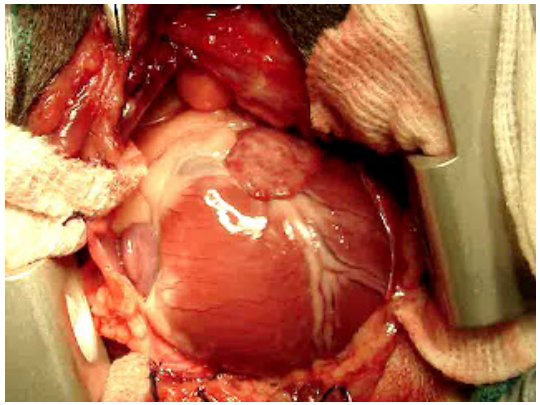
Controlling the Human Heart: Challenges and Opportunities

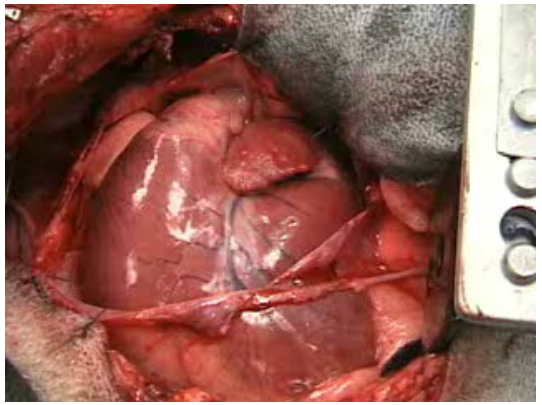
Radu Grosu

Stony Brook University
Vienna University of Technology

CPS: Electro-Mechanical Pump



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?

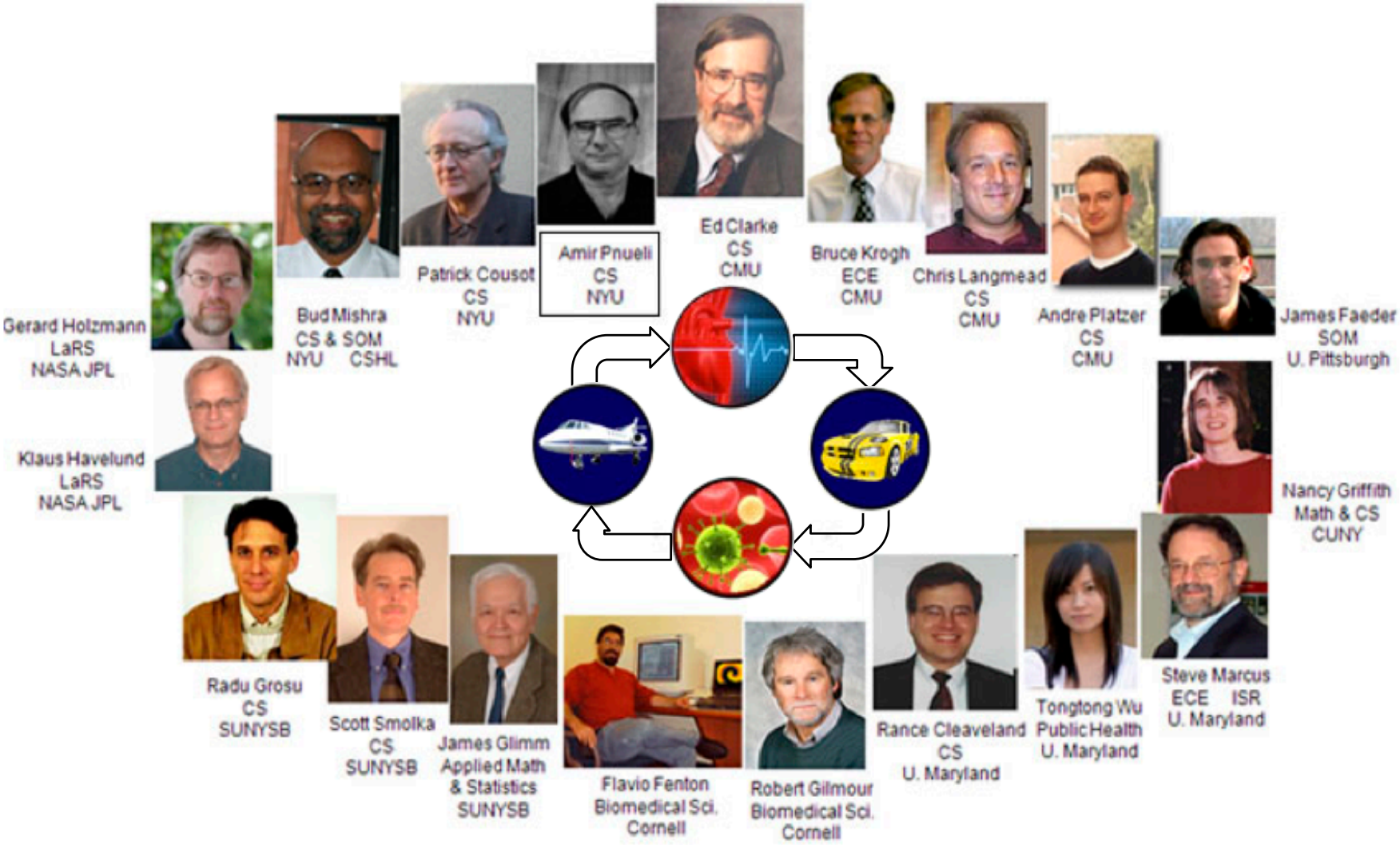
Given a disorder-specification and a model of the ventricle:

- 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?

CMACS: Multi-Institutional, -Disciplinary Team

7 Universities, 2 Colleges, 14 Departments/Schools



CMACS Atrial-Fibrillation Team

James Glimm
Stony Brook

Scott Smolka
Stony Brook

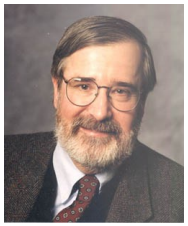
Radu Grosu
Stony Brook

Ezio Bartocci
Stony Brook

Abhishek Murthy
Stony Brook

Ariful Islam
Stony Brook

Sicun Gao
CMU



Edmund Clarke
CMU

Impossible Without
An Expeditions Project

Robert Gilmour
Cornell

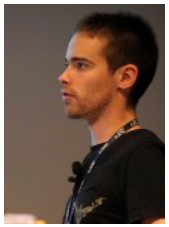
Flavio Fenton
Cornell

Elizabeth Cherry
Cornell

Gerard Holzmann
NASA

Klaus Havelund
NASA

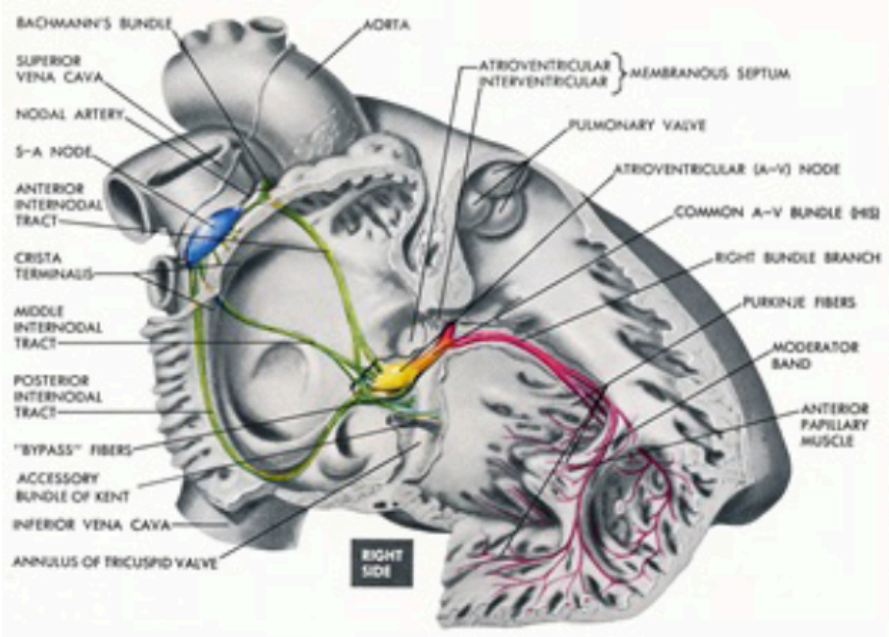
Nancy Griffeth
CUNY

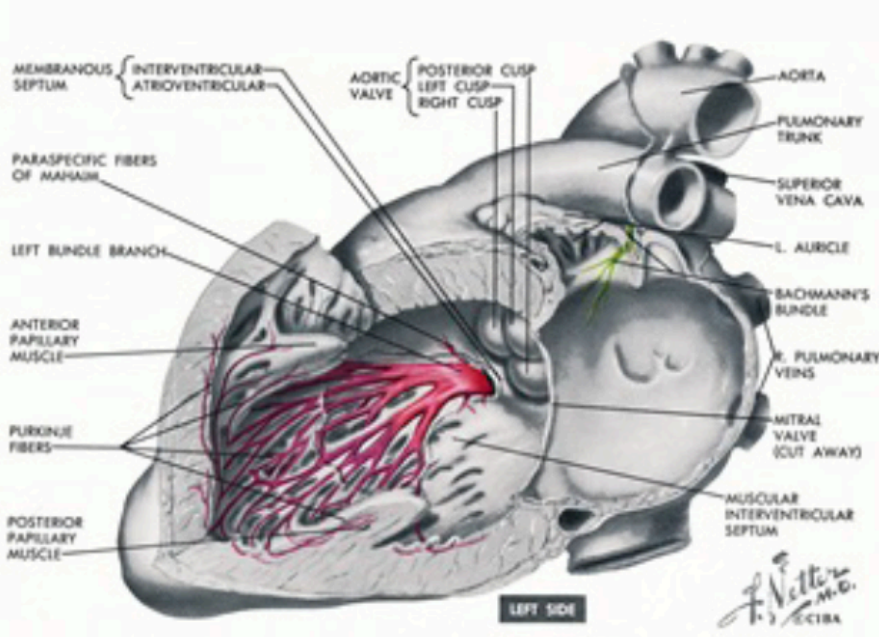


Colas Le Guernic
NYU

Patrick Cousot
NYU

It is a Communication-Structure Problem



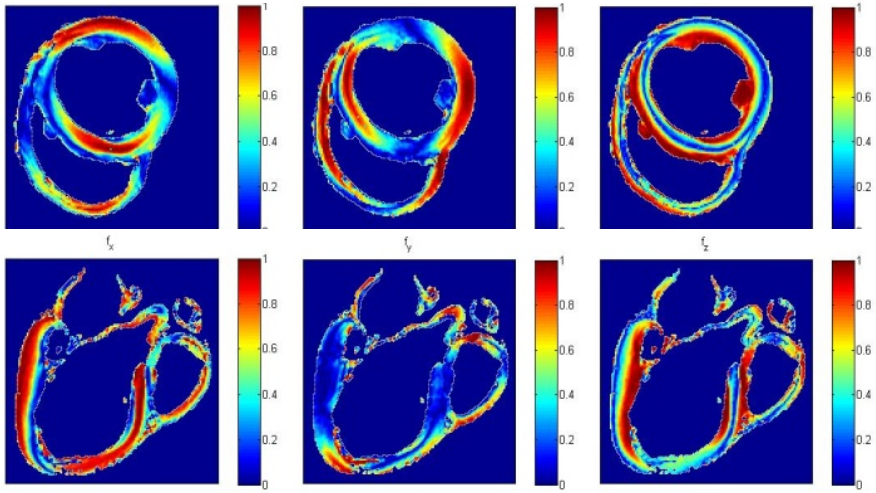


4 billion nodes interconnected in a very sophysticated way!

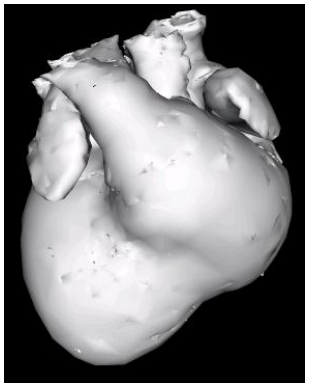
It is a Communication-Structure Problem

Complicated structure

Canine heart: slices
(DTMRI @ 250 microns resolution)



Anatomy



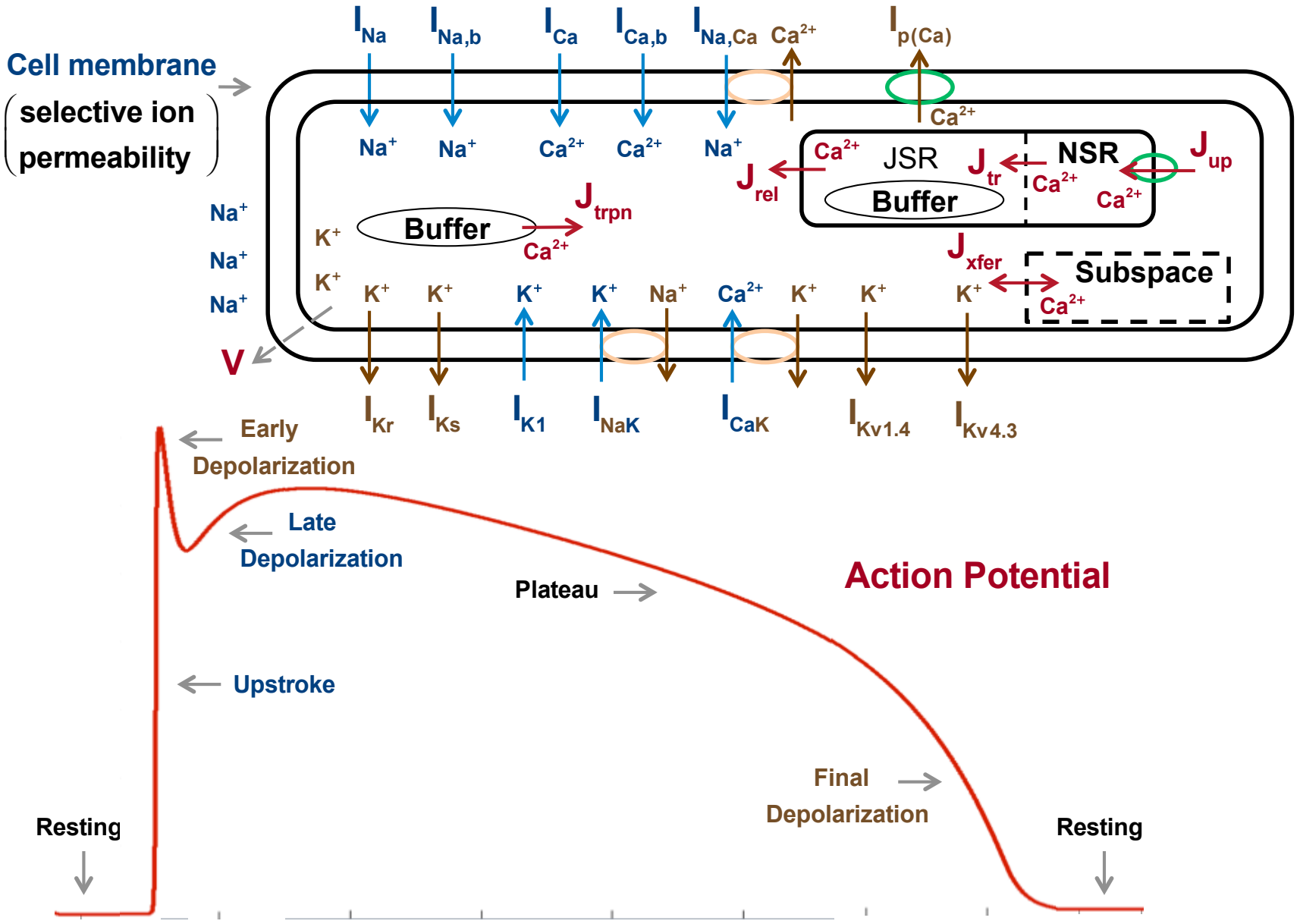
Fibers

Vessels

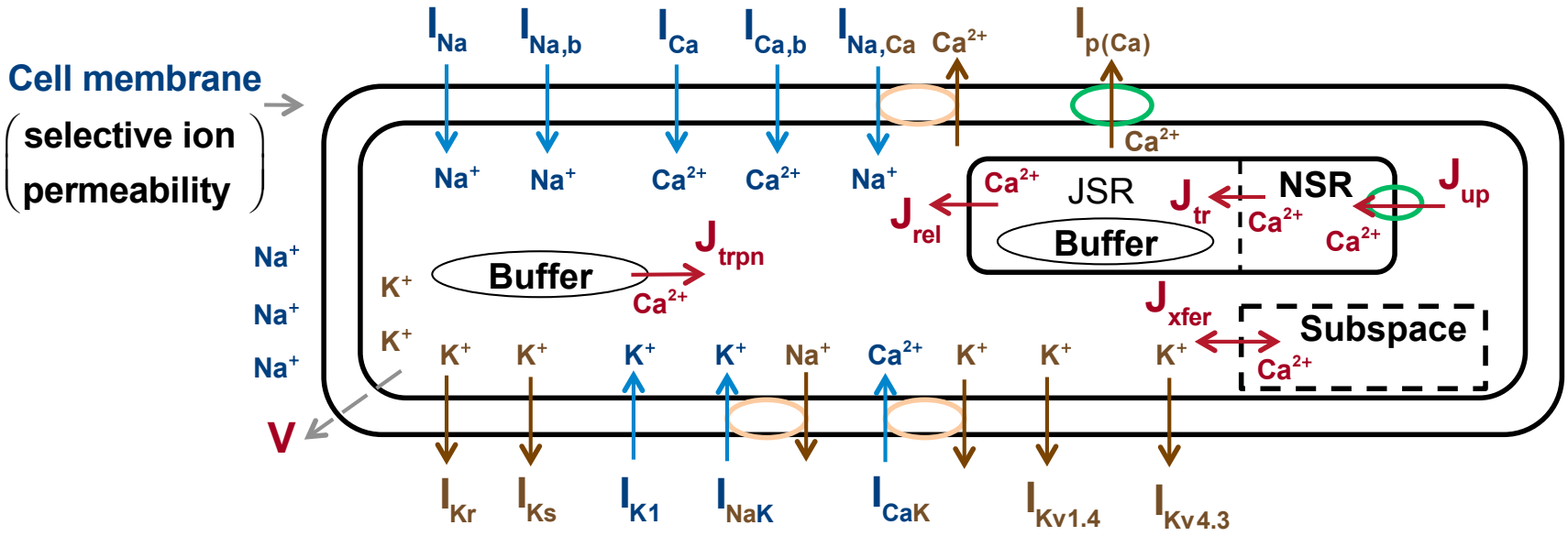
Pittsburgh NMR Center

MicroCT Cornell

It is a Cellular Problem



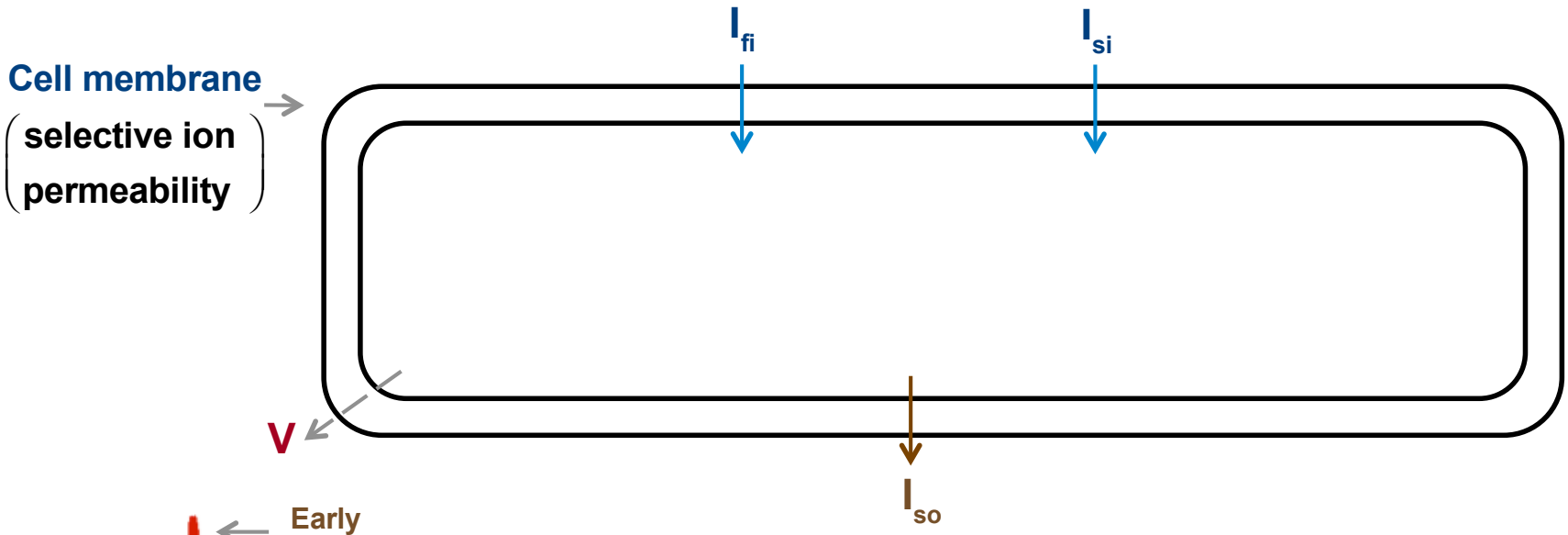
It is an Electrical Problem

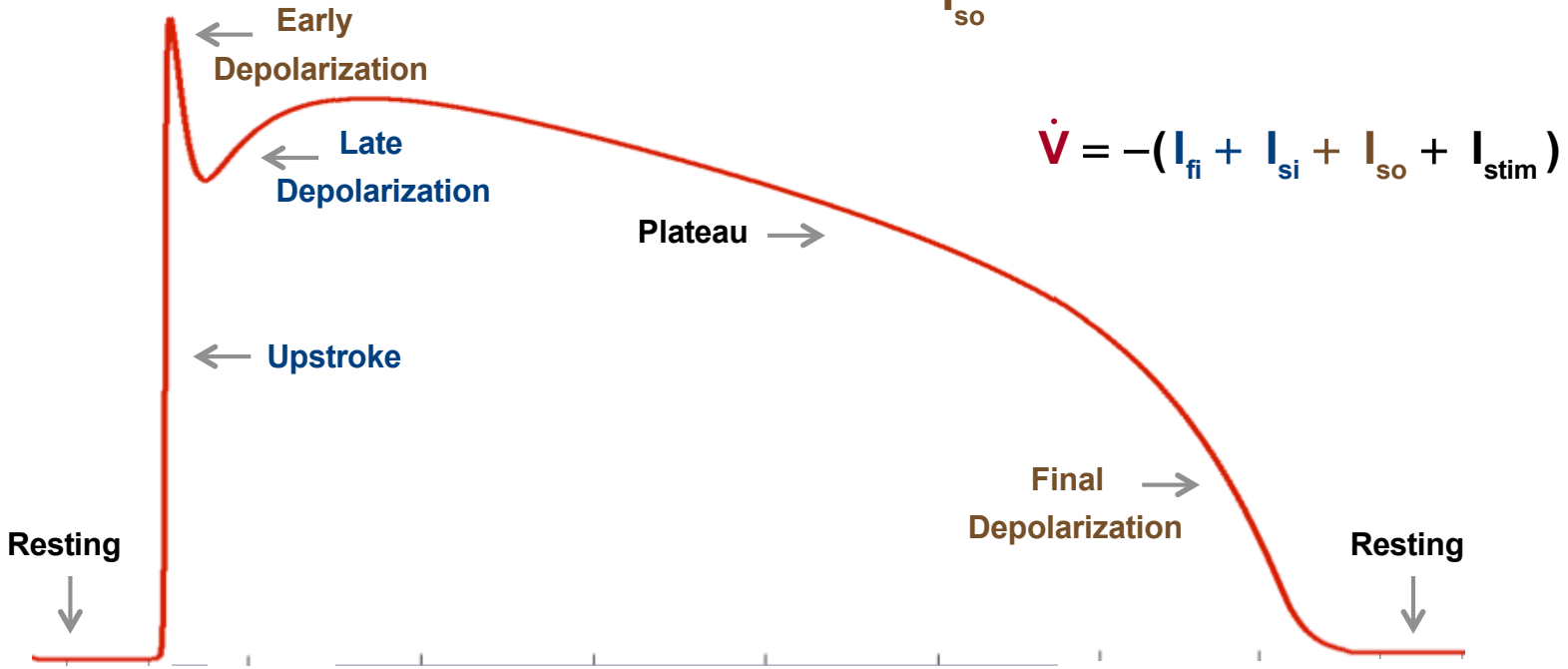


$$\dot{V} = -(I_{Na} + I_{Ca} + I_{CaK} + I_{K1} + I_{NaCa} + I_{NaK} + I_{Cab} + I_{Nab} + I_{Kr} + I_{Ks} + I_{Kv1.4} + I_{Kv4.3} + I_{p(Ca)} + I_{stim})$$

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

It is a Cellular-Abstraction Problem





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

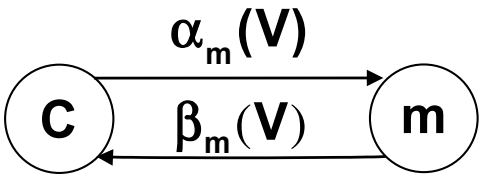
It is a Molecular Problem

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

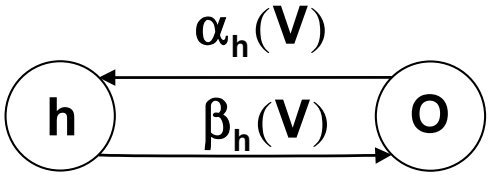
Na Channel Conductance

Nernst Potential

3 m-units 1 h-unit

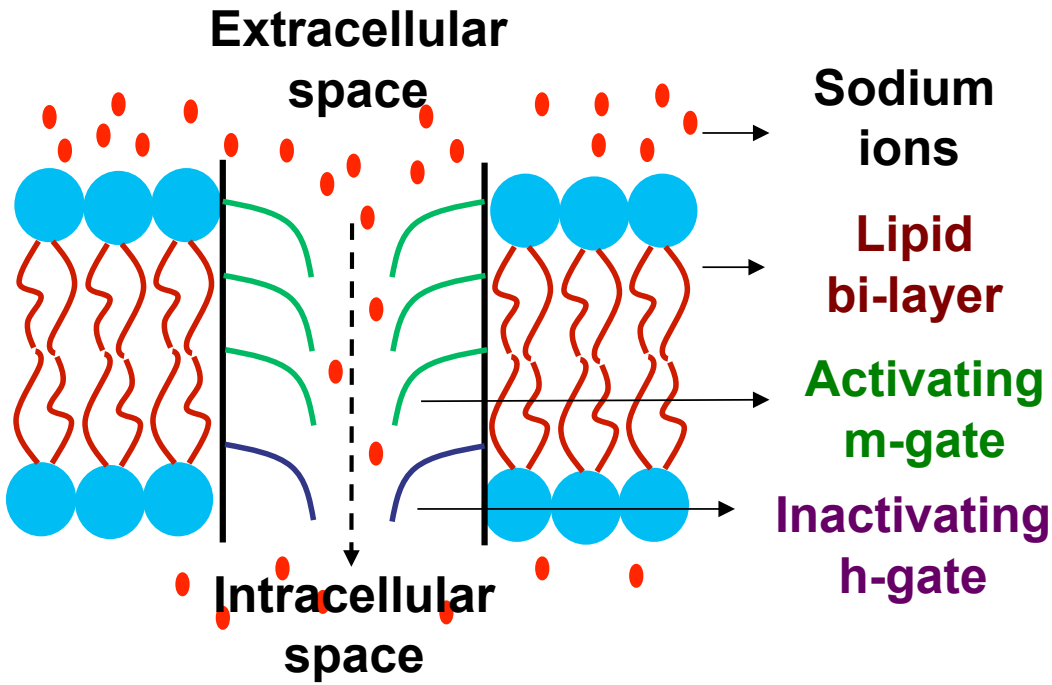


$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$$

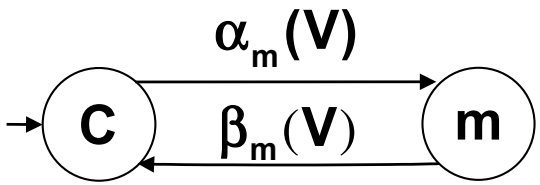


$$\dot{h} = \alpha_h(V)(1-h) - \beta_h(V)h$$

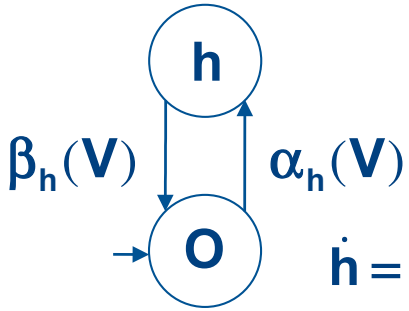
The Sodium Channel



It is a Molecular Abstraction Problem



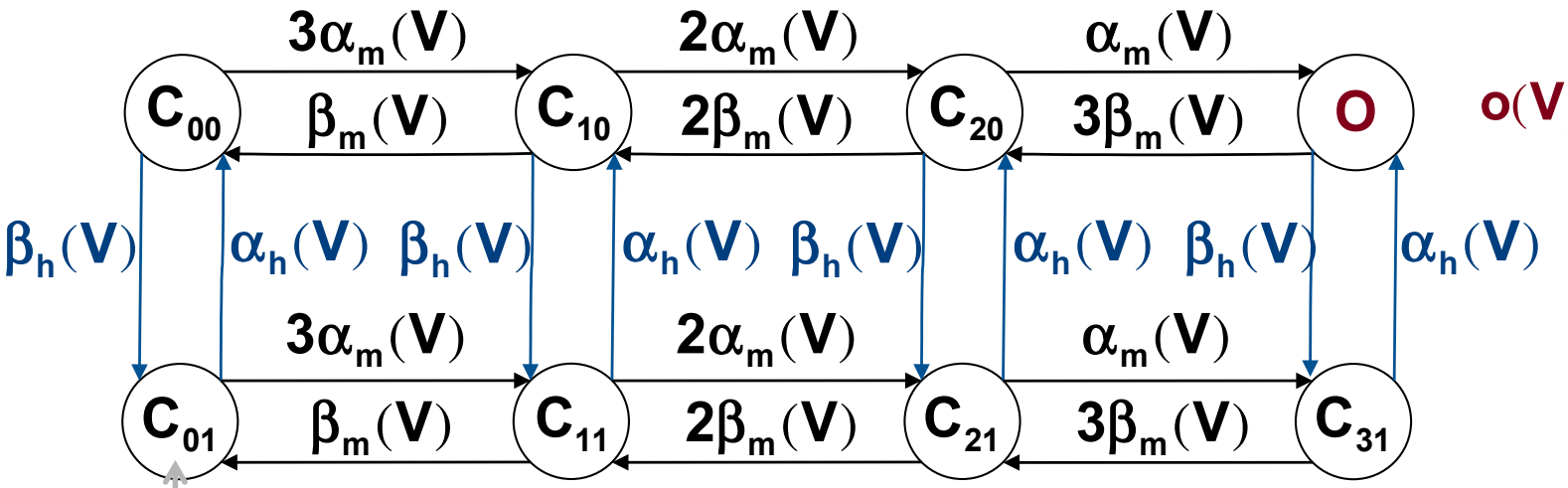
$$\dot{m} = \alpha_m(V)(1-m) - \beta_m(V)m$$



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

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

Independence between units ⇧ **Exact bisimulation: IMR**



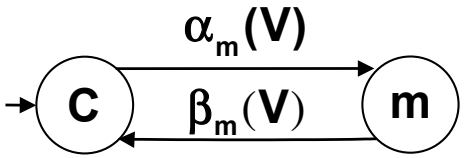
$$o(V) = O(V)$$

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

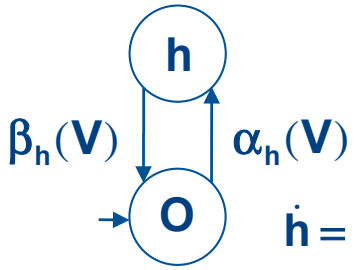
$$\dot{C}_{01} = -3\dot{m}(1-m)(1-h) - (1-m)^3\dot{h}$$

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

It is a Molecular Abstraction Problem



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

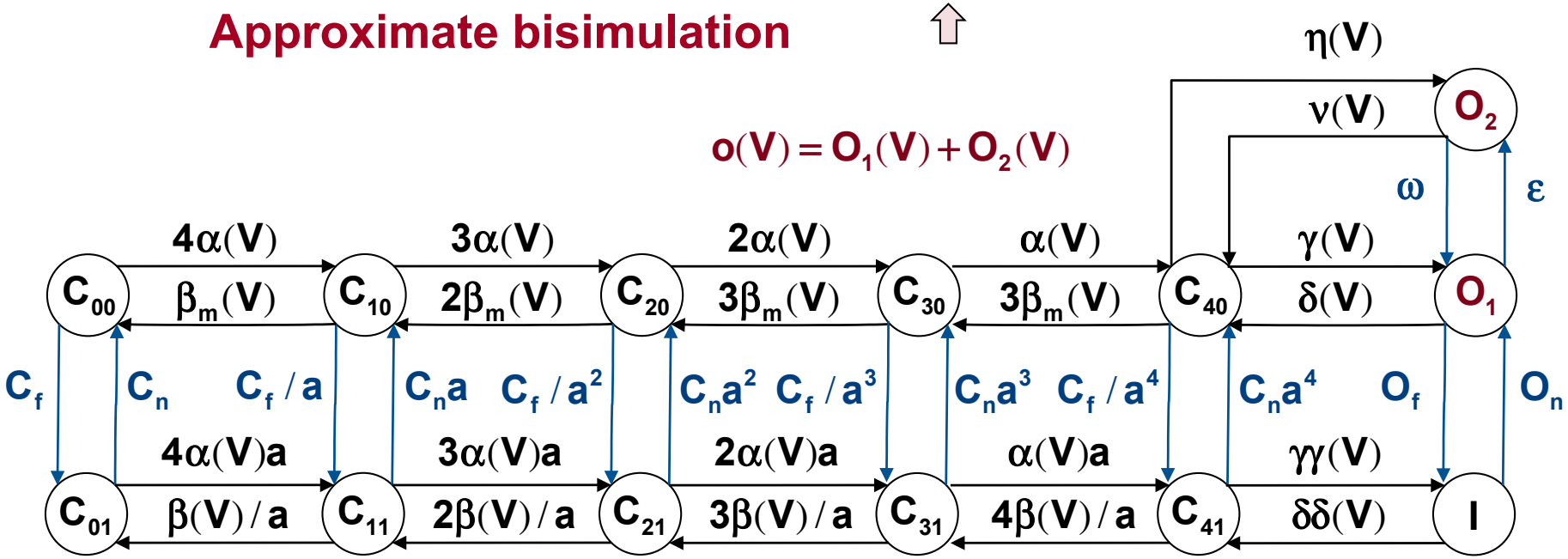


$$o(V) = m^3(V)h(V)$$

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

Approximate bisimulation ⇧

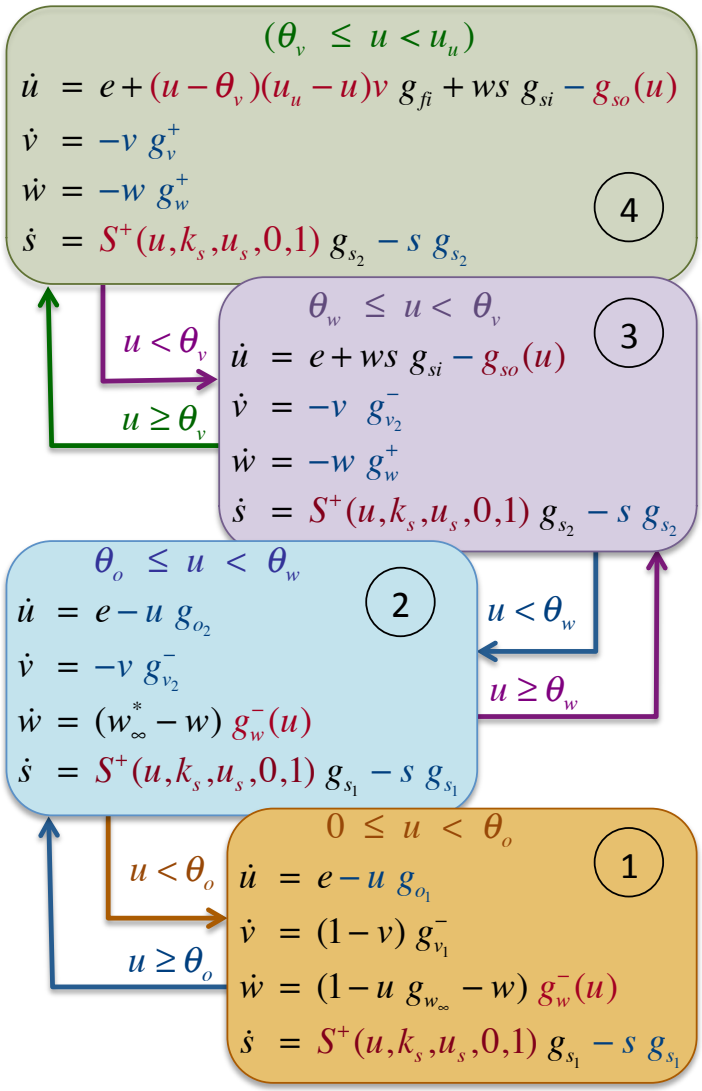
$$o(V) = O_1(V) + O_2(V)$$



These result appeared in **CMSB 2012**

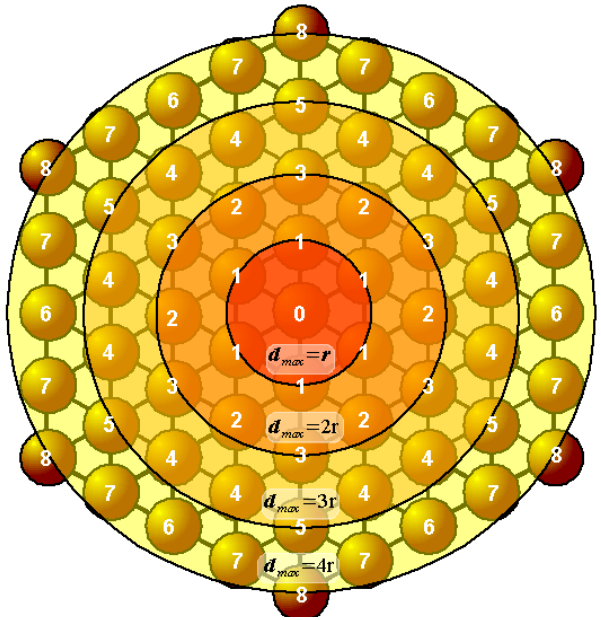
It is a Simulation Problem

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

$(\theta_v \le u < u_u)$

$\dot{u} = e + (u-\theta_v)(u_u-u)v\, g_{fi} + ws\, g_{si} - g_{so}(u)$

$\dot{v} = -v\, g_v^+$

$\dot{w} = -w\, g_w^+$

$\dot{s} = S^+(u,k_s,u_s,0,1)\, g_{s_2} - s\, g_{s_2}$

4

$u < \theta_v$

$u \ge \theta_v$

$\theta_w \le u < \theta_v$

$\dot{u} = e + ws\, g_{si} - g_{so}(u)$

$\dot{v} = -v\, g_{v_2}^-$

$\dot{w} = -w\, g_w^+$

$\dot{s} = S^+(u,k_s,u_s,0,1)\, g_{s_2} - s\, g_{s_2}$

3

$u < \theta_w$

$u \ge \theta_w$

$\theta_o \le u < \theta_w$

$\dot{u} = e - u\, g_{o_2}$

$\dot{v} = -v\, g_{v_2}^-$

$\dot{w} = (w_\infty^* - w)\, g_w^-(u)$

$\dot{s} = S^+(u,k_s,u_s,0,1)\, g_{s_1} - s\, g_{s_1}$

2

$u < \theta_o$

$u \ge \theta_o$

$0 \le u < \theta_o$

$\dot{u} = e - u\, g_{o_1}$

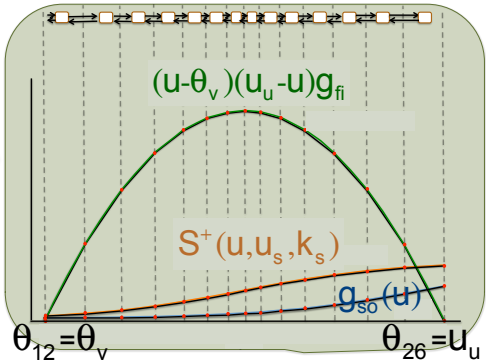
$\dot{v} = (1-v)\, g_{v_1}^-$

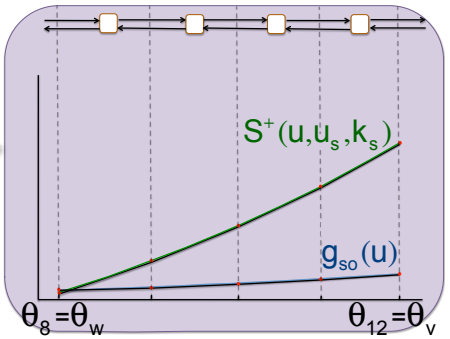
$\dot{w} = (1 - u\, g_{w_\infty} - w)\, g_w^-(u)$

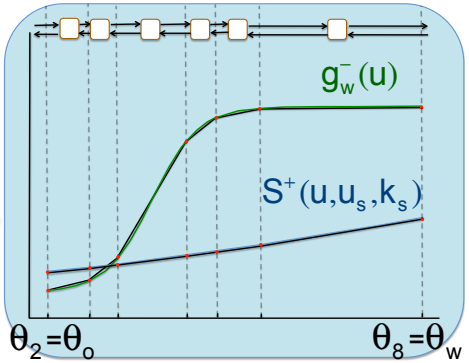
$\dot{s} = S^+(u,k_s,u_s,0,1)\, g_{s_1} - s\, g_{s_1}$

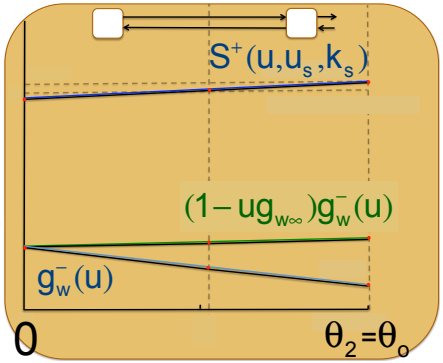
1

Optimal Linearization of Nonlinear Terms



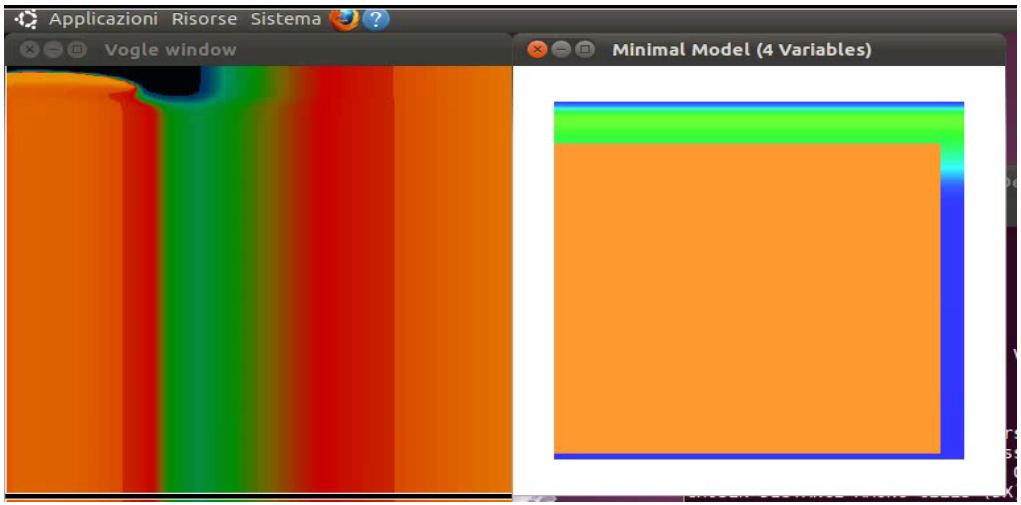




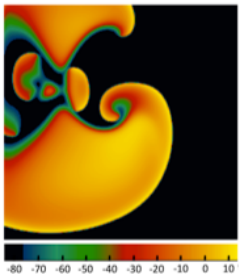


It is a Simulation Problem

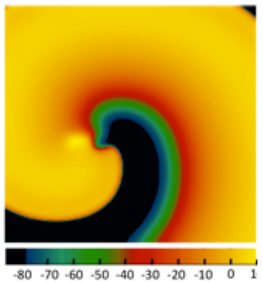
Minimal Model in Four State Variables (4V)



Beeler-Reuter (8 V)

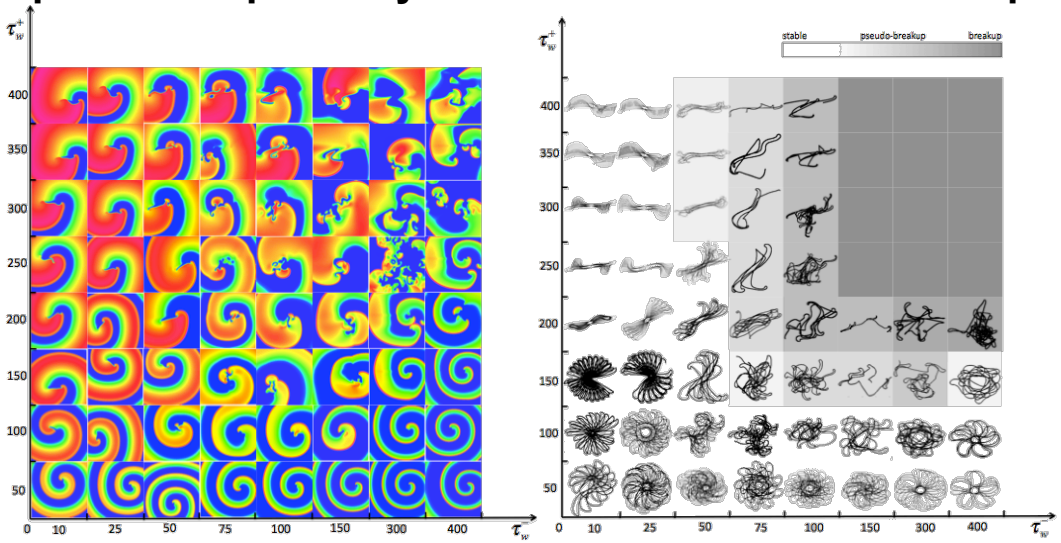


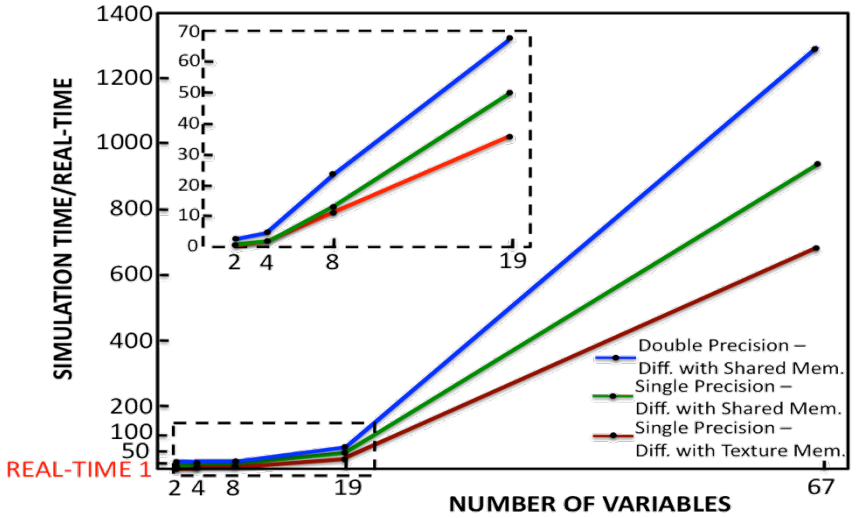
Ten-Tusscher-Panfilov (19V)



Iyer (67 V)

Spirals Computed by Students at CMACS Workshop





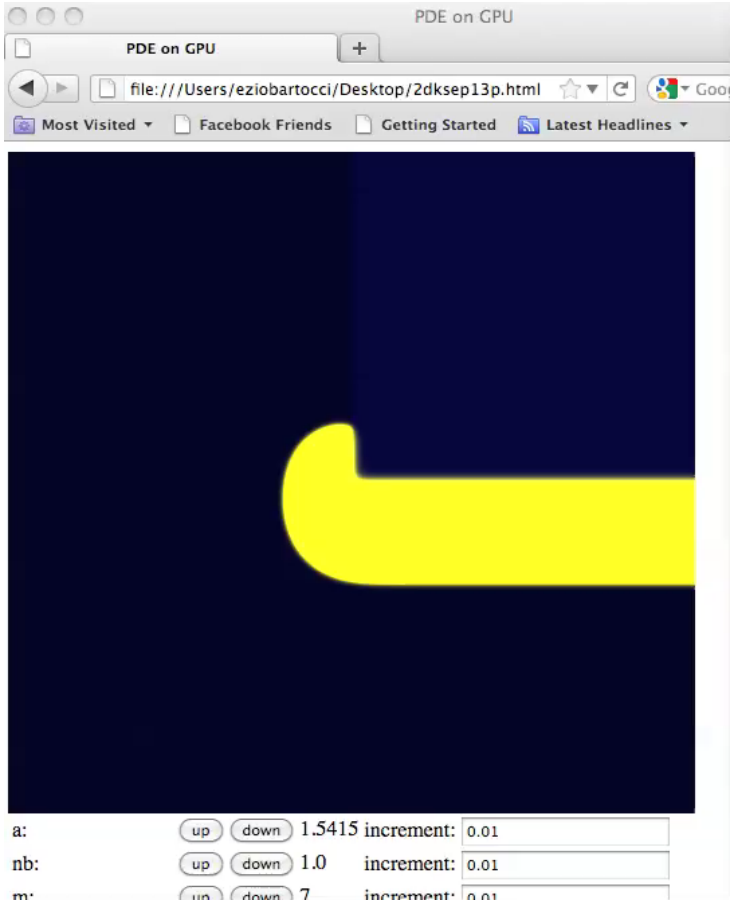
These results appeared in

CMSB 2011, pages 103-110, ACM, 2011

Advances in Physiology Education 35: 1-11, 2011

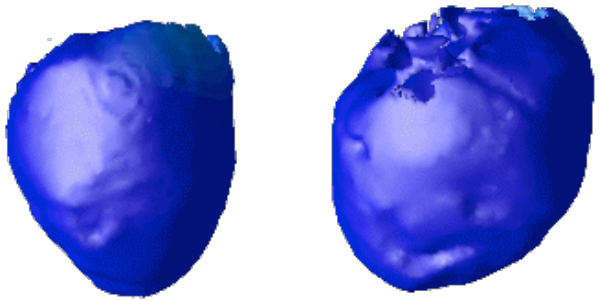
It is a Simulation Problem

Web Graphics Language (Fenton-Karma 2V)

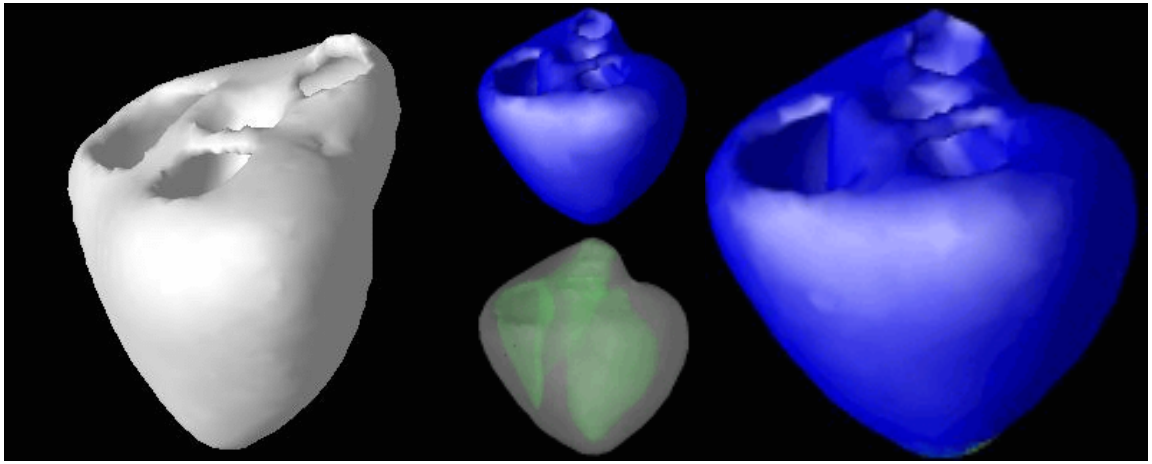


Runs in your Browser and Uses your own GPU

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

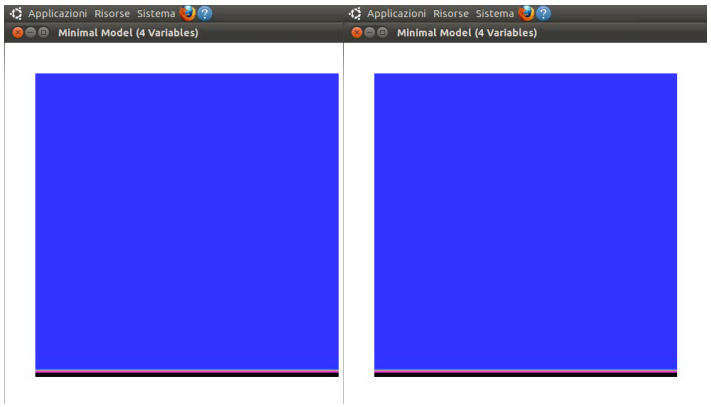


3D Model of a Pig Heart (Fenton-Karma 3V Model)



It is a Verification Problem

Spiral Wave Induced by Unexcitable Myocytes



Property to Check

$$G(u < \theta_v)$$

Uncertain Parameters

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

$$\theta_{12} = \theta_v < u \le u_u = \theta_{26}$$
$$\dot{u} = e + \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{fi_i},u_{fi_{i+1}})\, v\, g_{fi} + ws\, g_{si} - \sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\, g_{so}$$
$$\dot{v} = -v\, g_v^+$$
$$\dot{w} = -w\, g_w^+$$
$$\dot{s} = (\sum_{i=12}^{25} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\, g_{s_2}$$

4

$u < \theta_v$

$u \ge \theta_v$

$$\theta_8 = \theta_w \le u < \theta_v = \theta_{12}$$
$$\dot{u} = e + ws\, g_{si} - \sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{so_i},u_{so_{i+1}})\, g_{so}$$
$$\dot{v} = -v\, g_{v_2}^-$$
$$\dot{w} = -w\, g_w^+$$
$$\dot{s} = (\sum_{i=8}^{11} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\, g_{s_2}$$

3

$u < \theta_w$

$u \ge \theta_w$

$$\theta_2 = \theta_o \le u < \theta_w = \theta_8$$
$$\dot{u} = e - u\, g_{o_2}$$
$$\dot{v} = -v\, g_{v_2}^-$$
$$\dot{w} = (w_\infty^* - w)\, g_w^-$$
$$\dot{s} = (\sum_{i=2}^{7} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\, g_{s_1}$$

2

$u < \theta_o$

$u \ge \theta_o$

$$\theta_0 = 0 \le u < \theta_o = \theta_2$$
$$\dot{u} = e - u\, g_{o_1}$$
$$\dot{v} = (1 - v)\, g_{v_1}^-$$
$$\dot{w} = (1 - u g_{w_\infty} - w)\, g_w^-$$
$$\dot{s} = (\sum_{i=0}^{1} R(u,\theta_i,\theta_{i+1},u_{s_i},u_{s_{i+1}}) - s)\, g_{s_1}$$

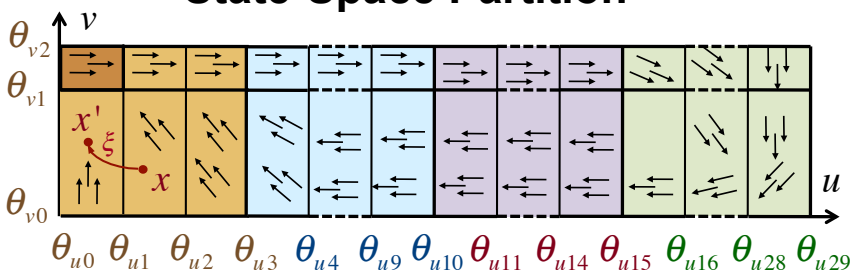
1

It is a Verification Problem

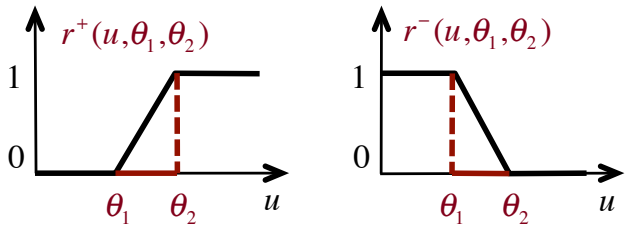
Genetic regulatory network with Parameters κ,γ

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

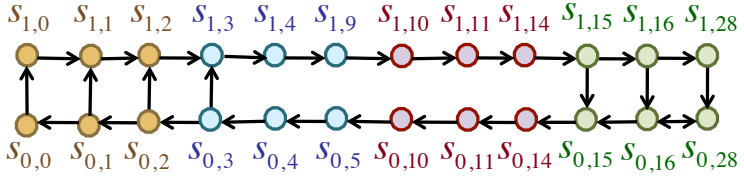
State-Space Partition



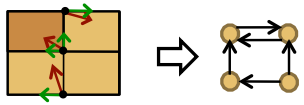
Ramps



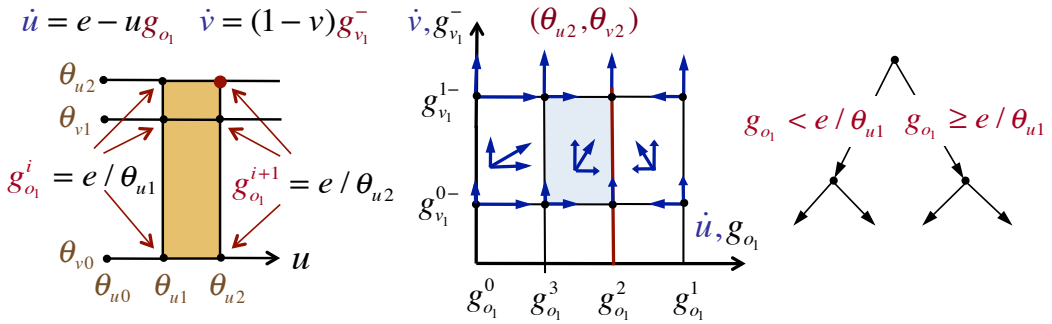
Kripke Structure for Fixed Parameters



Computation of transitions:
By examining corner flows



Parameter-Space Partition

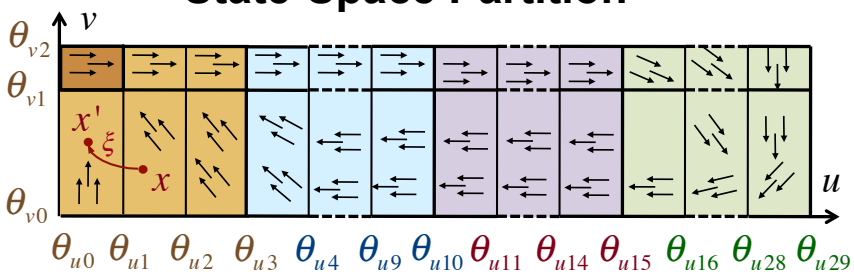


It is a Verification Problem

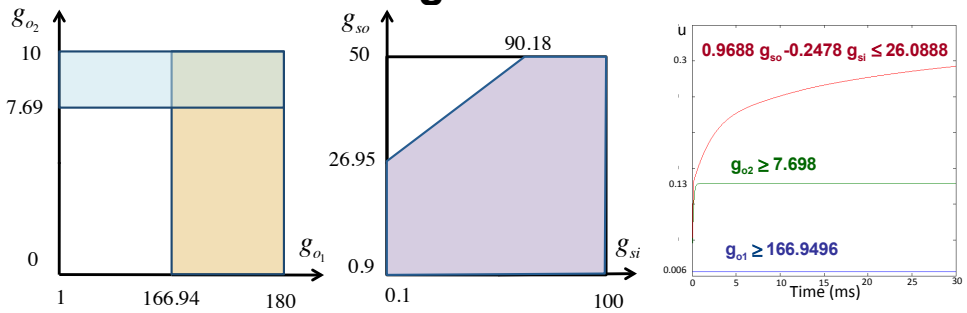
Genetic regulatory network with Parameters κ,γ

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

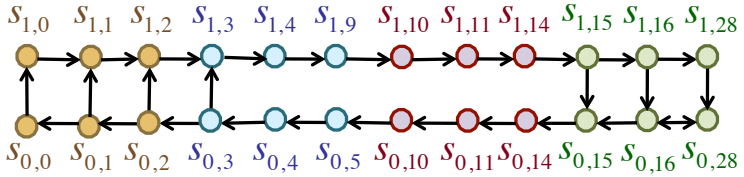
State-Space Partition



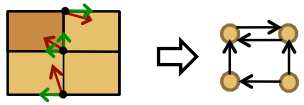
Parameter-Range Identification Results



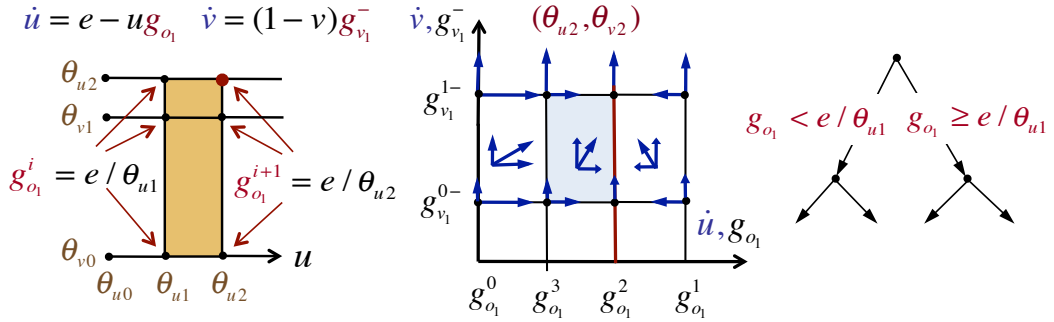
Kripke Structure for Fixed Parameters



Computation of transitions:
By examining corner flows

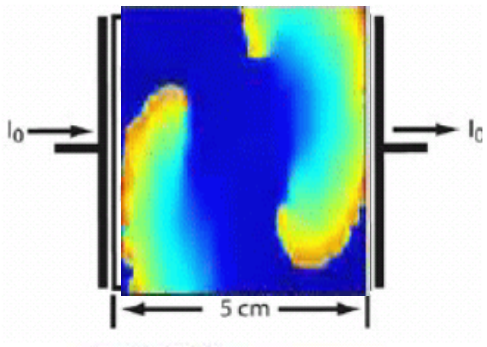


Parameter-Space Partition



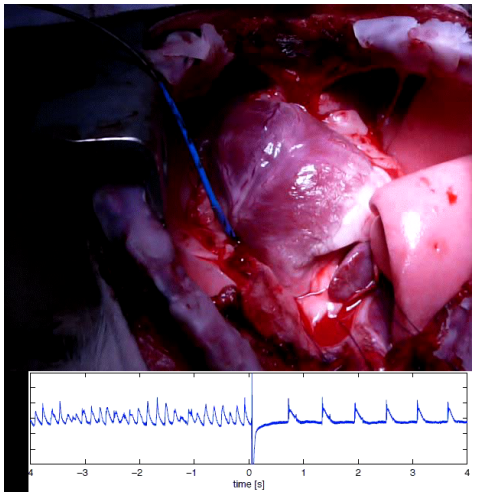
These results appeared in CAV 2011, LNCS 6806, pp. 396-411, 2011.

It is a Control Problem

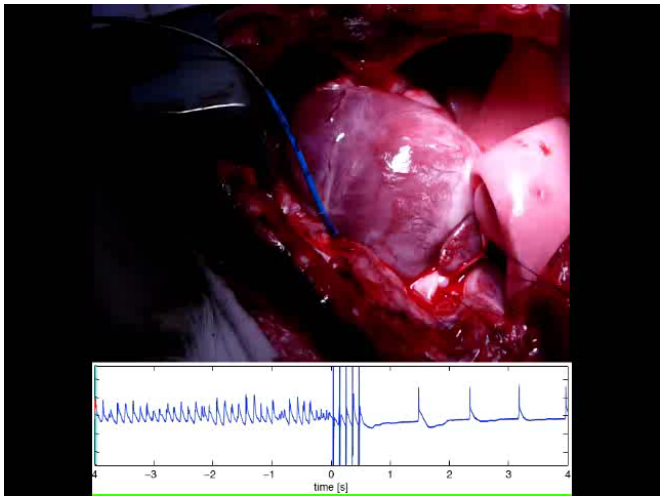


Computer simulation

1 Shock



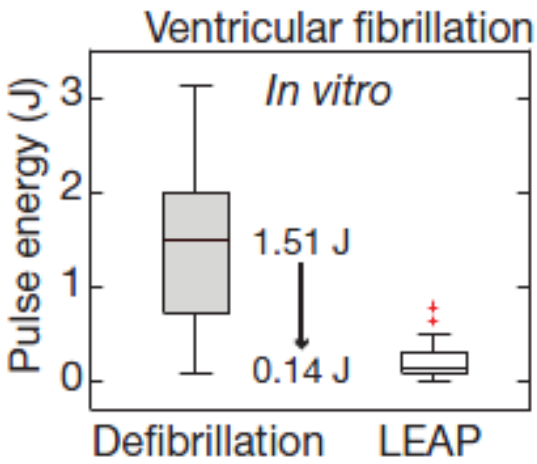
5 Low Energy Shocks

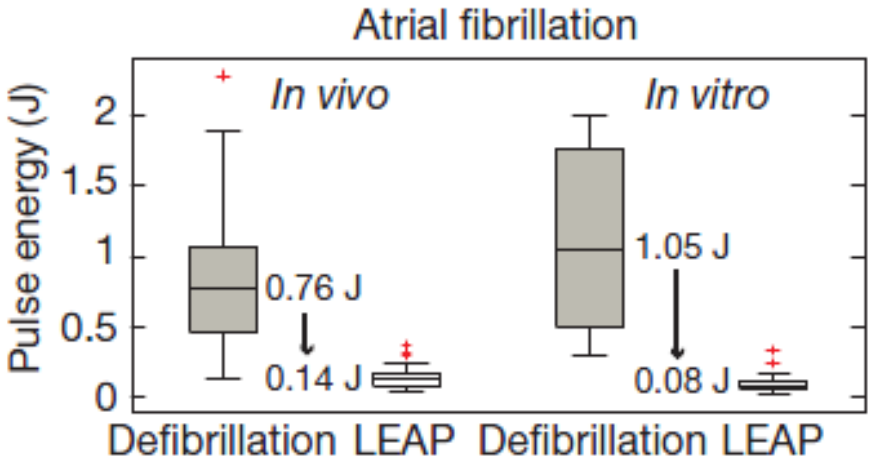


Defibrillation with 90% energy reduction

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!