In Silico Simulation Models of Human Physiology to Accelerate the Development and Verification of Medical Devices

Pourash Patel

Senior Application Engineer – Medical Device

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Largest pharmaceutical and biotech companies

Hospitals and medical research institutions

Agenda

i. Introduction - In-silico medicine
ii. Example – Heart + Pacemaker
iii. Case Studies

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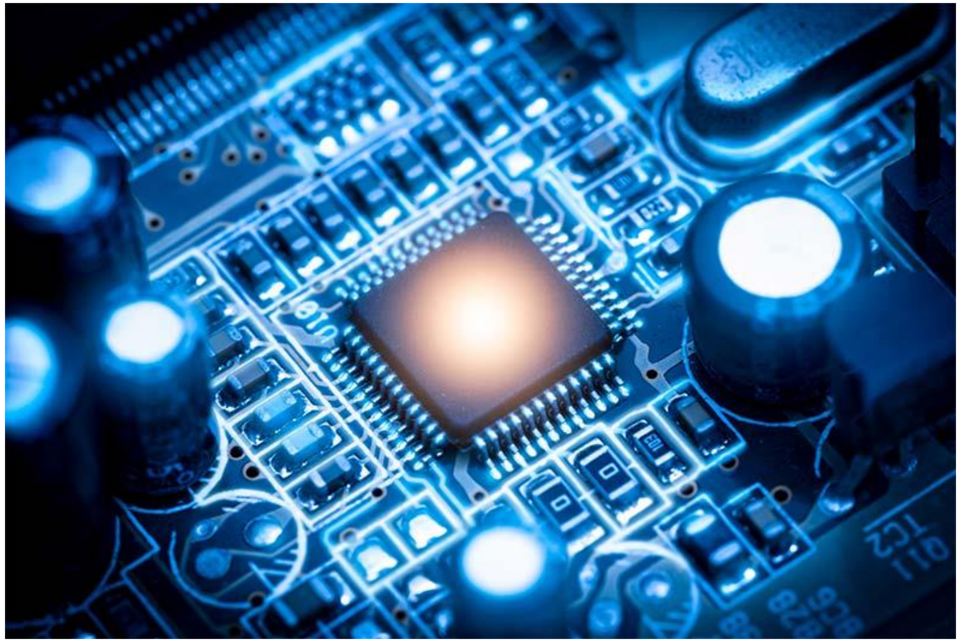
What is In Silico Medicine?

- **In Silico Medicine** uses computational modelling and simulation (CM&S) to replicate humans and medical devices
- **Virtual patients and organs** (aka Digital Twins) are utilised in R&D
- **Applications in medical devices:**
  - Design and verification
  - Clinical evaluation
  - Performance testing
  - Regulatory evidence



Benefits to all healthcare stakeholders

- Regulators see CM&S as a way to **provide supportive regulatory evidence**
  - Submission of virtual patient data

- Companies can use virtual human and organ models to **accelerate device development and testing**
  - Shorter time-to-market
  - Reduced R&D costs

- Patients benefit from **safer medical devices**
  - *In Silico Clinical Trials* with larger and more diverse patient cohorts

CM&S framework for medical devices

Medical device model

+

Physiological/anatomical model

+

Simulation

=

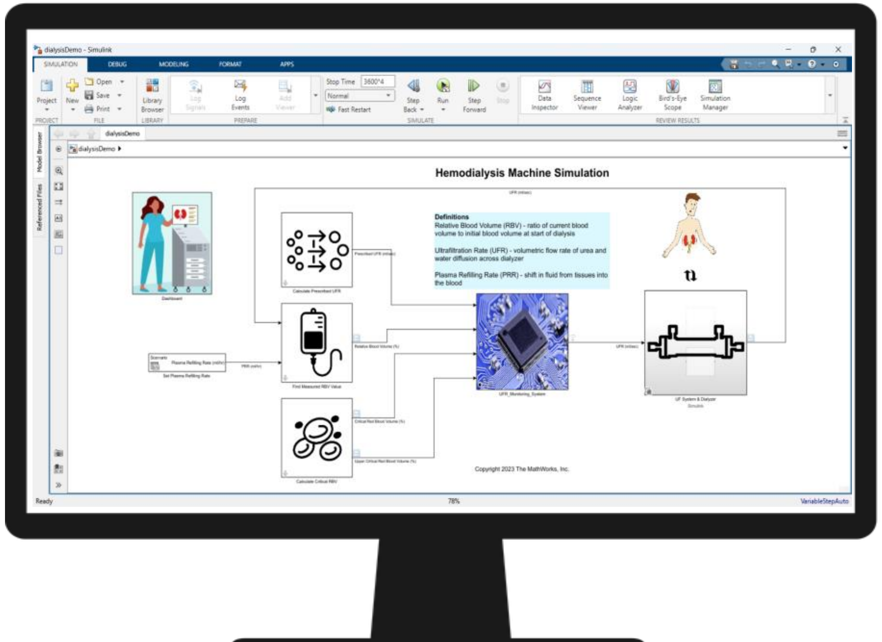
In Silico Medicine

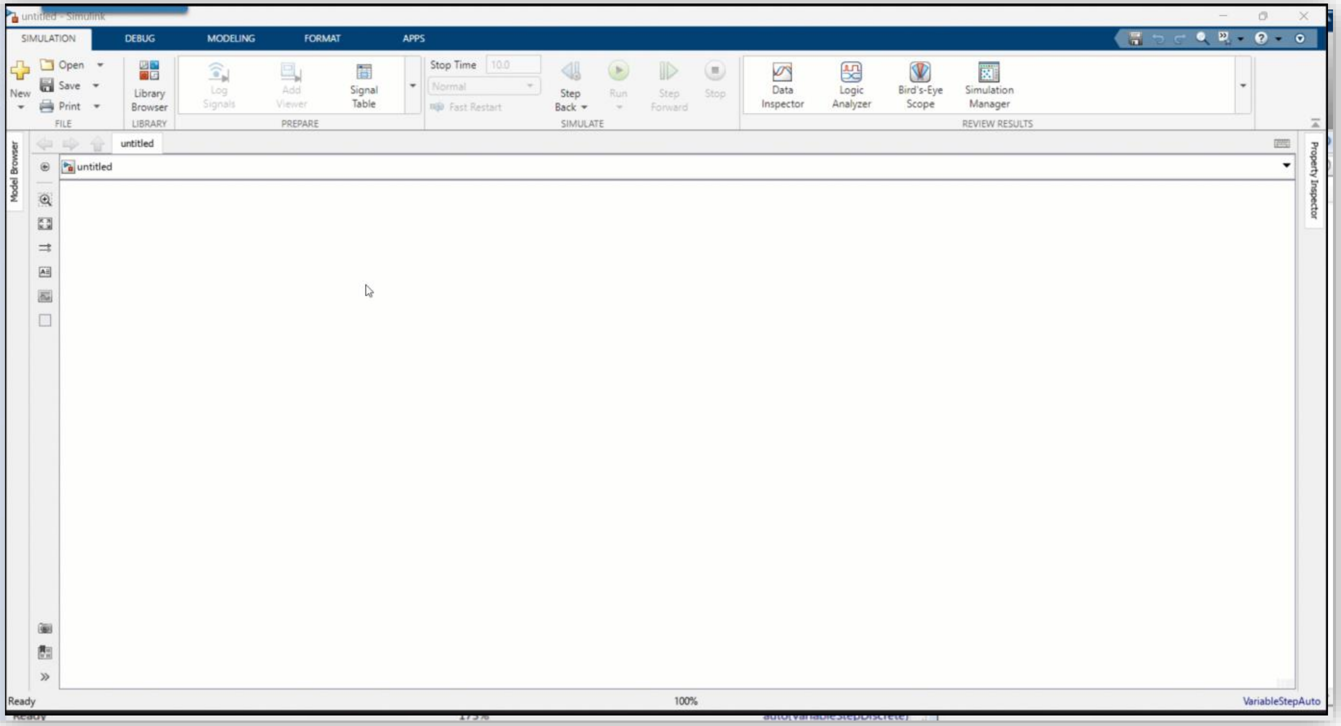
Simulink

Simulink: simulation & model based design

- dynamic system and control
- optimized model development
- grid design/integration
- code generation

Transforming the way Engineers work.





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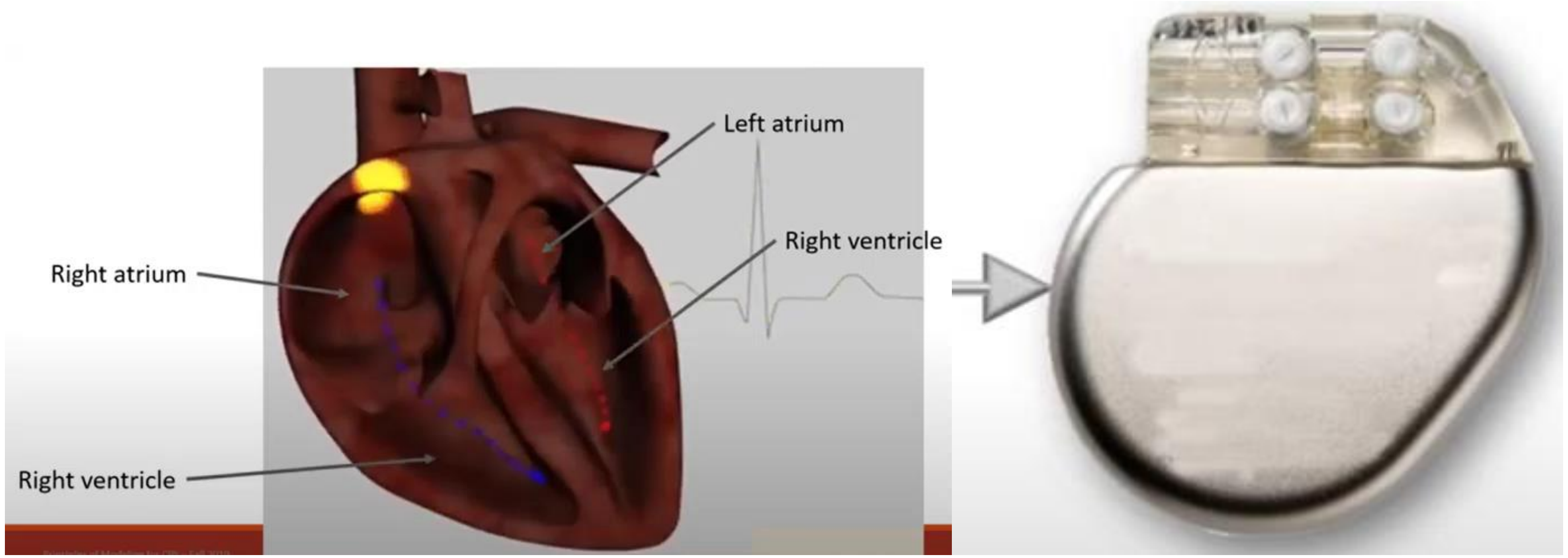
Why Study Cardiac Devices?

- These devices are life-critical → Must function correctly
- Are constrained in their energy consumption → must be low-power
- Are regulated by the FDA → must follow certain best practices

These are life-critical cyber-physical (embedded) systems

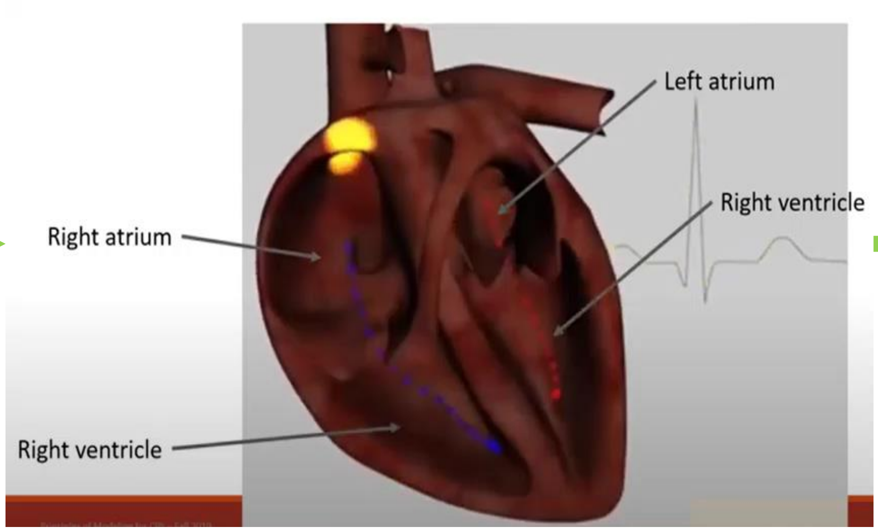
Open-Loop Evaluation



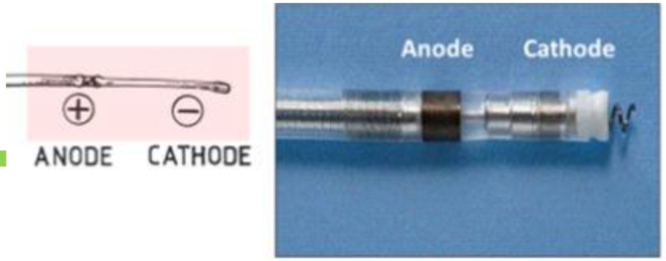
Closed-Loop Evaluation

Pacemaker (Controller)

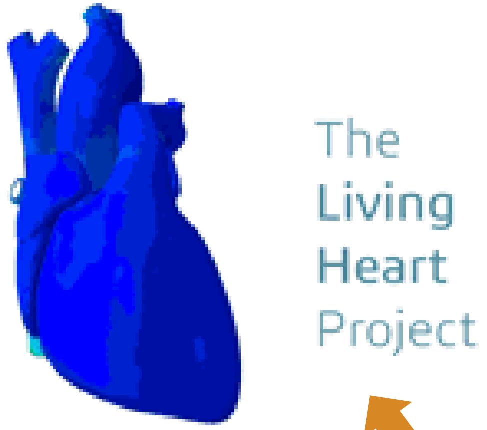
Heart Model (Plant)

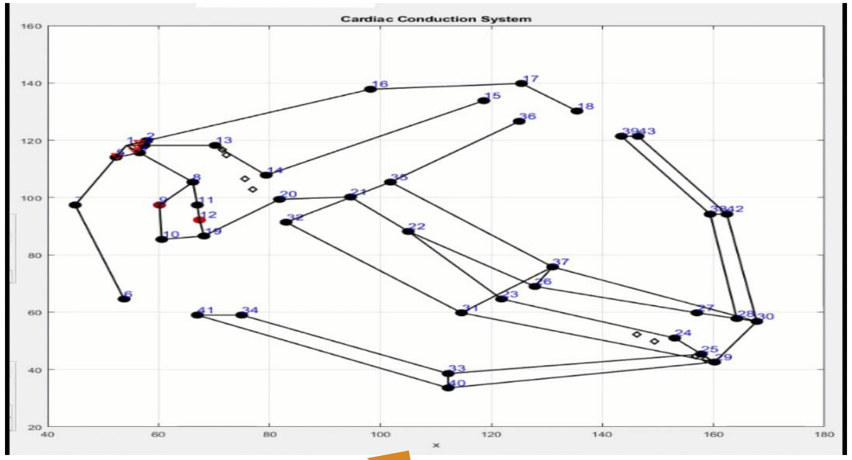


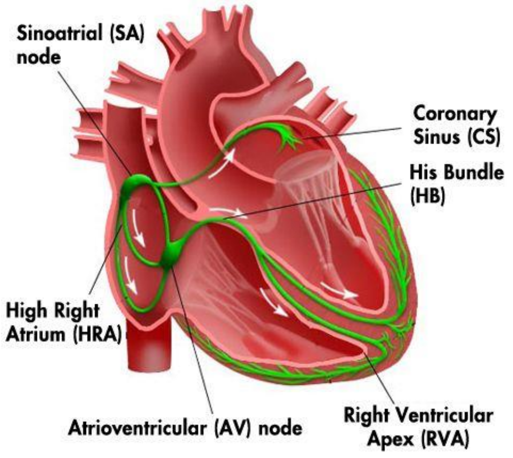
Bipolar Lead(Sensor)

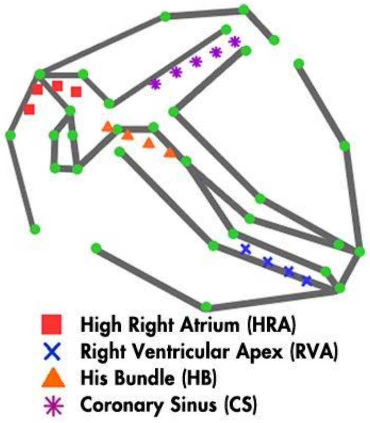


Various Modeling Efforts



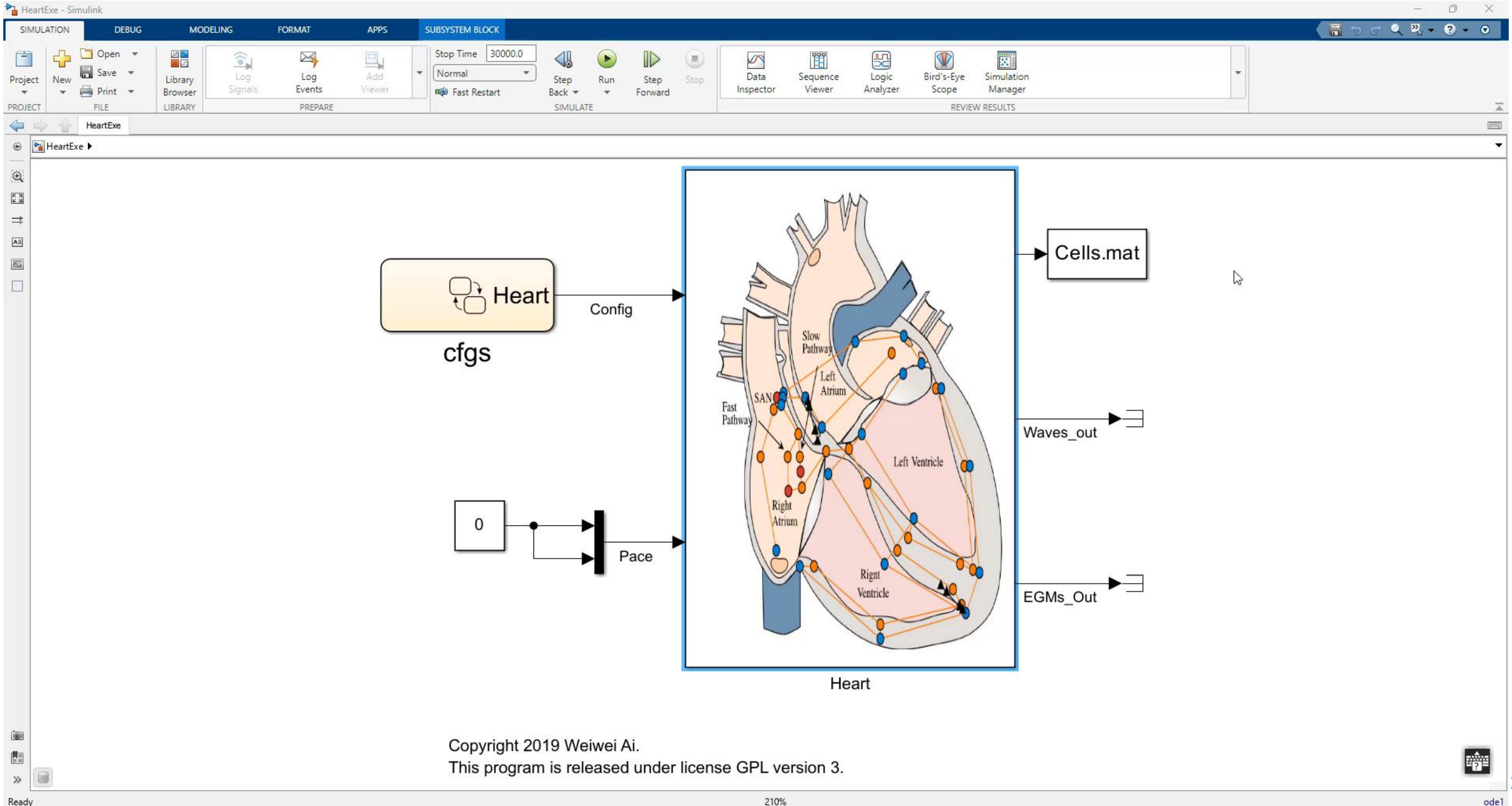






	Reality	Less Abstract ←		**Heart Models**			→ More Abstract
	Real Heart [22]	**Hi-Fi** [23], [24]	**UoA**	**Oxford** [6]	**UPenn** [3], [7]	**LORIA** [8]	**MES** [9]
Cell Model	Continuous APs from biophysical processes [25]	Continuous APs from biophysical models [25]	Continuous APs from improved Stony Brook HA [13]	Continuous APs from simplified Stony Brook HA [19]	Discrete APs from TA	Discrete APs from logico-mathematics	Continuous AV signal generators mimic whole heart electrical activity
Path Model	Continuous propagations from biophysical processes [10]	Continuous propagations from reaction-diffusion equations [25]	Continuous propagations from TA and contribution function	Continuous propagations from contribution function	Discrete propagations from TA	Discrete propagations from cellular automata	
Spatial Model	3D tissue (layers of bundles of fibers) that deforms	3D finite-volume that deforms	2D, static, and sparse network of cells along the conduction pathway				Black boxes of major heart components

Heart Model


HeartExe - Simulink
SIMULATION
DEBUG
MODELING
FORMAT
APPS
SUBSYSTEM BLOCK
Project
New
Open
Save
Print
Library Browser
Log Signals
Log Events
Add Viewer
Stop Time
30000.0
Normal
Fast Restart
Step Back
Run
Step Forward
Stop
Data Inspector
Sequence Viewer
Logic Analyzer
Bird's-Eye Scope
Simulation Manager
PROJECT
FILE
LIBRARY
PREPARE
SIMULATE
REVIEW RESULTS
HeartExe
Heart
cfgs
Config
0
Pace
Slow Pathway
Left Atrium
SAN
Fast Pathway
Left Ventricle
Right Atrium
Right Ventricle
Heart
Cells.mat
Waves_out
EGMs_Out
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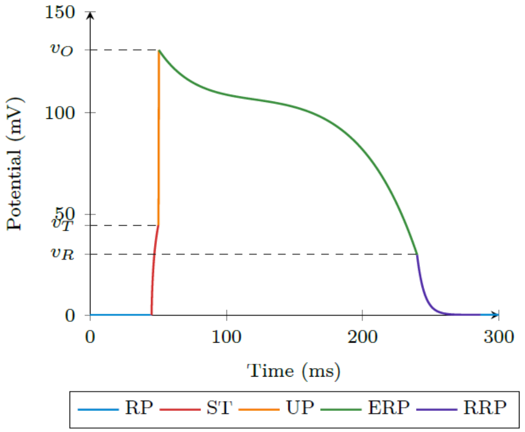
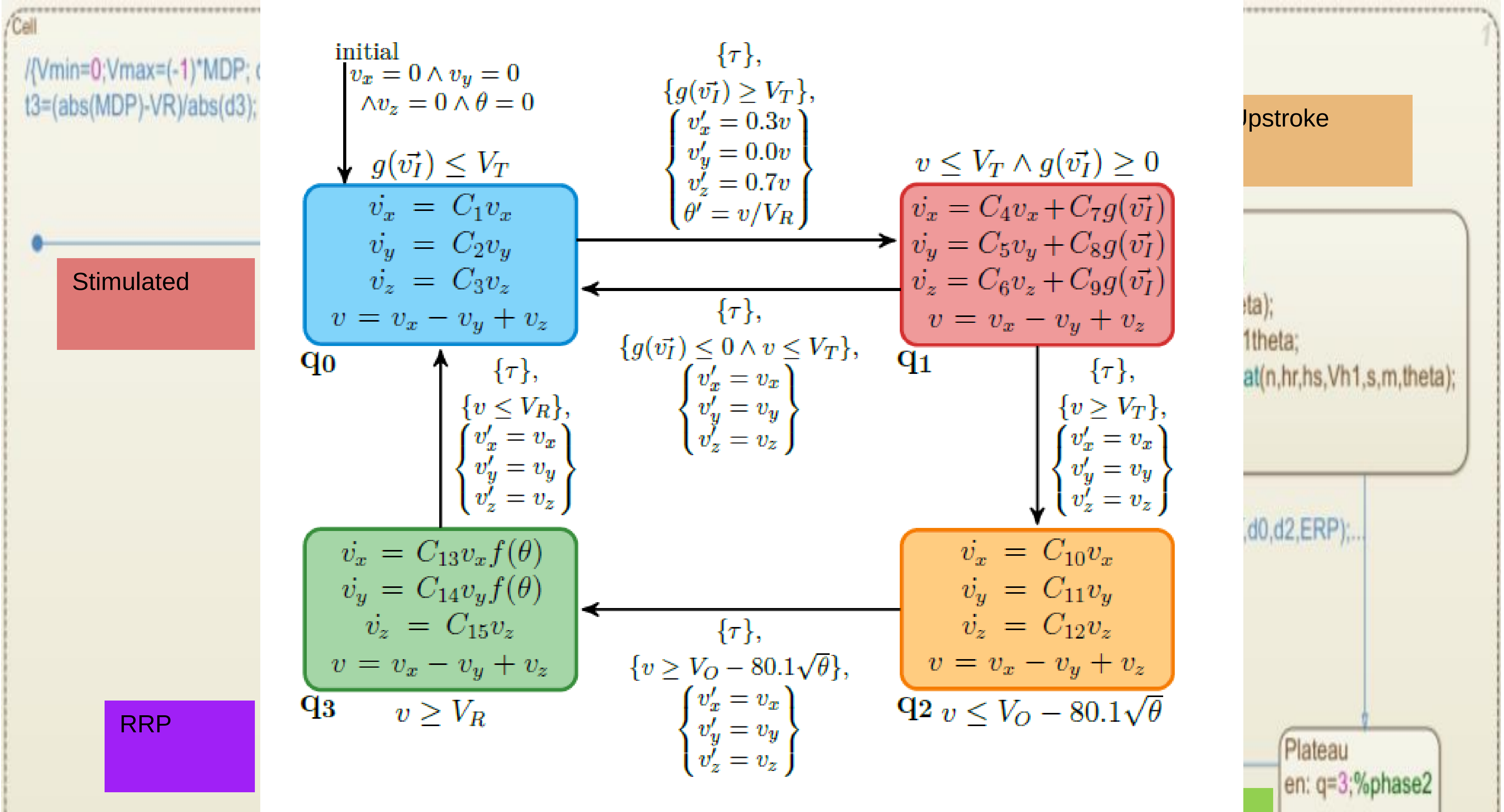
Ready
210%
ode1

Action Potential Generated by UOA Model

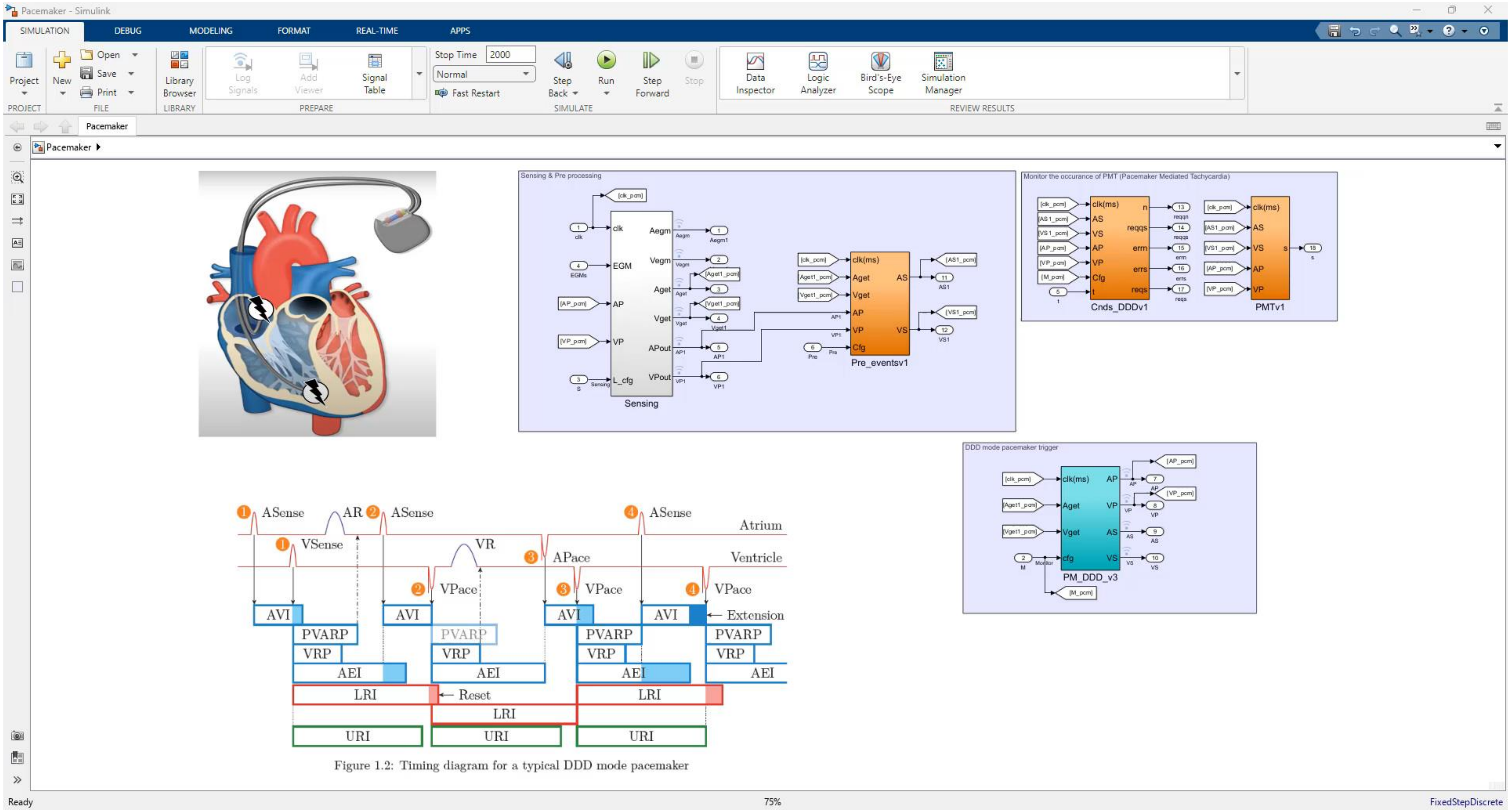


(b) An Action Potential generated by the UoA Model



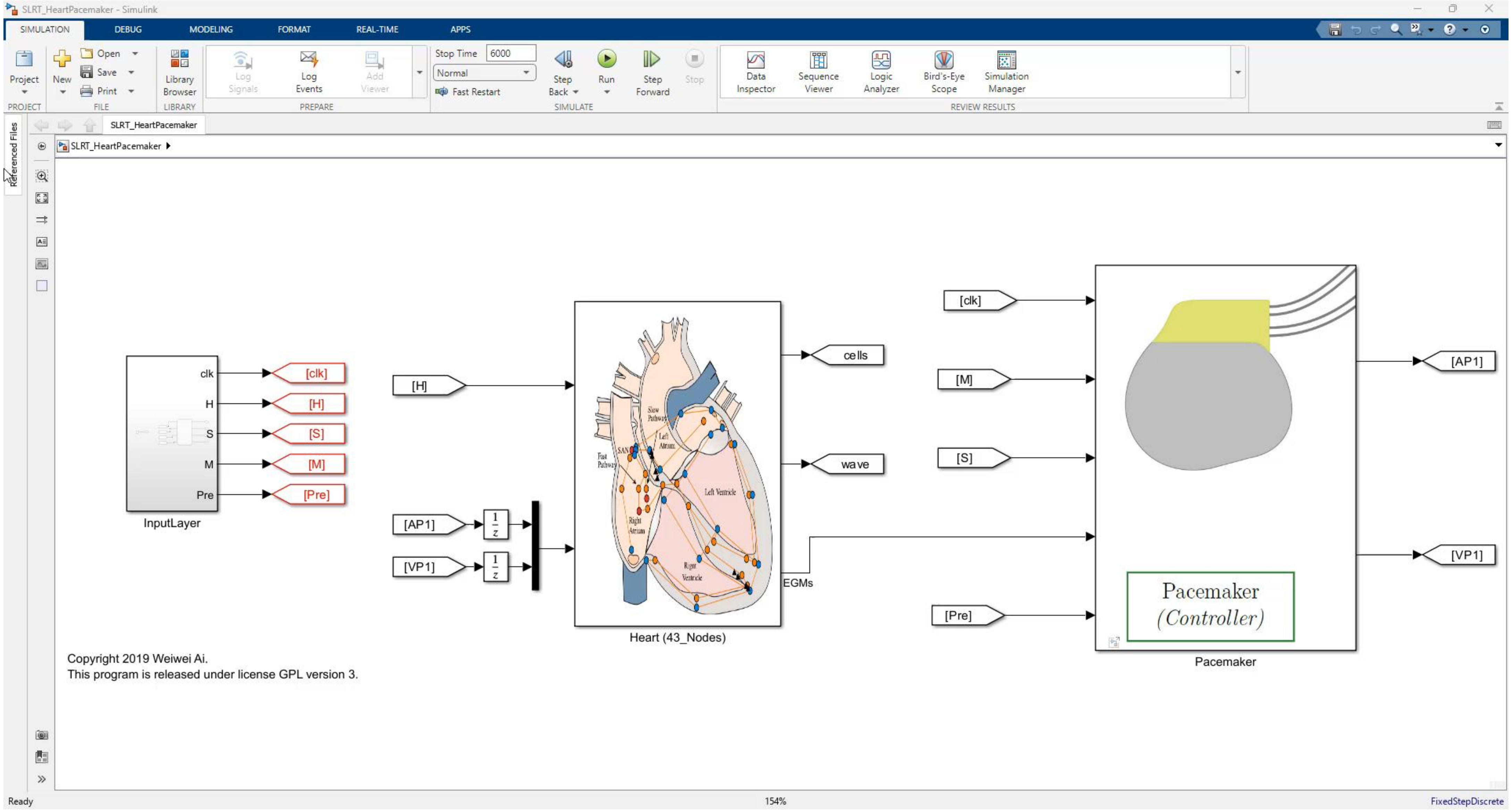
(a) The Hybrid Input-Output Automaton of the UoA Cell Model, reproduced from [37]

Pacemaker



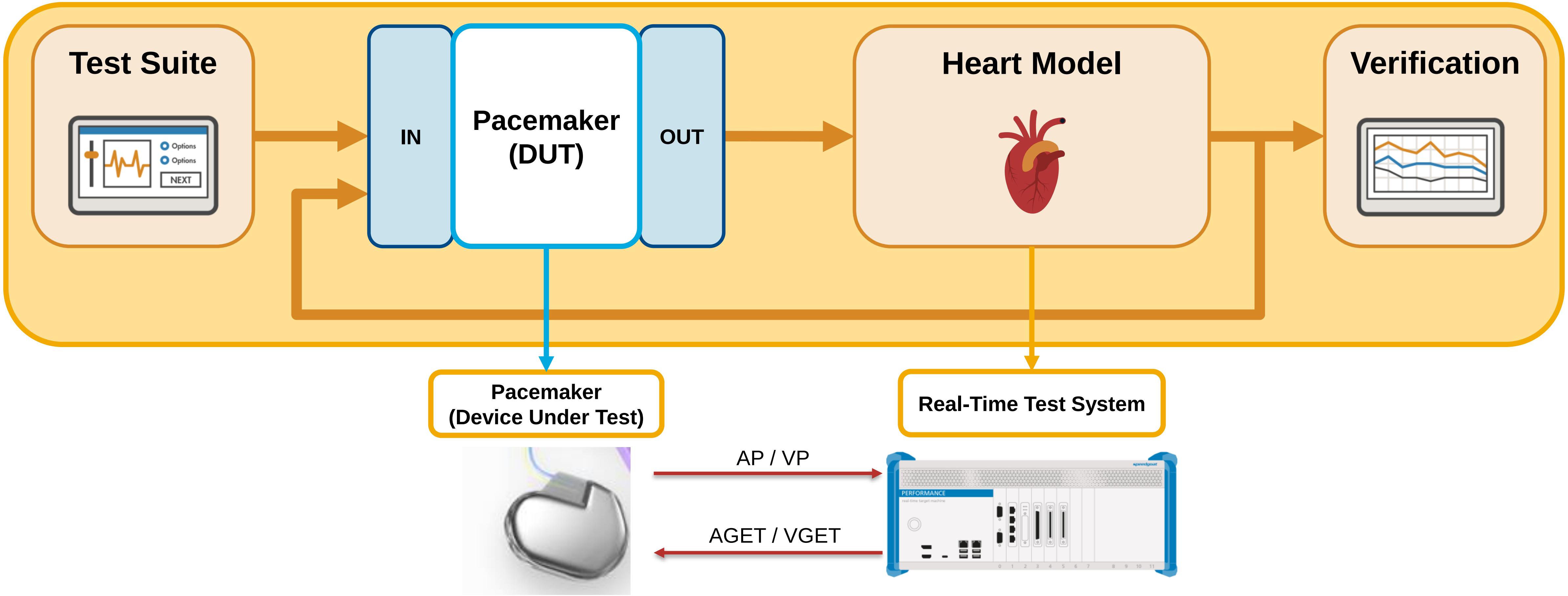
Pacemaker - Simulink
SIMULATION
DEBUG
MODELING
FORMAT
REAL-TIME
APPS
Stop Time 2000
Normal
Fast Restart
Data Inspector
Logic Analyzer
Bird's-Eye Scope
Simulation Manager
Sensing & Pre processing
Sensing
Pre_eventsv1
Monitor the occurance of PMT (Pacemaker Mediated Tachycardia)
Cnds_DDDv1
PMTv1
DDD mode pacemaker trigger
PM_DDD_v3
ASense
AR
VSense
VR
APace
VPace
Atrium
Ventricle
AVI
PVARP
VRP
AEI
LRI
URI
Reset
Extension
Figure 1.2: Timing diagram for a typical DDD mode pacemaker
Ready
75%
FixedStepDiscrete

System Simulation

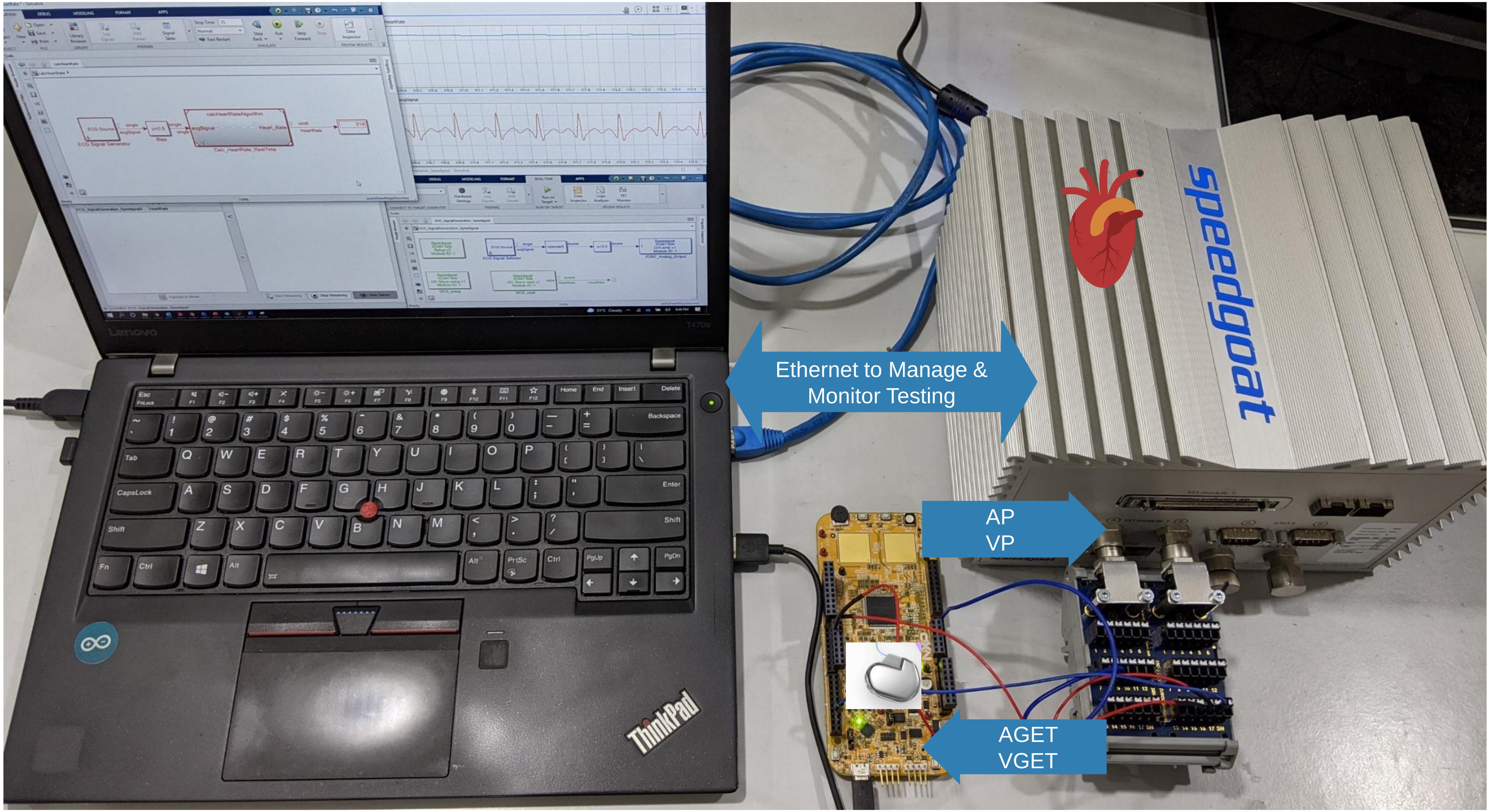


Hardware-in-the-loop Testing of Pacemaker Devices

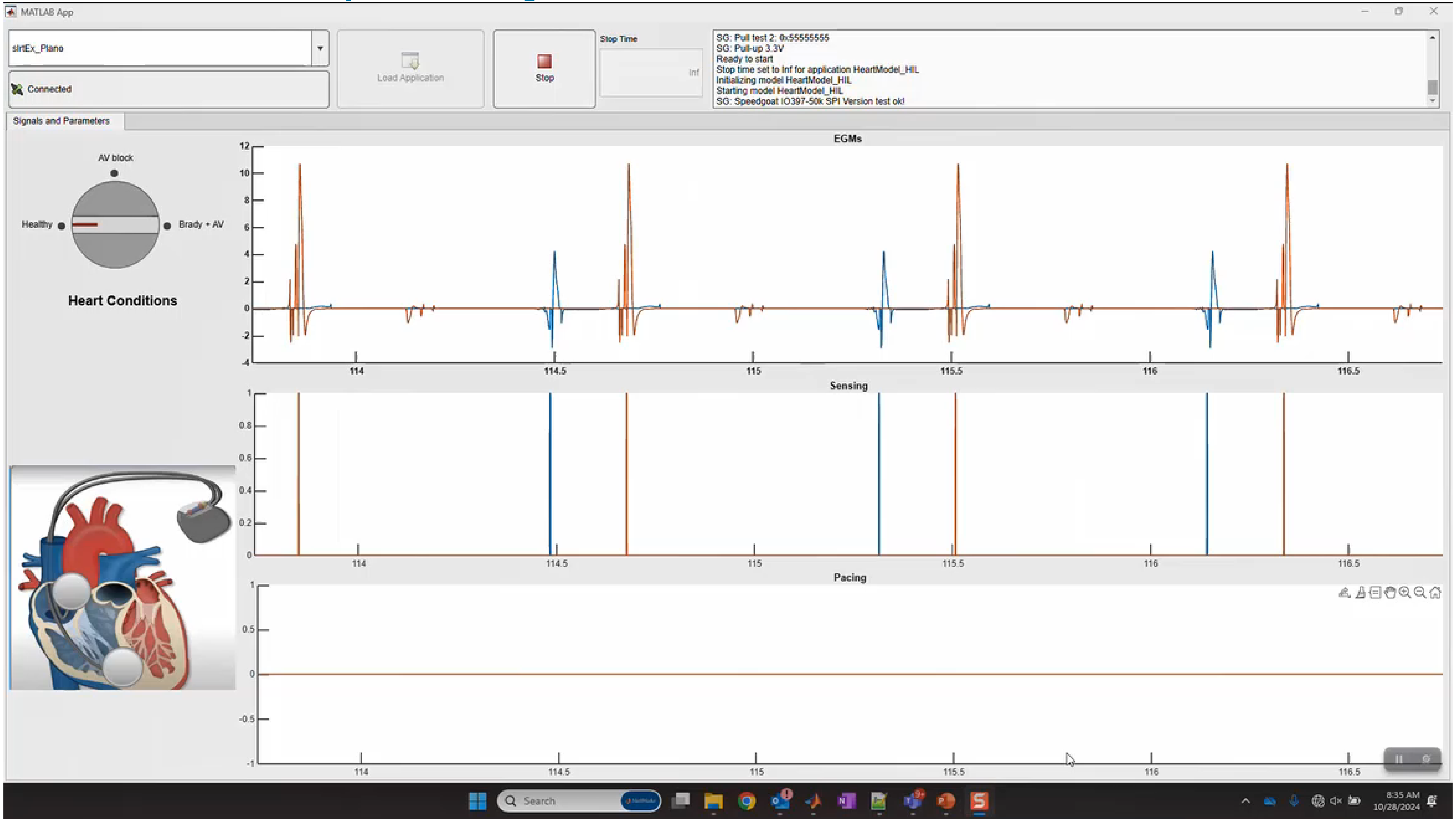
- Closed-Loop testing of pacemaker (DUT)
- Test different heart conditions and device failure modes
- Automate testing and reporting for certification



Hardware Setup



Hardware-In-Loop Testing



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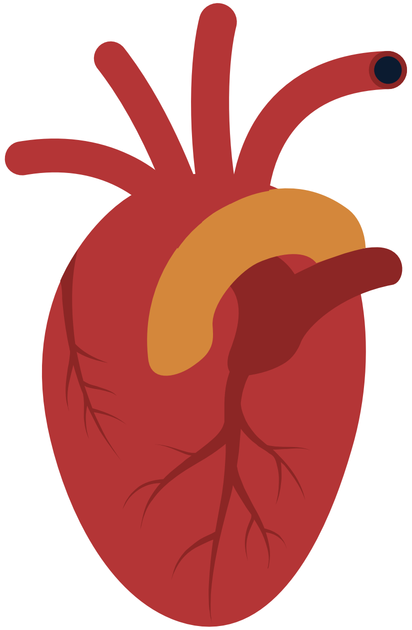
Case study: simulating an ECMO / heart-lung machine

- **ECMO / heart-lung machine**
  – Removes carbon dioxide and sends oxygen-filled blood back to tissues

- **FDA Class II device**

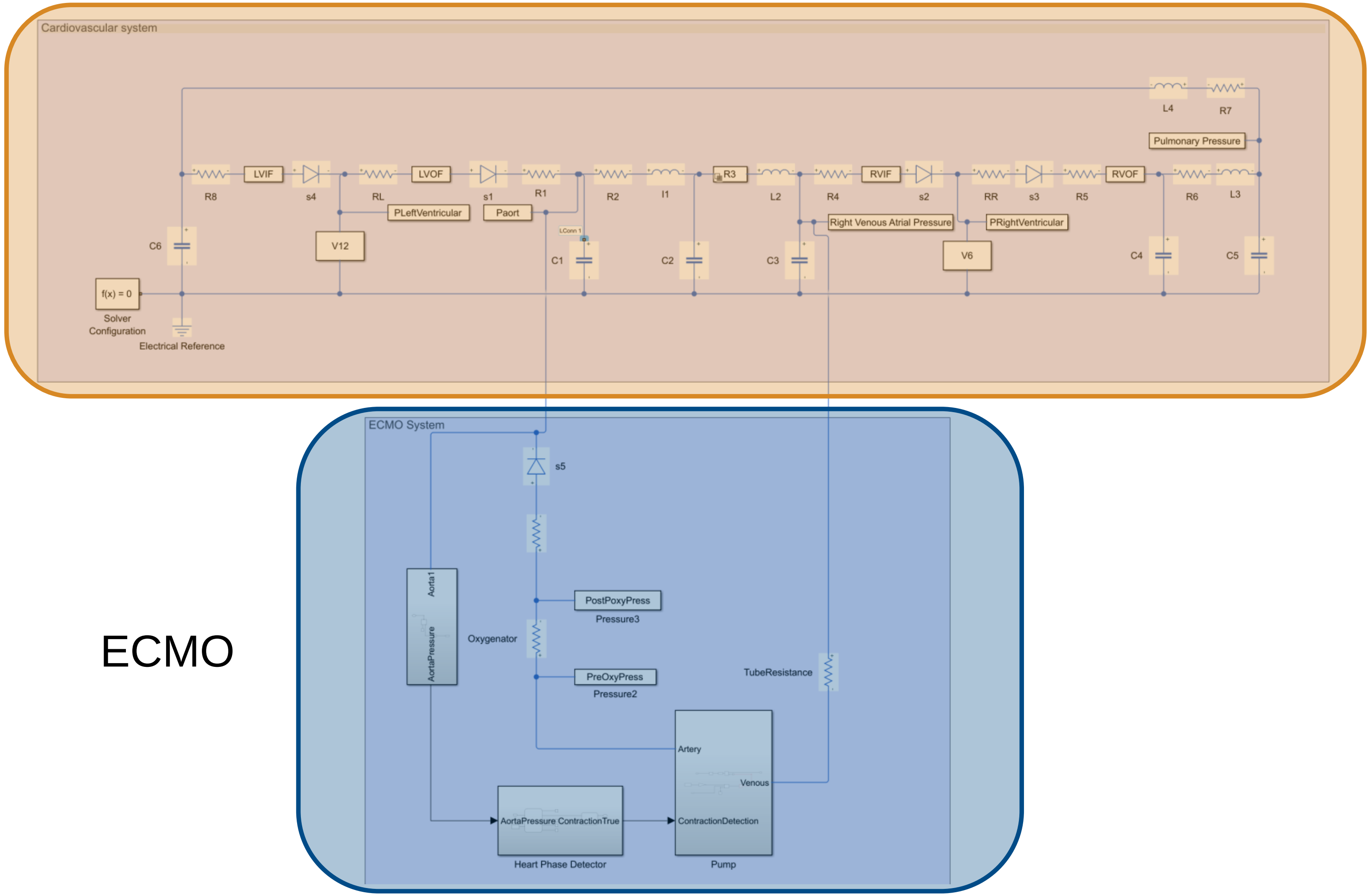
- **Simulation goals:**
  1. Build a complete representation of a cardiovascular system
  2. Verify and validate the ECMO machine using the patient model



Case study: simulating an ECMO / heart-lung machine

Patient model

ECMO



Source: [Cardiovascular System in Simscape with ECMO Machine]

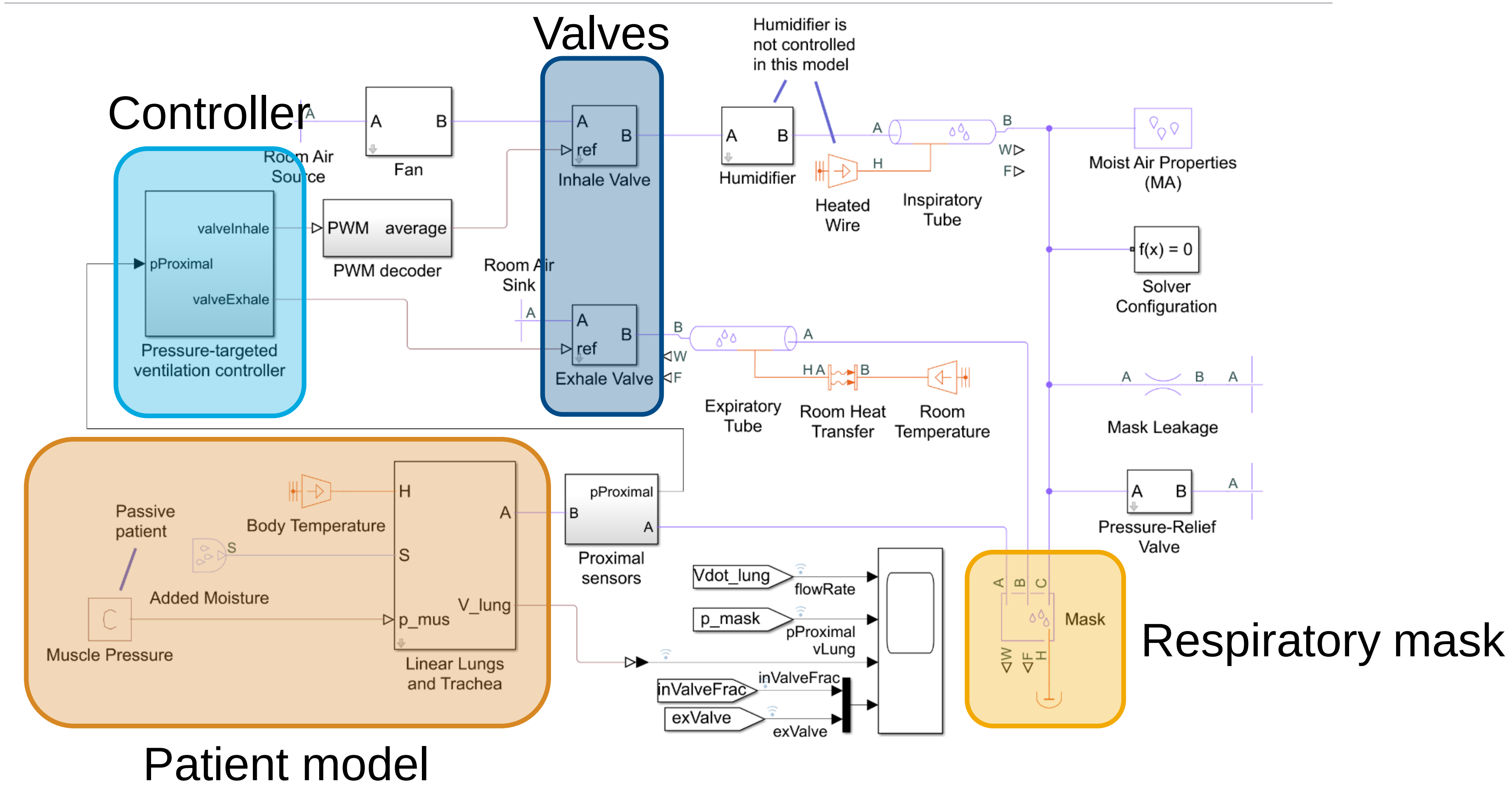
Case study: simulating a medical ventilator

- **Medical ventilator**
  – Replaces respiration by automatically moving air in and out of your lungs

- **FDA Class II device**

- **Simulation goals:**
  1. Create and tune a closed-loop control system for ventilation
  2. Generate certifiable embedded code for a production device

Case study: simulating a medical ventilator

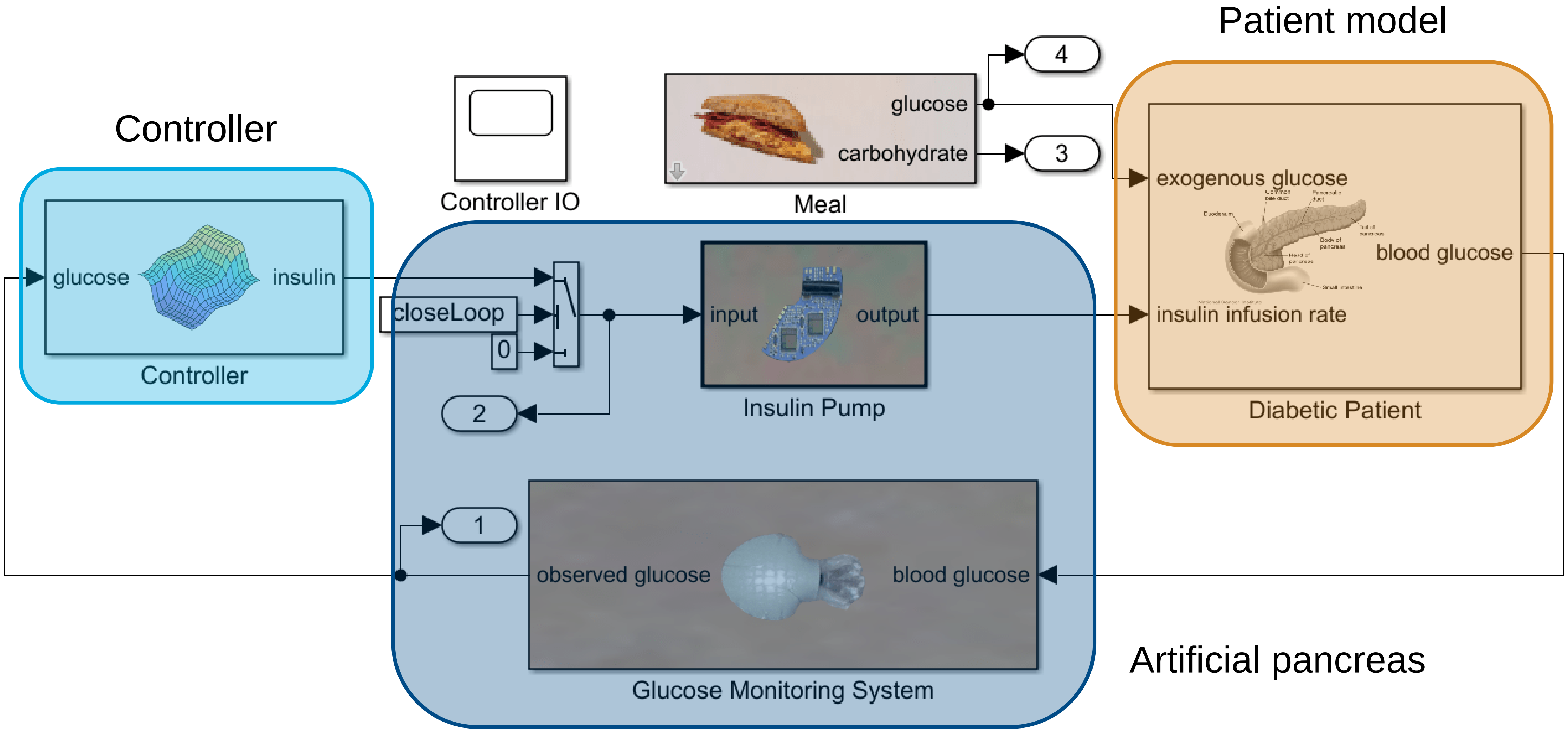


Source: Medical Ventilator Model in Simscape

Case study: simulating an artificial pancreas

- **Artificial pancreas**
  – Continuous glucose monitoring combined with insulin delivery
- **FDA Class III device**
- **Simulation goals:**
  1. Create and tune a closed-loop control system for insulin delivery
  2. Generate certifiable embedded code for production device

Case study: simulating an artificial pancreas

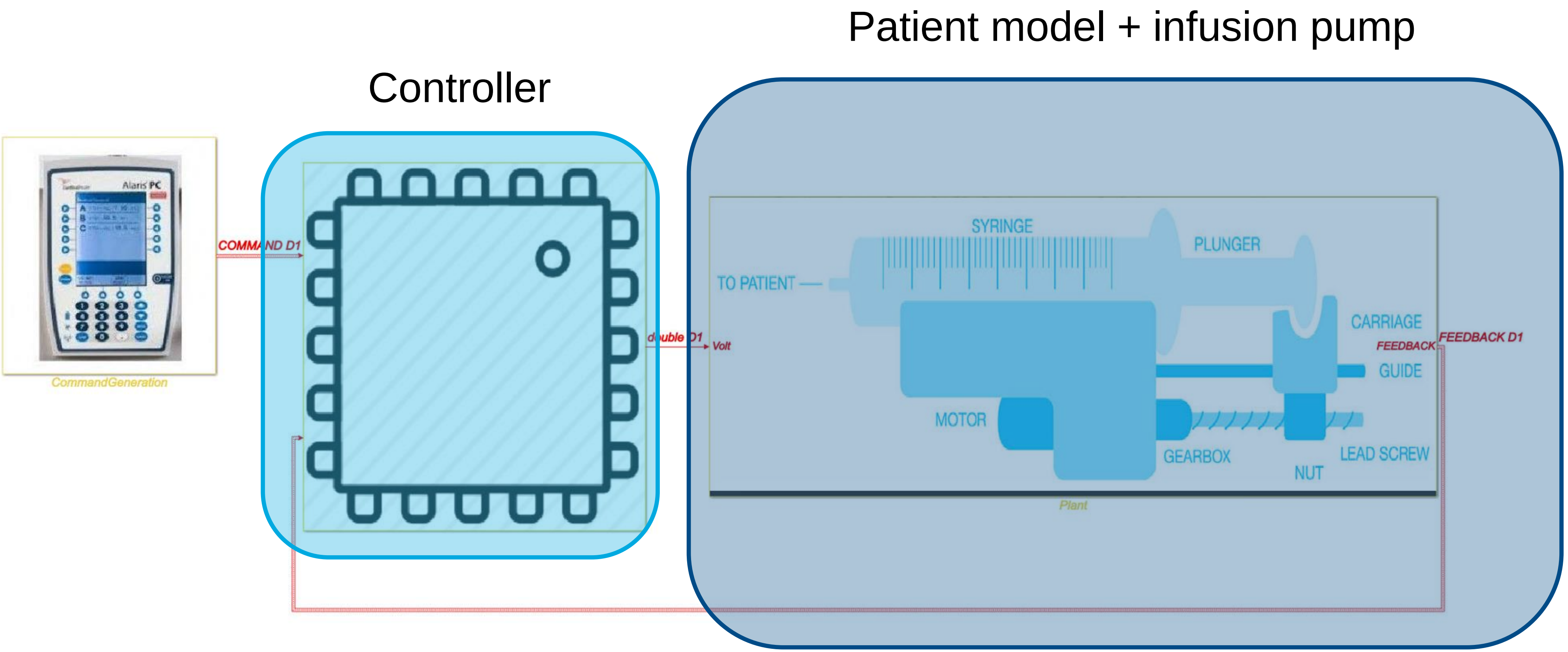


Source: [Artificial Pancreas Using Fuzzy Logic Controller]

Case study: simulating an infusion pump

- **Infusion pump**
  – Delivers drugs and nutrition into a patient's body in a controlled manner
- **FDA Class II device**
- **Simulation goals:**
  1. Verify and validate the pump behavior in different clinical scenarios
  2. Generate certifiable embedded code for production device

Case study: simulating an infusion pump



Source: Model-Based Design and Verification for Infusion Pump

Summary and key takeaways

- In Silico Medicine uses **simulations to verify and validate medical devices** with virtual humans or organs

- Using **simulations product design** will result in:
  - Shorter time-to-market
  - Reduced R&D costs and time
  - Safer medical devices

- Barriers to get started can be lowered with **end-to-end workflows, examples and technical support**

Examples on MathWorks File Exchange

- Medical Ventilator Model in Simscape
- Cardiovascular System in Simscape with ECMO Machine
- Artificial Pancreas Using Fuzzy Logic Controller
- Dialysis Machine in Simulink
- Model-Based Design and Verification for Infusion Pump

Learn more

- **White paper** on In Silico Medicine
- **Case studies** from the industry
- **Best practices** for getting started

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How In Silico Medicine Can Accelerate Innovation in Medical Devices

Dr. Visa Suomi, Medical Devices Industry Manager at MathWorks, explains how virtual human simulation models can benefit the development of next-generation medical devices.

From Physical to Virtual Humans

Modern medical devices are becoming ever more complex with better functionality, which provides patient benefit but also increases the risk of design errors. Therefore, it is important that new medical devices are tested for safety and efficacy several times throughout the development cycle. The validation and clinical evaluation of medical devices can be performed using living animals or humans, but this is expensive, time-consuming, and sometimes even risky to the test subjects. Alternatively, the testing can be conducted with tissue-mimicking phantoms or *in vitro*, which can reduce time and costs but does not accurately reflect a real human.

The question then arises: is it possible to eliminate the drawbacks of time, costs, and possible safety risks while maintaining the advantages of *in vivo* evaluation? One way to do this could be *in silico medicine*, which refers to the use of virtual human models to replace their physical counterparts in testing of new medical devices. The aim of these virtual humans is to replicate human anatomy and physiology so accurately that they can be used

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Start the project with the right support

- Trials and evaluations
- Consulting services
- Training services
- Technical support

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