LIVING STATE PHYSICS GROUP
DEPARTMENT OF PHYSICS AND ASTRONOMY, VANDERBILT UNIVERSITY

The Challenges of Spatial Scales in Modeling and Understanding Cardiac Fibrillation

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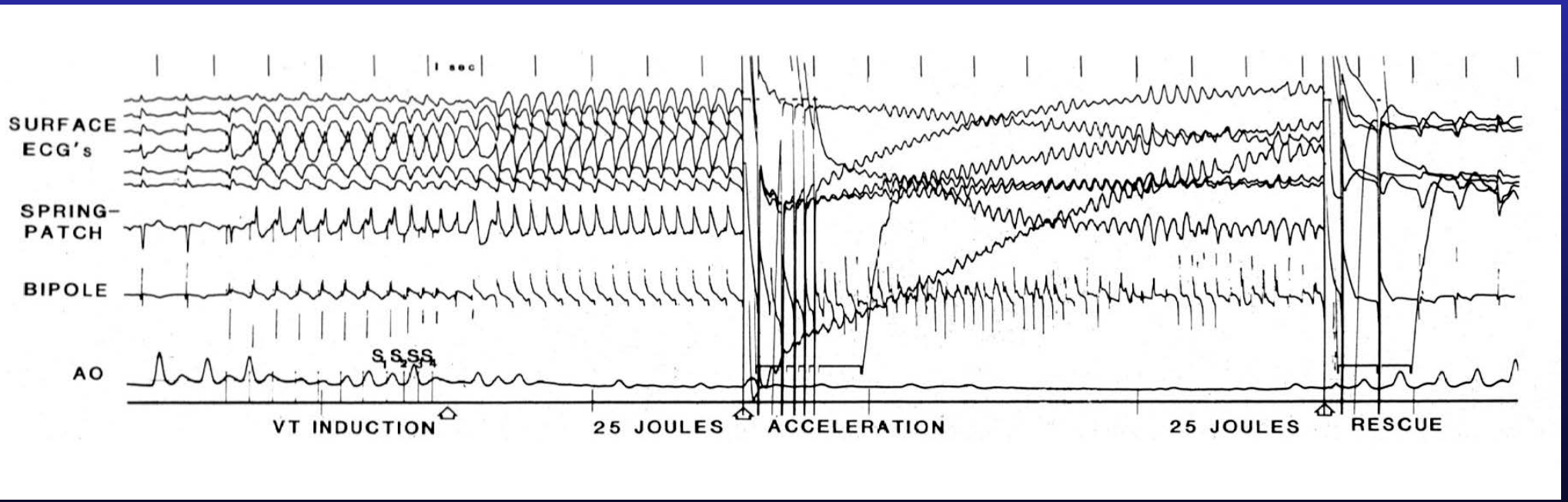
Theme

- The abrupt termination of the Cardiac Arrhythmia Suppression Trial (CAST) was the result of fatal drug effects that were not anticipated by model or experiment
- There is a rapidly growing knowledge base on the structure and function of membrane ion channels
- What is involved in providing a stronger numerical connection between the ion channel and the electrophysiology of the entire heart?
- Models of the electrical activity of the heart during cardiac fibrillation provide serve as a valuable example of just how hard this might be.

Will a particular antiarrhythmic drug alter either the fibrillation or defibrillation thresholds?

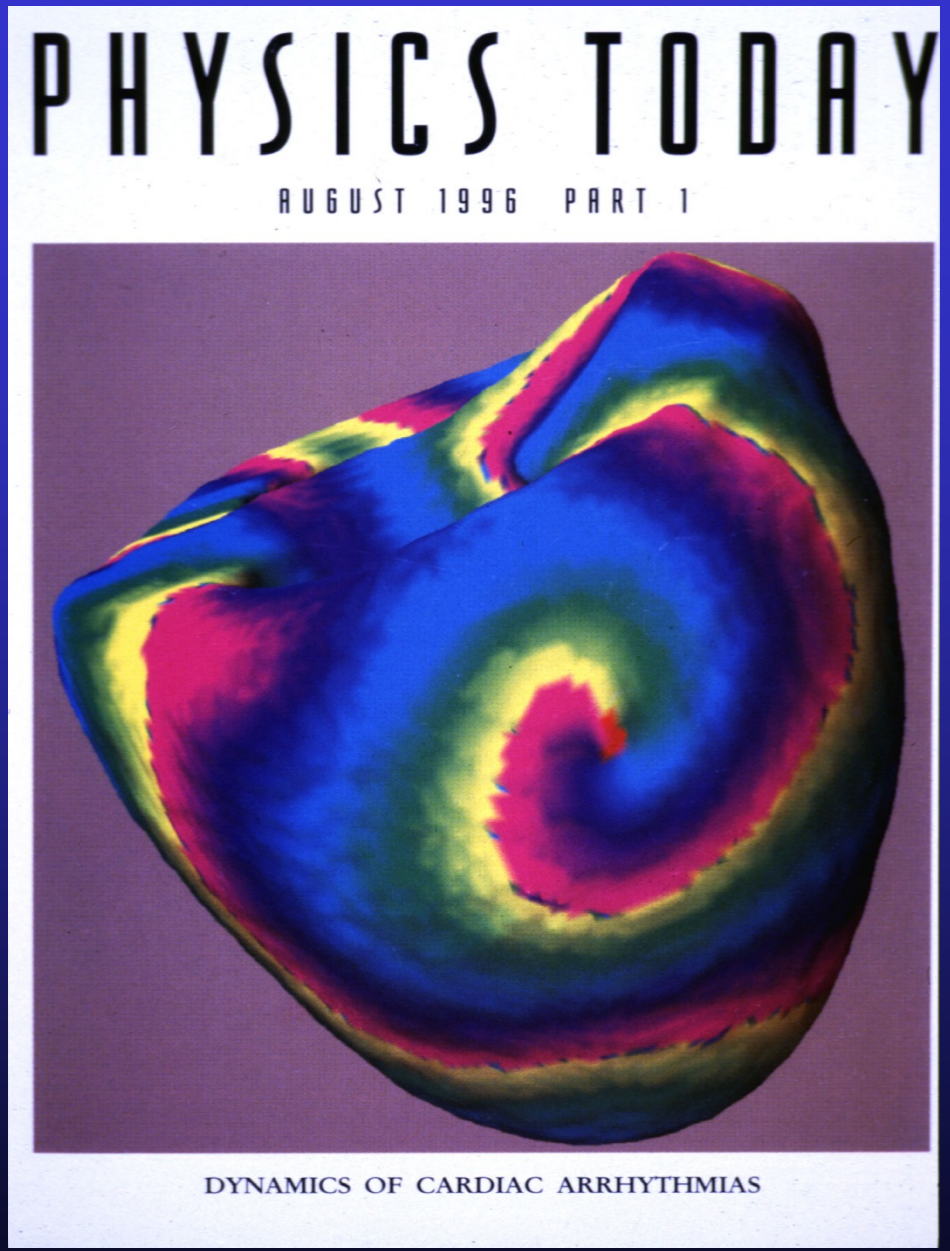
- Or… Why I use rabbit hearts as analog computers.



The Ultimate Forward Problem:

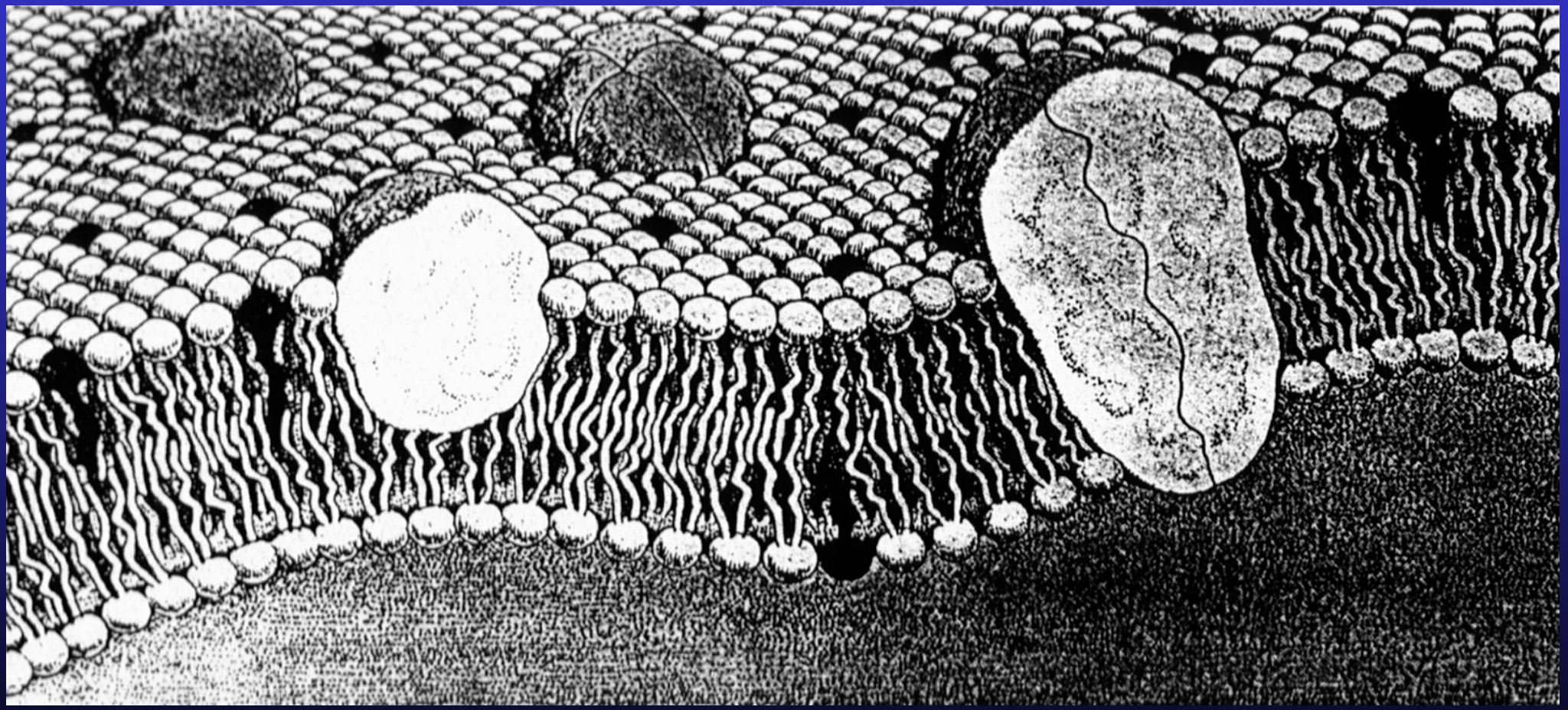
How can we use knowledge of the protein sequence for voltage-gated ion channels to predict numerically the electrocardiogram during a long episode of fibrillation?

The characteristics of cardiac fibrillation are set by the spatial scale of the entire heart



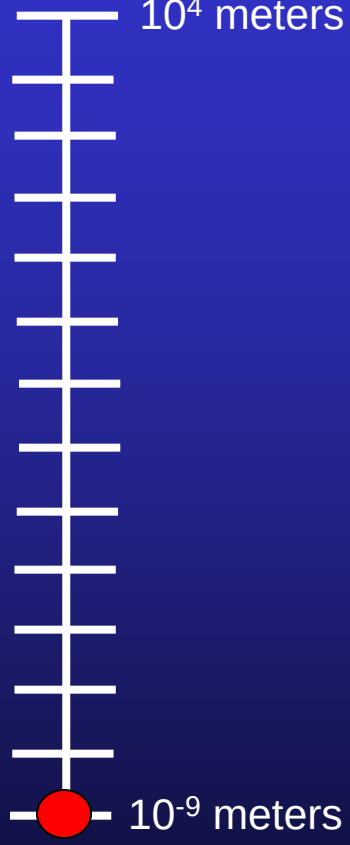
Leon Glass

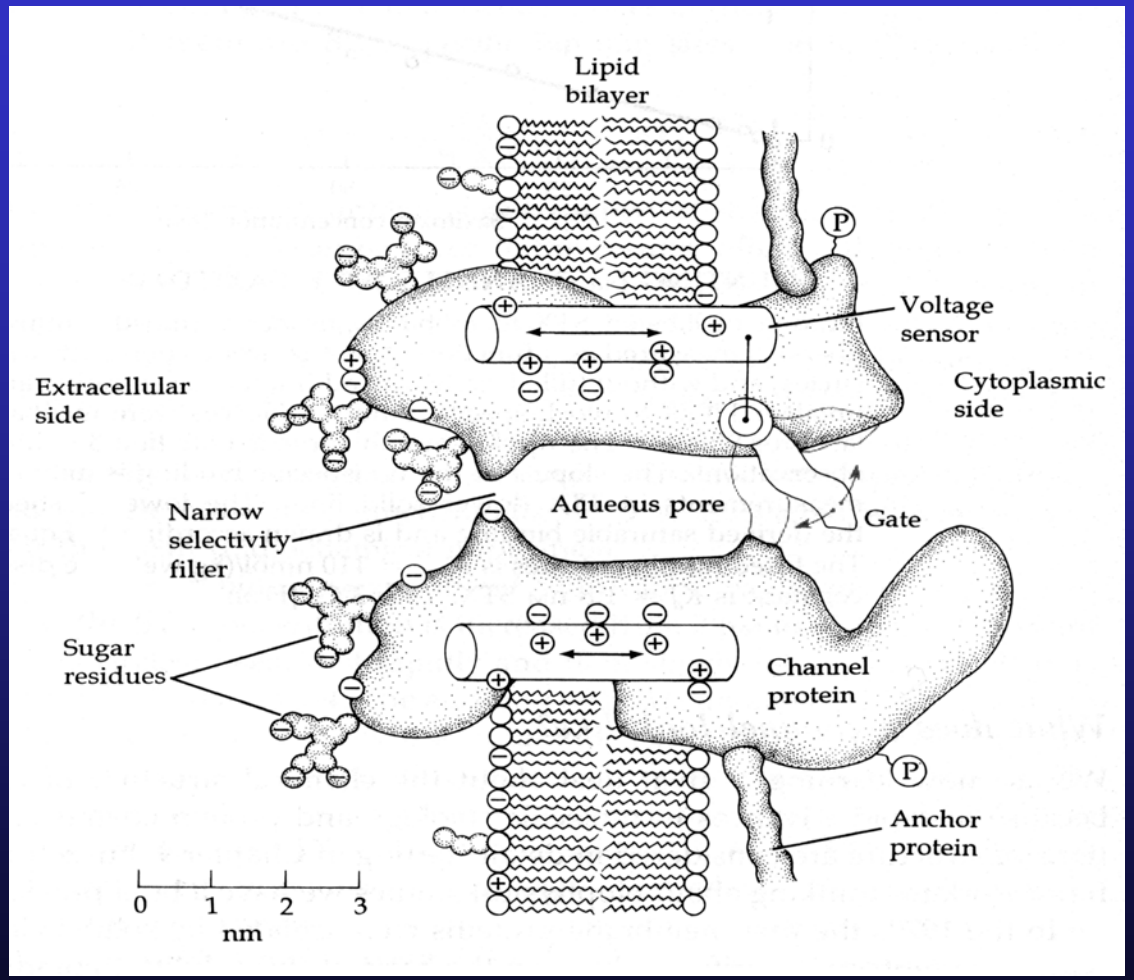
10 nanometers: Ion channels are in control

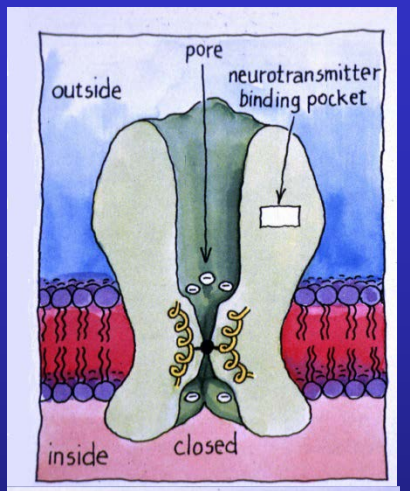


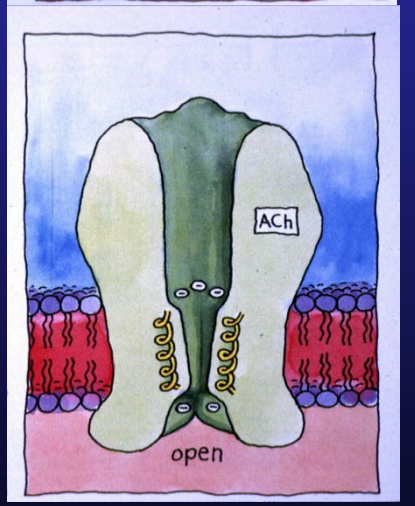
The Ultimate Device

1 nanometer: Pore in a gated ion channel

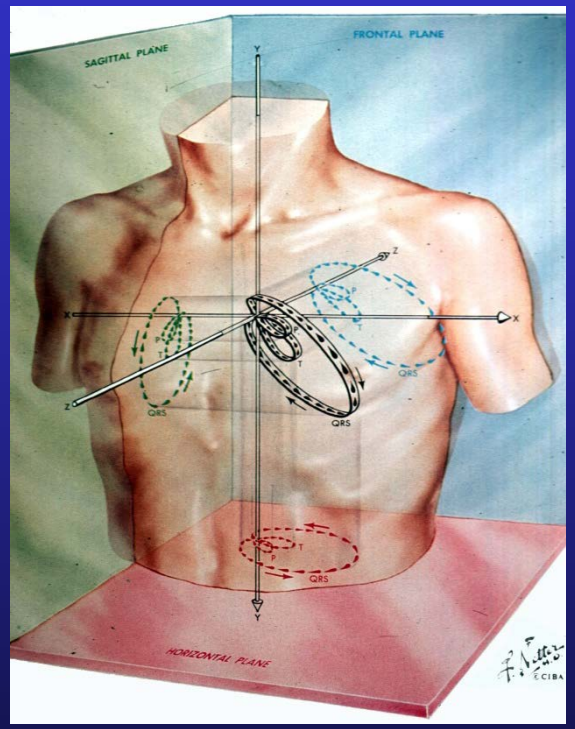






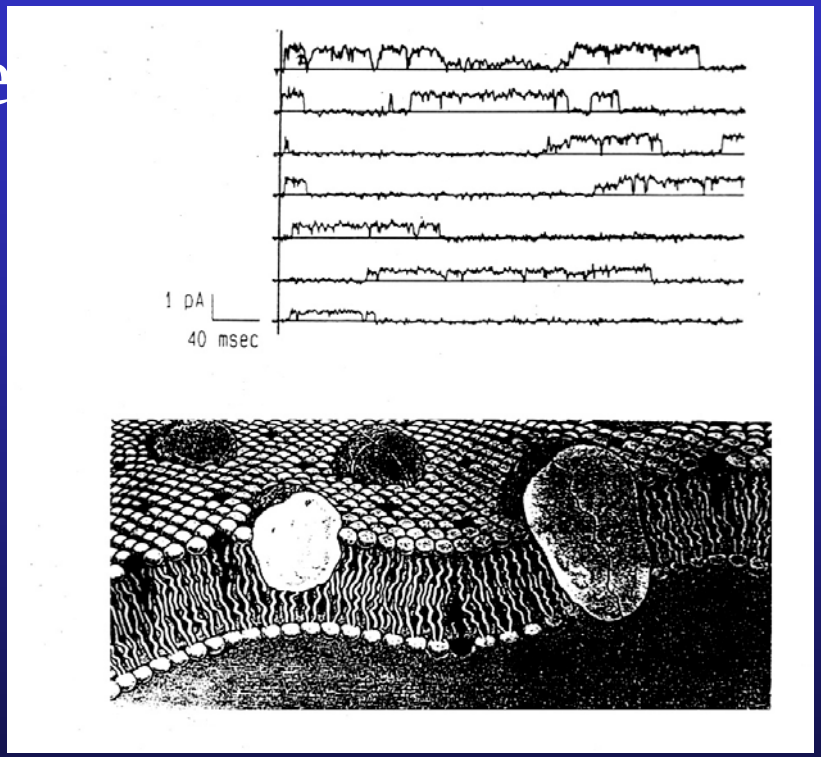


Two extremes: Models of cardiac activity



← Einthoven triangle and the cardiac dipole moment

1 m, 10 sec



→ Channel kinetics from patch clamp

10 nm, 1-10 nsec

The problem of scales:

The characteristic lengths and times in biological systems span MANY orders of magnitude.

- An ion channel: 10 nm ~ 1 channel/μm^2
- Cardiac cell: 150 μm x 15 μm x 15 μm
  500 to 30,000 channels per cell depending upon cell type
- The heart: 10 cm
  4×10^9 cells
  2×10^{14} channels
- The body: 1 m
- **Ratio of spatial scales: 10^8 in distance, 10^{24} in volume**
- Channels change in 1 - 10 ns, fibrillation time scale ~10 s
- **Ratio of temporal scales: 10^9 in time**

The Ultimate Forward Problem:

- Assume gated ion-channel protein sequence: **1 nm**
- Assume that you can compute
  - Protein structure: **1 – 10 nm**
  - Protein kinetics: **1 ns – 100 ms**
  - Channel response to antiarrhythmic drugs: **10 nm, 1 ns – 100 ms**
  - Cellular, tissue and cardiac electrodynamics: **10 mm, 10 ms**
  - Electrocardiogram: **1 m, 10 s**
  - Fibrillation and defibrillation thresholds: **1 m, 10 s**
- **What will this involve?**

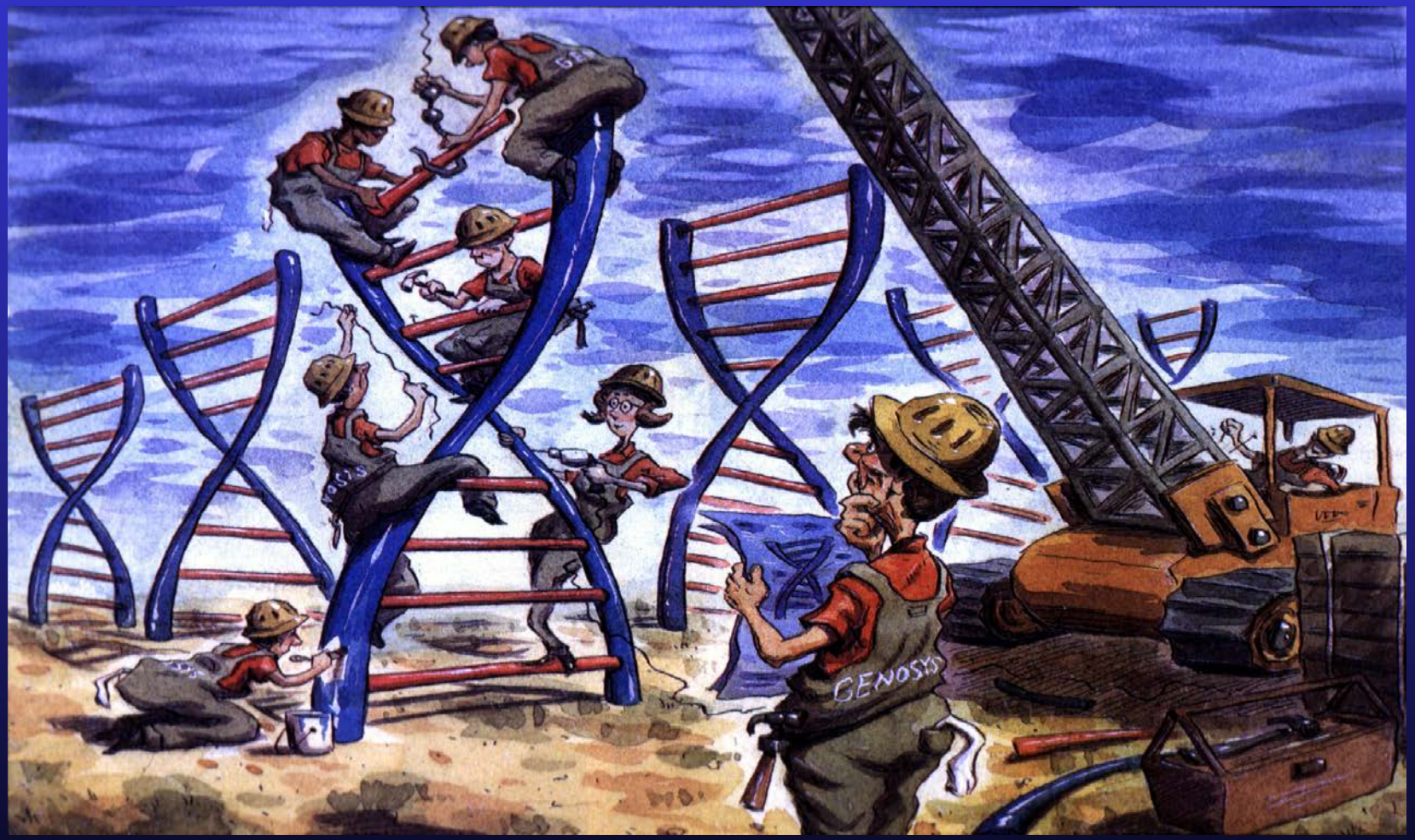
Start with the DNA sequence for a potassium channel…

human Kv1.5

GCGGCCGCGCGGCTTTTTGACGTCAGGGCCAAGCGAGGGGATCGCGCCAGCAACCCCAGCTCTCCCCAGAGAGGGGCCGG
CCGACCGCTGGAGCGGAGCCTGACGCCAGGCGCCCGCGGAGCGTGAGTAGGGGGCGCGGGAGCCGGTCAGCTGGGGCGCA
GCATGCCCTCTGCTCCCGCGCCATGGAGATCGCCCTGGTGCCCCTGGAGAACGGCGGTGCCATGACCGTCAGAGGAGGCG
ATGAGGCCCGGGCAGGCTGCGGCCAGGCCACAGGGGGAGAGCTCCAGTGTCCCCCGACGGCTGGGCTCAGCGATGGGCCC
AAGGAGCCGGCGCCAAAGGGGCGCGCGCAGAGAGACGCGGACTCGGGAGTGCGGCCCTTGCCTCCGCTGCCGGACCCGGG
AGTGCGGCCCTTGCCTCCGCTGCCAGAGGAGCTGCCACGGCCTCGACGGCCGCCTCCCGAGGACGAGGAGGAAGAAGGCG
ATCCCGGCCTGGGCACGGTGGAGGACCAGGCTCTGGGCACGGCGTCCCTGCACCACCAGCGCGTCCACATCAACATCTCC
GGGCTGCGCTTTGAGACGCAGCTGGGCACCCTGGCGCAGTTCCCCAACACACTCCTGGGGGACCCCGCCAAGCGCCTGCC
GTACTTCGACCCCCTGAGGAACGAGTACTTCTTCGACCGCAACCGGCCCAGCTTCGACGGTATCCTCTACTACTACCAGT
CCGGGGGCCGCCTGCGAGGGGTCAACGTCTCCCTGGACGTGTTCGCGGACGAGATACGCTTCTACCAGCTGGGGGACGAG
GCCATGGAGCGCTTCCGCGAGGATGAGGGCTTCATTAAAGAAGAGGAGAAGCCCCTGCCCCGCAACGAGTTCCAGCGCCA
GGTGTGGCTTATCTTCGAGTATCCGGAGAGCTCTGGGTCCGCGCGGGCCATCGCCATCGTCTCGGTCTTGGTTATCCTCA
TCTCCATCATCACCTTCTGCTTGGAGACCCTGCCTGAGTTCAGGGATGAACGTGAGCTGCTCCGCCACCCTCCGGCGCCC
CACCAGCCTCCCGCGCCCGCCCCTGGGGCCAACGGCAGCGGGGTCATGGCCCCCGCCTCTGGCCCTACGGTGGCACCGCT
CCTGCCCAGGACCCTGGCCGACCCCTTCTTCATCGTGGAGACCACGTGCGTGATCTGGTTCACCTTCGAGCTGCTCGTGC
GCTTCTTCGCCTGCCCCAGCAAGGCAGGGTTCTCCCGGAACATCATGAACATCATCGATGTGGTGGCCATCTTCCCCTAC
TTCATCACCCTGGGCACCGAACTGGCAGAGCAGCAGCCAGGGGGCGGAGGAGGCGGCCAGAATGGGCAGCAGGCCATGTC
CCTGGCCATCCTCCGAGTCATCCGCCTGGTCCGGGTGTTCCGCATCTTCAAGCTCTCCCGCCACTCCAAGGGGCTGCAGA
TCCTGGGCAAGACCTTGCAGGCCTCCATGAGGGAGCTGGGGCTGCTCATCTTCTTCCTCTTCATCGGGGTCATCCTCTTC
TCCAGTGCCGTCTACTTCGCAGAGGCTGACAACCAGGGAACCCATTTCTCTAGCATCCCTGACGCCTTCTGGTGGGCAGT
GGTCACCATGACCACTGTGGGCTACGGGGACATGAGGCCCATCACTGTTGGGGGCAAGATCGTGGGCTCGCTGTGTGCCA
TCGCCGGGGTCCTCACCATTGCCCTGCCTGTGCCCGTCATCGTCTCCAACTTCAACTACTTCTACCACCGGGAAACGGAT
CACGAGGAGCCGGCAGTCCTTAAGGAAGAGCAGGGCACTCAGAGCCAGGGGCCGGGGCTGGACAGAGGAGTCCAGCGGAA
GGTCAGCGGGAGCAGGGGATCCTTCTGCAAGGCTGGGGGGACCCTGGAGAATGCAGACAGTGCCCGAAGGGGCAGCTGCC
CCCTAGAGAAGTGTAACGTCAAGGCCAAGAGCAACGTGGACTTGCGGAGGTCCCTTTATGCCCTCTGCCTGGACACCAGC
CGGGAAACAGATTTGTGAAAGGAGATTCAGGCAGACTGGTGGCAGTGGAGTAGGGAATGGGAGGCTTCTGAACATGGATA
TCTACATTATCCGCAGAGTATTTGACTCACTCCTCT

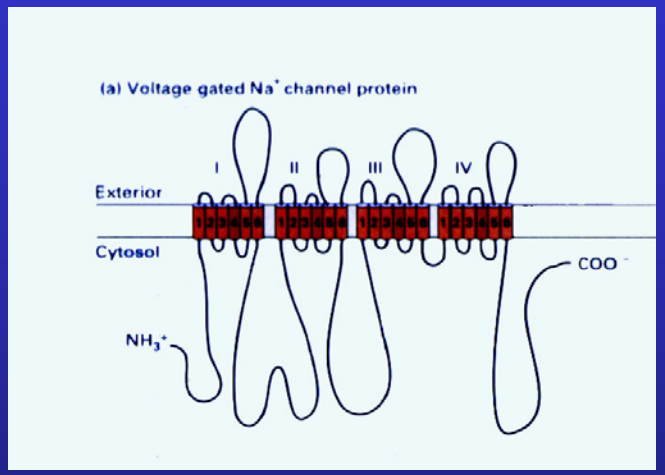
Courtesy of Dirk Schneiders

Assemble the proteins

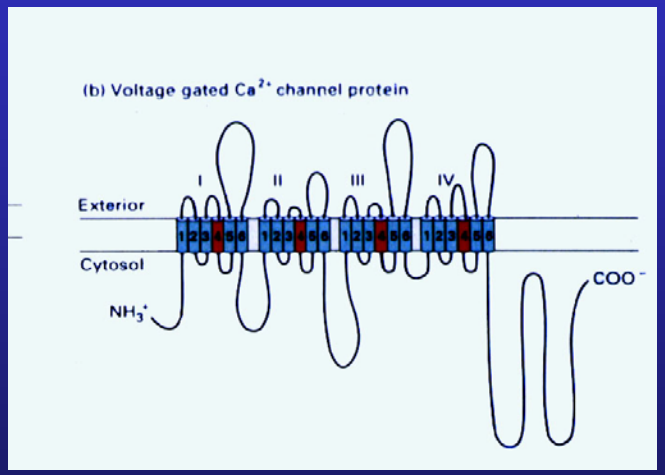


And we solve the protein folding problem…

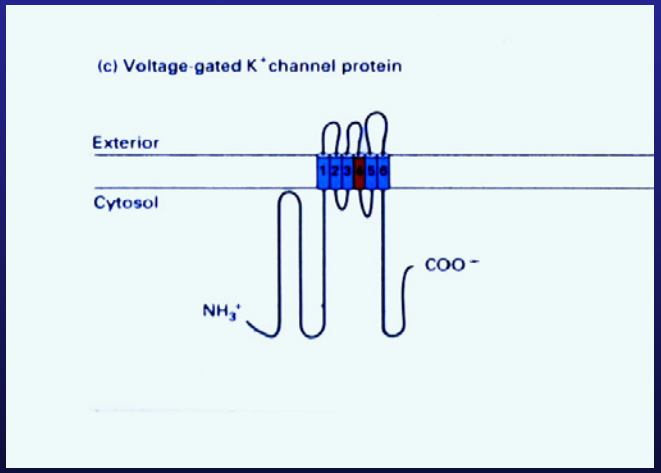
Insert the folded proteins into the membrane



Voltage-gated Na^+ channel

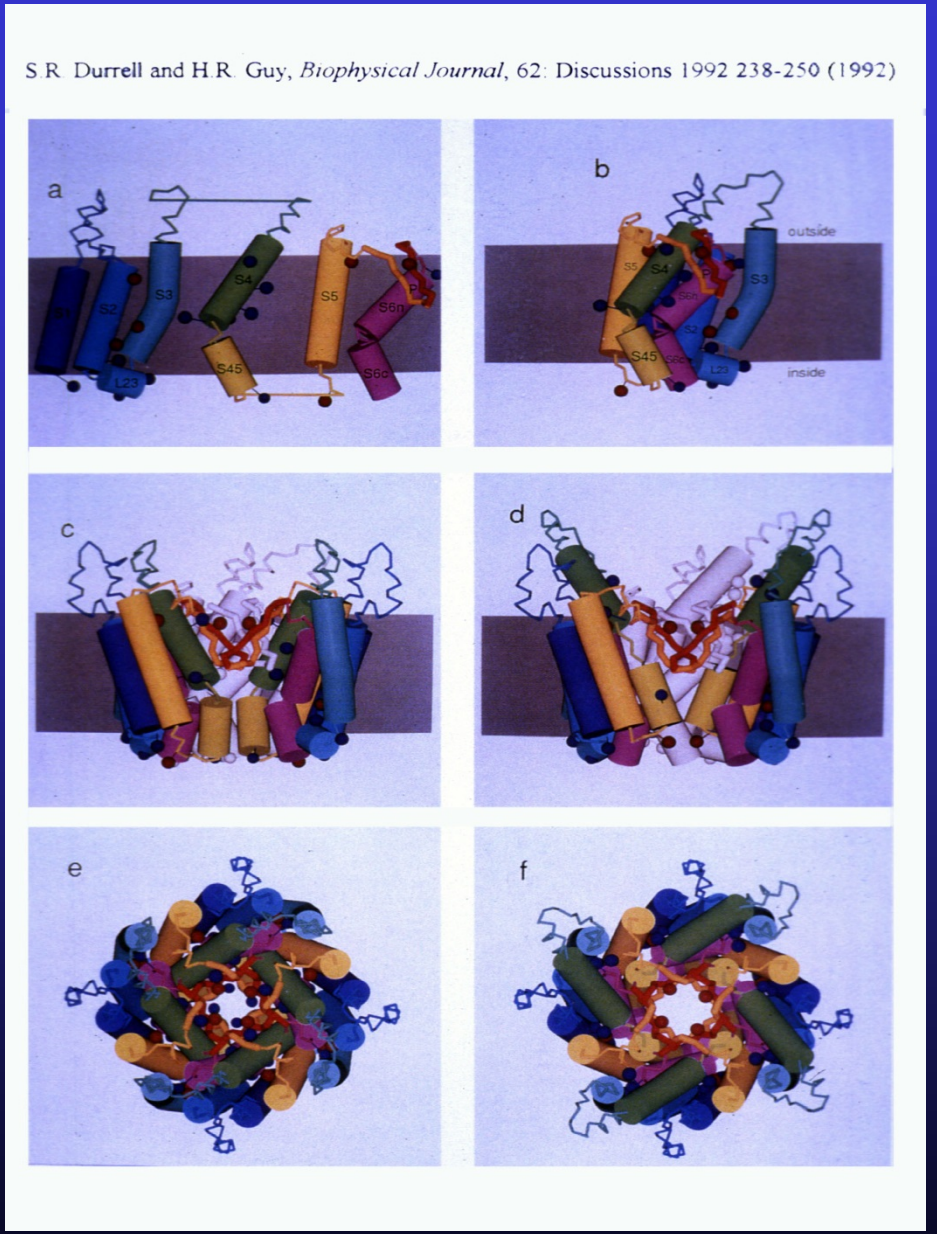


Voltage-gated Ca^{++} channel

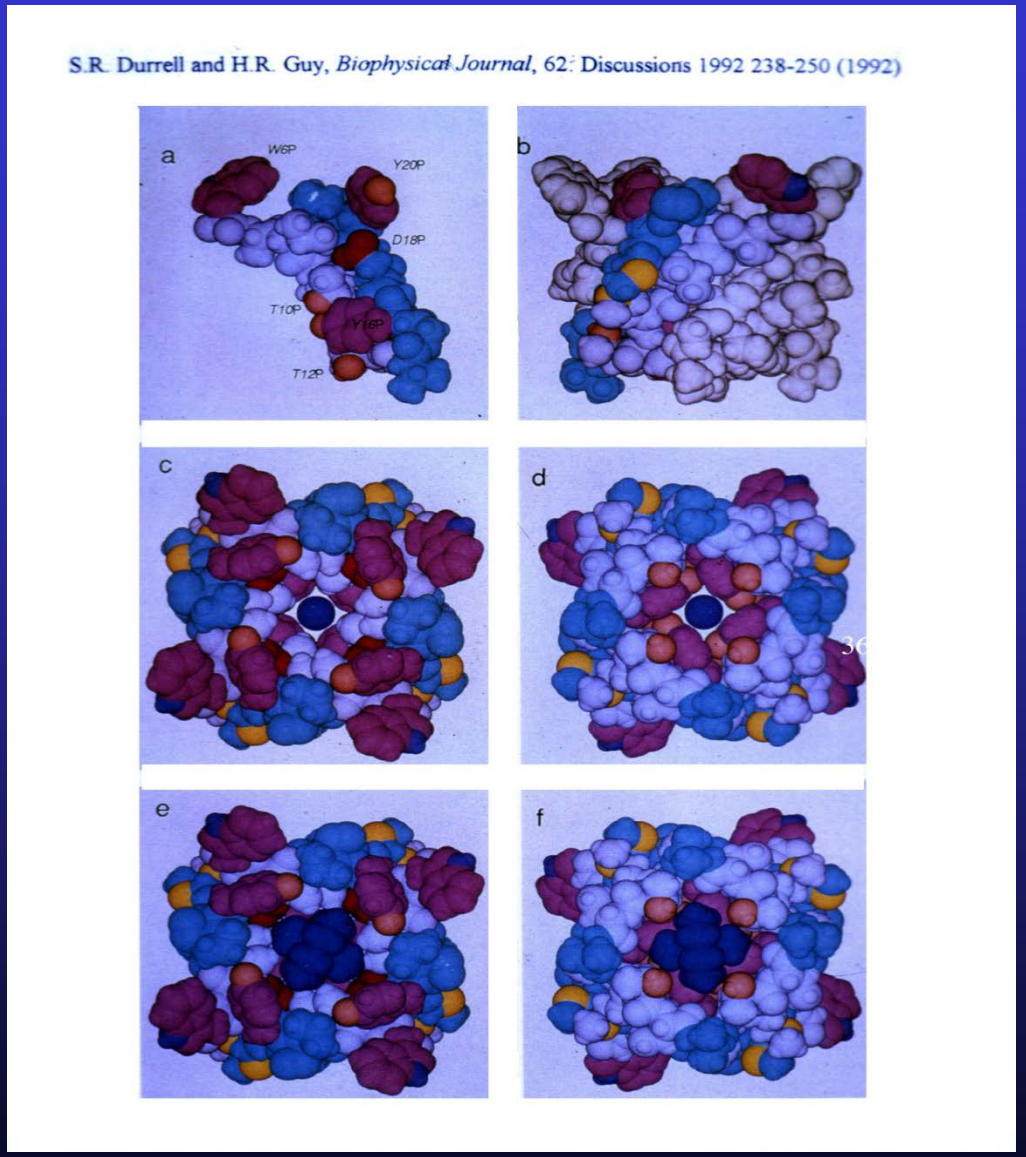


Voltage-gated K^+ channel

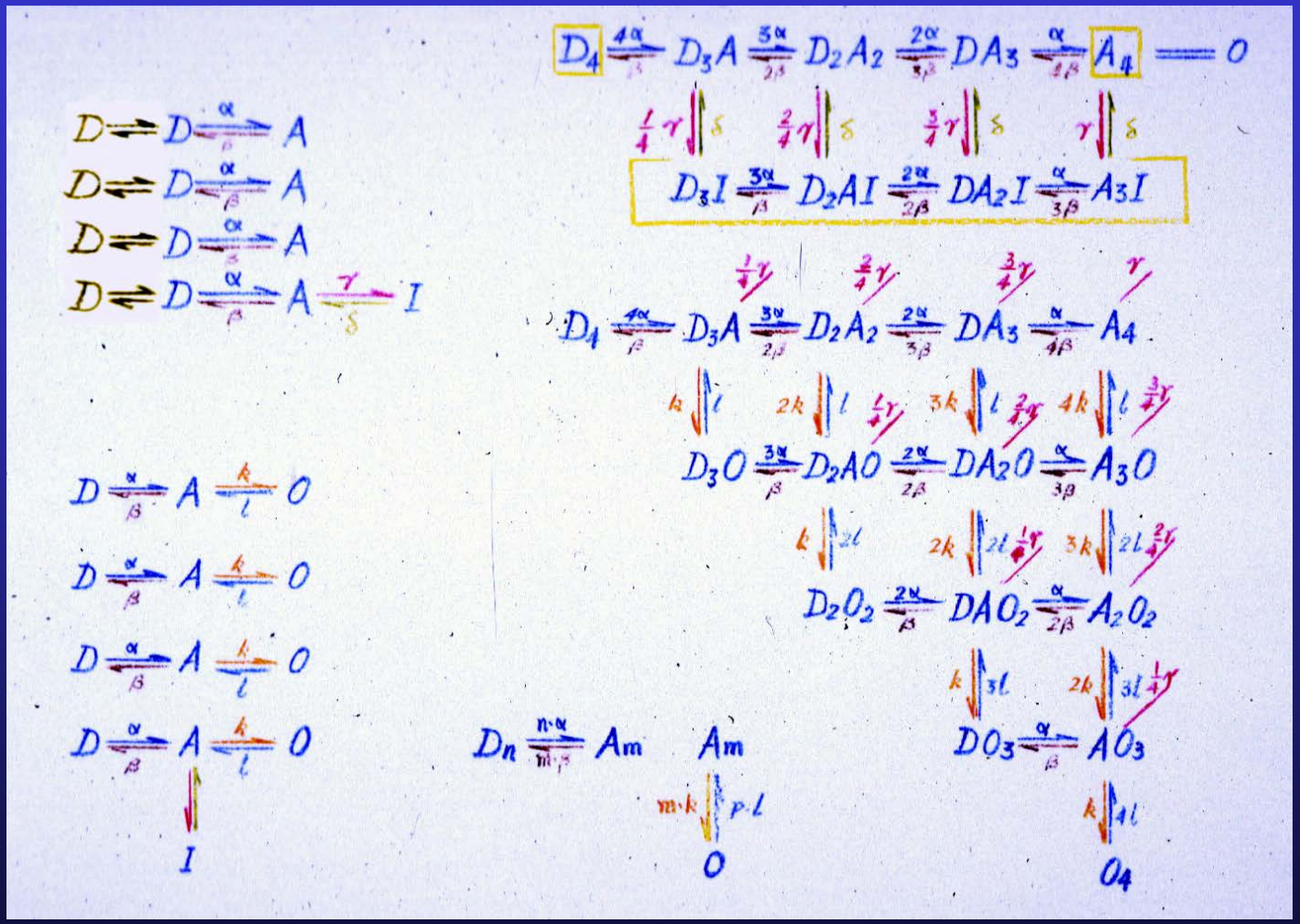
Compute how the protein conformation depends upon voltage or ligand binding



See which drugs block the channel

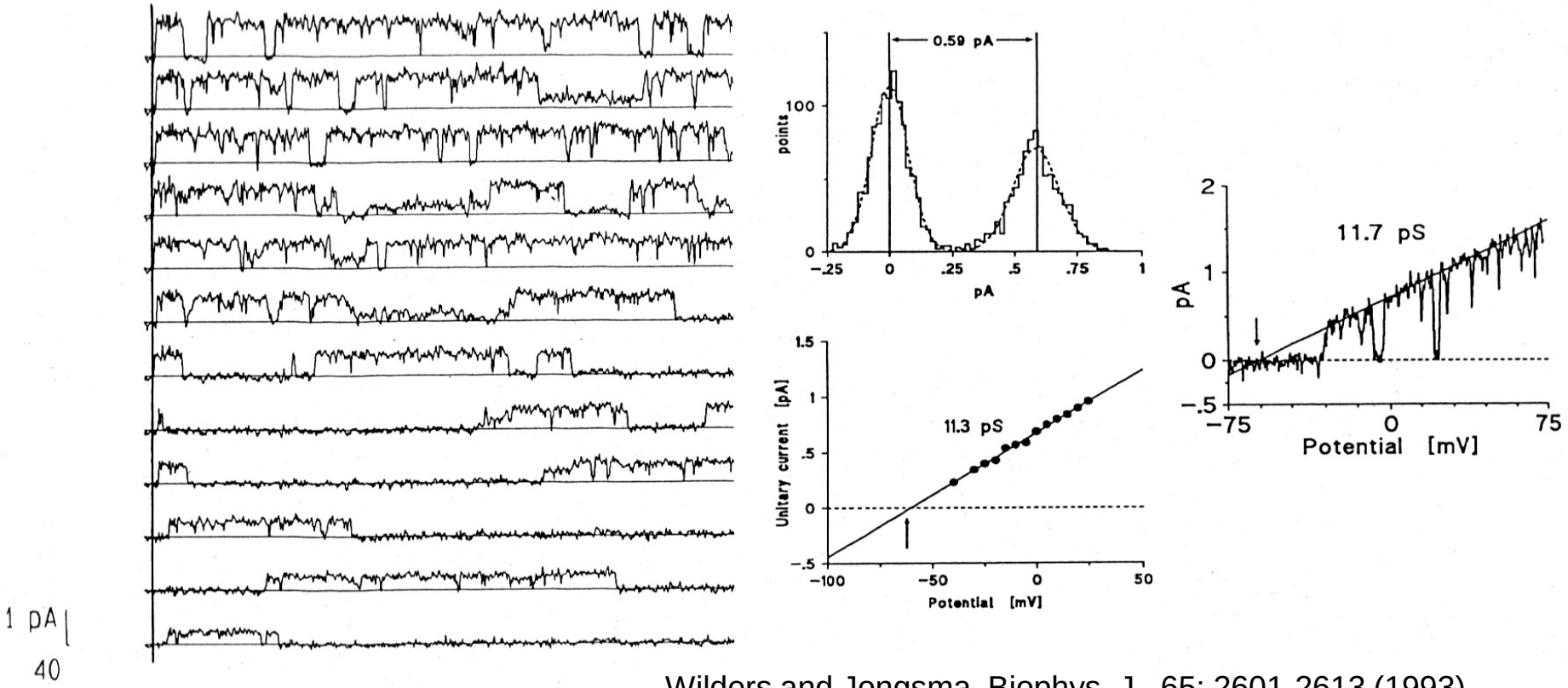


Compute the channel kinetics to determine the switching behavior



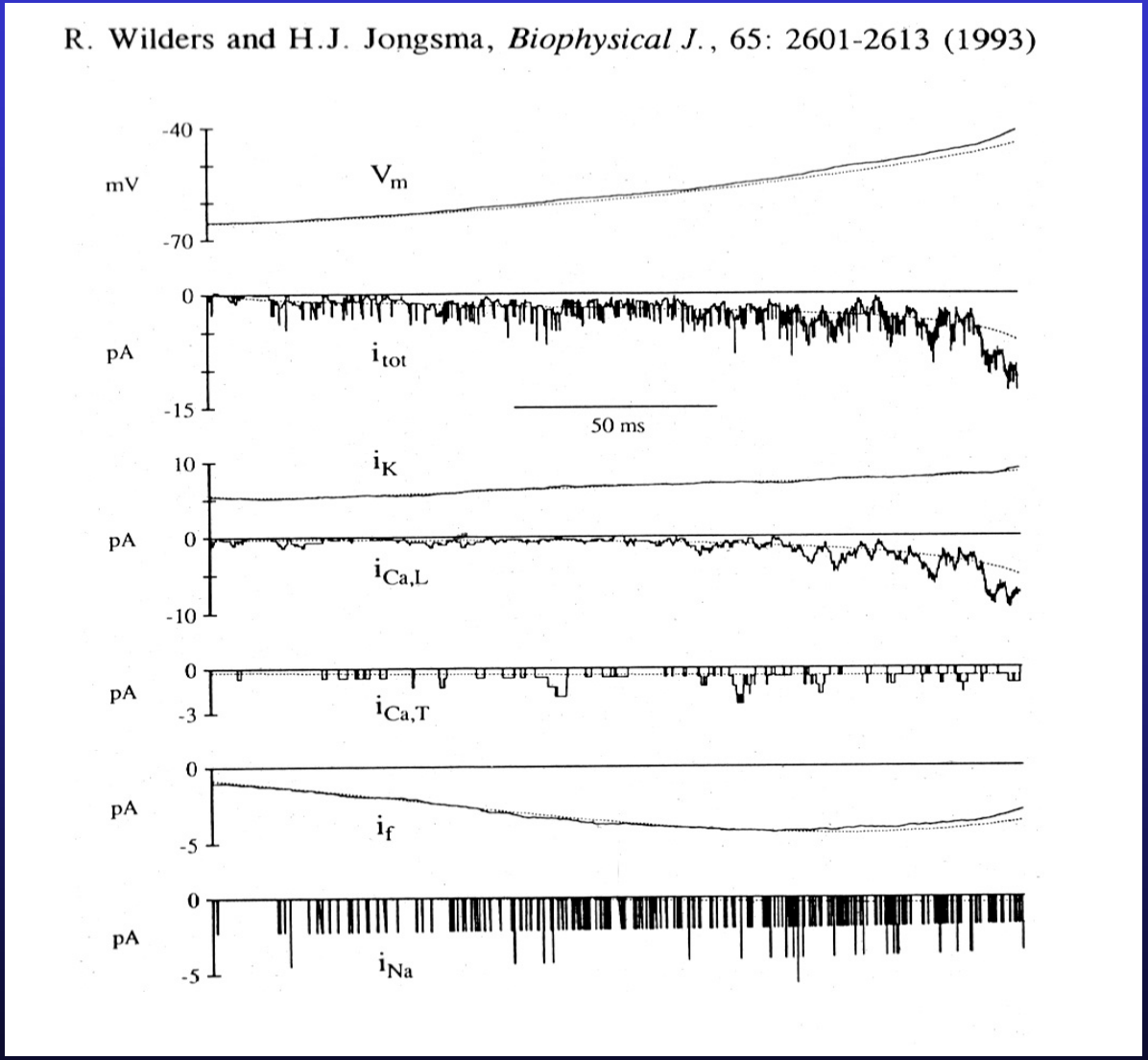
Courtesy of Dirk Schneiders

Compute the time-dependent channel conductance



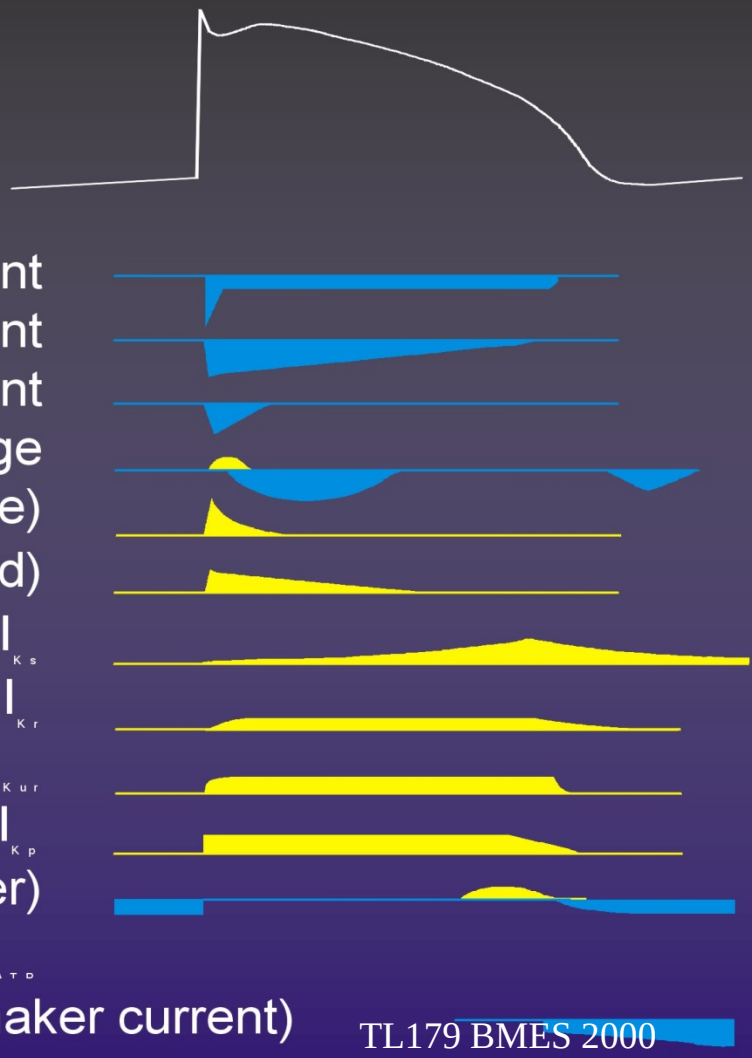
Wilders and Jongsma, Biophys. J., 65: 2601-2613 (1993)

Stochastically activate the channels



Describe the channel currents in terms of a Hodgkin-Huxley-like model such as Luo-Rudy I or II

Courtesy of Dan Roden

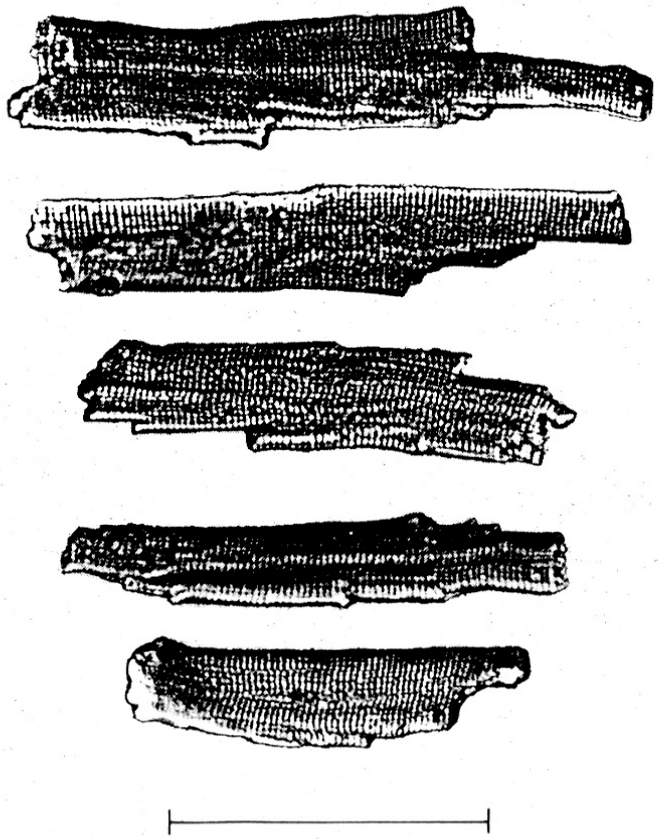


Current	Probable clone
sodium current	H1, SCN5A*
L-type calcium current	✓*
T-type calcium current	✓
Na-Ca exchange	Na-Ca exchanger
I_{TO1} (4-AP-sensitive)	Kv4.3 (?1.2, 1.4, 1.5, 2.1, 4.2)*?
I_{TO2} (Ca-activated)	--
I_{Ks}	KvLQT1 + minK (IsK)
I_{Kr}	HERG + MiRP1
I_{Kur}	Kv1.5
I_{Cl} or I_{Kp}	CFTR, TWIK (?others)
I_{K1} (inward rectifier)	Kir2.x
I_{K-ACh}; I_{K-ATP}	Kir3.1/3.4; Kir6.x/SUR
I_f (pacemaker current)	hCNG

*+sub-units

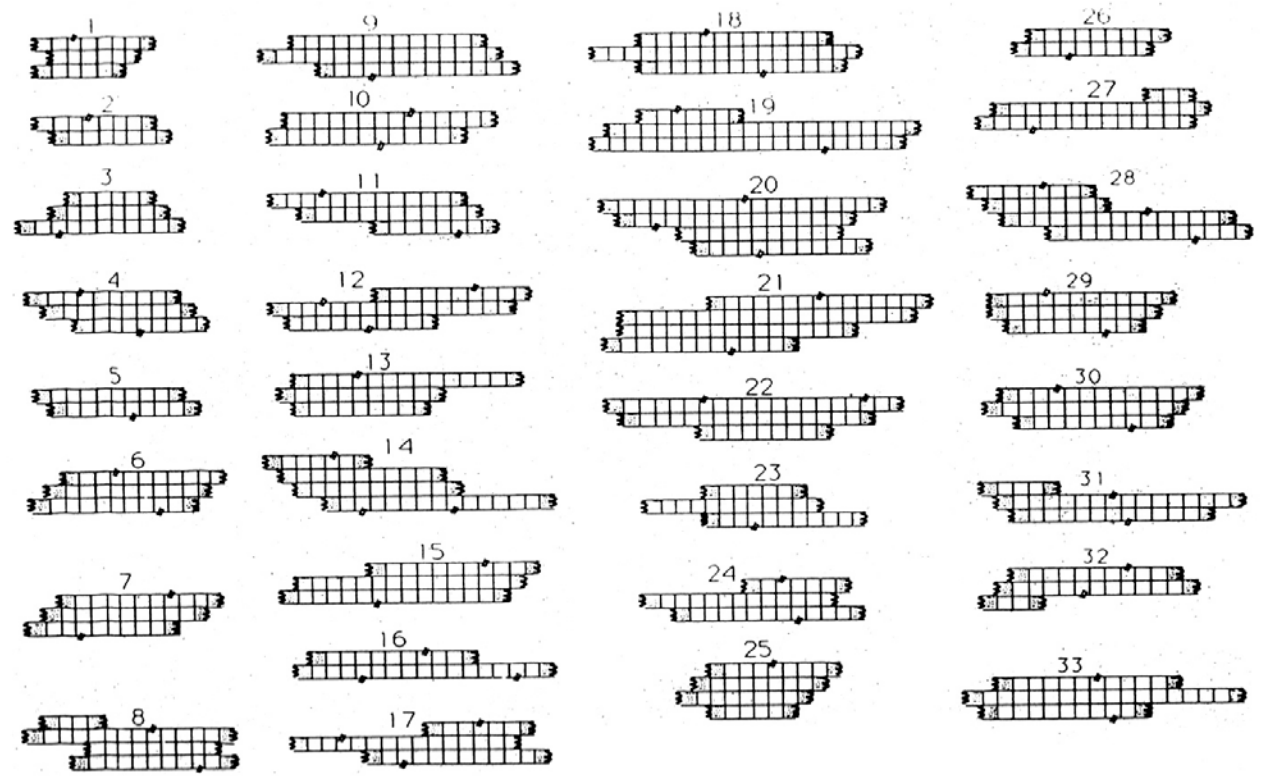
Sprinkle the channels and their currents onto a family of virtual cardiac cells

M.S. Spach and J.F. Heidlage, in *High Performance Computing in Biomedical Research*, T.C. Pilkington *et al.*, Eds., (CRC, Boca Raton, 1993) pp 289-317

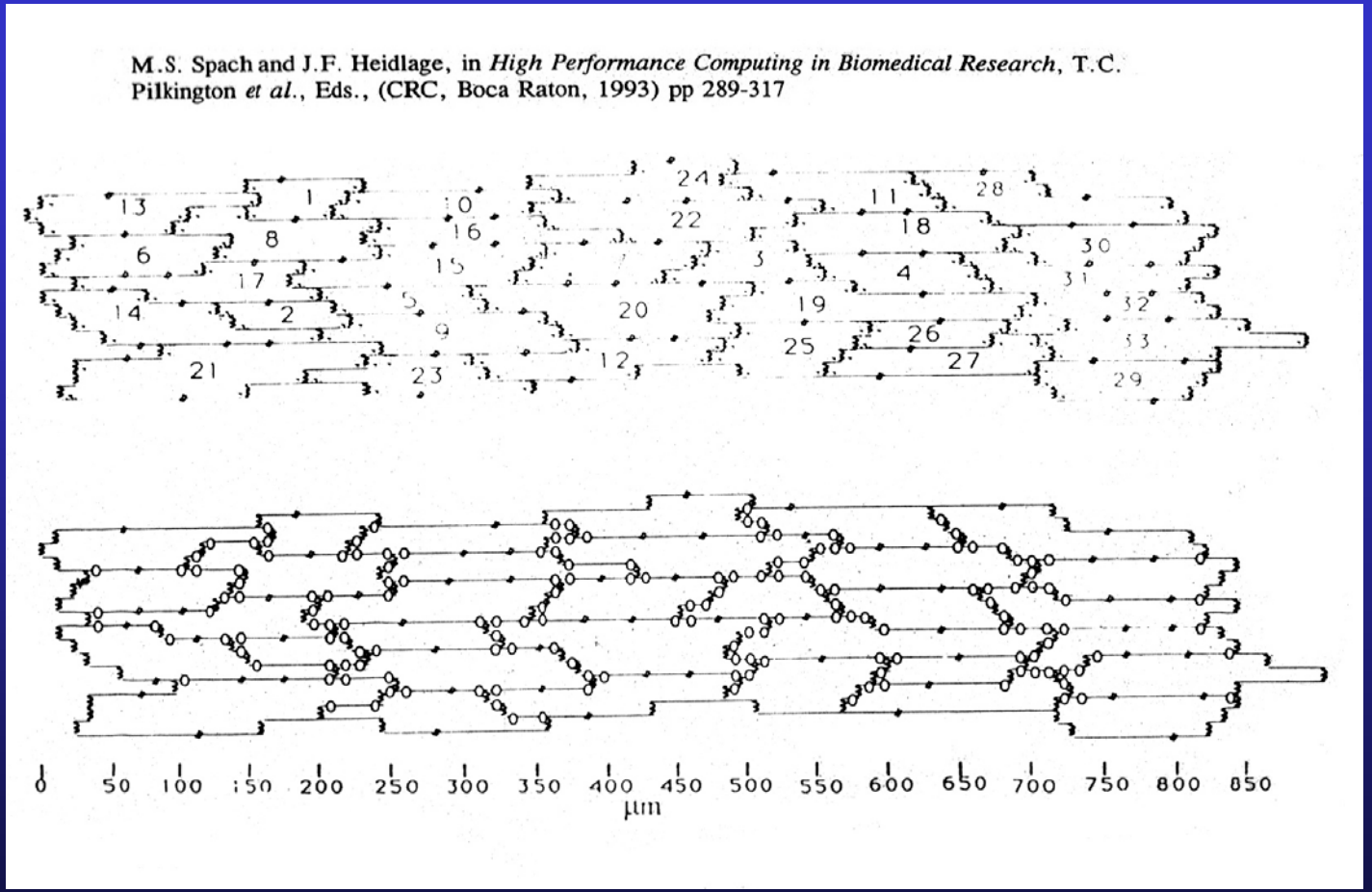


Divide each cell into a numerically stable subunit

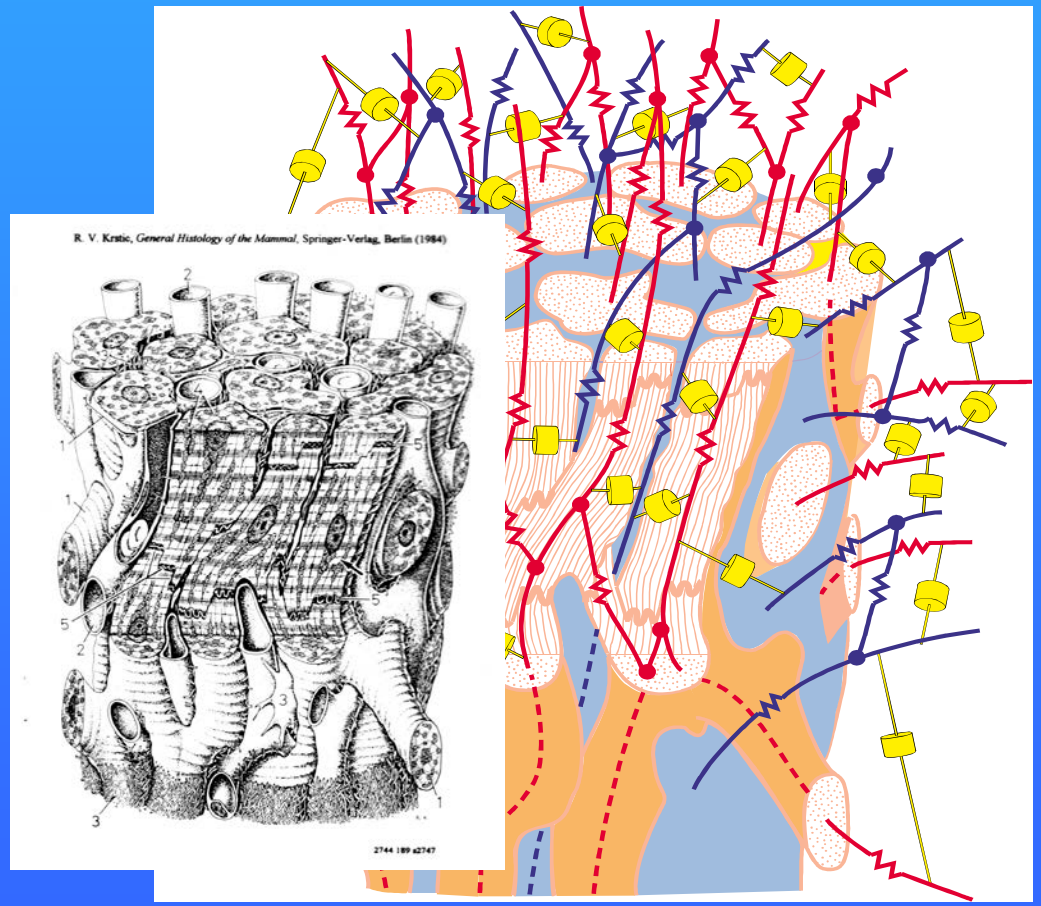
M.S. Spach and J.F. Heidlage, in *High Performance Computing in Biomedical Research*, T.C. Pilkington *et al.*, Eds., (CRC, Boca Raton, 1993) pp 289-317

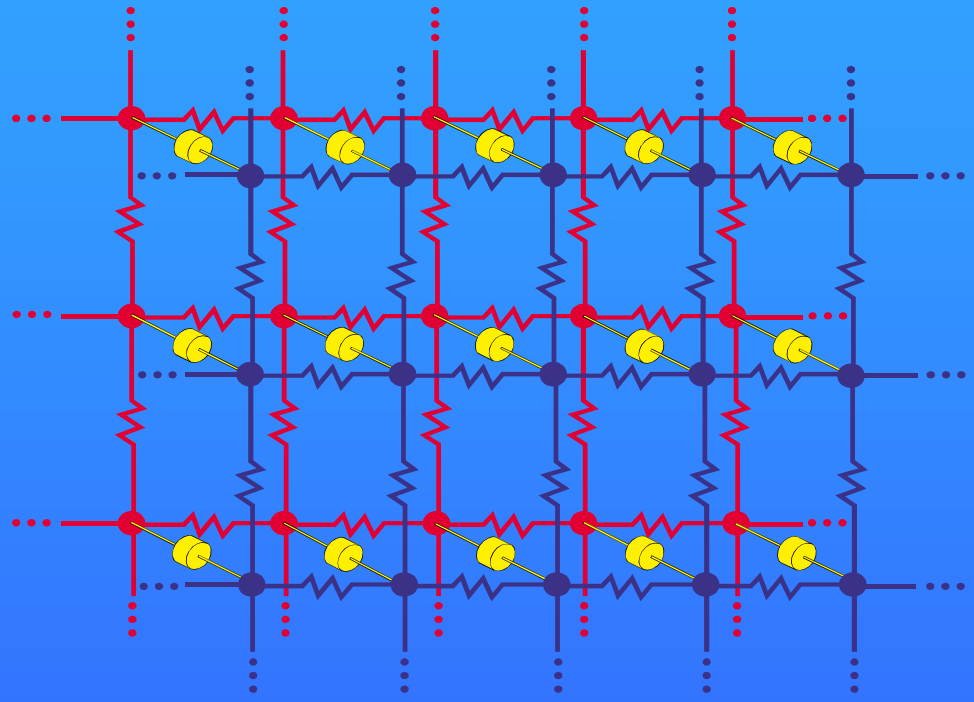


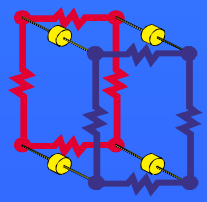
Assemble the cells into small regions of cardiac tissue



Include the three-dimensional cable properties of the anisotropic cardiac syncytium







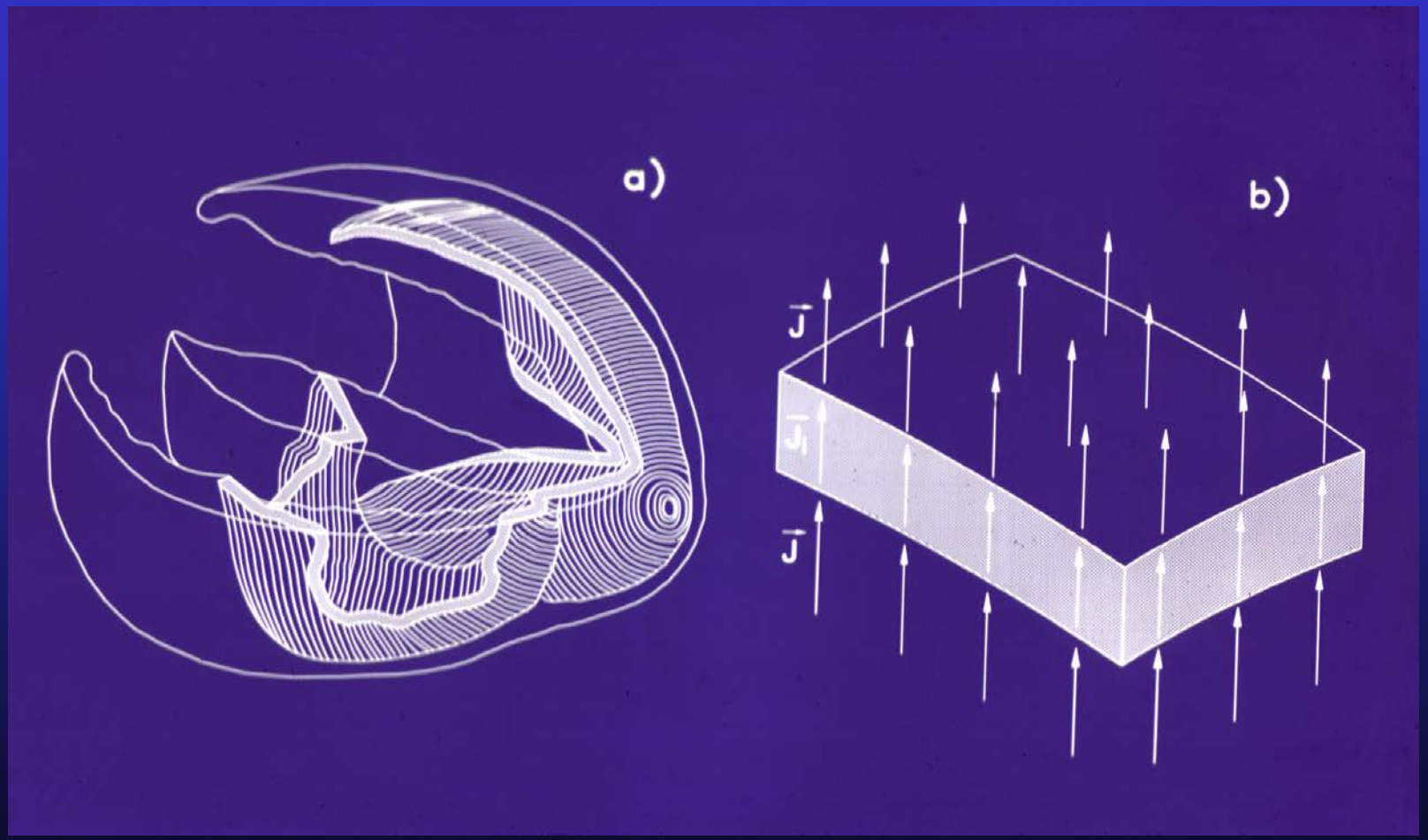
Unit Block

Intracellular

Extracellular

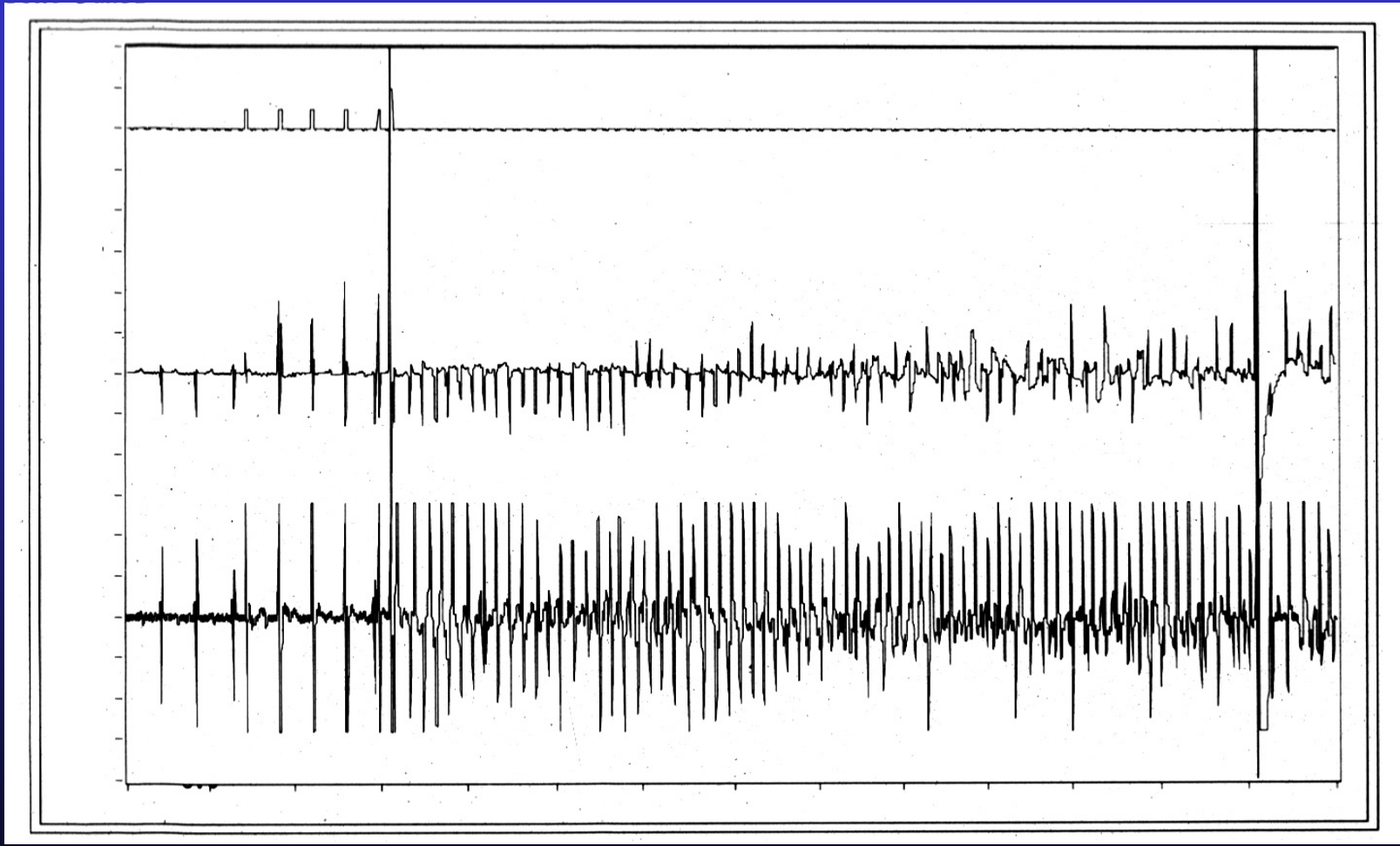
Non-linear membrane

Assemble the regions into a whole heart



Compute 10 seconds of fibrillation …

Traces of experimental data



The computer runs forever…. Look at the model

81 free parameters for each volume element in the model

Potentials	(2)
V_i, V_e	
Anisotropy tensors	(3 × 6 = 18)
conductivity, stress, strain	
Volume fractions	(3)
vol_e/vol_i, vol_{sr}/vol_i, $area_m/vol_i$.	
Concentrations	(12)
$[Na^+]_i$, $[Na^+]_e$, $[K^+]_i$, $[K+^-]_e$, $[K^+]_{cleft}$, $[Cl^-]_i$, $[Cl^-]_e$, $[Ca^{+2}]_i$, $[Ca^{+2}]_e$, $[Ca^{+2}]_{sr}$, $[ATP]_i$, $[ACh]_e$, $[H^+]_i$, $[H^+]_e$	
Currents with activation and inactivation	(6 × 3 = 18)
I_{Na}, I_{Ca}, $I_{Ca,Na}$, $I_{Ca,K}$, I_{rel}, $I_{Cl,Ca}$	
Currents with activation	(7 × 2 = 14)
I_{K1}, I_{Kp}, I_K, $I_{ns,Na}$, $I_{ns,K}$, I_{tr}, $I_{stretch}$	
Steady-state currents	(7)
$I_{Ca,b}$, $I_{Na,b}$, I_{leak}, $I_{k,ATP}$, $I_{k,ACh}$, $I_{k,PC}$, $I_{k,AA}$	
Pumps	(7)
I_{NaK}, $I_{p(Ca)}$, I_{up}, I_{NaCa}, I_{ATPCa}, I_{HK}, I_{HCl}	
Total	**81**

2791 188 s2794

The Problem of Scale: Numerical Models

- Divide each cardiac cell into 10 segments:
  4×10^{10} segments/heart
- At least 50 currents and other variables/segment
  2×10^{12} variables/heart
- 5 μs/timestep: 2×10^{6} timesteps/10s of fibrillation
- 4×10^{18} equations to solve … micromoles ….
- 46,000 years on a 25 MFLOP workstation
- 10 years on 1200 100 MFLOP workstations
- 1 year on a 1 TFLOP workstation
- At 100 bytes/segment, 4 Tbytes of memory or disk to store the model

Cherry, Greenside, Henriquez PRL 2/7/00: Whole-heart, minimal adaptive mesh LR1 estimated 10^{-5} real time with a 533 MHz DEC a; 70x increase with a 100-parallel computer.

Discussion

- Whole-heart cardiac models involve brute-force solution of partial differential equations, using either HH-type models (LR, etc), or eikonal equations
- At present, there are few if any numerical, theoretical, or analytic connections between the molecular description of the channel and either HH-type or eikonal models

Solutions to the *Ultimate Forward Problem*

- Develop efficient multiscale/mesoscale models to span the full range of space and time
  - Molecular dynamics vs. statistical mechanics vs. thermodynamics
  - Eikonal equations for the wave front properties
  - Direct physiological determination of eikonal equation parameters
- An isolated rabbit heart: **a self-assembling, multivarible, multistate, massively parallel, non-linear analog computer**
  - Solves ~10^{17} equations/second at $30/hour
  - Requires improved programming techniques
  - Requires improved readout of the answer

Characterizing the Cardiac State

What do you do with all the data?

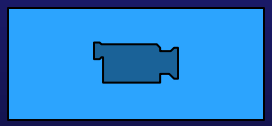
- Ontological failure: "The phenomena you are interested in requires elements or laws outside of the set you have been given."
- Epistimological Failure: "You have enough elements and the laws do apply, but you yourself cannot understand the explanation that they provide."

D Bray, TIBS 22, pp 325-326 (1997)

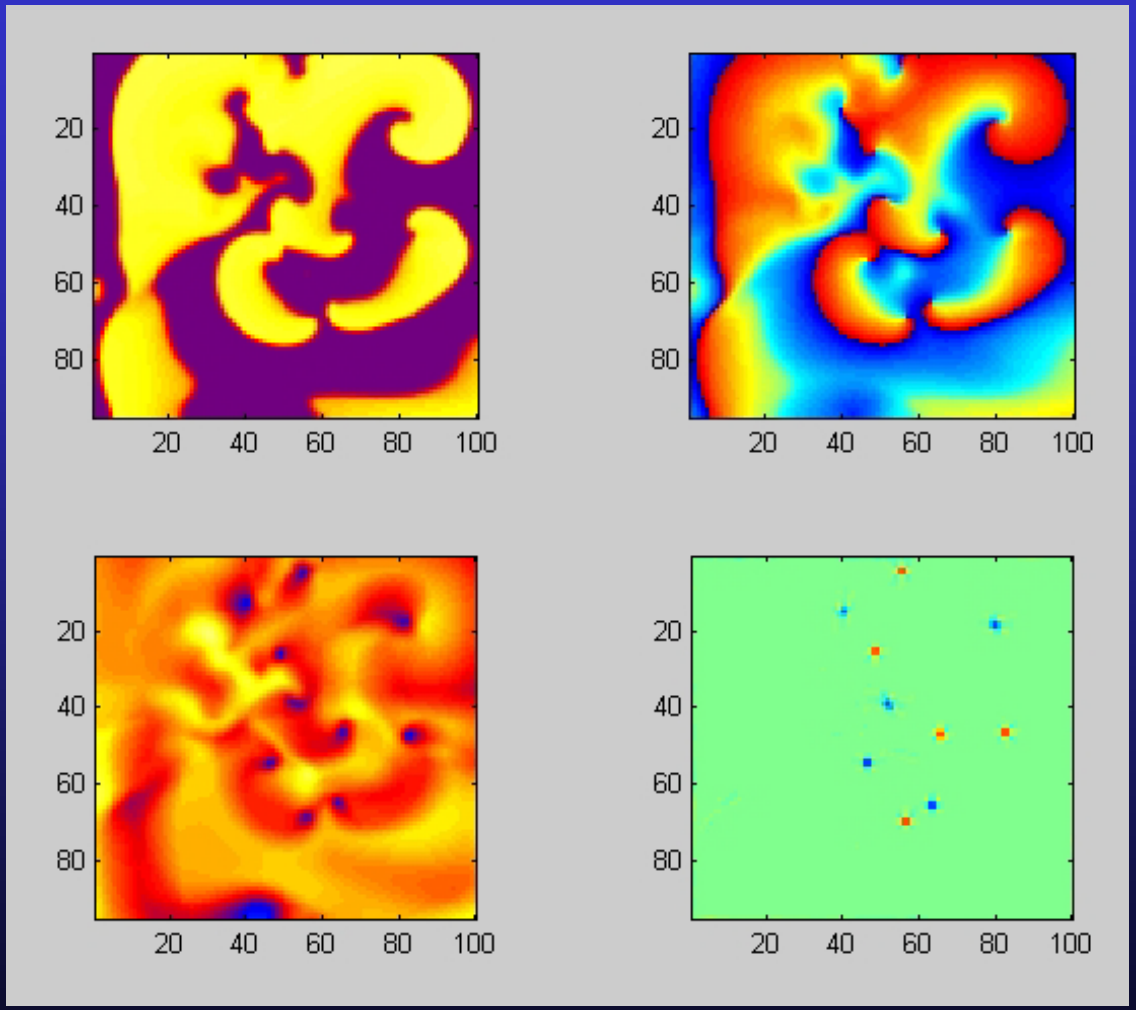
Visualizing Fibrillation

V_m Phase

Variance Curl

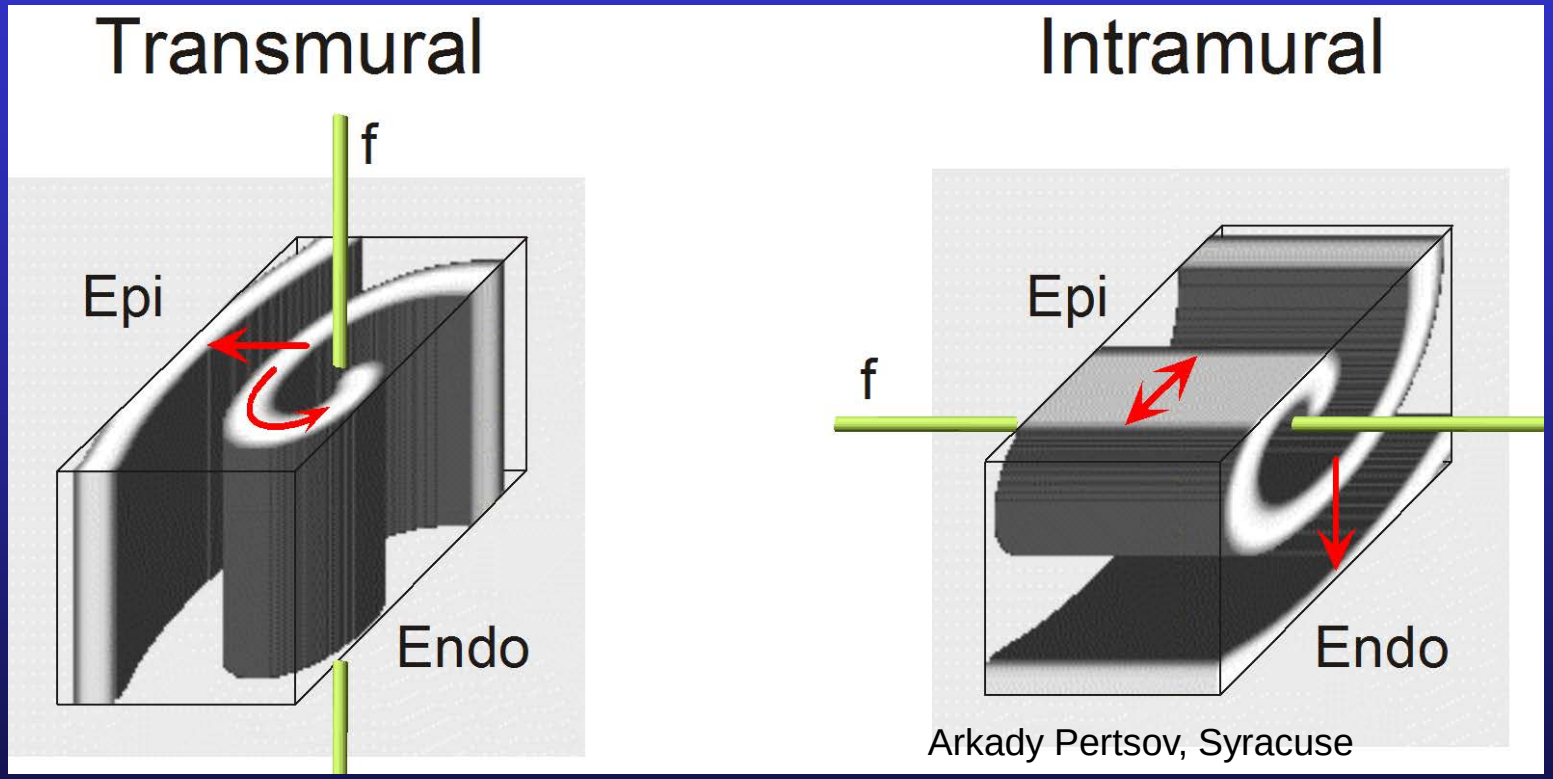


Vm_Var_Phase_Curl.mp4



And the Third Dimension…

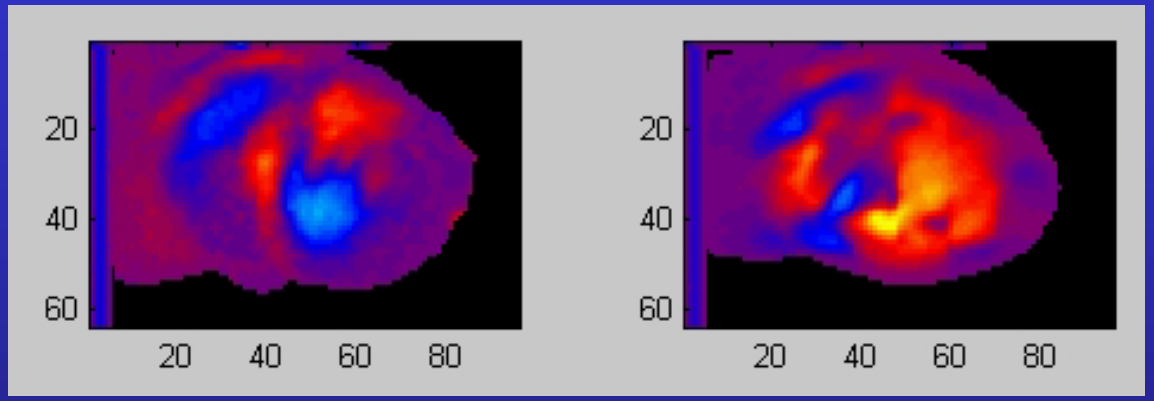
Spiral vs Scroll Waves

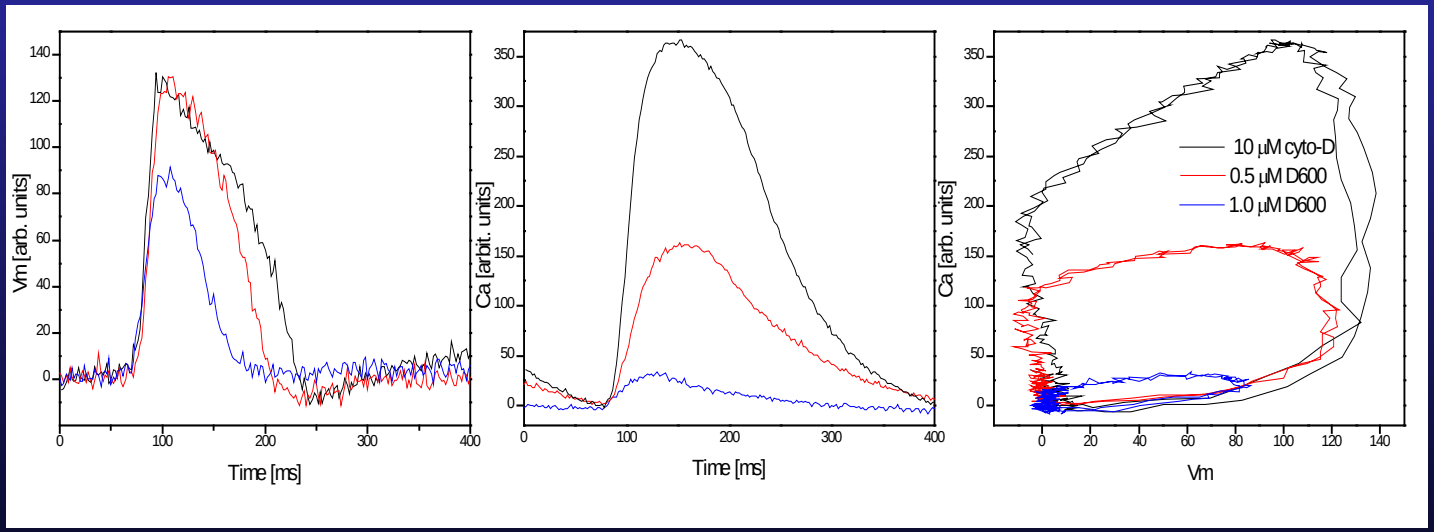


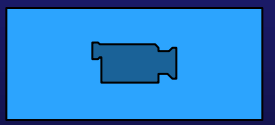
- Transmural waves can exist in 2-D (thin) or 3-D (thick)
- Intramural waves require ~1 cm wall thickness

Understanding Cardiac Dynamics

V_m & Ca^{++}
vs.
Methoxyverapamil
(D-600)







Vm_Ca.mp4

Questions

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