The Human Heart
An Ultimate Cyber-Physical System

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CMACS Atrial-Fibrillation Team so Far


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Impossible Without An Expeditions Project


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Elizabeth Cherry
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Gerard Holzmann
NASA


Klaus Havelund
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Patrick Cousot
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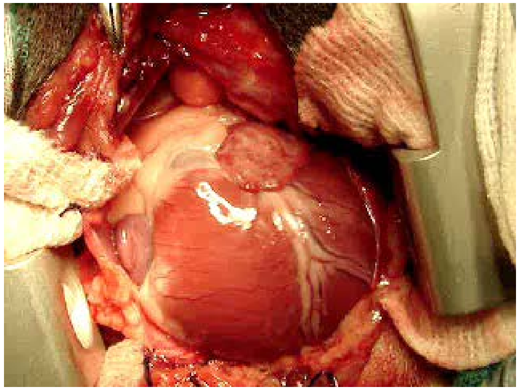
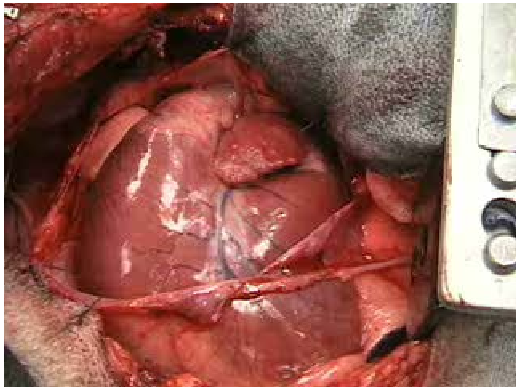
Consider the Following CP-EM-Systems



Error-Free System



Error-Prone System

Whose problem is this to solve?

It is a Medical Problem

National Vital Statistics Report, Vol.49, No.11, October 12, 2006
Deaths and percent of total deaths for the 10 leading causes of death: USA

Rank	Cause of death	Total Deaths	Percentage
	All causes	2,391,399	100.0
1	**Diseases of heart**	**725,192**	**30.3**
2	Malignant neoplasms	549,838	23.0
3	Cerebrovascular diseases	167,366	7.0
4	Chronic lower respiratory diseases	124,181	5.2
5	Accidents (unintentional injuries)	97,860	4.1
6	Diabetes mellitus	68,399	2.9
7	Influenza and pneumonia	63,730	2.7
8	Alzheimer's disease	44,536	1.9
9	Nephritis, nephrotic syndrome and nephrosis	35,525	1.5
10	Septicemia	30,680	1.3
	All other causes	484,092	20.2

http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf

What are the Fundamental Questions?

For cardiologists, pharmacologists and patients:

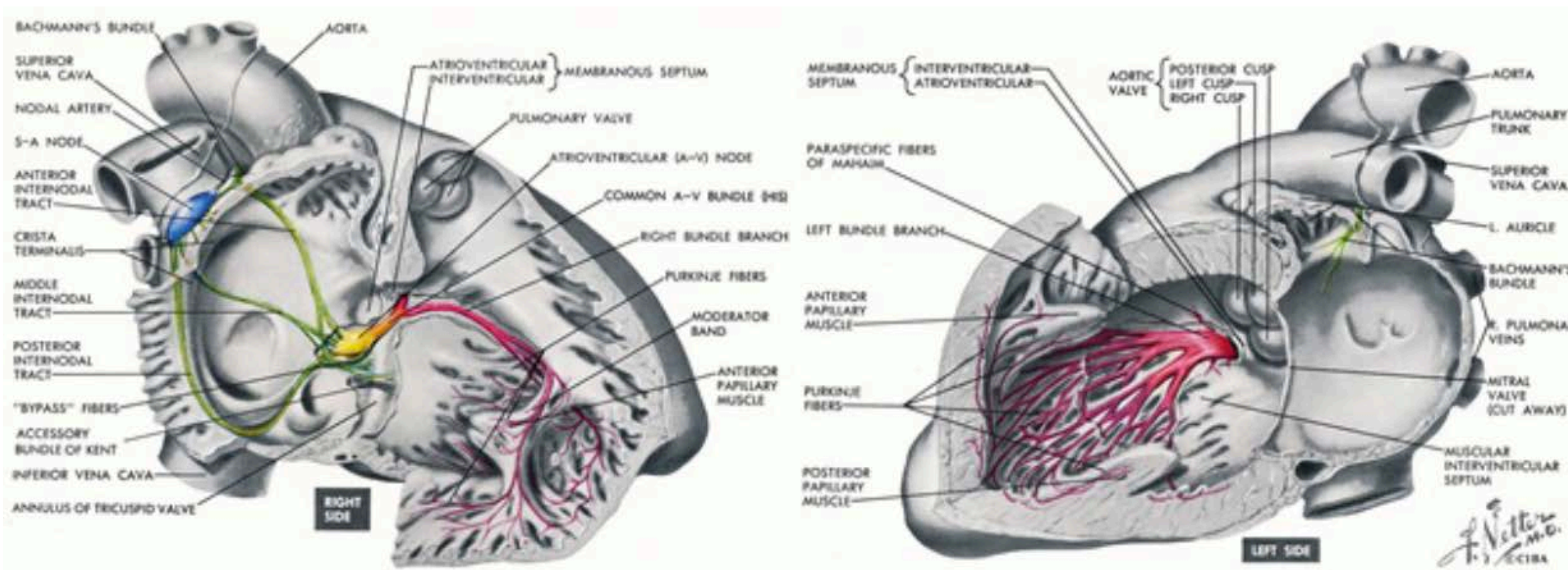
- What is the risk of a patient to develop the disorder?
- Under what circumstances will such a disorder arise?

Given a disorder-specification and a model of the ventricle:

- What is the probability of the model to satisfy the specification?
- For what parameter-ranges does it satisfy the specification?

Whose problem is this to solve?

It is a Communication-Structure Problem

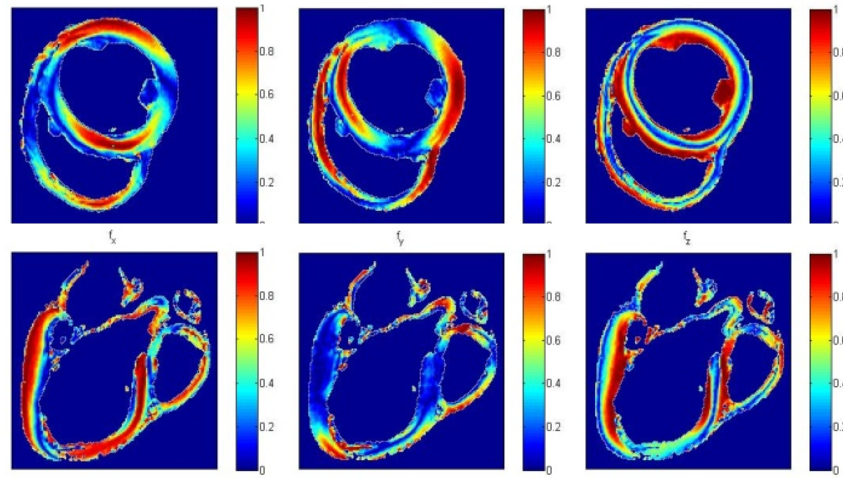


4 billion nodes interconnected in a very sophysticated way!

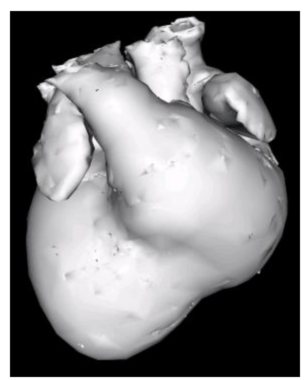
It is a Communication-Structure Problem

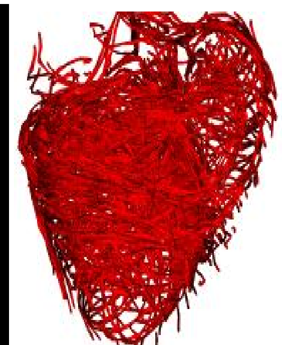
Complicated structure

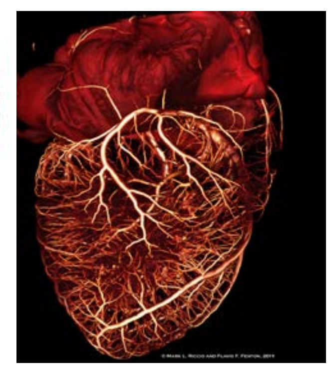
Canine heart: slices
(DTMRI @ 250 microns resolution)



Anatomy **Fibers** **Vessels**

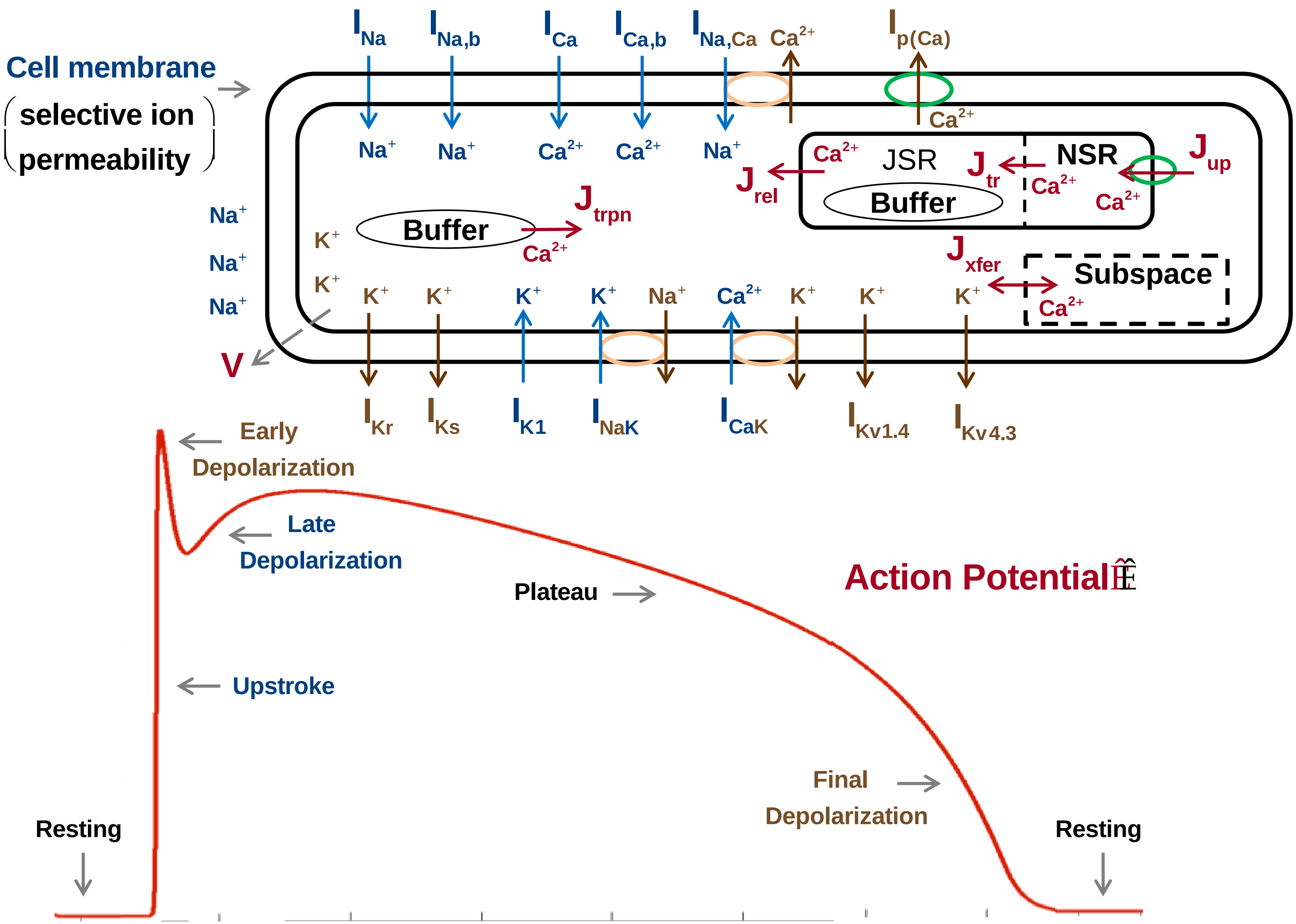




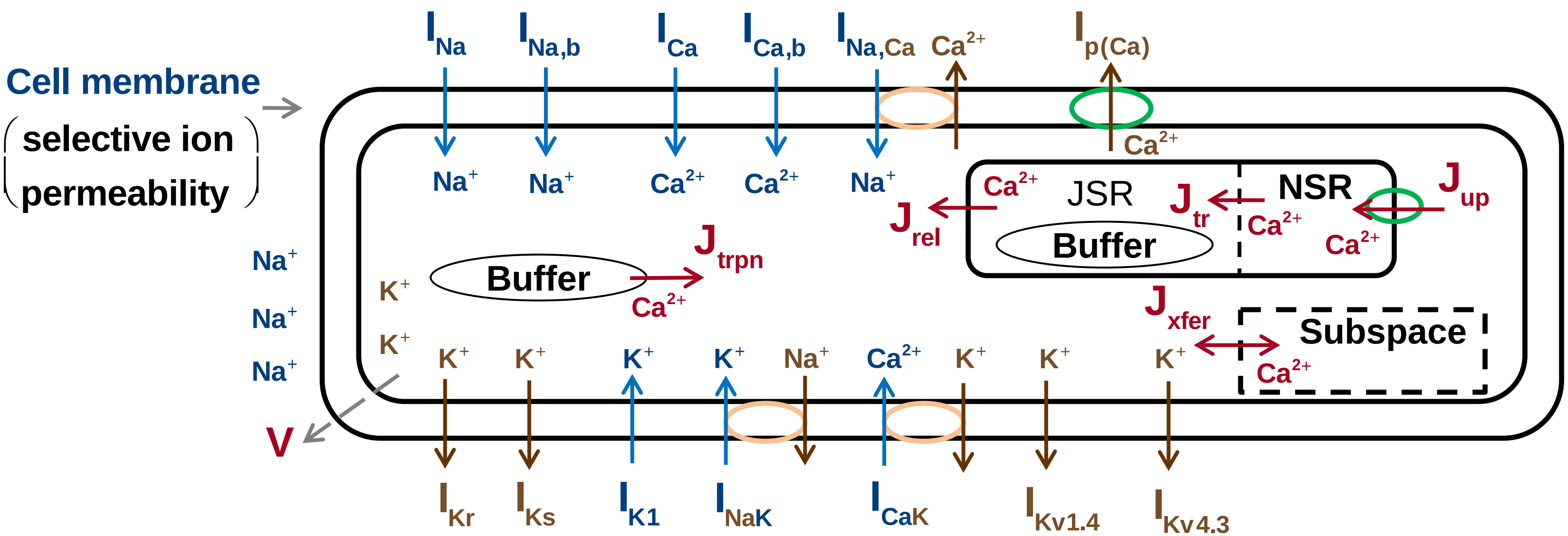


Pittsburgh NMR Center **MicroCT Cornell**

It is a Cellular Problem



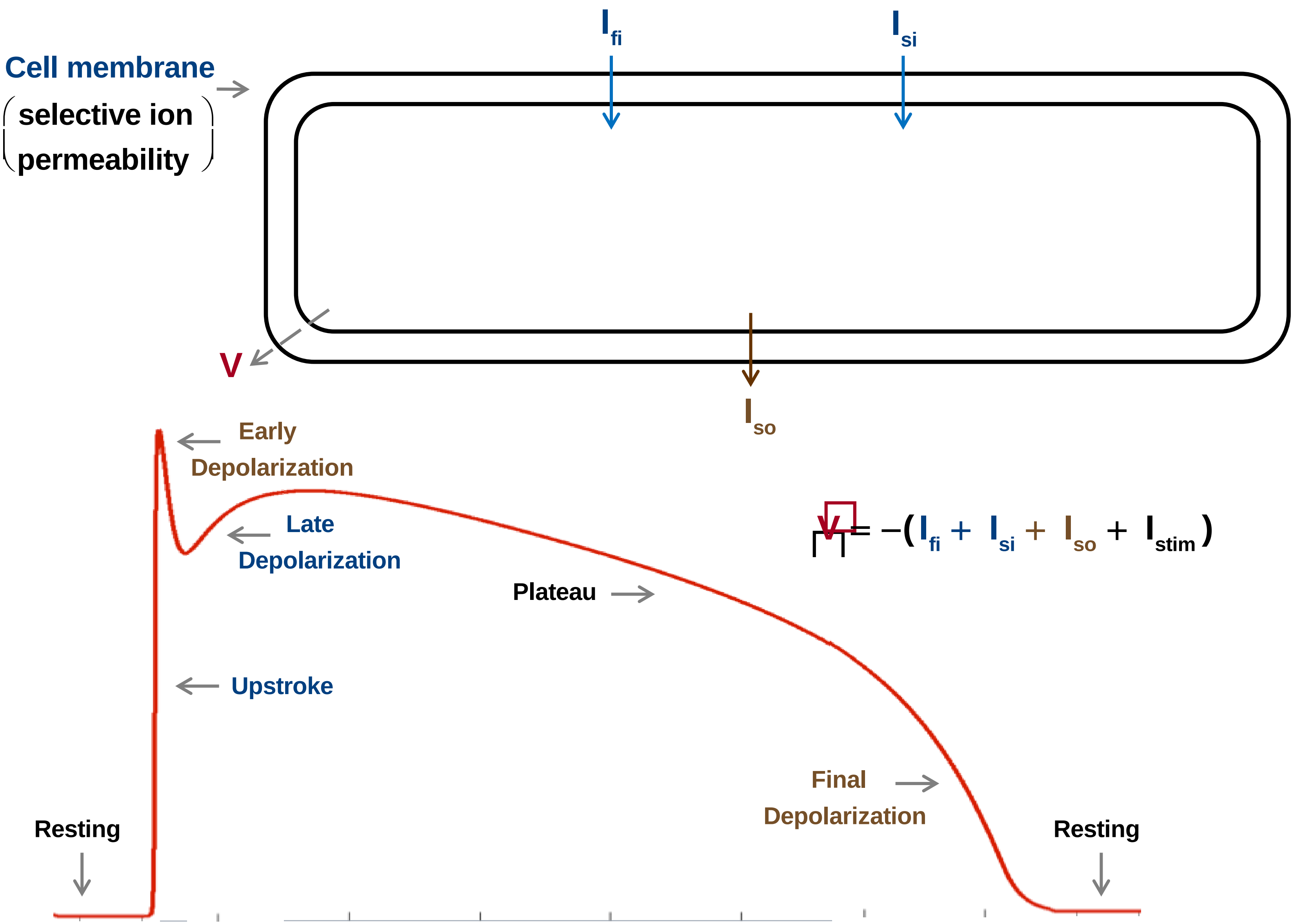
It is an Electrical Problem



$$\dot{V} = -(I_{Na} + I_{Ca} + I_{CaK} + I_{K1} + I_{NaCa} + I_{NaK} + I_{Cab} + I_{Nab} + I_{Kr} + I_{Ks} + I_{Kv1.4} + I_{Kv4.3} + I_{p(Ca)} + I_{stim})$$

- **Rate of change in membrane potential (V):**
  - **Sum of physiological currents due to ion flows across membrane**
- **Physiological detailed: 67 variables**
  - **Difficult to simulate and formally analyze**

It is a Cellular-Abstraction Problem

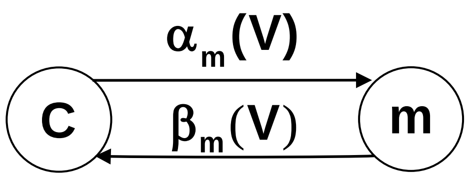


$$\dot{V} = -(I_{fi} + I_{si} + I_{so} + I_{stim})$$

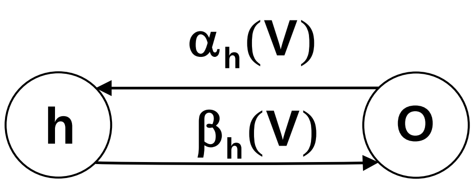
It is a Molecular Problem

$$I_{Na} = g_{Na}(V - V_{Na}) = \bar{g}_{Na} m^3 h (V - V_{Na})$$

Na Channel Conductance | **Nernst Potential** | **3 m-units, 1 h-unit**

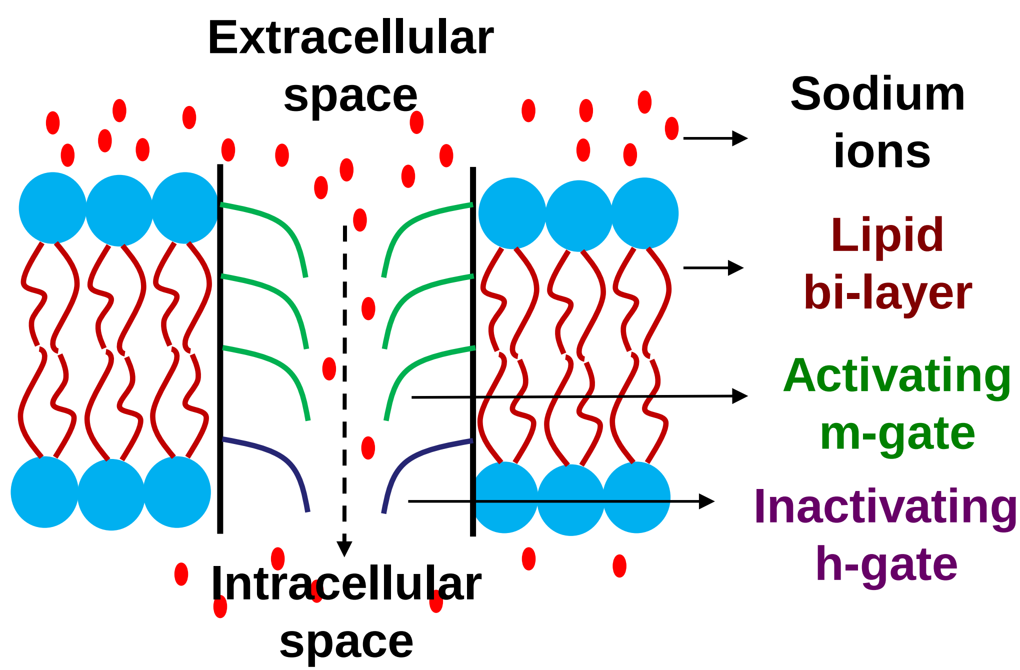


$$\dot{m} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

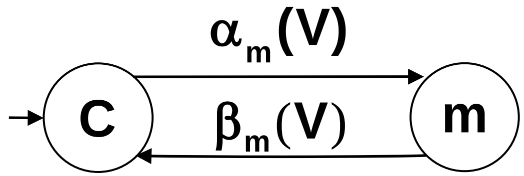


$$\dot{h} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

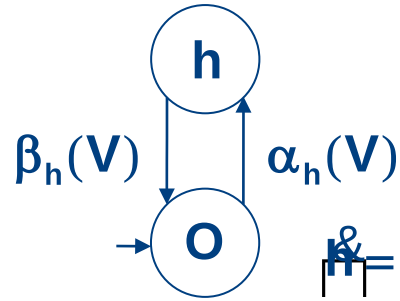
The Sodium Channel



It is a Molecular Abstraction Problem



$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$$

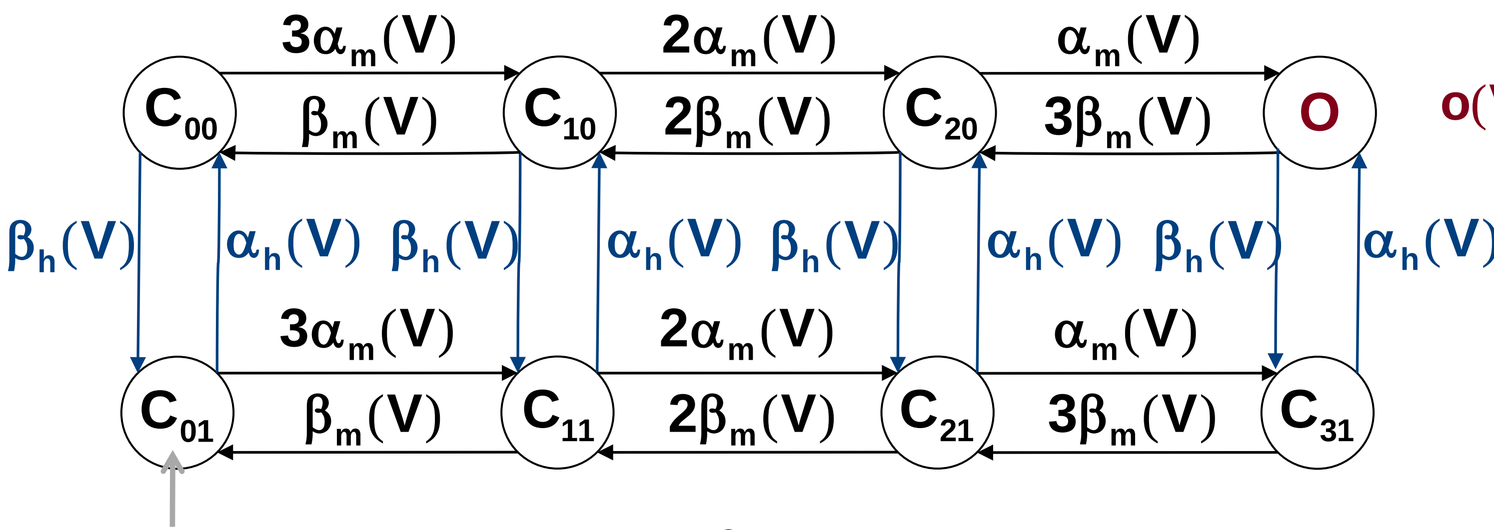


$$o(V) = m^3(V)h(V)$$

$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$$

Independence between units

Exact bisimulation: IMR



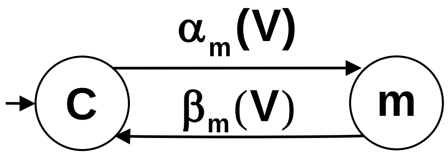
$$o(V) = O(V)$$

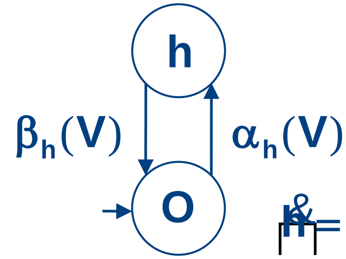
$$C_{01} = C_3^3(1-m)^3(1-h)$$

$$\dot{C}_{01} = -3\dot{m}(1-m)(1-h) - (1-m)^3\dot{h}$$

$$\dot{C}_{01} = -3\alpha_m C_{01} + \beta_m C_{11} - \alpha_h C_{01} + \beta_h C_{00}$$

It is a Molecular Abstraction Problem





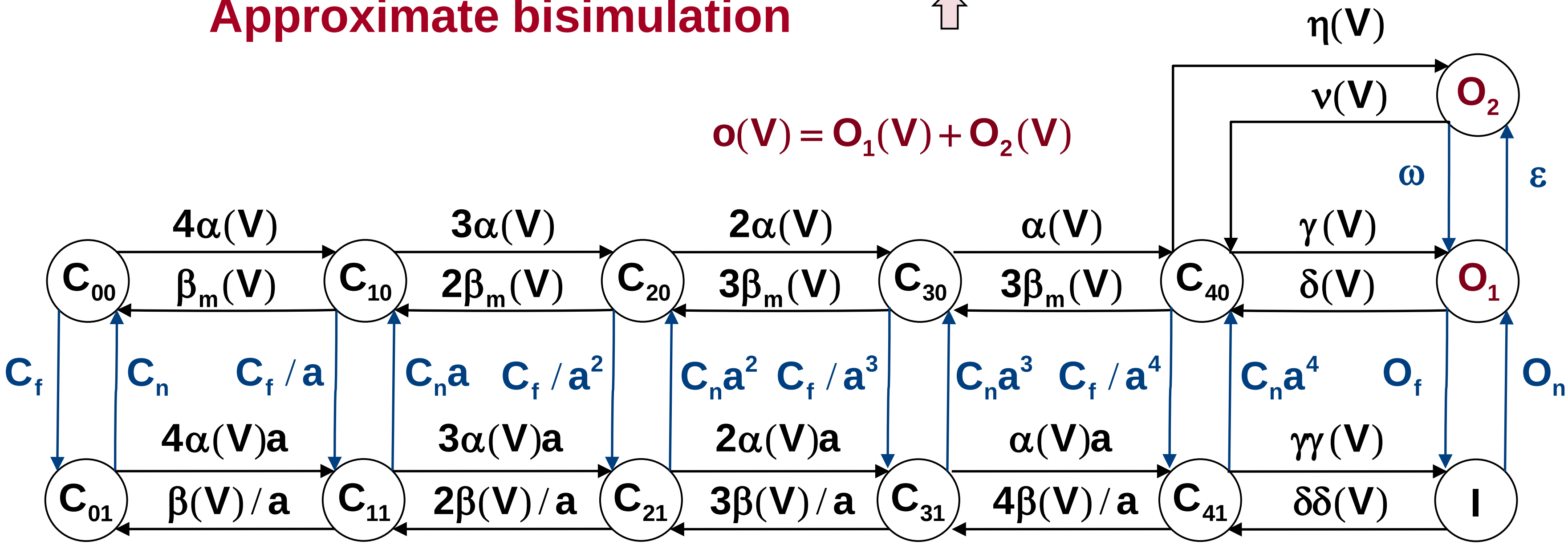
$o(V) = m^3(V)h(V)$

$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$

$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$

Approximate bisimulation

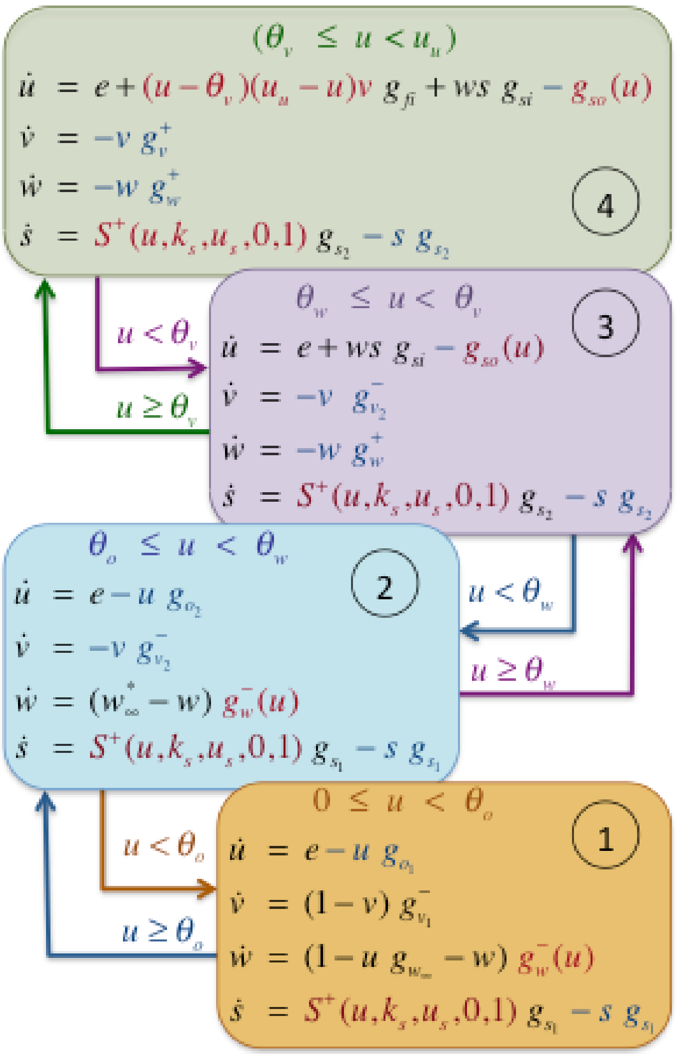
$o(V) = O_1(V) + O_2(V)$



These result will appear in **CMSB 2012**

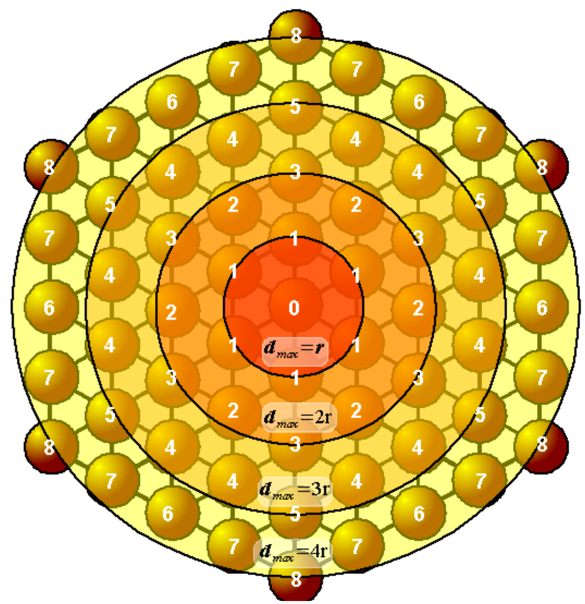
It is a Simulation Problem

Nonlinear Hybrid Automaton



2D/3D Simulation of Partial Differential Equations

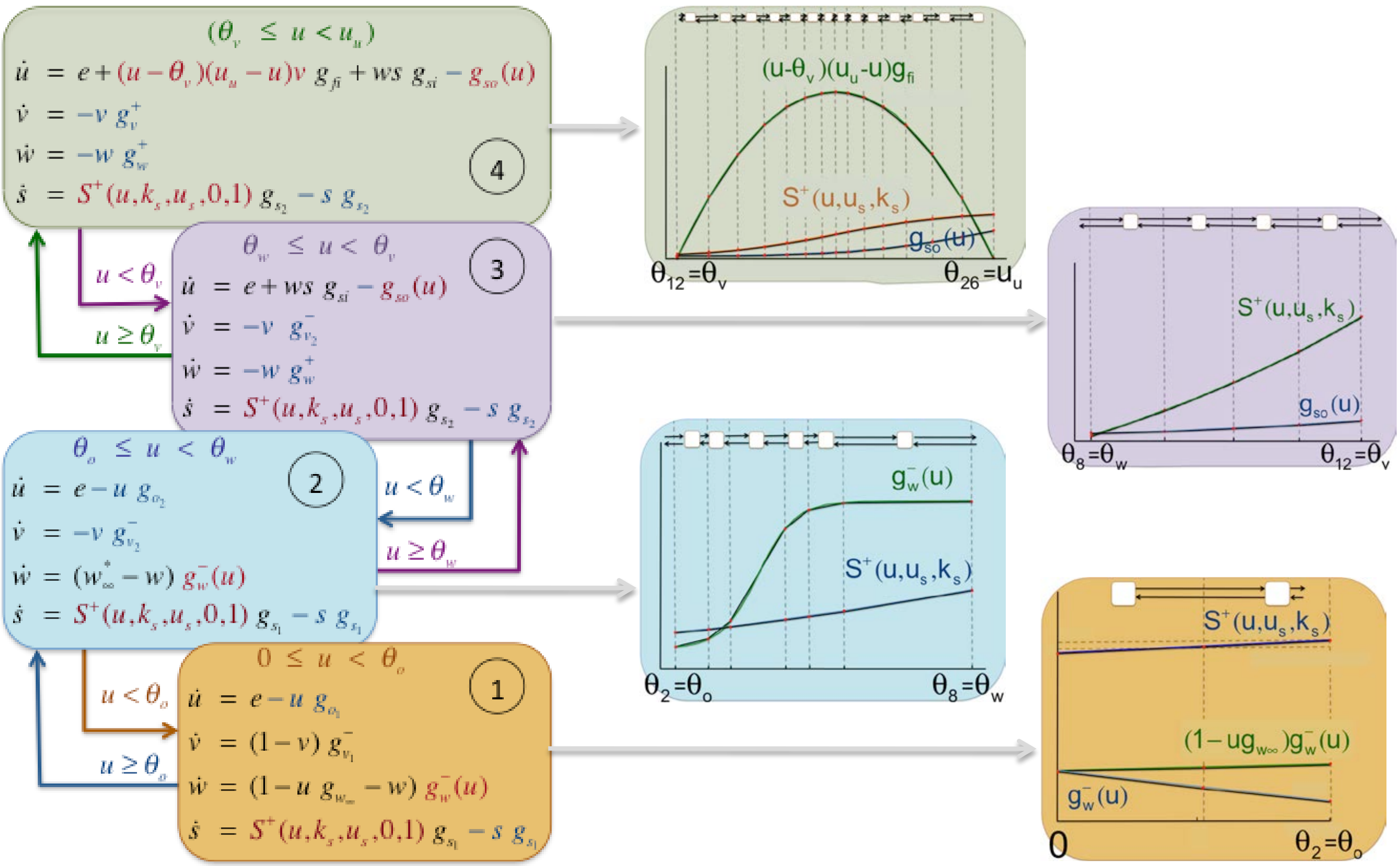
$$\dot{u} = \nabla(D\nabla u) - (J_{fi} + J_{si} + J_{so})$$



PDEs are simulated as Finite Difference Equations

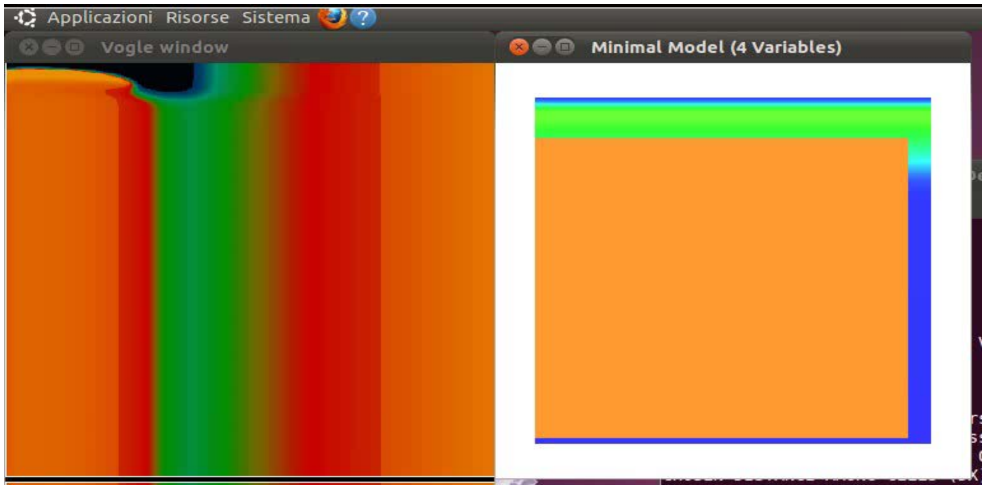
It is a Simulation Problem

Nonlinear Hybrid Automaton | **Optimal Linearization of Nonlinear Terms**

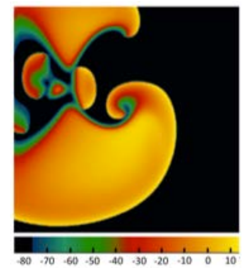


It is a Simulation Problem

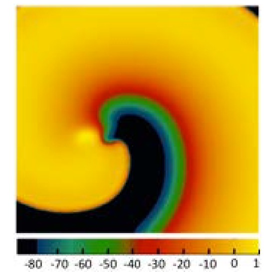
Minimal Model in Four State Variables (4V)



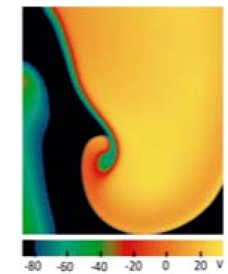
Beeler-Reuter (8 V)

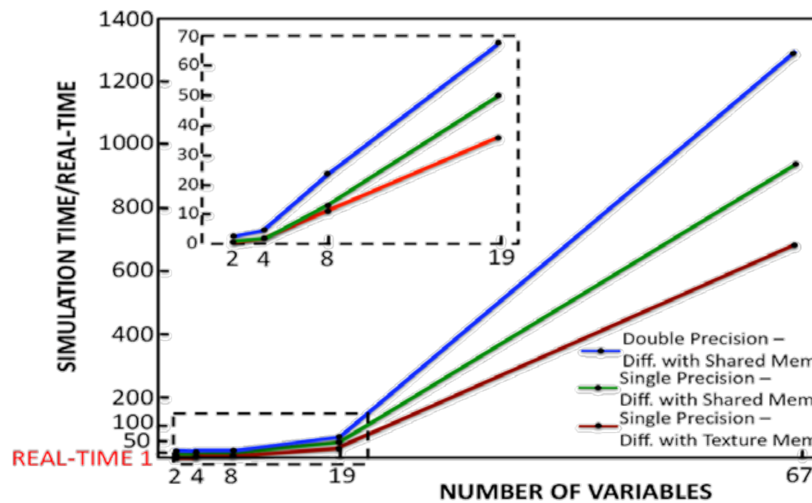


Ten-Tusscher-Panfilov (19V)

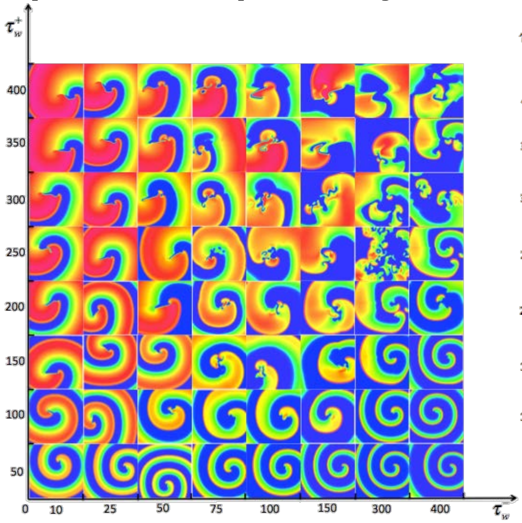


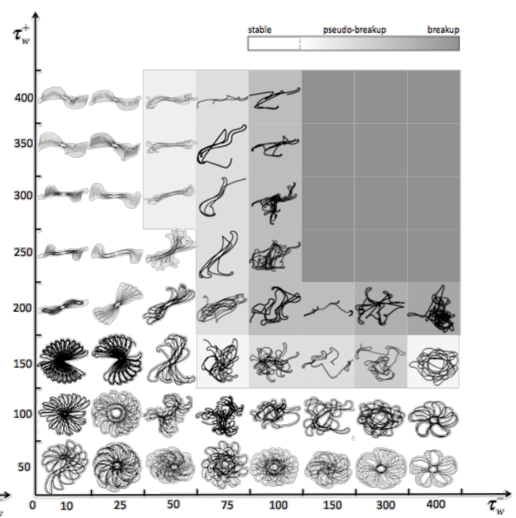
Iyer (67 V)





Spirals Computed by Students at CMACS Workshop





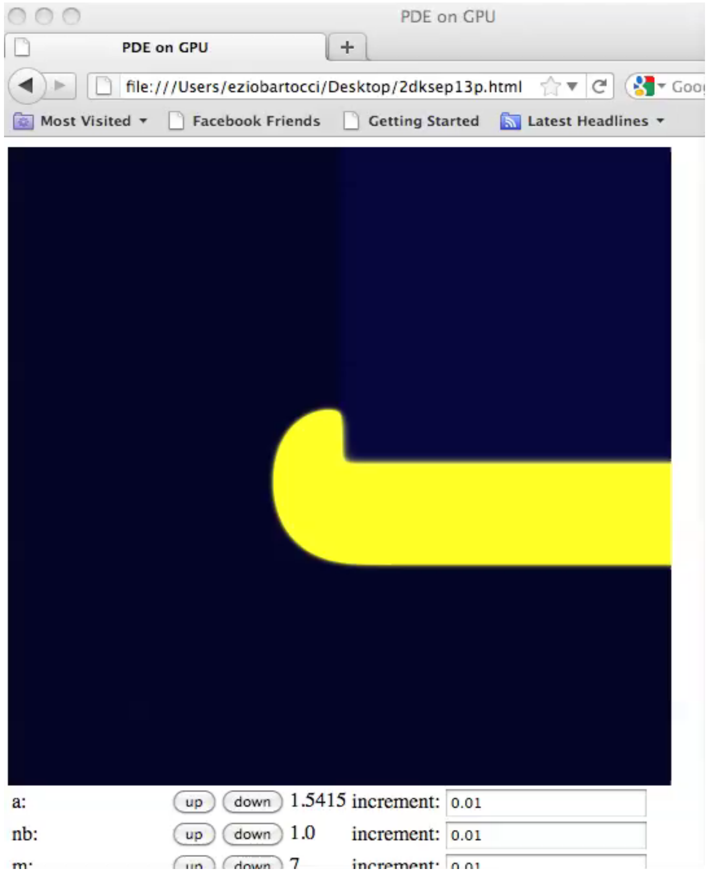
These results appeared this year in

CMSB 2011, pages 103-110, ACM, 2011

Advances in Physiology Education 35: 1-11, 2011

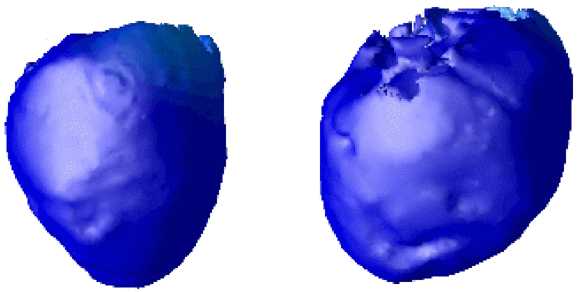
It is a Simulation Problem

Web Graphics Language (Fenton-Karma 2V)

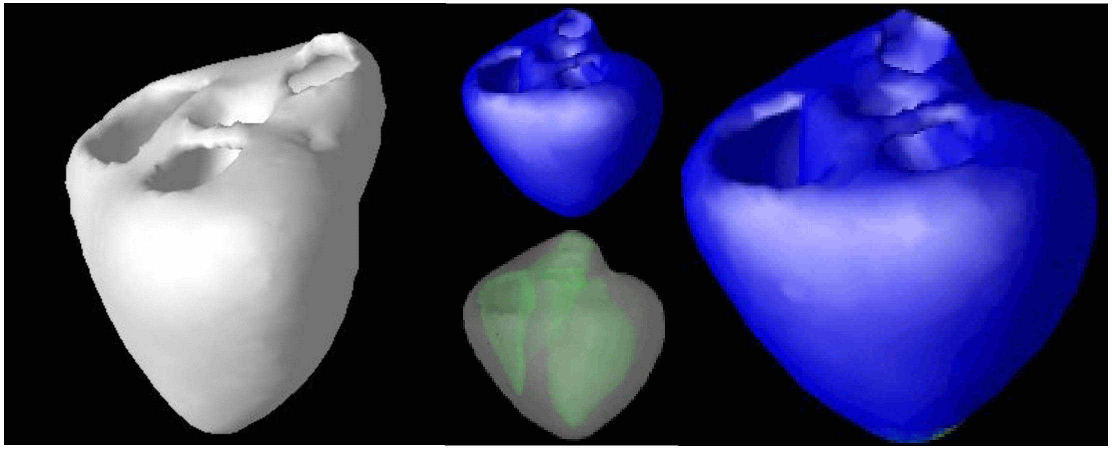


Runs in your Browser and Uses your own GPU

3D Model of a Mouse Heart (Fenton-Karma 3V Model)

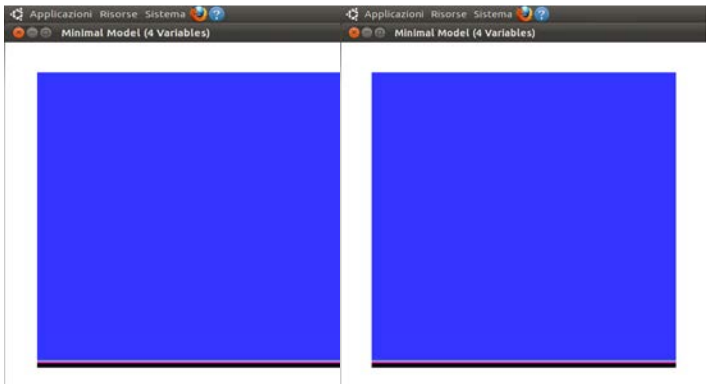


3D Model of a Pig Heart (Fenton-Karma 3V Model)



It is a Verification Problem

Spiral Wave Induced by Unexcitable Myocytes

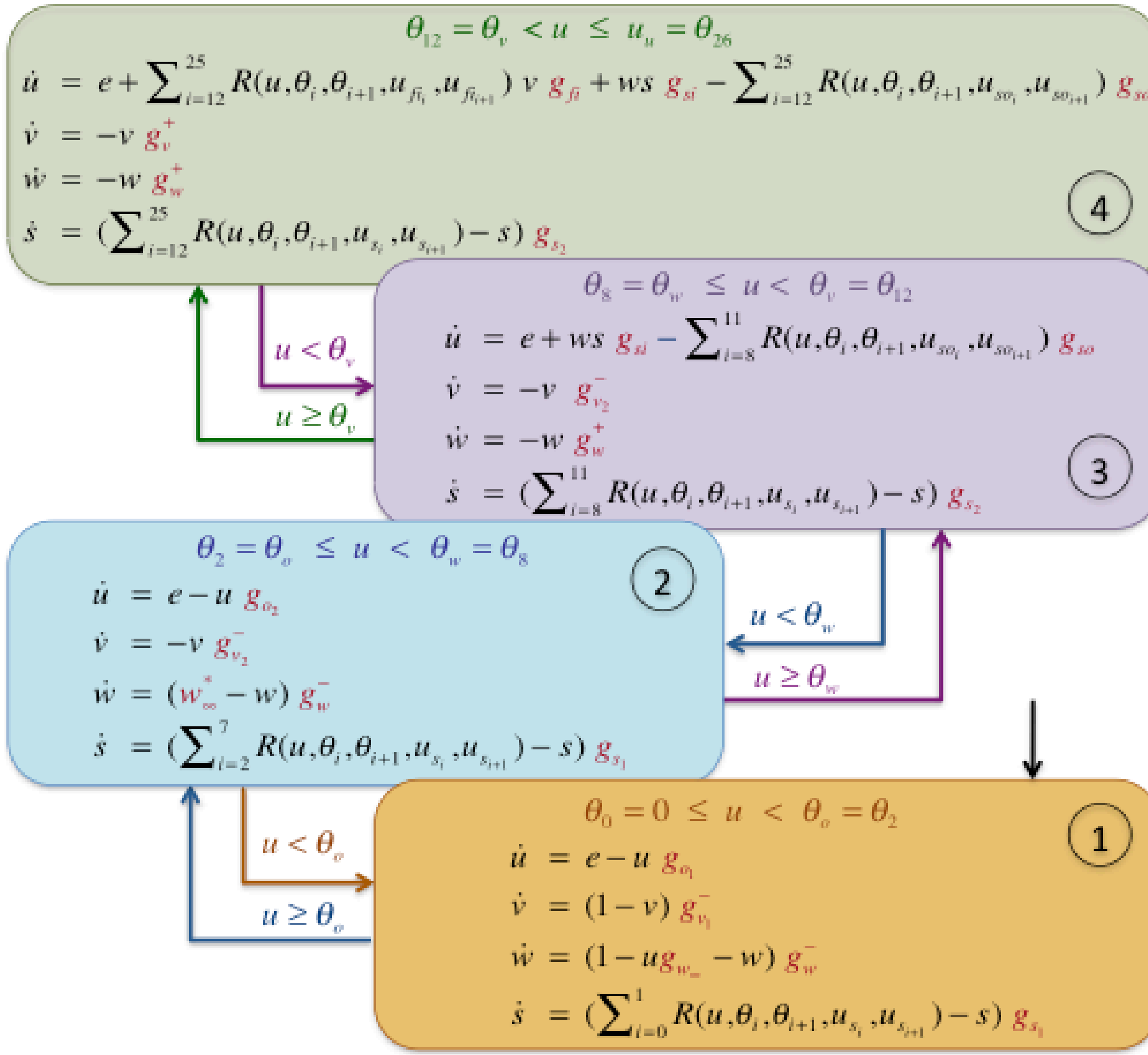


Property to Check

$$G(u < \theta_v)$$

Uncertain Parameters

$$g_{o_1} \in [0,180], \quad g_{o_2} \in [0,10]$$
$$g_{si} \in [0.1,100], \quad g_{so} \in [0.9,50]$$

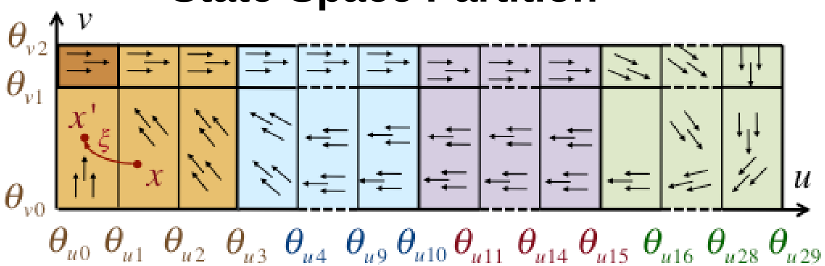


It is a Verification Problem

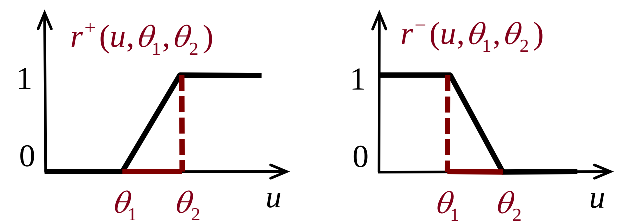
Genetic regulatory network with Parameters *κ,γ*

$$\dot{x}_i = f_i(x,p) = \sum_{j \in P_i} \kappa_{ij} r_{ij}(x) - \sum_{j \in D_i} \gamma_{ij} r_{ij}(x) x_i$$

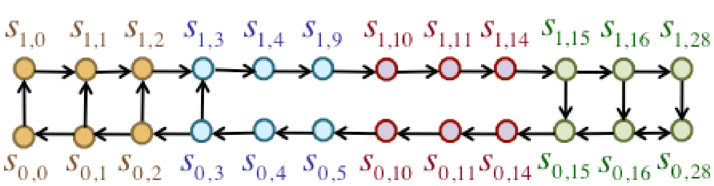
State-Space Partition



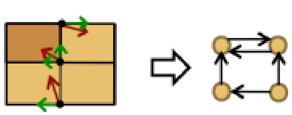
Ramps



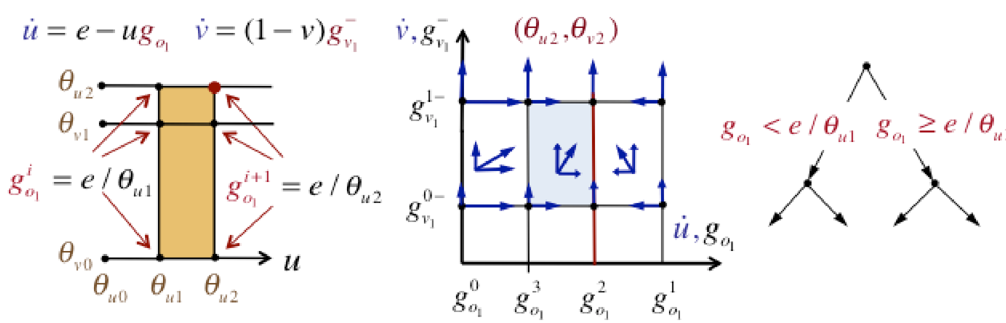
Kripke Structure for Fixed Parameters



Computation of transitions:
By examining corner flows



Parameter-Space Partition



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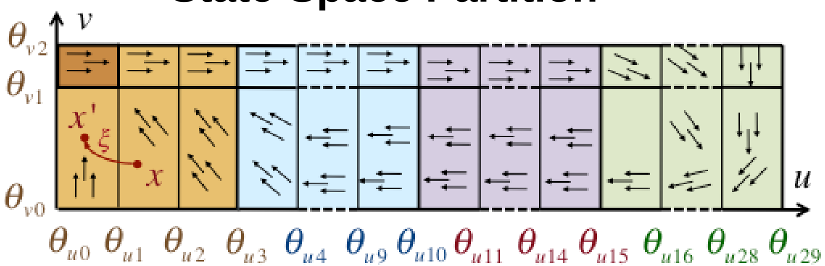
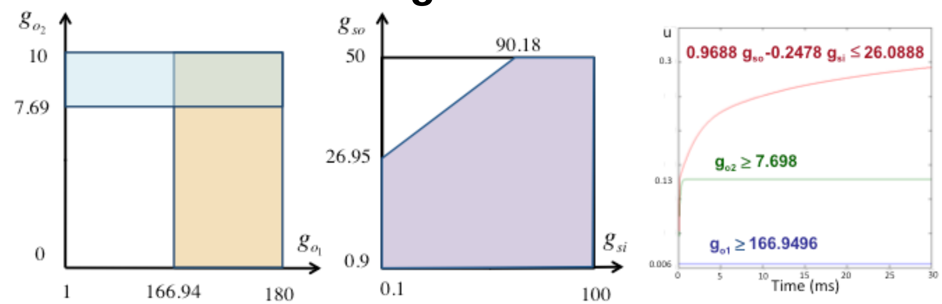
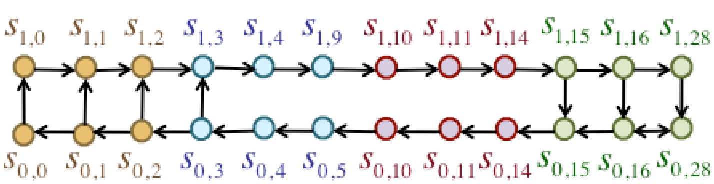
State-Space Partition



Parameter-Range Identification Results



Kripke Structure for Fixed Parameters



Computation of transitions:
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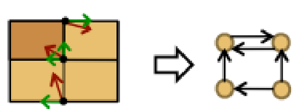
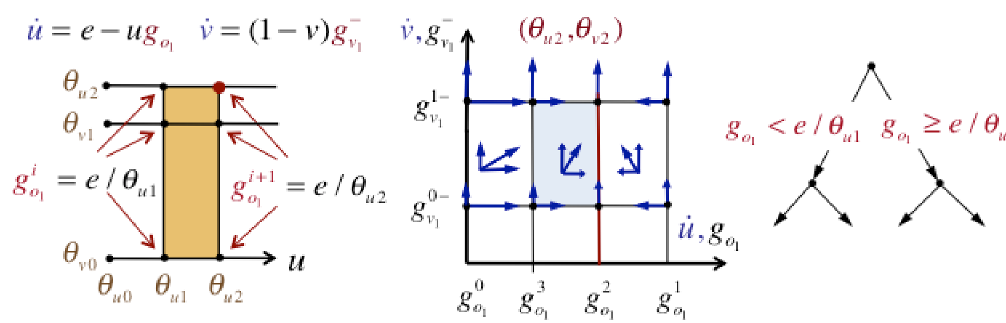
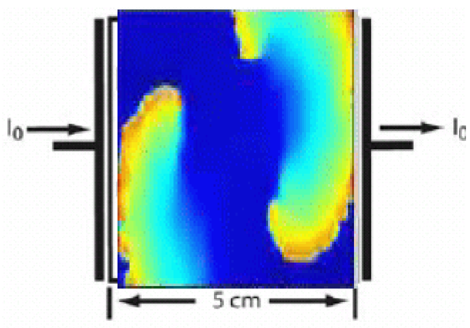


Parameter-Space Partition



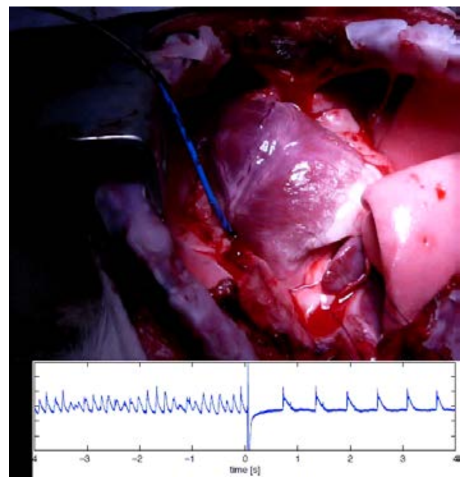
These results appeared in CAV 2011, LNCS 6806, pp. 396-411, 2011.

It is a Control Problem

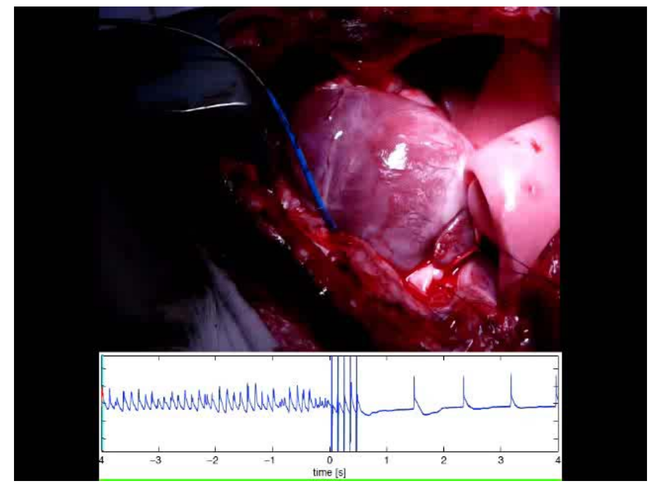


Computer simulation

1 Shock



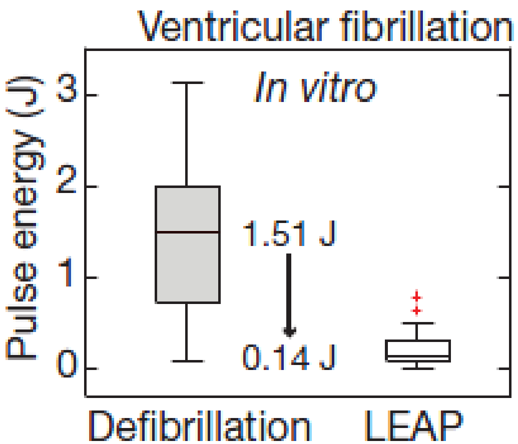
5 Low Energy Shocks

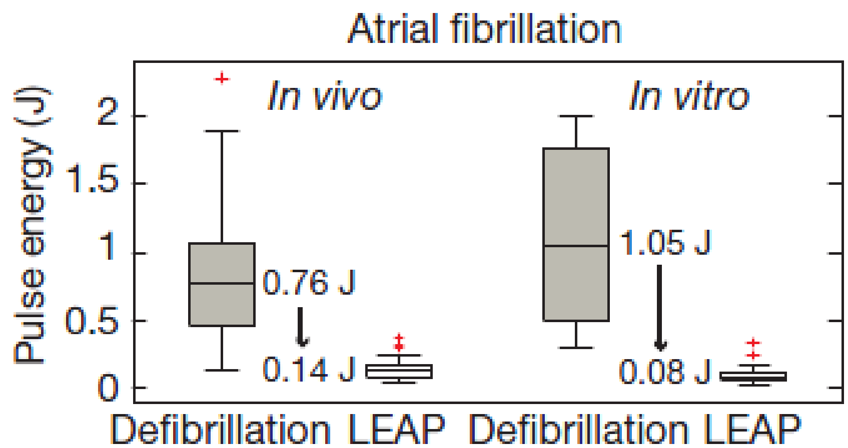


Defibrillation with 90% energy reduction

It is a Control Problem

Low Energy Defibrillation (LEAP) tested for Canine Hearts





For Both AF and VF we have found successful defibrillation with LEAP using about10% of the energy required by the standard 1 shock defibrillation protocol

Furthermore, using high resolution mCT We obtained detail vessel distribution of the heart and found a scaling law which was used to obtain a theory that explains the mechanism behind LEAP.

These results appeared this year in Nature, Jul 13 475(7355):235-9; 2011

It is a CPS Problem

We are on the brink of a paradigm shift in the Diagnosis and treatment of cardiac disorders

It is up to us in to make it happen!