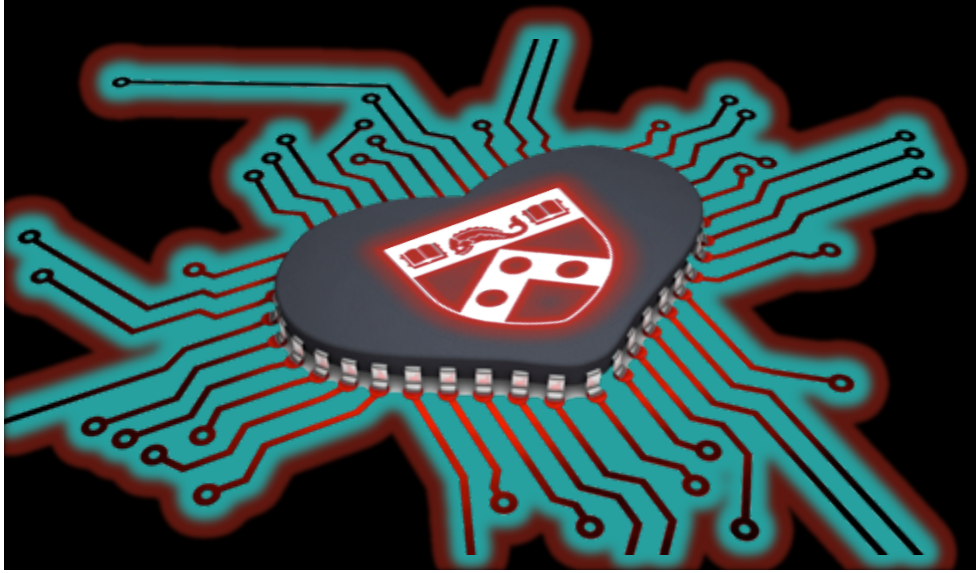
Model-based Clinical Trials
for Implantable Cardiac Devices



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Dept. Electrical & Systems Engineering
Dept. Computer & Information Science
University of Pennsylvania
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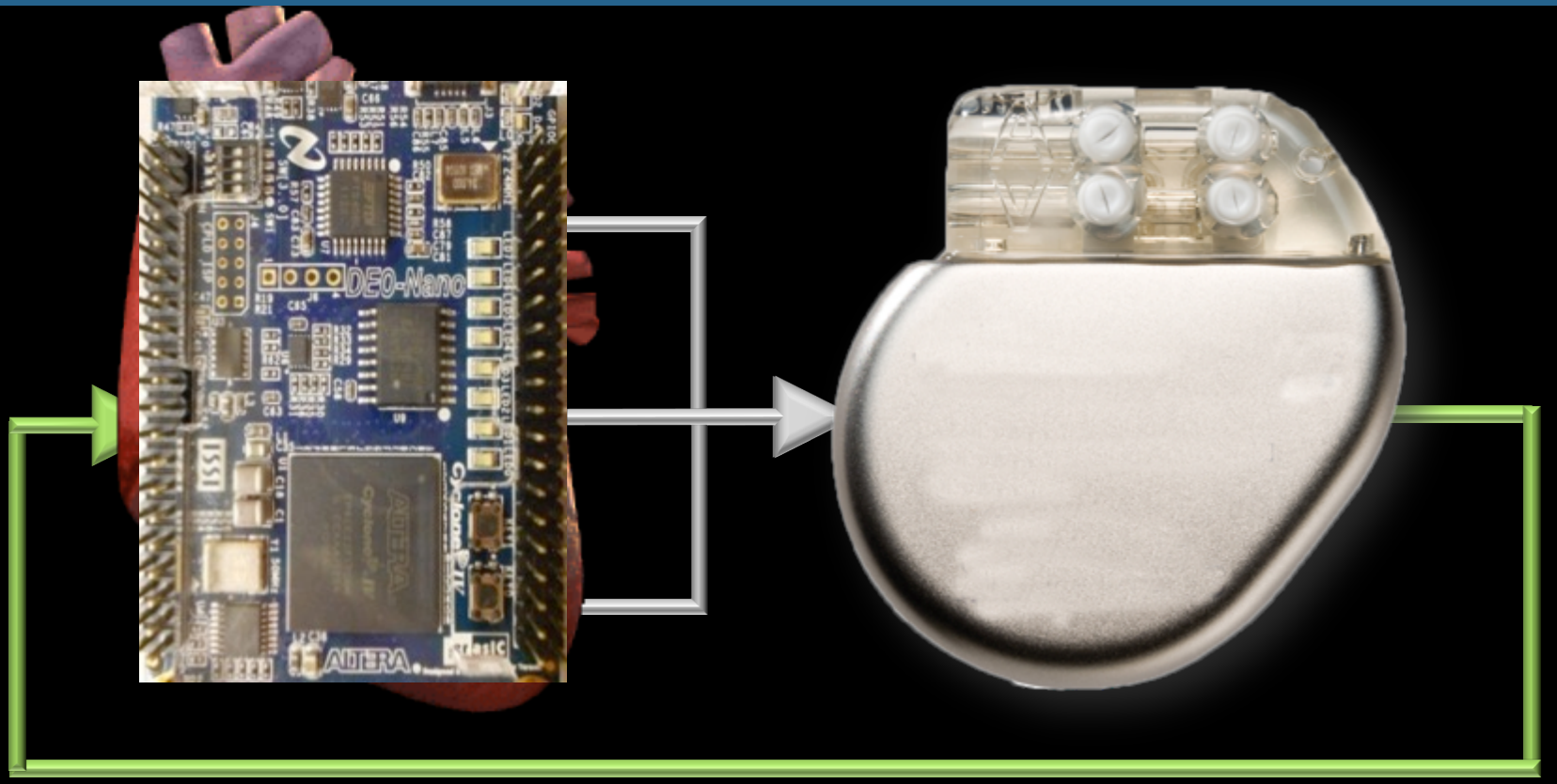
- Demo

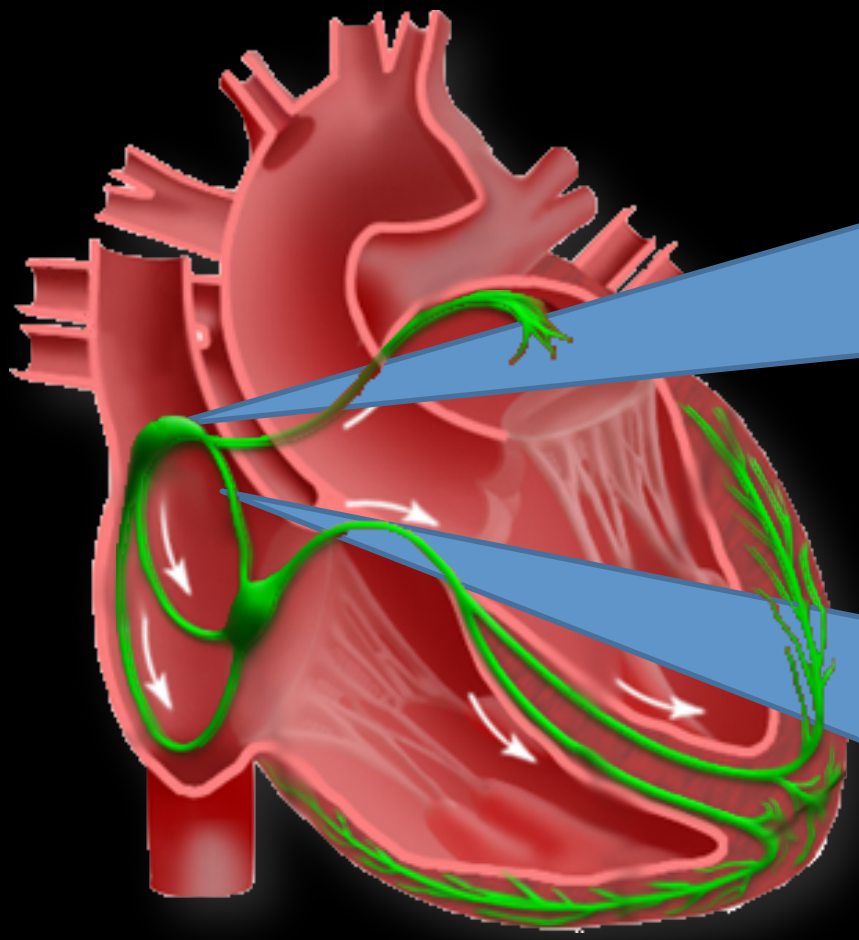
The Problem – Software Recalls

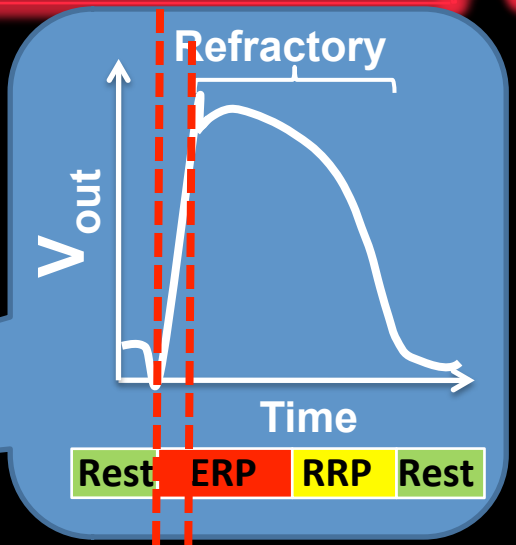
1990-2000: **600,000** cardiac devices recalled.
41% of recalls due to software issues

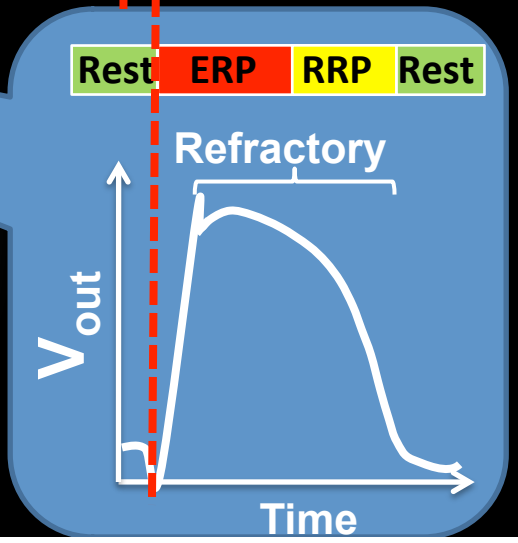
2008-12: **15% of *all*** the medical device recalls (Class I, II & III) due to software

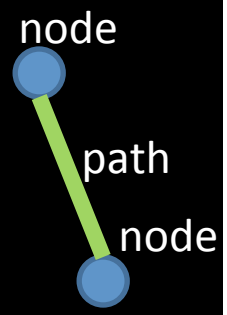


Electro-physiological Heart Model



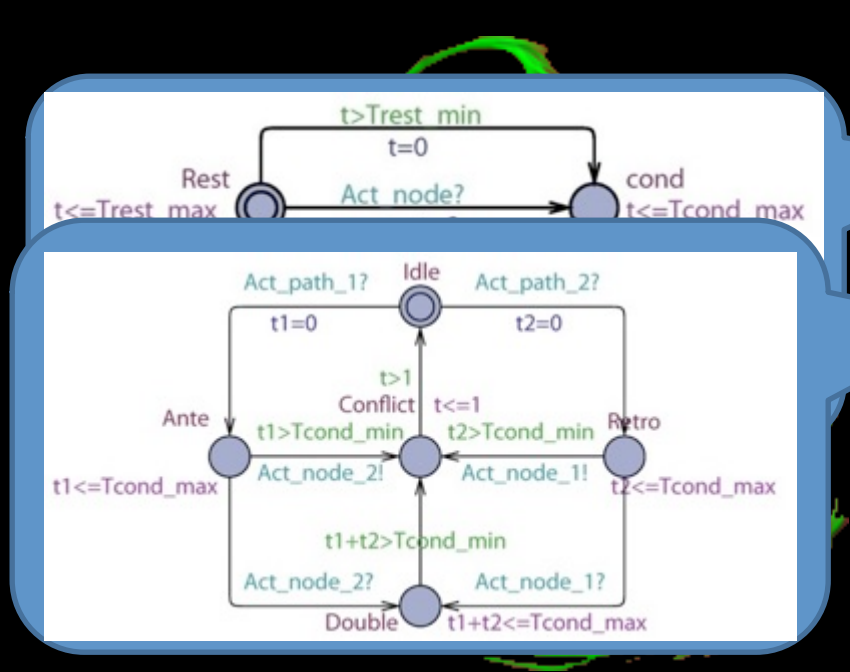


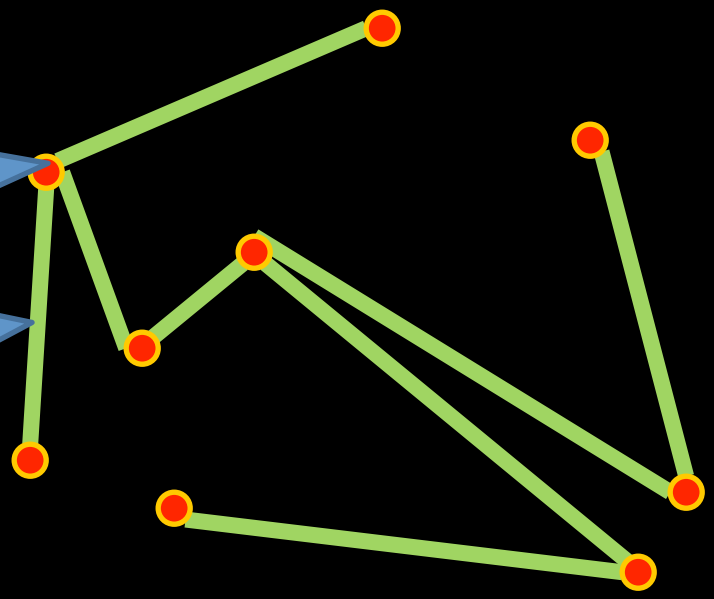




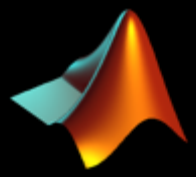
Timed Automata Heart Model

Node Automata



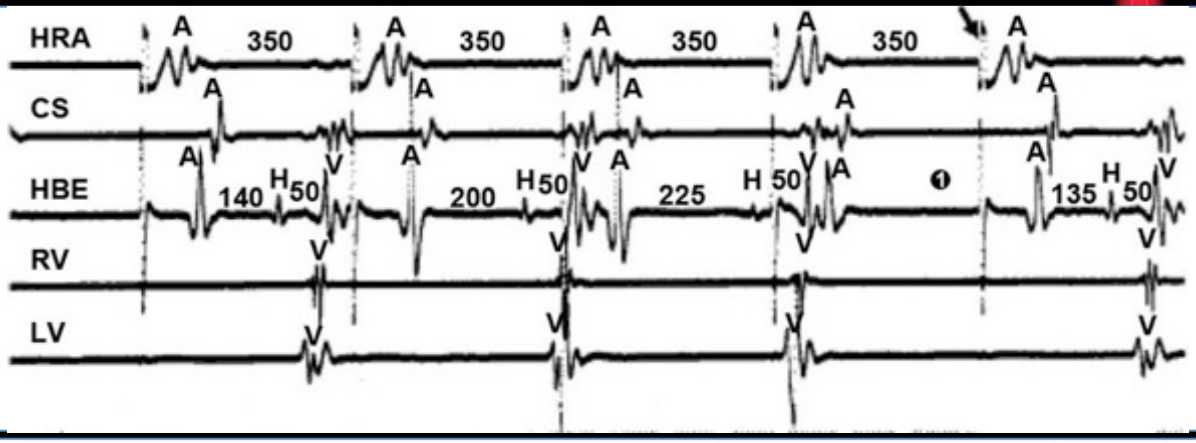


Closed-loop Heart Modeling

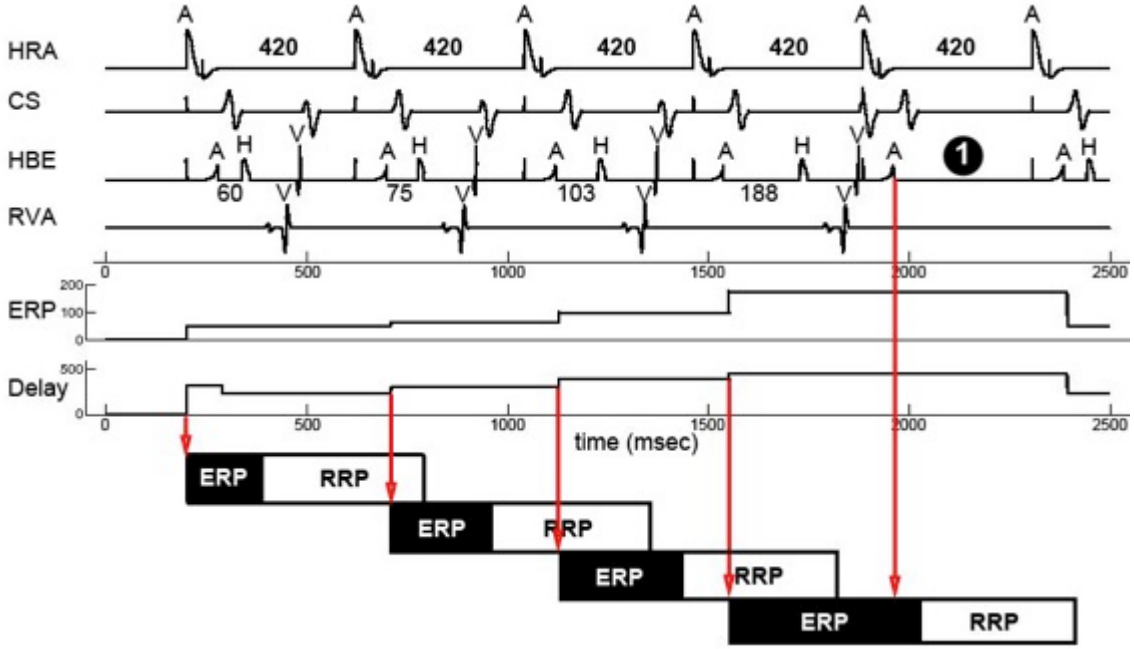


Validation Cases:
Wenckebach AV nodal response

Real Patient



Heart Model



This case shows that our model is not a signal generator.
It responds to a sequence of stimuli interactively

Closed-loop Heart – Pacemaker
illustrating Pacemaker Mediated Tachycardia

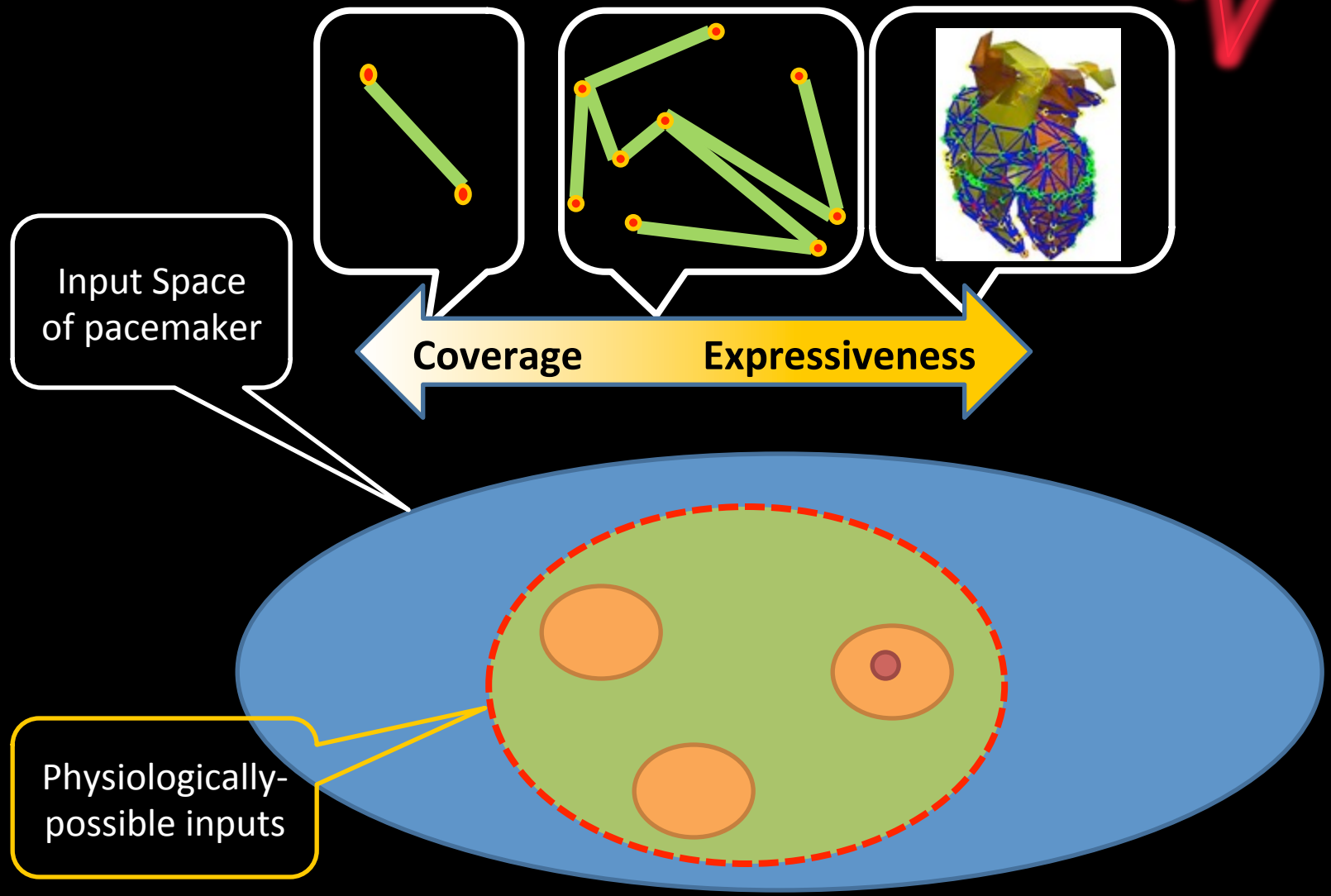
- Demo

Heart Conditions Modeled

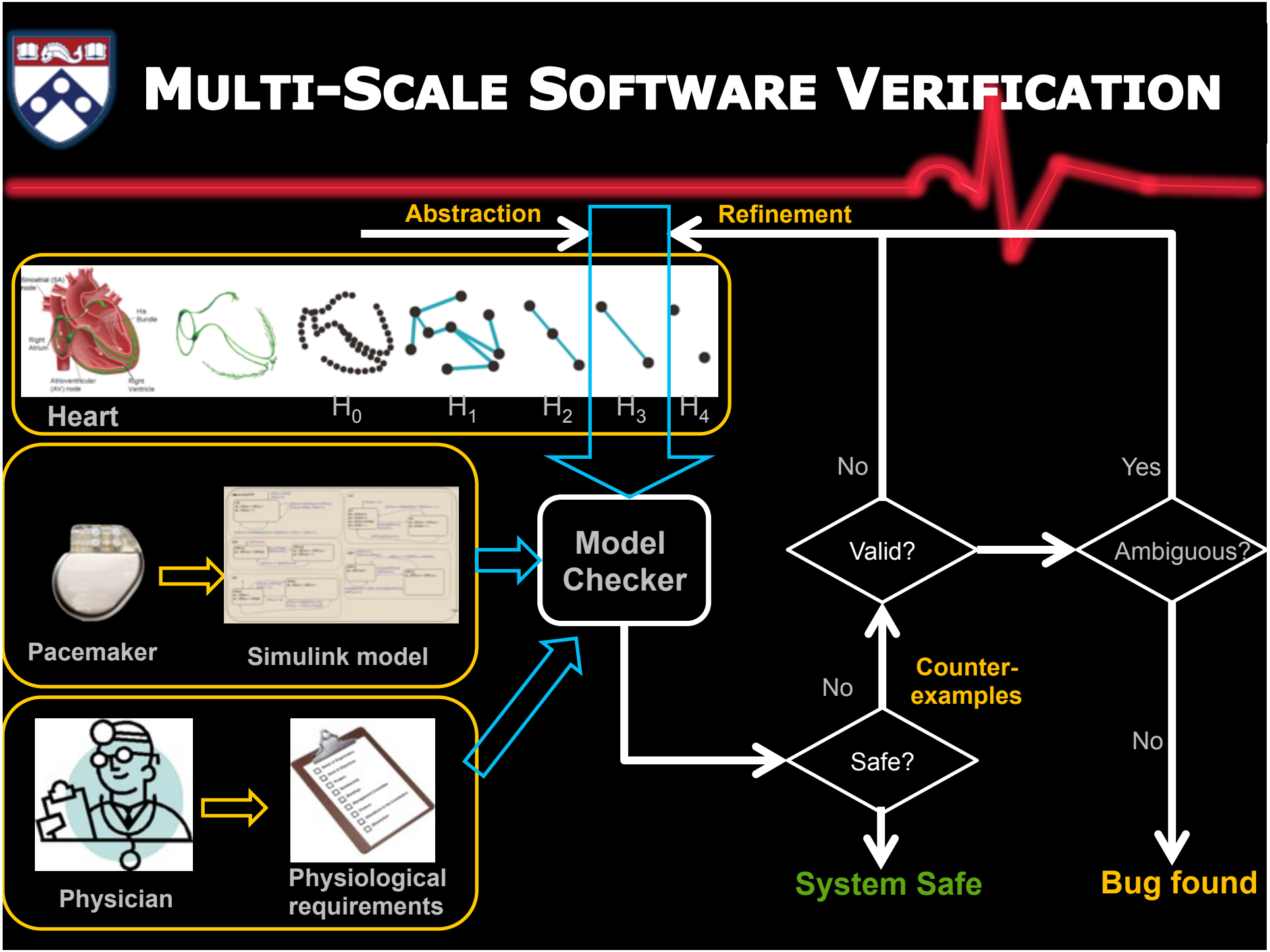
1. Normal Sinus Rhythm
2. Bradycardia
3. Heart block
4. Supraventricular Tachycardia
5. Lead displacement
6. Lead Cross-talk and race conditions
7. Pacemaker Mediated Tachycardia
8. Endless-loop Tachycardia
9. Pacemaker Mode-switch

Validated

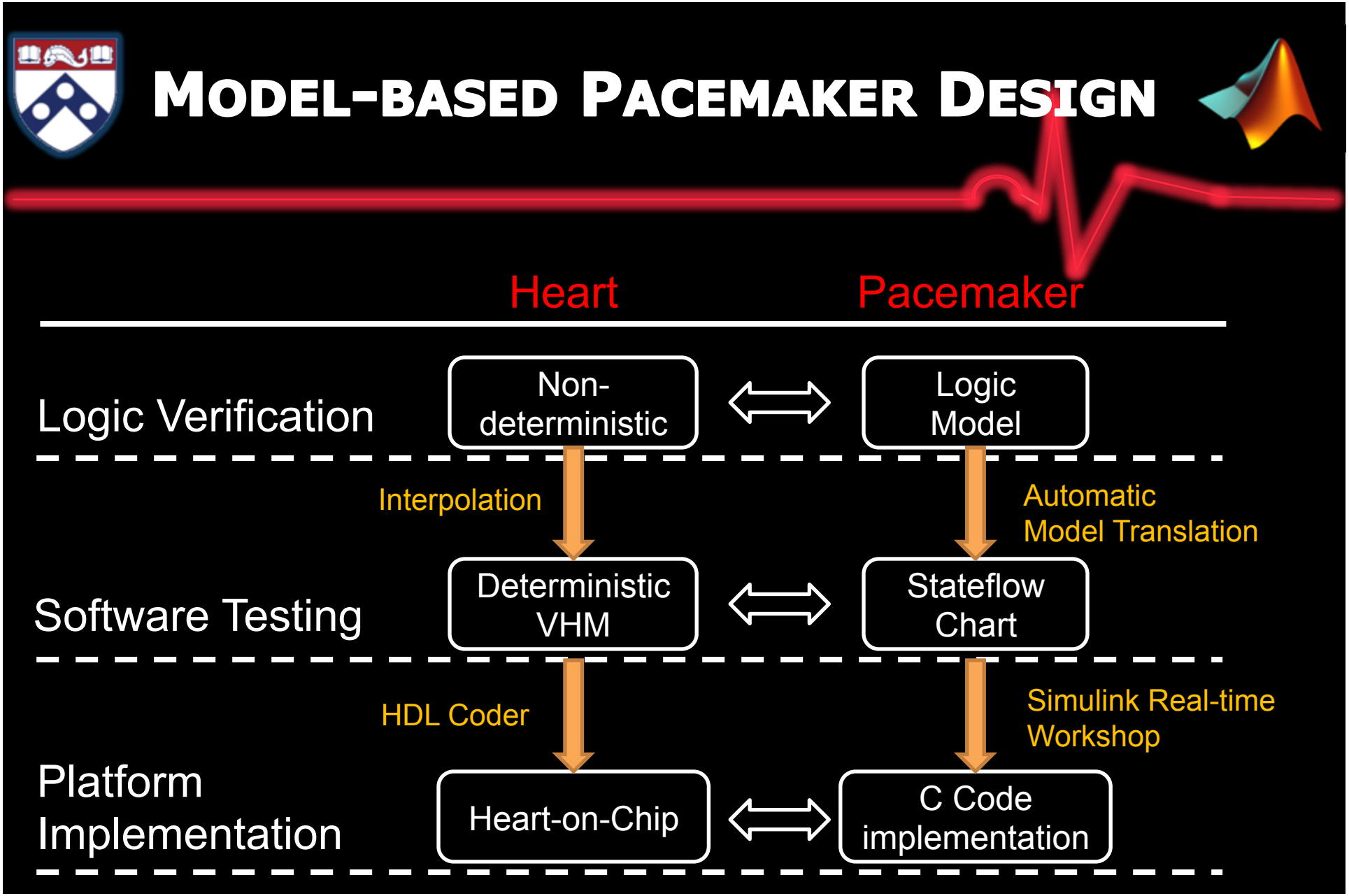
Multi-Scale Heart Modeling



Multi-Scale Software Verification

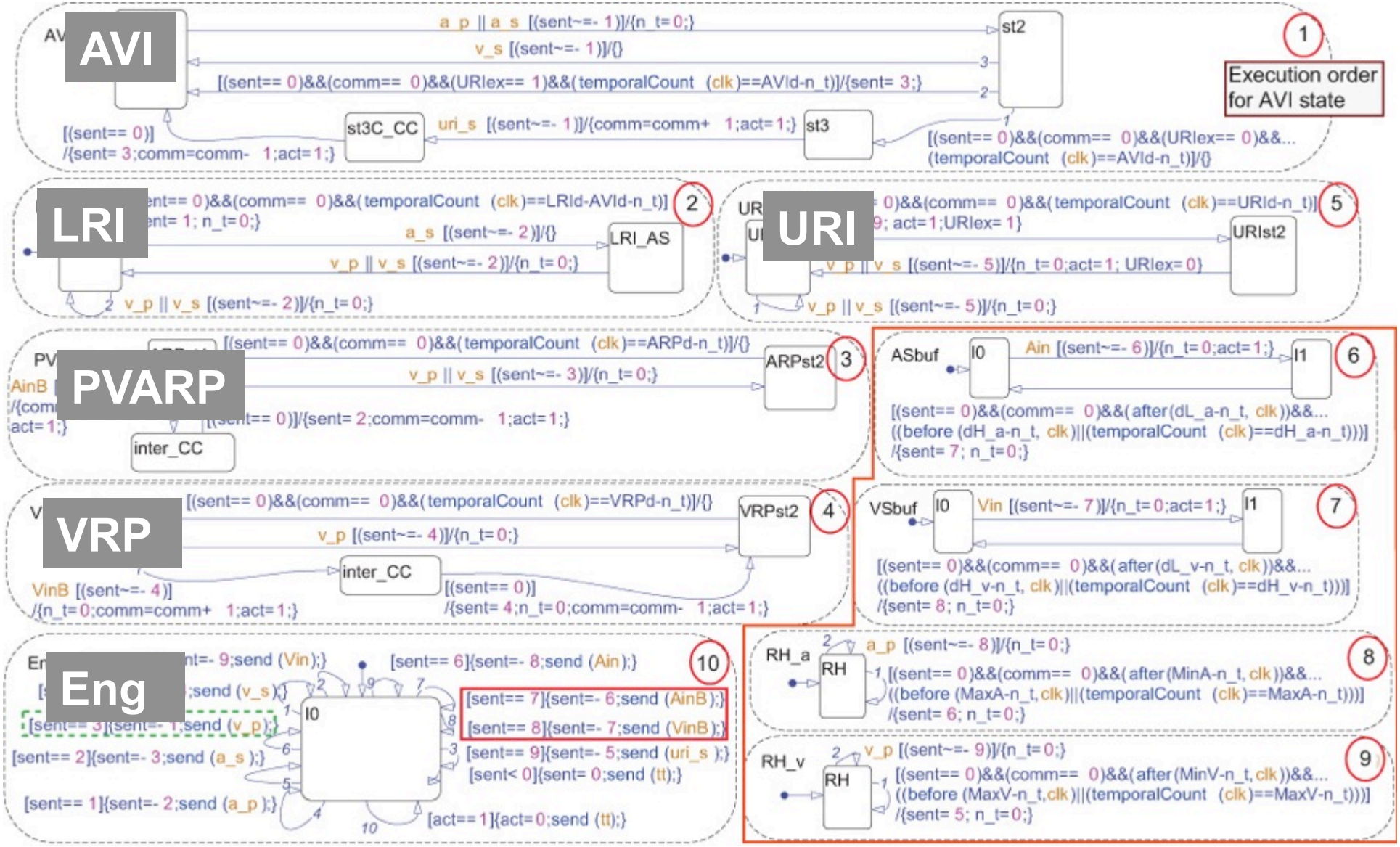


Model-based Pacemaker Design



Published in: IEEE ECRTS'10, EMBC'10, Proceedings of IEEE'11, ICCPS'11, EMBC'11, TACAS'12, RTAS'12, STTT'13, BMES'14, Frontiers of EDA'15

Pacemaker Case Study – Extracted Stateflow Model of the Closed-loop Systems



Generated C Code

Listing 1. `bitsForTID0` definition

```
struct {
    uint_T is_AVI:3;
    uint_T is_LRI:2;
    uint_T is_PVARP:2;
    uint_T is_VRP:2;
    uint_T is_URI:2;
    uint_T is_active_AVI:1;
    uint_T is_active_LRI:1;
    uint_T is_active_PVARP:1;
    uint_T is_active_VRP:1;
    uint_T is_active_URI:1;
    uint_T is_active_Eng:1;
    uint_T is_Eng:1;
    uint_T URI_ex:1;
  } bitsForTID0;
```

Listing 2. `Rt_OneStep` procedure

```
detect active inputs;
for each of the input events {
  if EventName is active   {
    sf_previousEvent = _sfEvent_;
    _sfEvent_ = EventName;
    c1_ChartName();
    _sfEvent_ = sf_previousEvent;
  }
}

update the outputs;
update the input events states;
```

Listing 4. `processState()` procedure

```
if (rtDWork.bitsForTID0.is_active_NAME != 0){
  switch (rtDWork.bitsForTID0.is_NAME) {
    case SubStateName1:
      /* the loop below is - checkTrans();*/
      for all transitions in ex. order {
       if transition enabled {
         execution transition actions;
         reset corresponding temporal counters;
         update rtDWork.bitsForTID0.is_NAME;
         break for
       }
      }
      break;
    case SubStateName2:
      checkTrans();
      break;
    ...
    default:
     rtDWork.bitsForTID0.is_NAME=NoActiveChild;
     break;
   }
  }
```

Listing 5. `broadcast_tt()` procedure

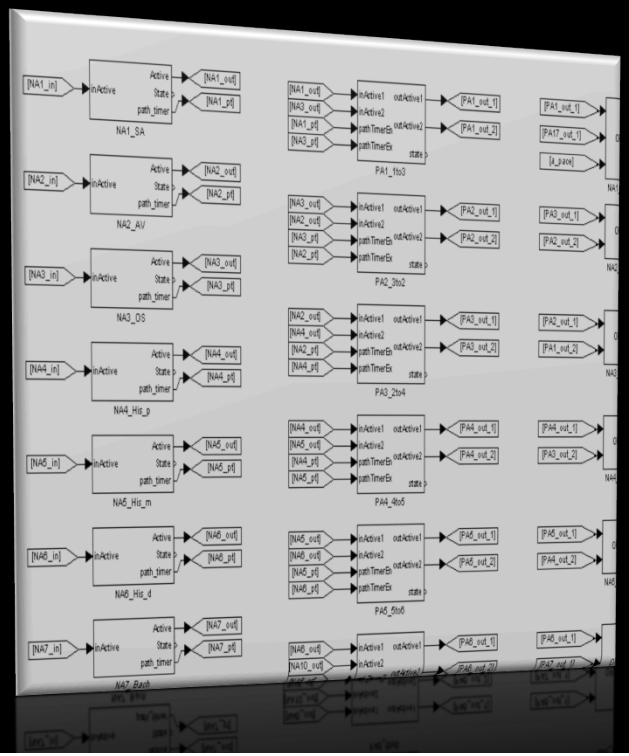
```
static void broadcast_tt(void) {
  int16_T sf_previousEvent;
  sf_previousEvent = _sfEvent_;
  _sfEvent_ = event_tt;
  c1_ChartName();
  _sfEvent_ = sf_previousEvent;
}
```

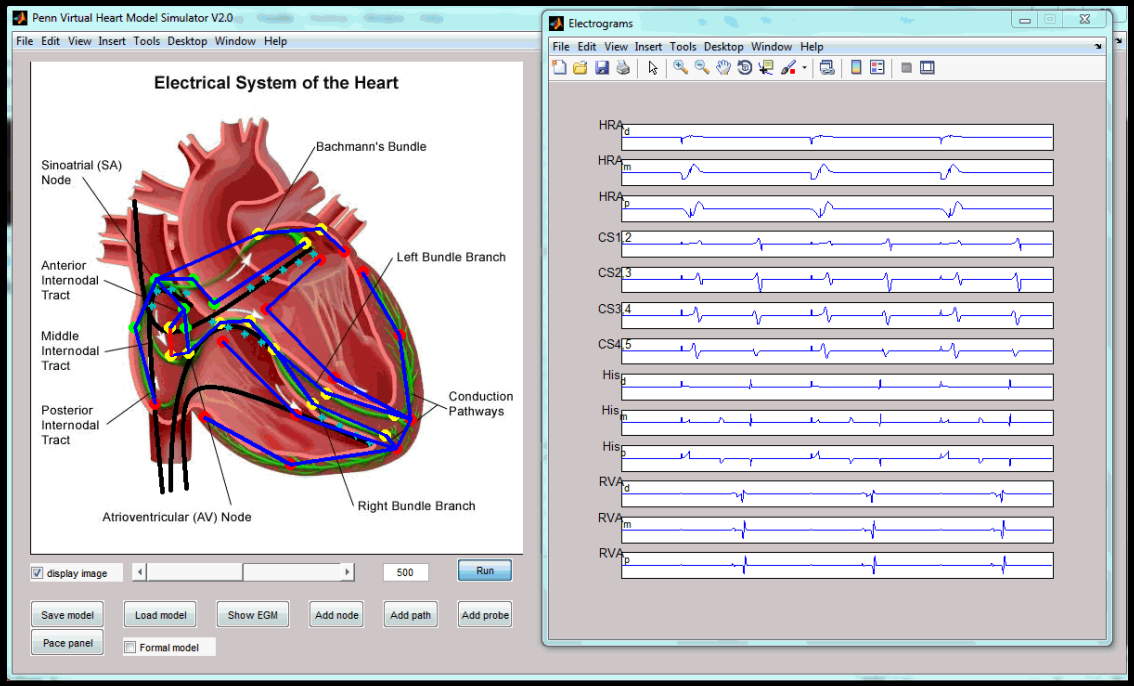
Listing 3. `c1_ChartName()` procedure

```
increase counters for _sfEvent_;
for each parallel state {
  processState();
}
```

Heart Implementation

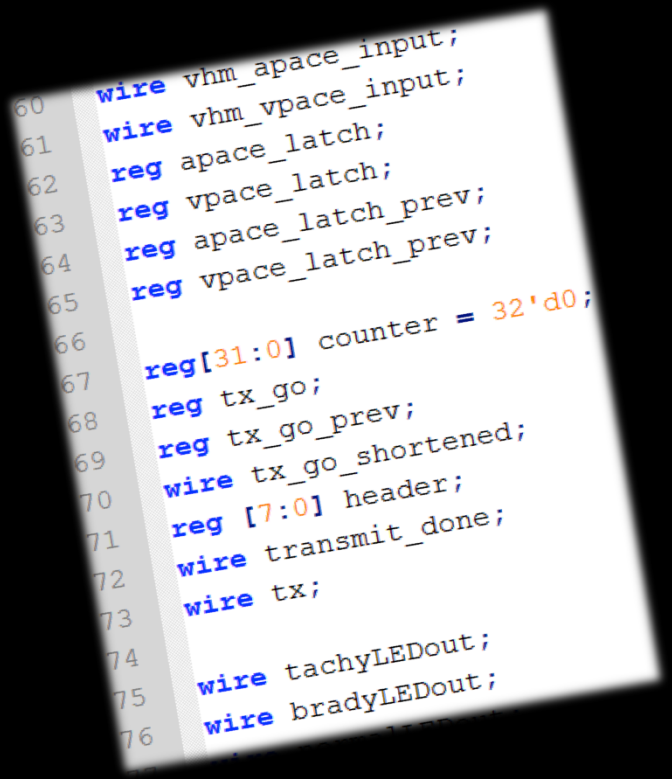
Heart Model Assembly (Heart → Model) → HDL Generation (Model → Code) → FPGA Synthesis (Code → Hardware)





Heart Implementation

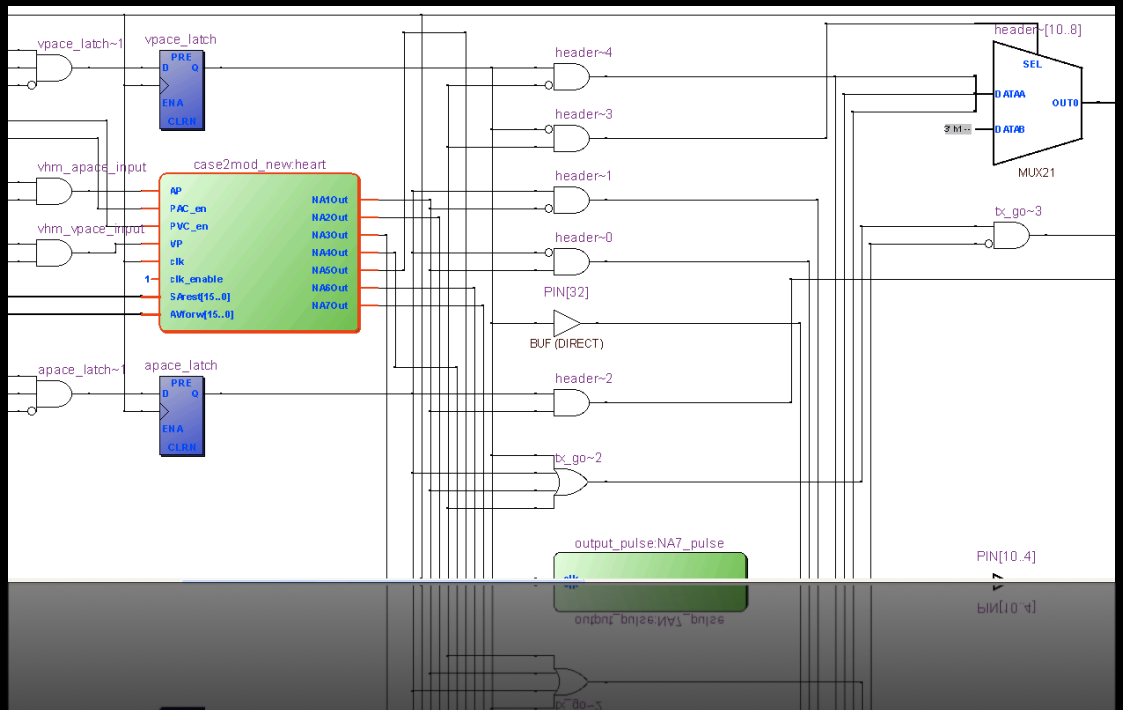
Heart Model Assembly (Heart → Model) → HDL Generation (Model → Code) → FPGA Synthesis (Code → Hardware)

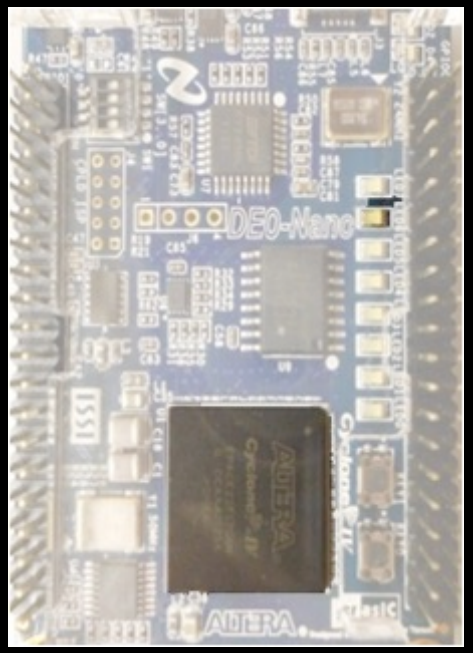


```
wire vhm_apace_input;
wire vhm_vpace_input;
reg apace_latch;
reg vpace_latch;
reg apace_latch_prev;
reg vpace_latch_prev;

reg[31:0] counter = 32'd0;
reg tx_go;
reg tx_go_prev;
wire tx_go_shortened;
reg [7:0] header;
wire transmit_done;
wire tx;

wire tachyLEDout;
wire bradyLEDout;
```

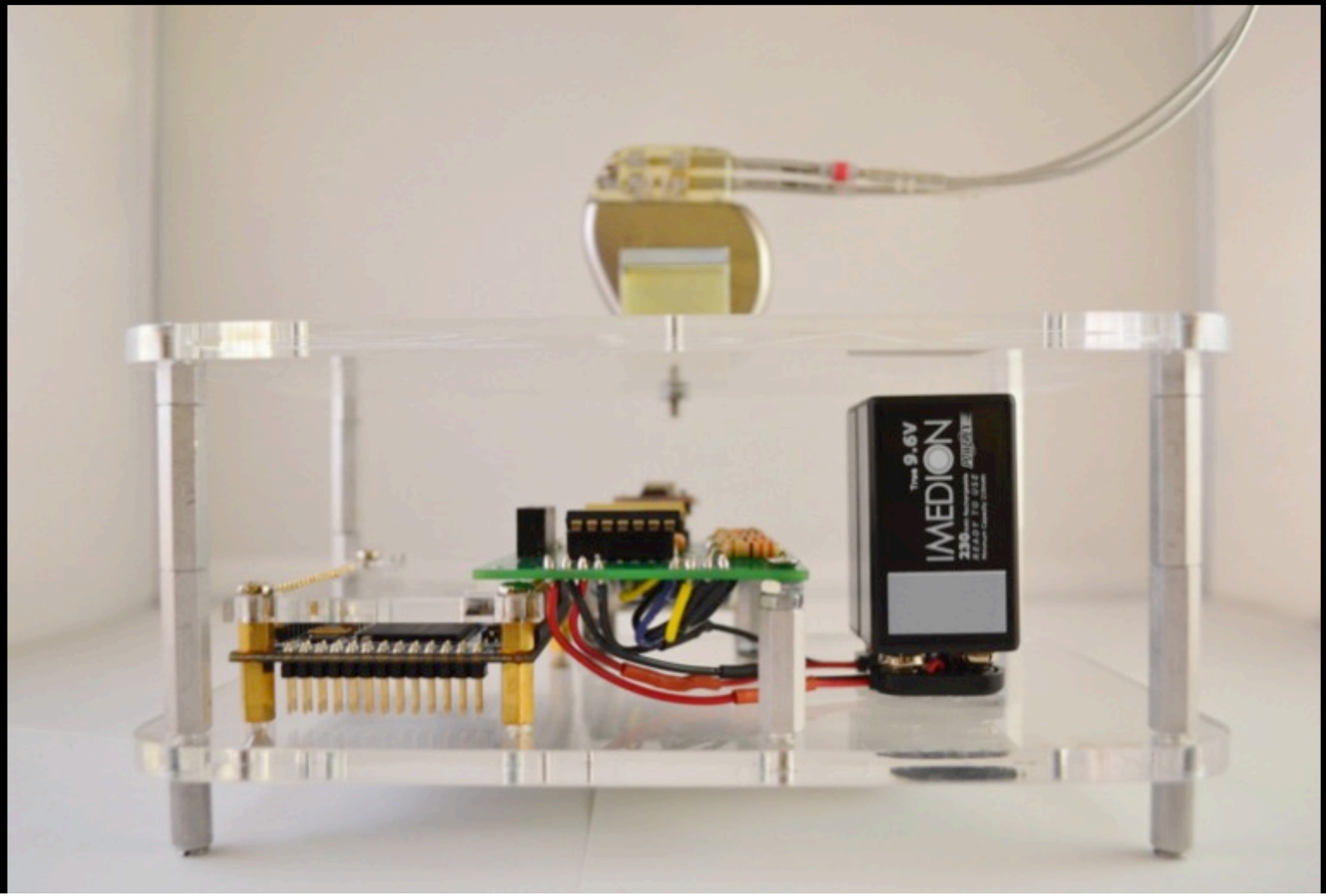
Heart Implementation

Heart Model Assembly (Heart → Model) → HDL Generation (Model → Code) → FPGA Synthesis (Code → Hardware)





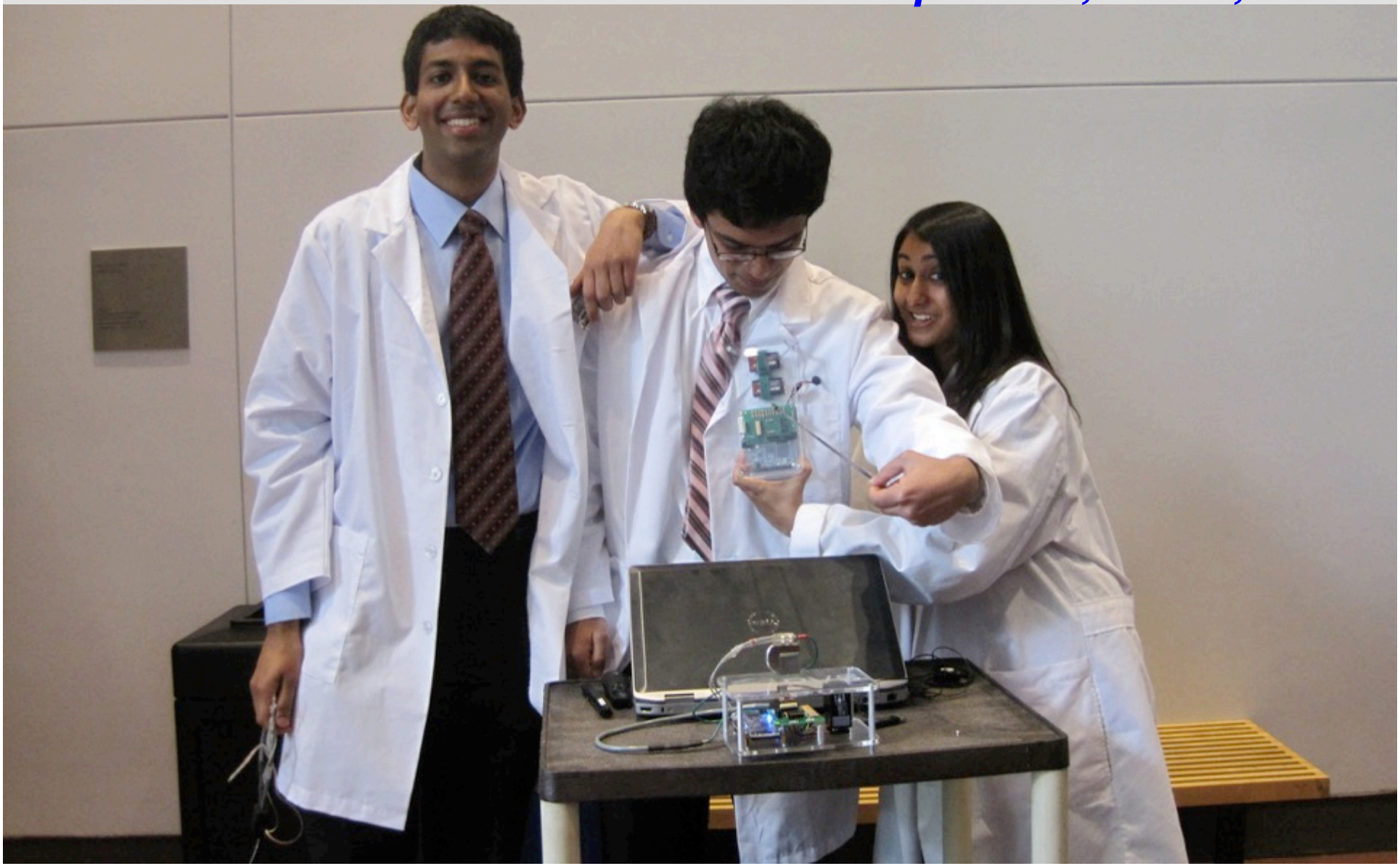
Heart-on-Chip Platform for Closed-loop Testing



Pacemaker Verification System

1st Prize UPenn Senior Design Competition 2012

1st Prize World Embedded Software Competition, Seoul, Korea

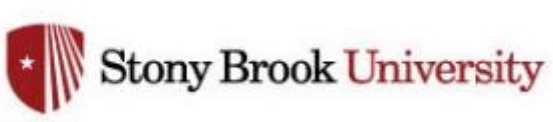


So what next?

Compositional, Approximate & Quantative Reasoning for Medical Cyber-Physical Systems

NSF Cyber-Physical Systems Frontier [May 2015-2020]

Scott Smolka	*Stony Brook University*
Rance Cleaveland	*University of Maryland*
James Glimm	*Stony Brook University*
Radu Grosu	*Stony Brook University*
Edmund M. Clarke	*Carnegie Mellon University*
Sicun Gao	*Carnegie Mellon University*
Rahul Mangharam	*University of Pennsylvania*
Sanjay Dixit	*University of Pennsylvania*
Arnab Ray	*Fraunhofer USA Center*
Flavio Fenton	*Georgia Institute of Technology*
Elizabeth Cherry	*Rochester Institute of Technology*
Richard Gray	*U.S. Food and Drug Administration*



Scott Smolka
Stony Brook

Rance Cleaveland
UMD / Fraunhofer

Rick Gray
FDA

Elizabeth Cherry
RIT

Ed Clarke
CMU

James Glimm
Stony Brook

Sean Gao
MIT

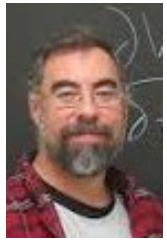
CyberHeart

NSF CPS Frontier

Radu Grosu
Stony Brook /
Vienna

Arnab Ray
Fraunhofer

Rahul Mangharam
Penn



Flavio Fenton
Gatech

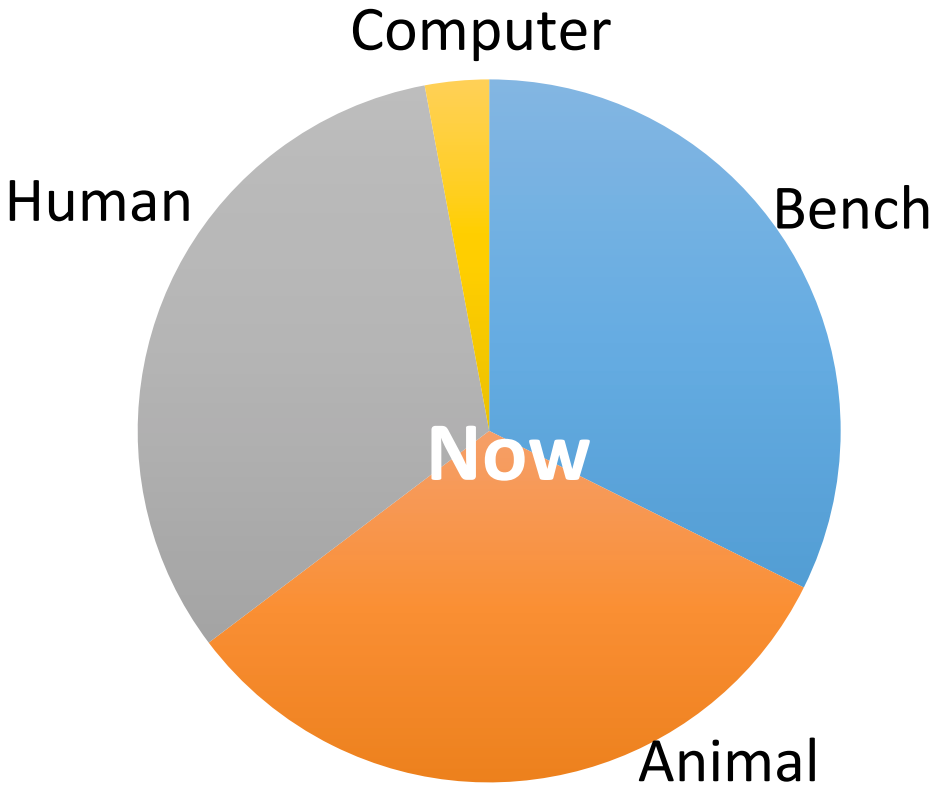
Sanjay Dixit
Director of Cardiac
Electrophysiology
Philadelphia VA Hospital

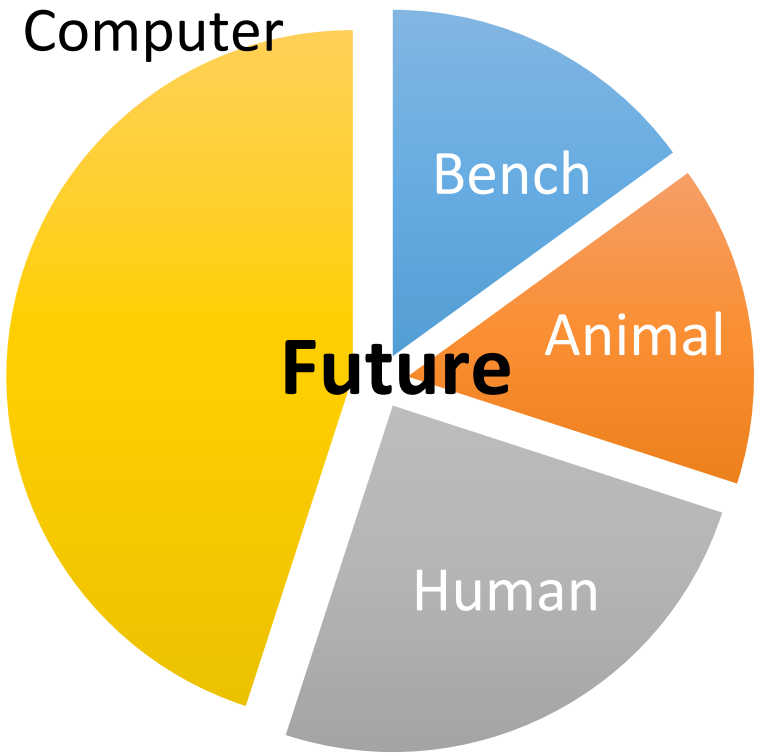
5 Computer Scientists, 1 Cardiologist, 1 Physicist, 1 BioMed Engineer, 2 Mathematicians, 1 Electrical Engineer

Impact on Medical CPS Foundations in 5 Years

1. **Model-based Clinical Trials**
   - Regulatory-grade modeling and simulation with closed-loop testing for pre-clinical trial evidence
   - Reduce the scope and cost of randomized clinical trials
   - Identify bugs and reduce the probability of a failed trial

Medical Device Pre-Market Evaluation





Increasing use of Computer Simulation and Modeling evidence

Roadmap:
Increasing use of Computer Simulation and Modeling evidence

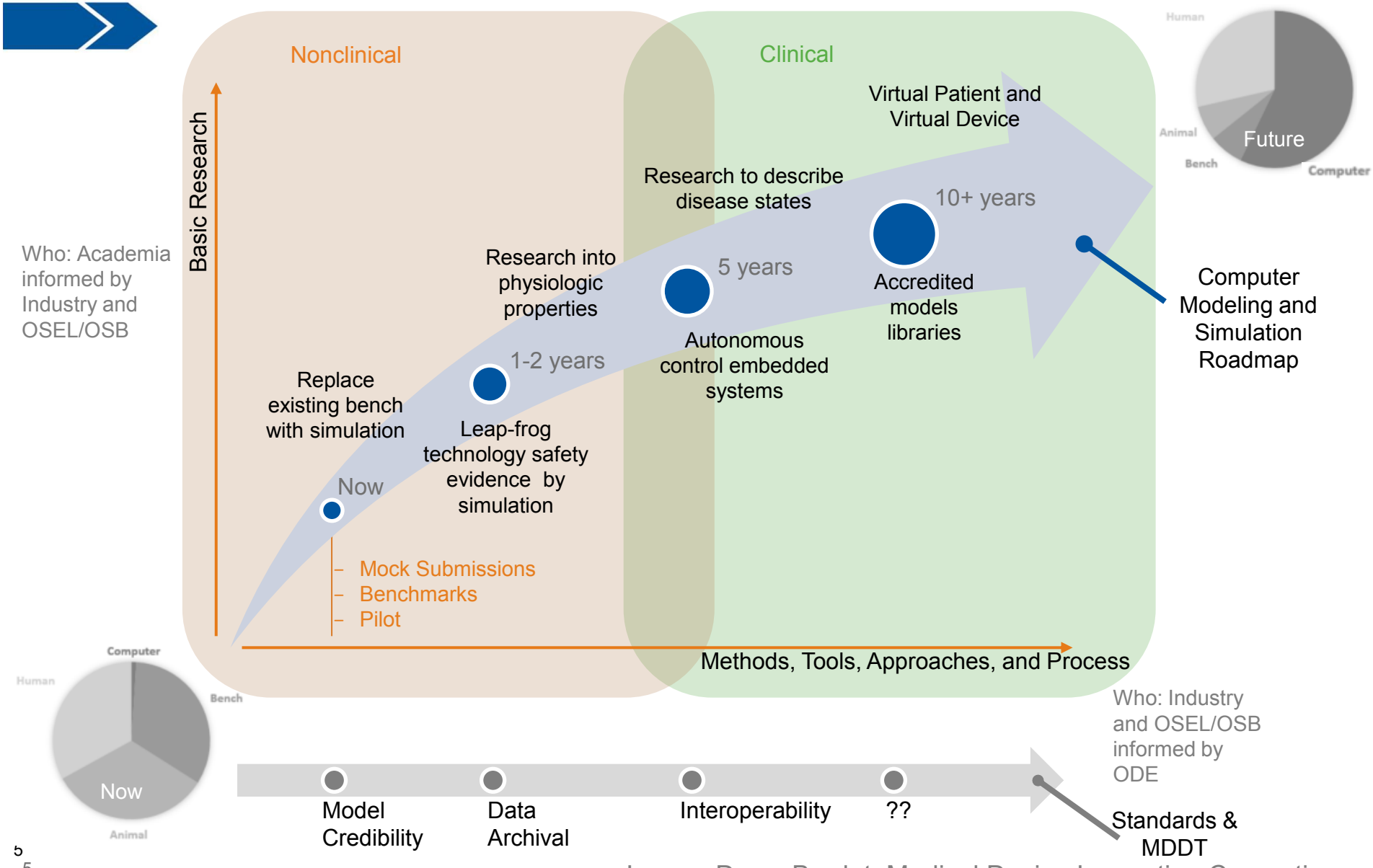
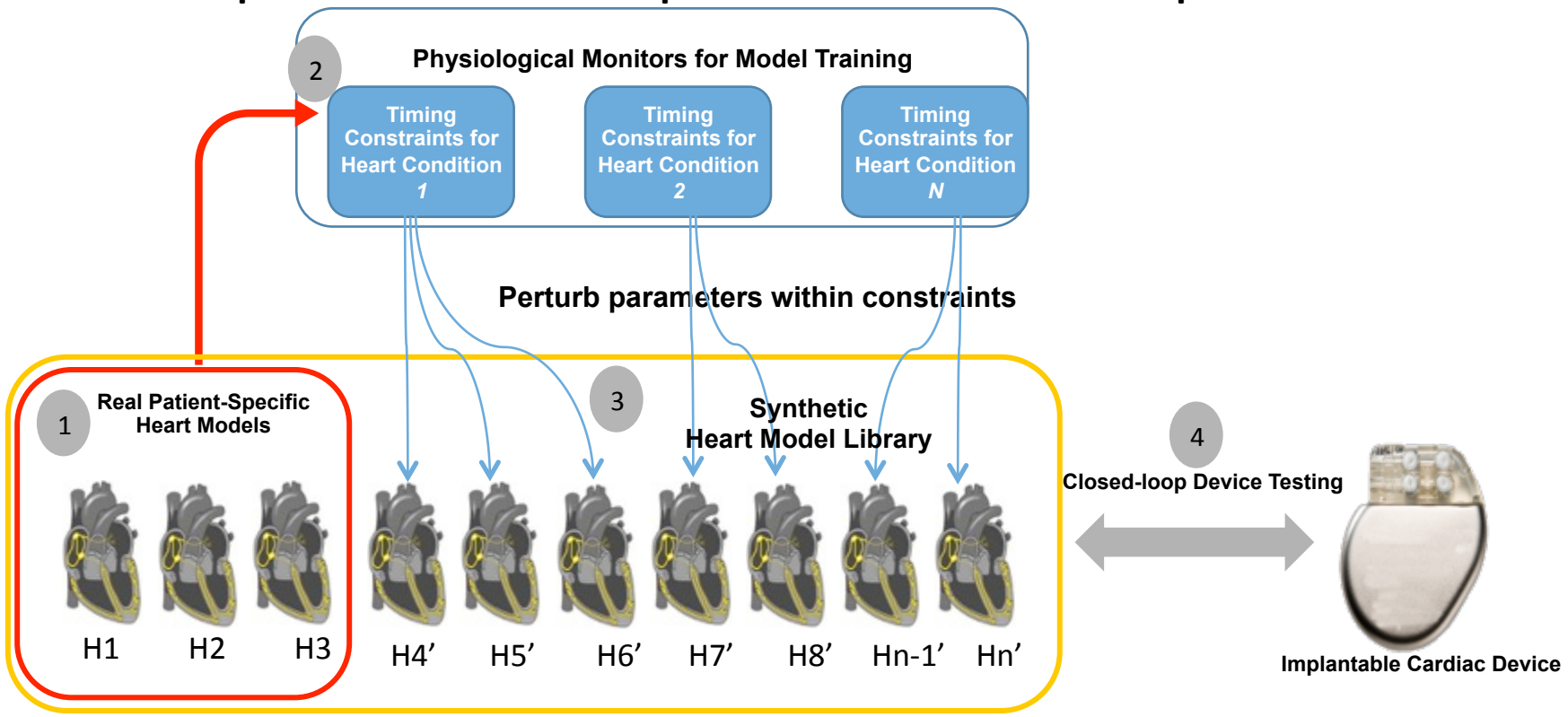


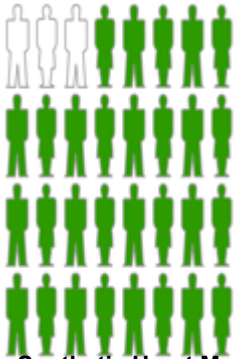
Image: Dawn Bardot, Medical Device Innovation Consortium

Model-based Clinical Trials

From Patient-specific data to Patient-specific models for Closed-loop Device Certification



Real Patient Heart Models



Generate Synthetic Heart Models

Complete Population/Parameter Analysis

Impact on Medical CPS Foundations in 5 Years

1. **Model-based Clinical Trials**
   - Regulatory-grade modeling and simulation with closed-loop testing for pre-clinical trial evidence
   - Reduce the scope and cost of randomized clinical trials
   - Identify bugs and reduce the probability of a failed trial

Access to safe and effective medical device technology through Regulatory Grade computer models & simulations

Impact on Medical CPS Foundations in 5 Years

1. Model-based Clinical Trials

- Regulatory-grade modeling and simulation with closed-loop testing for pre-clinical trial evidence
- Reduce the scope and cost of randomized clinical trials
- Identify bugs and reduce the probability of a failed trial

2. Quantative Verification of ICD Efficacy

- Early Rhythm Therapy evaluation of safety, efficacy & energy tradeoffs

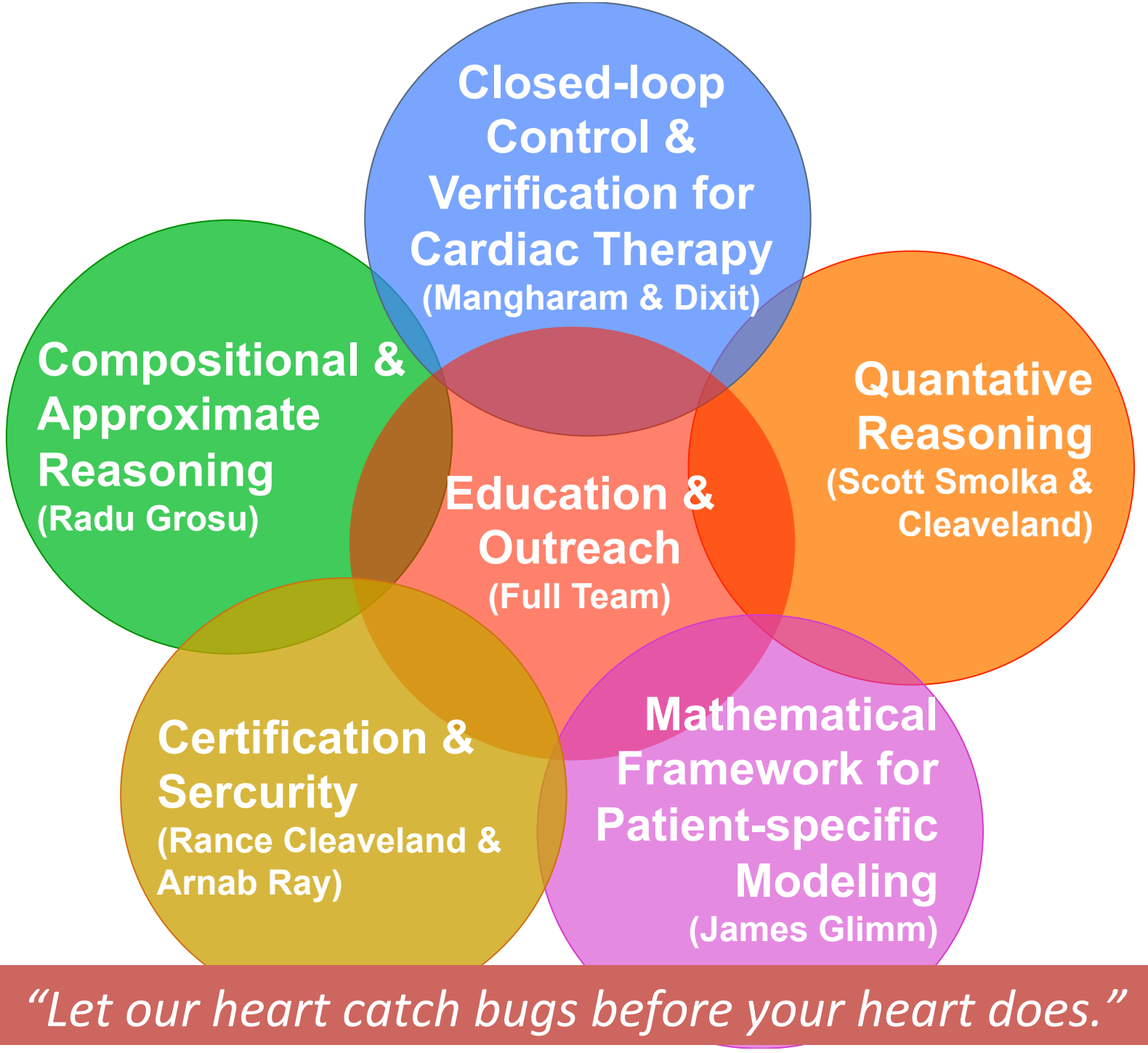
3. Patient-specific Therapy Guidance & Device Configuration

- Automated ablation therapy guidance and device configuration

4. Patient Heart Model in Electronic Health Records

- Lifelong functional record for pre/post operation evaluation

CyberHeart: Thrusts and Tasks



"Let our heart catch bugs before your heart does."

CyberHeart: Thrusts and Tasks

CAR: Compositional and Approximate Reasoning – *Radu Grosu*

- CAR1 Bisimulation-based abstraction – *Smolka*
- CAR2 Numerical reasoning for model checking – *Clarke*
- CAR3 Reasoning about stochastic hybrid systems – *Grosu*

QR: Quantitative Reasoning – *Scott Smolka*

- QR1 Unified event-based and frequency-domain methods for detecting emergent cardiac phenomena – *Smolka*
- QR2 Combining qualitative and quantitative measurements of spatio-temporal cardiac behavior - *Smolka*
- QR3 Predicate equation systems as a unified basis for analyzing spatio-temporal behavior – *Cleaveland*

CCV: Closed-loop Control and Verification for Cardiac Therapy – *Rahul Mangharam*

- CCV1 Abstraction techniques for heart models – *Mangharam*
- CCV2 Parameter inference for cardiac devices – *Mangharam*
- CCV3 Probabilistic heart modeling – *Grosu*

FDT: A Framework for Devices, Therapies and Ultimately Patient-Specific Modeling – *Jim Glimm*

- FDT1 Numerical, accurate simulation models of cardiac electrical wave propagation – *Glimm*
- FDT2 Model validation via experimentation – *Cherry, Fenton*
- FDT3 Patient-specific heart / device modeling – *Fenton, Dixit*

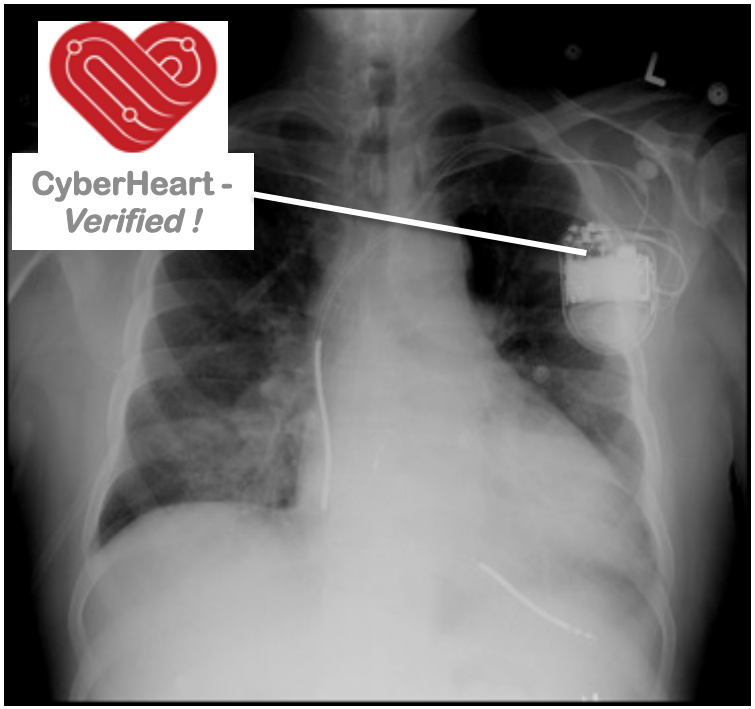
CS: Certification and Security Concerns – *Arnab Ray*

- CS1 In silico verification and safety-assurance cases – *Ray, Cleaveland*
- CS2 Integrating security and safety case reasoning – *Ray*

EO: Education and Outreach – *Elizabeth Cherry*

- EO1 Undergraduate workshops – *Cherry*
- EO2 Virtual classroom teaching - *Fenton*
- EO3 Exhibits for general-public science events – *Cherry, Fenton*
- EO4 Course development - *Mangharam*
- EO5 Advisory panel formation and relations – *Cleaveland, Smolka*
- EO6 Industrial workshops – *Cleaveland, Smolka*

CyberHeart V&V for Medical CPSs



in vivo

What is Closed-Loop V&V?

(AD, AH)
in vitro

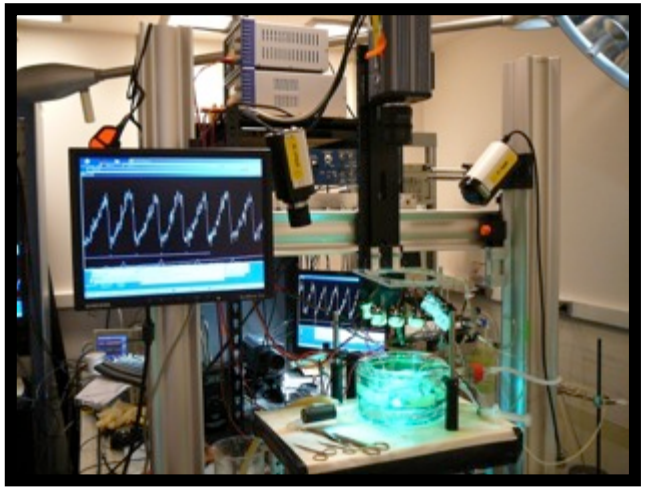
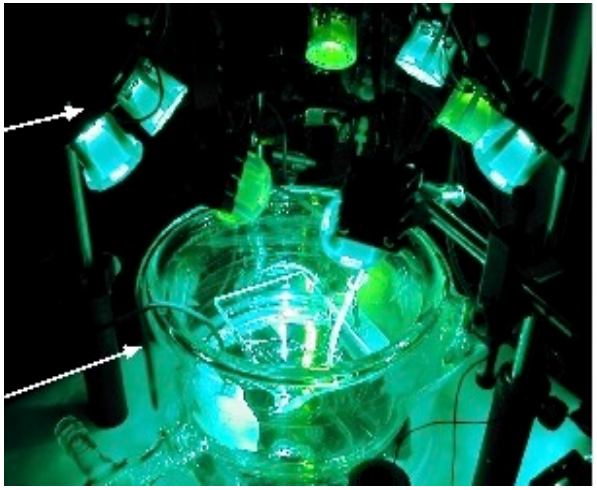
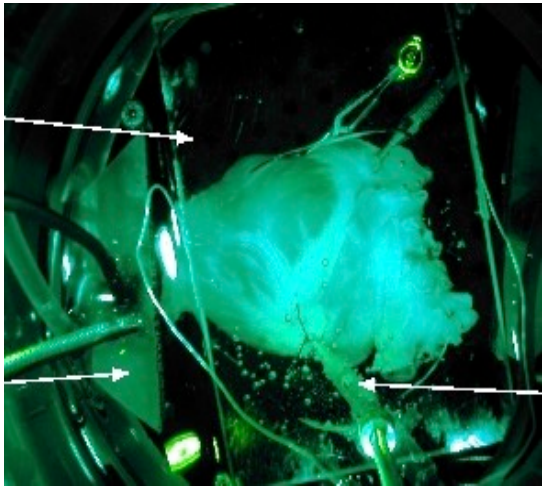
(AD,VH)
Device-in-the-loop

(VD,AH)
Heart-in-the-loop

(VD,VH)
in silico

AD=Actual Device VD=Virtual Device
AH=Actual Heart VH=Virtual Heart

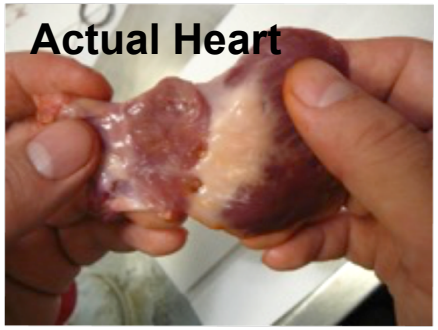
In Vitro: Actual Heart, Actual Device

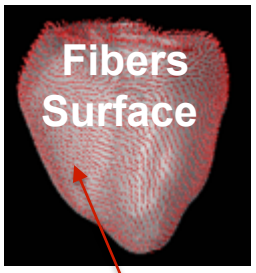




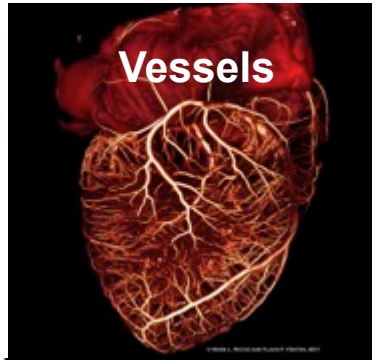
Optical-mapping wet-lab setup (Flavio Fenton, GT) where:

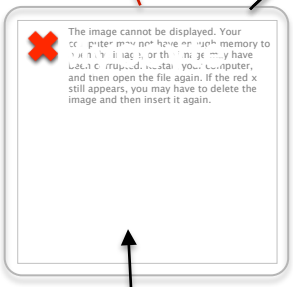
- **Surgically removed heart** *will be* in the loop with actual device
- **V&V possible** in this setup by repeatedly running experiments

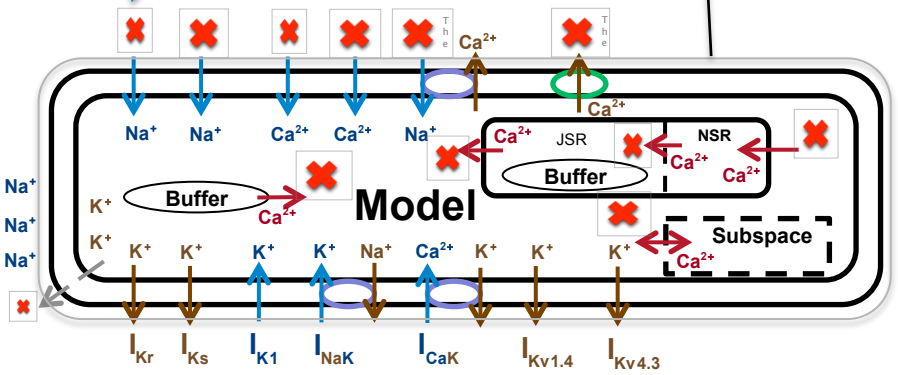
The Complexity of the Heart
Multi-Scale CPS

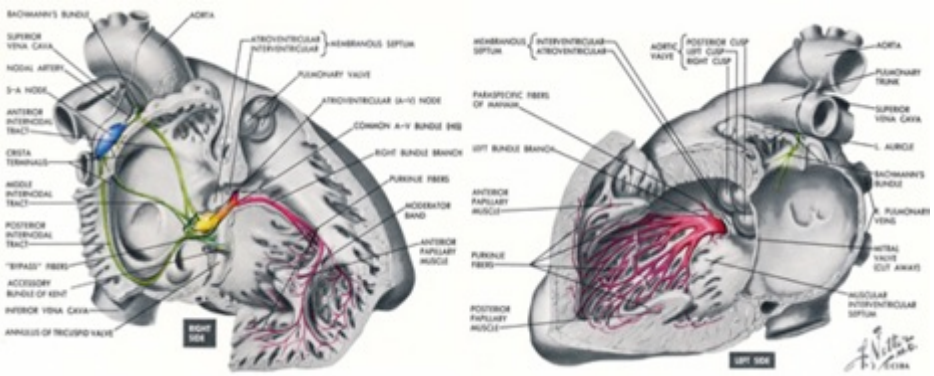




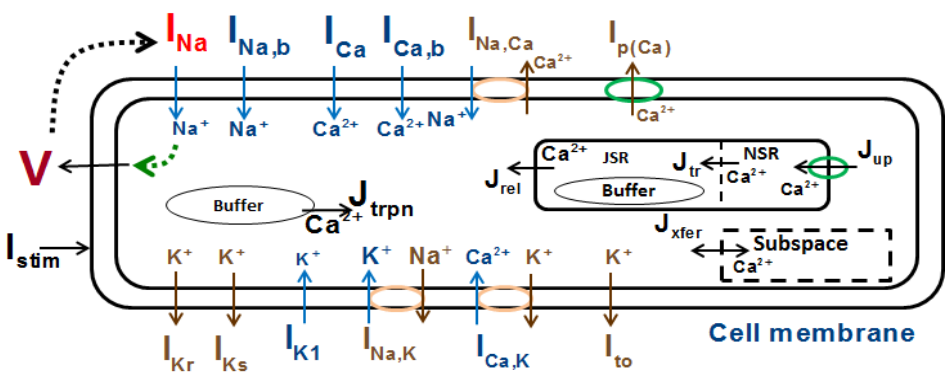






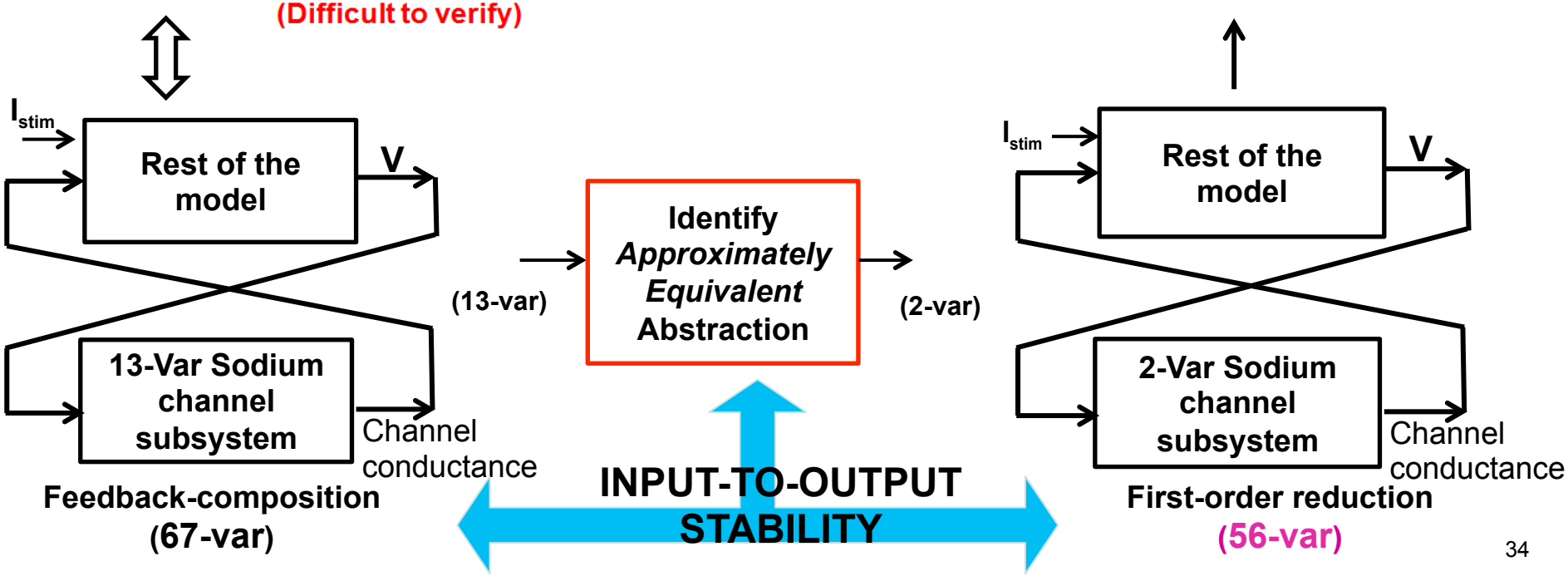


Proposed Research:
Compositional & Approximate Verification



67-Var Detailed Cardiac Cell Model
(Difficult to verify)

4-Var Minimal Model
(Easier to verify)



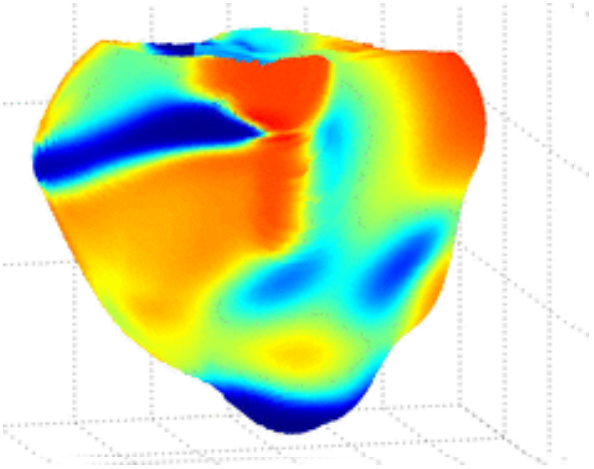
Feedback-composition (67-var)

First-order reduction (56-var)

Sharp boundary method for cardiac tissue modeling including defibrillation

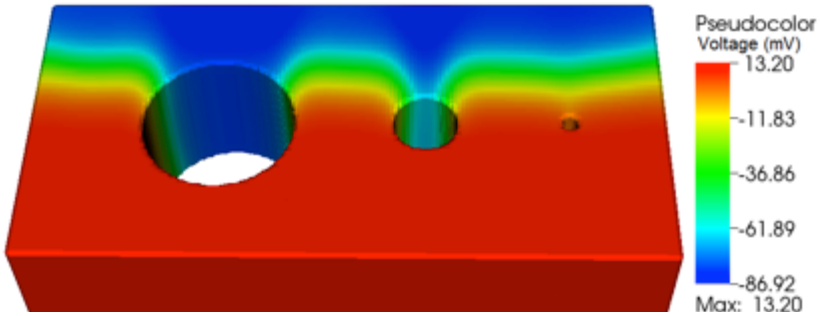
Method already optimized to handle:

- Irregular domains

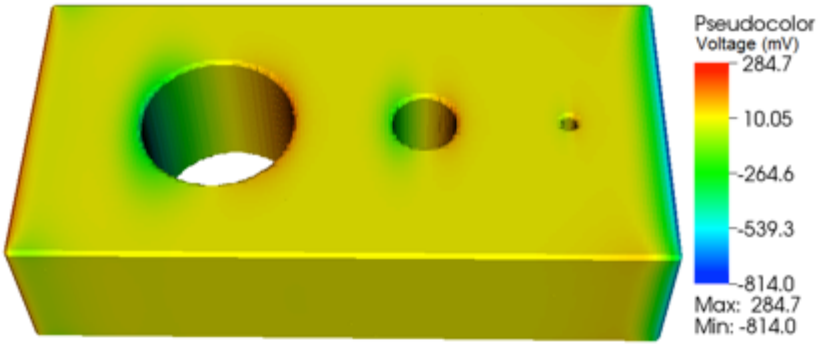


Simulated VF in rabbit ventricles

- Resolved very small vessels



Propagating wave



Defibrillating shock

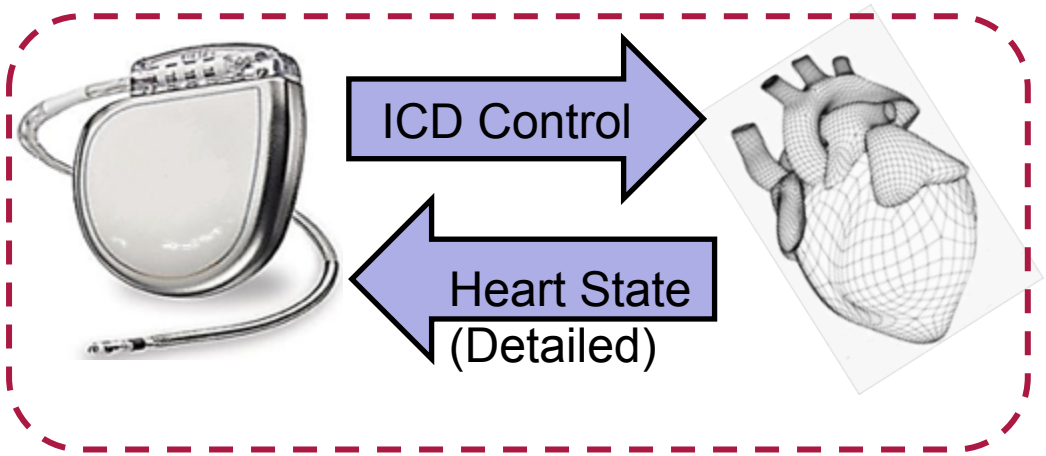
4000x2000x1000 microns

Method will be used to study arrhythmias and interaction with ICDs

Bridging in-vitro and simulation models
Simulation of fibrillation and in-vitro experiment

Work by Richard Gray (FDA), Flavio Fenton (GA-Tech) and others

Proposed Research:
Closed-loop Control & Verification for Cardiac Therapy

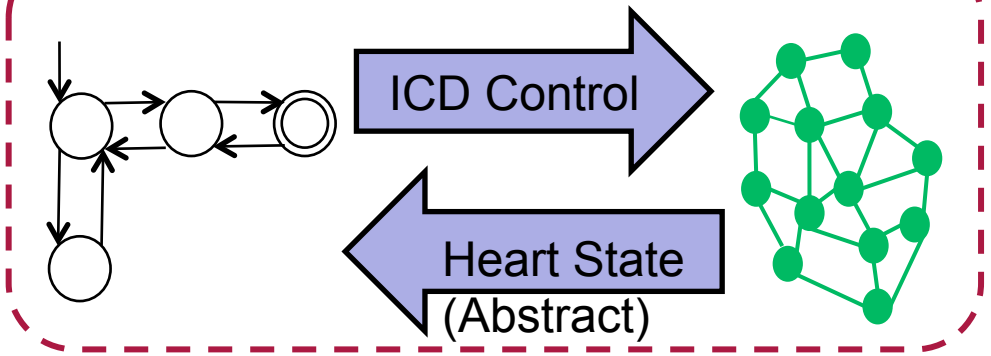


: Difficult to verify

Detailed feedback-composed
closed-loop model of
device () & heart ()

Functional Model

Formal Model



: Easier to verify

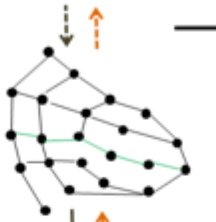
Abstract feedback-composed
closed-loop model of
device () & heart ()

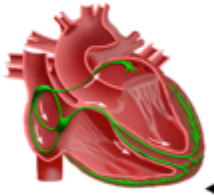
CyberHeart

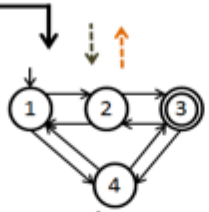
Counter Example-Guided
Abstraction & Refinement:
Complexity v. Fidelity

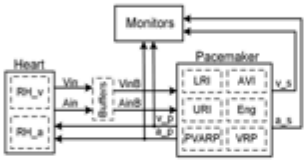
Modeling & Verification Technologies for CPS

- *Compositional Reasoning*
- *Quantitative Reasoning*
- *Approximate Reasoning*
- *Patient-Specific Modeling & Verification*









Closed-Loop V&V

Applications

- *Low-Energy Anti-fibrillation Pacing*
- *Inappropriate Shocking*
- *Rhythm Management*
- *Device Interaction*
- *Alternans*

Enabling Platforms

Patient Data & Model Repository

- *Heart-on-a-Chip*
- *dReach*
- *HySim*
- • • •

We CyberHeart Education & Outreach!

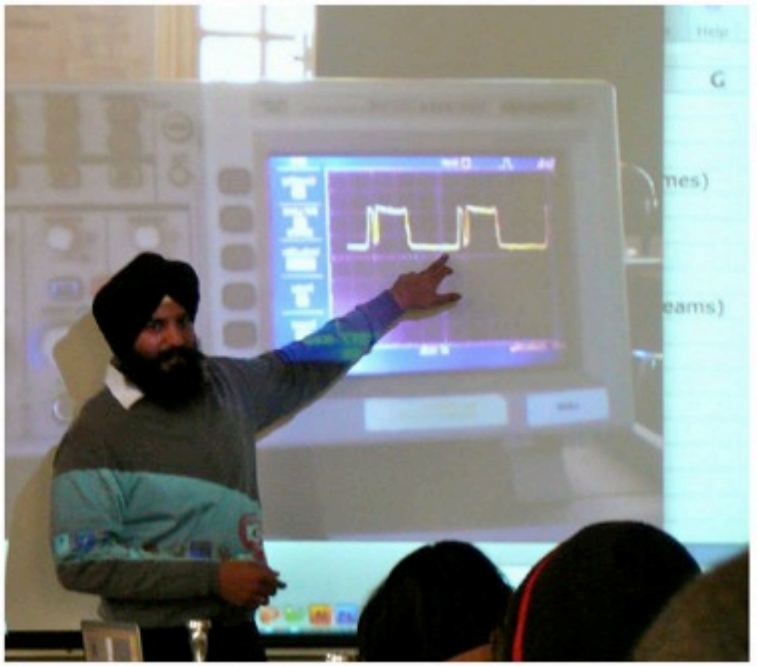
a. *2011 workshop on Cellular Signaling Pathways*

b. *2012 workshop on Atrial Fibrillation*

c. *2013 workshop on Cellular Signaling Pathways*

d. *2014 workshop on Atrial Fibrillation*

6th Year of Medical CPS Workshop – in the next room ☺



Adv Physiol Educ 35: 427–437, 2011;
doi:10.1152/advan.00034.2011.

Teaching cardiac electrophysiology modeling to undergraduate students: laboratory exercises and GPU programming for the study of arrhythmias and spiral wave dynamics

All student participants co-authors

Ezio Bartocci,[1] Rupinder Singh,[2] Frederick B. von Stein,[3] Avessie Amedome,[4] Alan Joseph J. Caceres,[4] Juan Castillo,[4] Evan Closser,[4] Gabriel Deards,[4] Andriy Goltsev,[4] Roumwelle Sta. Ines,[4] Cem Isbilir,[4] Joan K. Marc,[4] Diquan Moore,[4] Dana Pardi,[4] Sandeep Sadhu,[4] Samuel Sanchez,[4] Pooja Sharma,[4] Anoopa Singh,[4] Joshua Rogers,[4] Aron Wolinetz,[4] Terri Grosso-Applewhite,[4] Kai Zhao,[4] Andrew B. Filipski,[5] Robert F. Gilmour, Jr.,[3] Radu Grosu,[6] James Glimm,[1] Scott A. Smolka,[6] Elizabeth M. Cherry,[3,7] Edmund M. Clarke,[8] Nancy Griffeth,[4] and Flavio H. Fenton[3]

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Bartocci E, Singh R, von Stein FB, Amedome A, Caceres AJ, Castillo J, Closser E, Deards G, Goltsev A, Ines RS, Isbilir C, Marc JK, Moore D, Pardi D, Sadhu S, Sanchez S, Sharma P, Singh A, Rogers J, Wolinetz A, Grosso-Applewhite T, Zhao K, Filipski AB, Gilmour RF Jr, Grosu R, Glimm J, Smolka SA, Cherry EM, Clarke EM, Griffeth N, Fenton FH. Teaching cardiac electrophysiology modeling to undergraduate students: laboratory exercises and GPU programming for the study of arrhythmias and spiral wave dynamics. *Adv Physiol Educ* 35: 427–437, 2011; doi:10.1152/advan.00034.2011.— As part of a 3-wk intersession workshop funded by a National Science Foundation Expeditions in Computing award, 15 undergraduate students from the City University of New York[1] collaborated on a study aimed at characterizing the voltage dynamics and arrhythmogenic behavior of cardiac cells for a broad range of physiologically relevant conditions using an in silico model. The primary goal of the

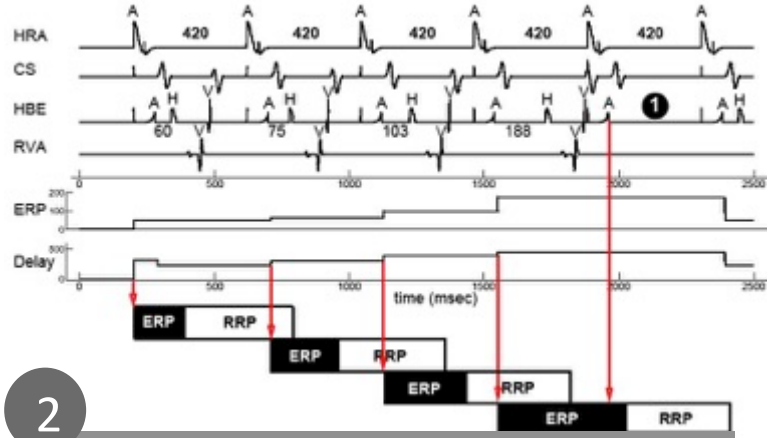
ventricular fibrillation; atrial fibrillation; graphics processing unit simulations

THE 2011 ATRIAL FIBRILLATION WORKSHOP was one of a series of annual workshops affiliated with the Computational Modeling and Analysis of Complex Systems (CMACS), a multi-institutional (8) and multi-principal investigator (19) project led by Edmund Clarke. CMACS is funded by a National Science Foundation Expeditions in Computing award. The objective of the workshops is to develop the scientific interest and skills of students from urban minority-serving institutions and especially to motivate them to study the kinds of computational modeling techniques and applications used and developed in

Integration of Research with Education for Cross-disciplinary Projects

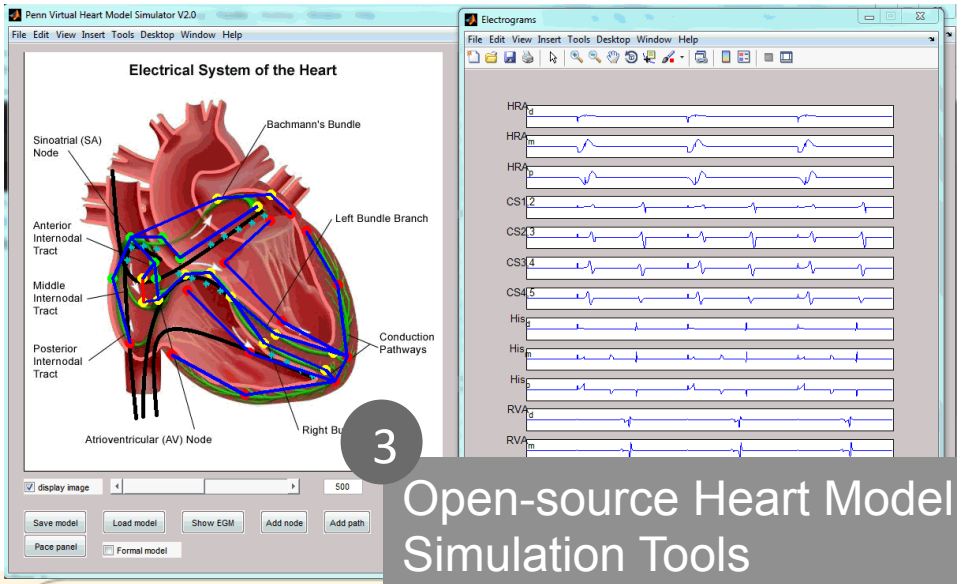
1

Open-source Closed-loop Pacemaker/ICD Testing Platforms



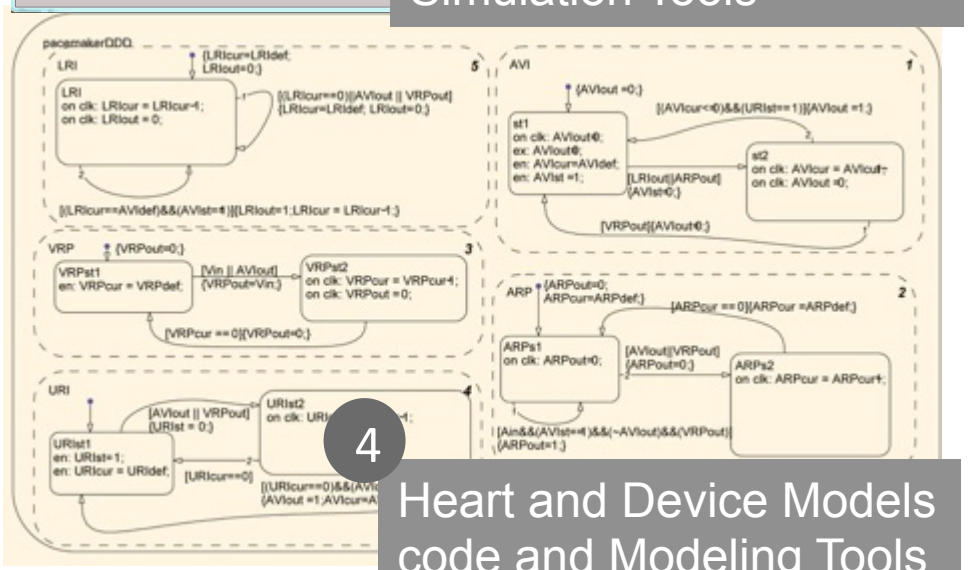
2

Open Datasets of electrograms and device signal traces



3

Open-source Heart Model Simulation Tools

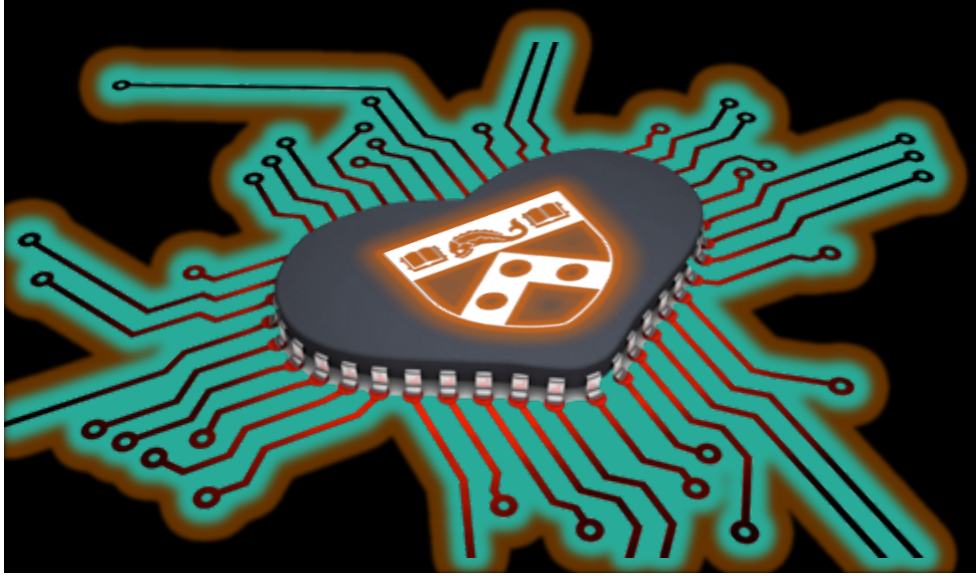


4

Heart and Device Models code and Modeling Tools

Essentially, all models are wrong,
but some are useful.

- George E. P. Box



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Patient-specific Therapy Guidance & Device Configuration

1. Model-guided ablation therapy
   - Data-driven timing anomaly heatmap

2. Patient-model based device selection and configuration
   - Automated timing extraction and device parameter mapping

3. Arrhythmia risk stratification and optimization of treatment
   - Better procedure planning for ablation therapy