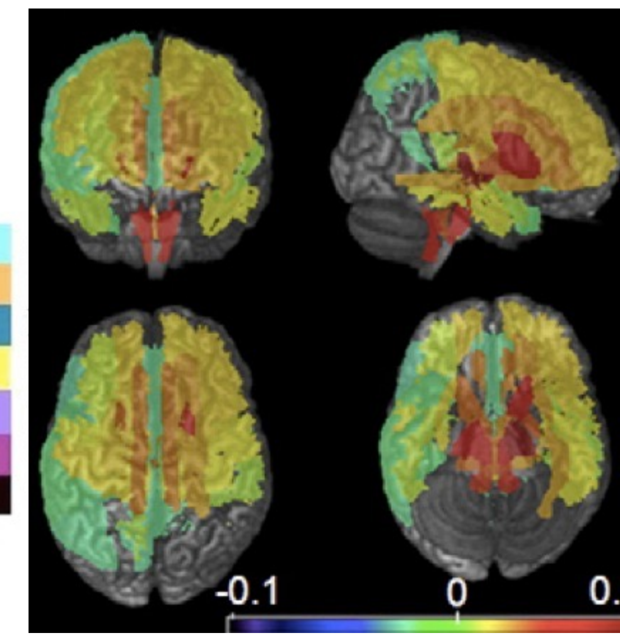
Human White Matter (fiber tract) Atlas[1]



Sub-Cortical Volume Atlas[2]



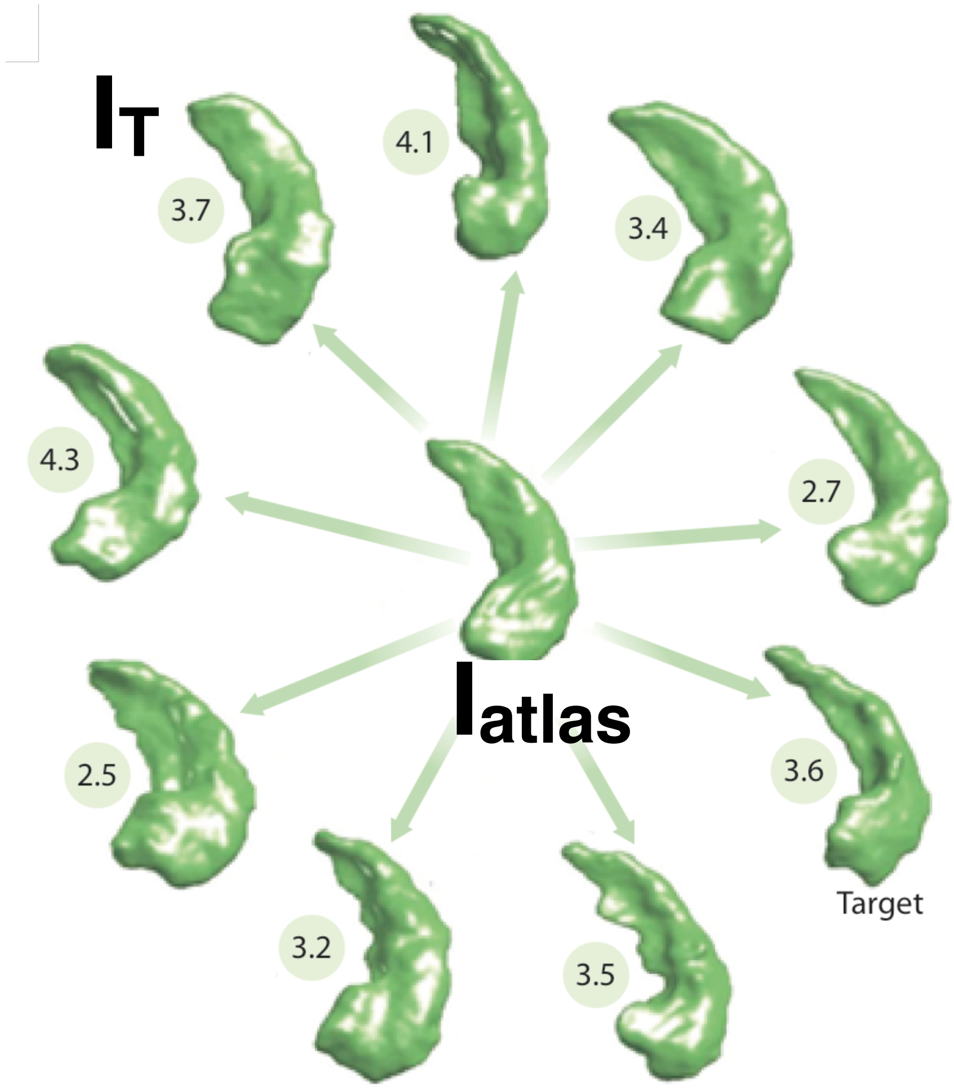
Human Neonatal Brain Atlas[3]



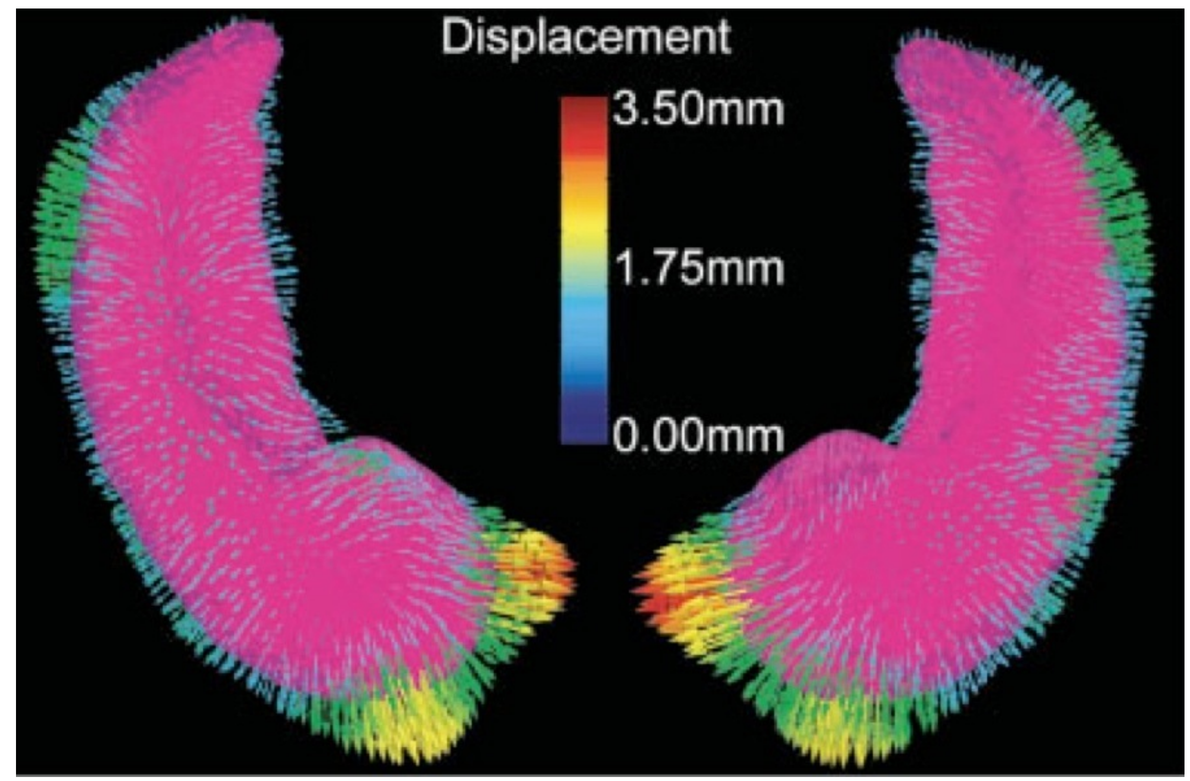
[1]Oishi et al (2008) *Neuroimage* 44(3): 447
[2]Qiu et al (2010) *IEEE TIP* 19(6): 1539
[3]Oishi et al (2011) *Neuroimage* 56(1): 8

Computational Anatomical Medicine

Modeling anatomic shape and its variations



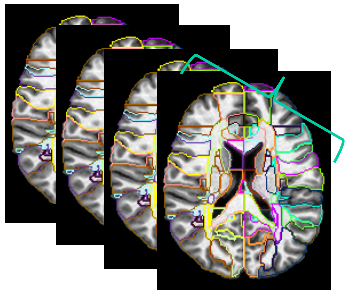
Hippocampal Shape
Alzheimer's = purple, Normal = arrows



Miller, Trouve, Younes (2006) *J. Math. Imaging Vis.* 24: 209

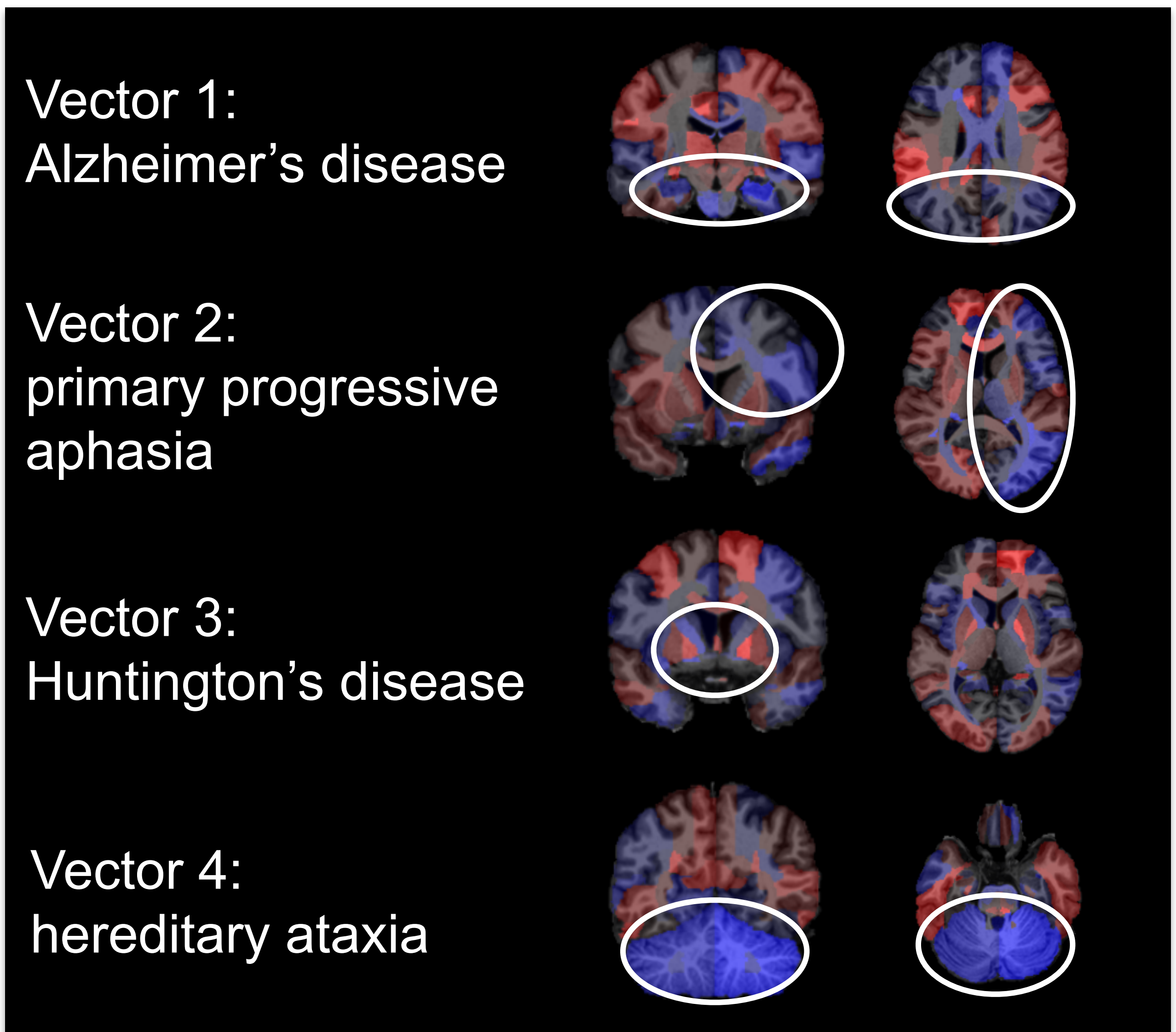
Computational Anatomical Medicine

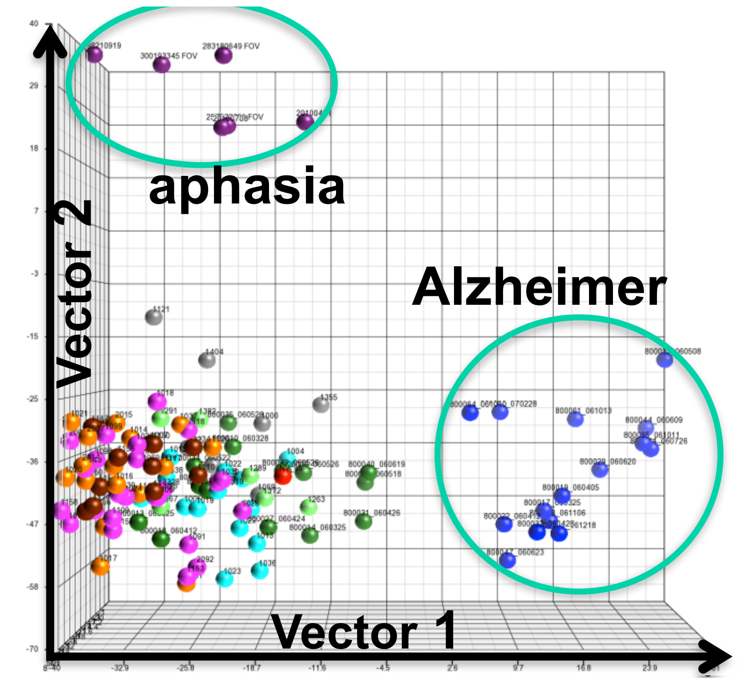
Non-Invasive Detection of Brain Diseases

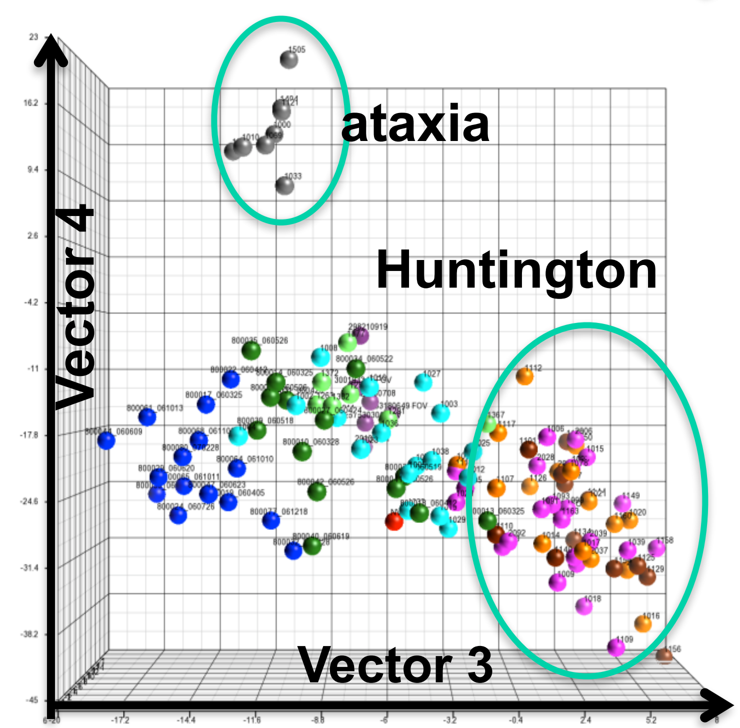


~ 1000 images, ~ 17 GBs

177 anatomical areas → PCA 60 components → LDA 4 feature vectors → Image categorization







Qin et al (2013) Gross feature recognition of Anatomical Images based on Atlas grid (GAIA): Using the Degree of Local Atlas-Image Segmentation Disagreement to Capture the Features of Anatomic Brain MRI, *NeuroImage Clin. 3: 202-211*

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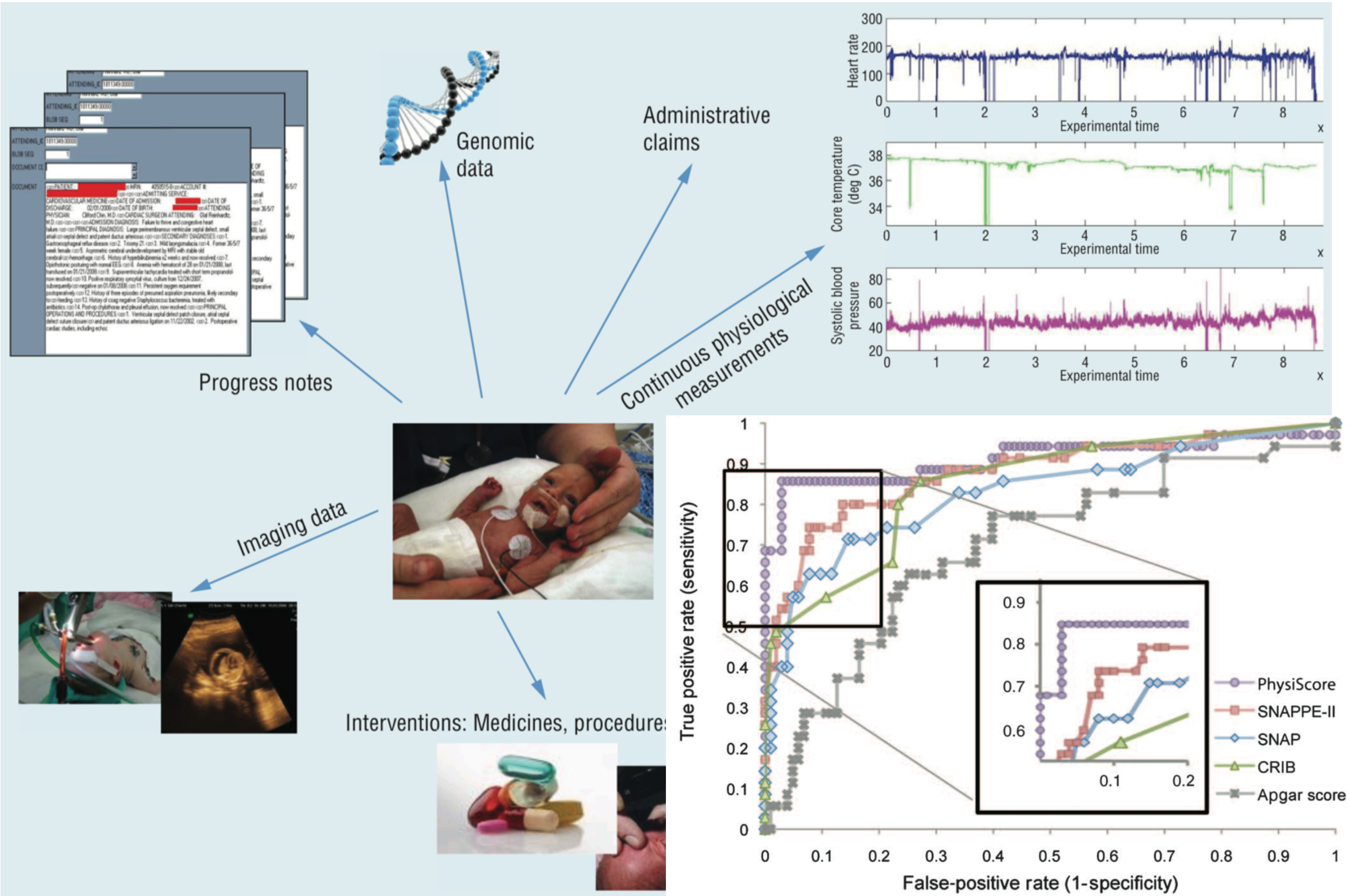
Computational Healthcare

Learning From Big Data



Computational Healthcare

Spread of Infectious Disease and PH Policy

300 Million Agents H1N1
Origin southern CA US

The US National Large Scale Agent Model

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

Parker & Epstein (2011) A distributed platform for global-scale agent-based modeling of disease transmission. *Trans. Model. Comp. Sim.* 22(1).

The Future of Medicine

- Medicine is becoming a computational science and the consequences will be profound
  - practice
  - training
  - outcomes
  - cost
- 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?

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ICM Core Faculty

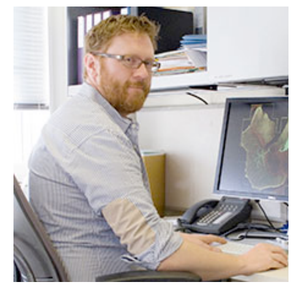
School of Engineering

Ardekani

Bader

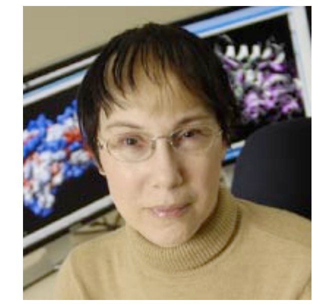
Charon

Mac Gabhann



Geman

Karchin



Miller

Mittal

Ratnanather

Sarma

Trayanova

Vidal

Vogelstein

Younes

Saria

School of Medicine

Anderson

Barta

Epstein

Winslow

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BME 580.431:

Introduction to Computational Medicine I

- TA
  - Kristin Gunnarsdottir
  - kgunnar1@jhu.edu
- Office Hours
  - Rm 111 Hackerman Hall 11:00 - 12:00 Wednesdays

BME 580.431: Overview

- Weeks 1-6 Computational Physiological Medicine
  - Winslow, Greenstein, Sarma
  - Weeks 7-12 Computational Anatomy
  - Miller, Ratnanather, Vogelstein
- Course materials on Github

BME 580.431: Weeks 1-6

Computational Physiological Medicine (Sept 2 - Oct 14)

- Two projects, “hands on”
- De-emphasize lectures, no exams or homework per se
- Projects involve analysis & modeling of real clinical data (EHR, physiological waveforms), modeling of disease
- Form project groups of 3-4, work on projects together
- Bring laptops with Matlab
- Oral presentation (graded)

BME 580.431: Weeks 1-6

Computational Anatomy (Oct 17 - Nov 4)

Shape Analysis

- 2 homeworks, 1 project, “hands on”
- no exams

Computational Anatomy (Nov 6 - Dec 4)

Statistical Connectomics

- Homeworks that build to a final project, no exams

Minor in Computational Medicine

HUB article here

Description on ICM website here

Minor in Computational Medicine: Prerequisites

- Calculus I
- Calculus II
- Probability and Statistics: either a single course covering both (e.g. 550.310), or a course devoted to each (e.g., 550.420 and 550.430) – this may be taken concurrent with Introduction to Computational Medicine (see below).
- At least one additional course math or applied mathematics (at least 3 credits)
- At least one course on programming (at least 3 credits)
- At least one course on biological sciences (at least 3 credits)

Minor in Computational Medicine: Requirements

Required Core:

- Introduction to Computational Medicine I (BME 580.431)
- Introduction to Computational Medicine II (BME 580.432)
  - *Computational Molecular Medicine (AMS 550.450)*

Minor in Computational Medicine: Requirements

- 6 CM courses (including core), ≥ 18 credits, 300-level or above, at least C-
- At most 3/18 credits independent research, as agreed to by minor advisor;
- At least 2 non-core courses must be outside student's home department
- At least 4 courses (can include core electives) with substantial biology or medicine component
- At least 1 non-core course with substantial programming component ("C" designation in electives list)