The Physics of the Heart

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XXV Encontro Nacional de Física da Matéria Condensada
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Department of Molecular Physiology and Biophysics
http://medschool.mc.vanderbilt.edu/mpb/

Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE)
http://www.vanderbilt.edu/viibre (coming soon)

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DEPARTMENT OF PHYSICS AND ASTRONOMY, VANDERBILT UNIVERSITY

Cardiac Inventory

- Arrhythmias or antiarrhythmic drugs
- Atrial tachycardia
- Atrial fibrillation
- Ventricular tachycardia
- Ventricular fibrillation
- Conduction block
- Chagas disease
- Pacemakers
- Cardioverter or automatic defibrillator
- Angina
- Nitroglycerin
- Heart attack (myocardial infarction)
- Coronary bypass
- Coronary stents
- Open heart surgery
- Artificial valves
- Smoking? Cardiac problems and smoking? Ex-smoking

Self

Family

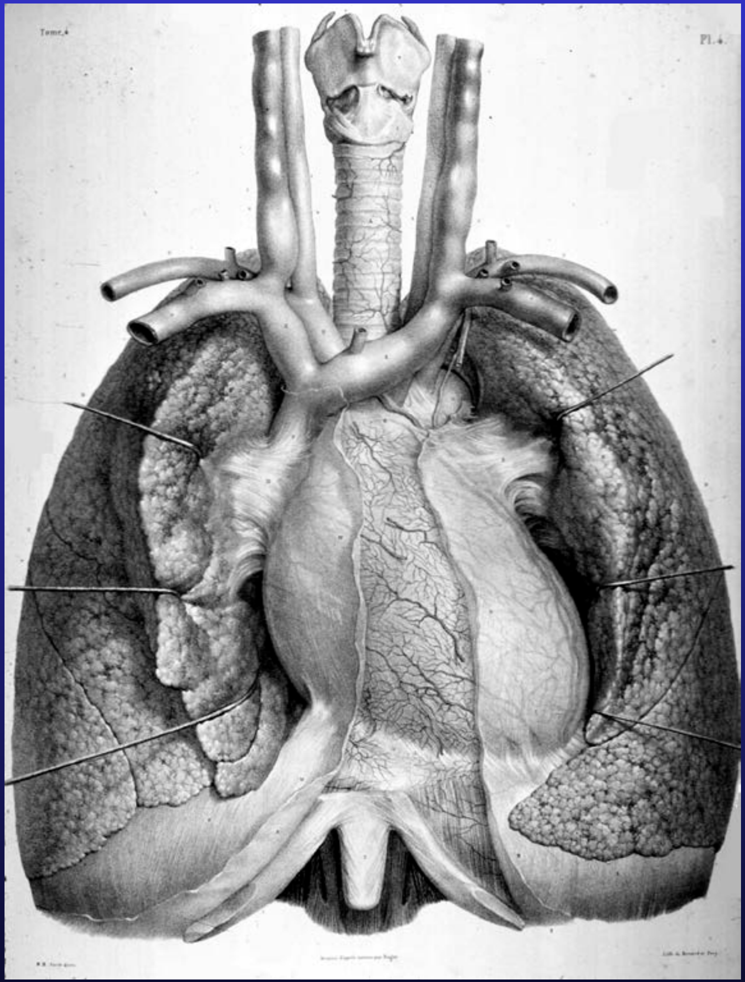
Friends

Goals

- To demonstrate, from the perspective of a physicist, the elegance of cardiac electrophysiology and biophysics
- To show how multiple spatial scales govern the behavior of the heart

The Heart is a…

- Self-assembling,
- Biochemically powered,
- Electrically activated,
- Electrically non-linear,
- Pressure- and volume-regulated,
- Two-stage,
- Tandem,
- Mechanical pump
- With a mean time-to-failure of approximately two billion cycles.



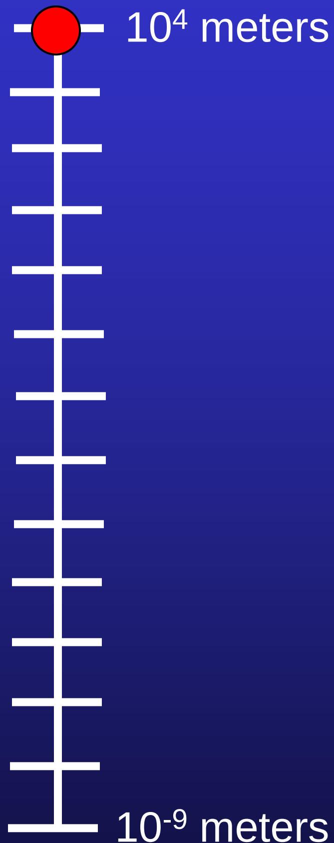
A flying tour of cardiac biophysics, …

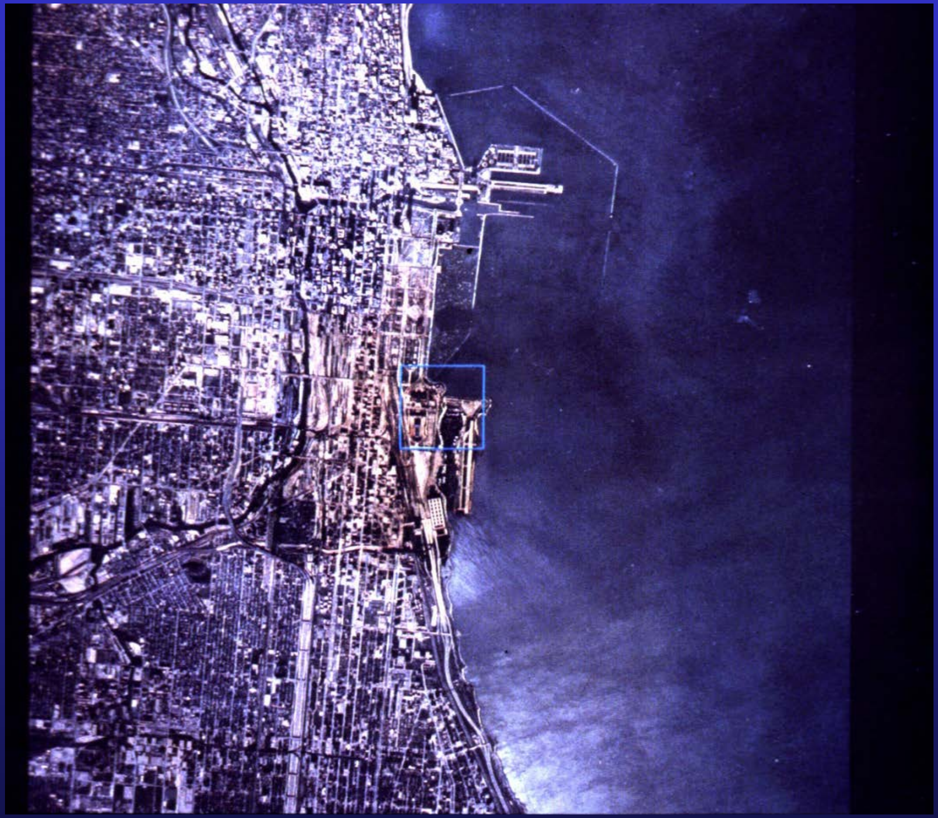
with occasional stops…

The Spatial Scales

- 10 km — Chicago
- 1 km — Soldiers Field
- 100 m — A park
- 10 m — A picnic
- 1 m — People
- 10 cm — Diameter of the heart
- 1 cm — Thickness of the left ventricular wall
- 1 mm — Electrical length scale of cardiac tissue
- 100 μm — Length of a cardiac cell
- 10 μm — Width of a cardiac cell
- 1 μm — Cardiac sarcomere spacing
- 100 nm — Intercalated disk thickness
- 10 nm — Proteins; Cell membrane thickness
- 1 nm — Pore diameter in a membrane protein

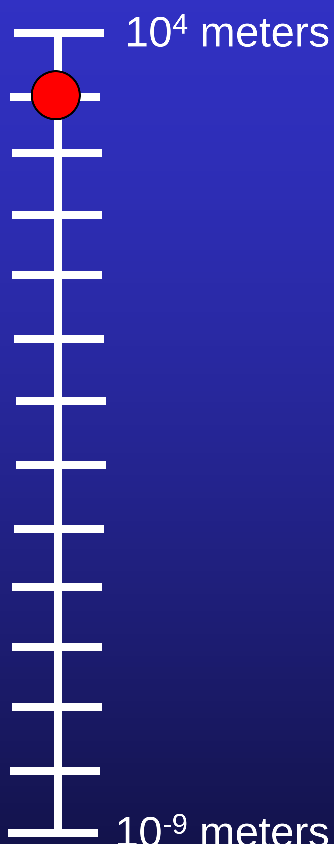
10 kilometers: Chicago

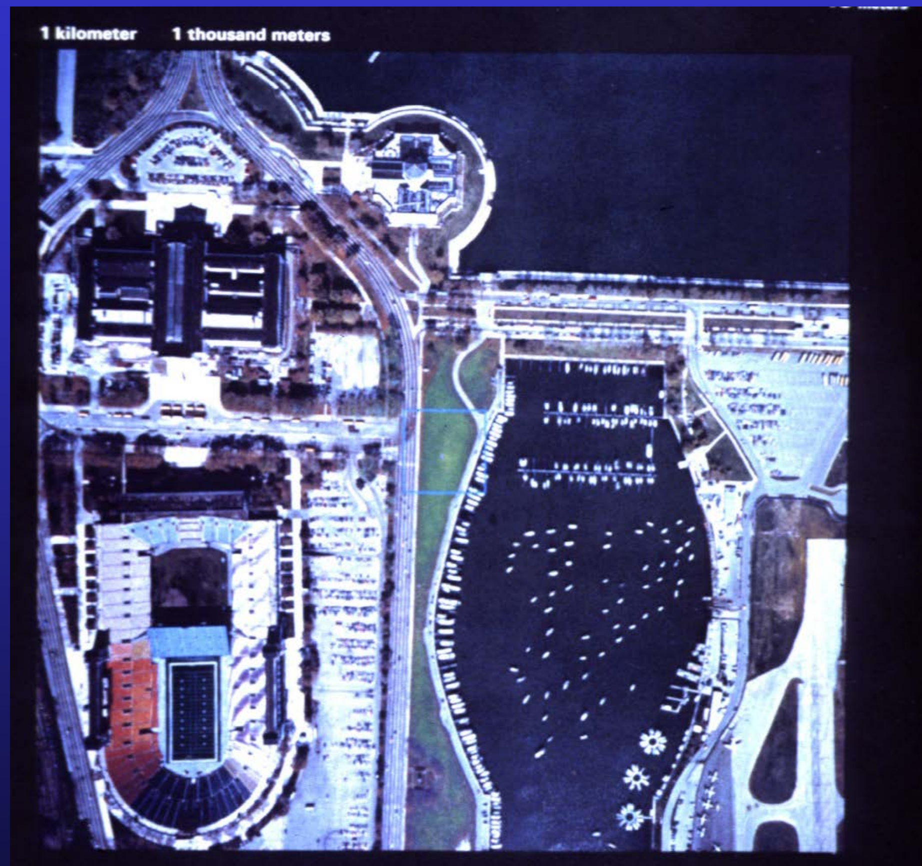




From Powers of Ten by Philip Morrison

1 kilometer: Soldiers Field





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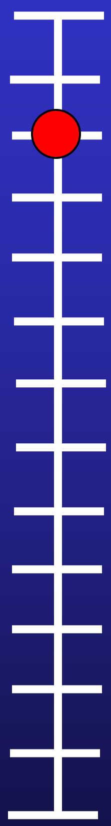
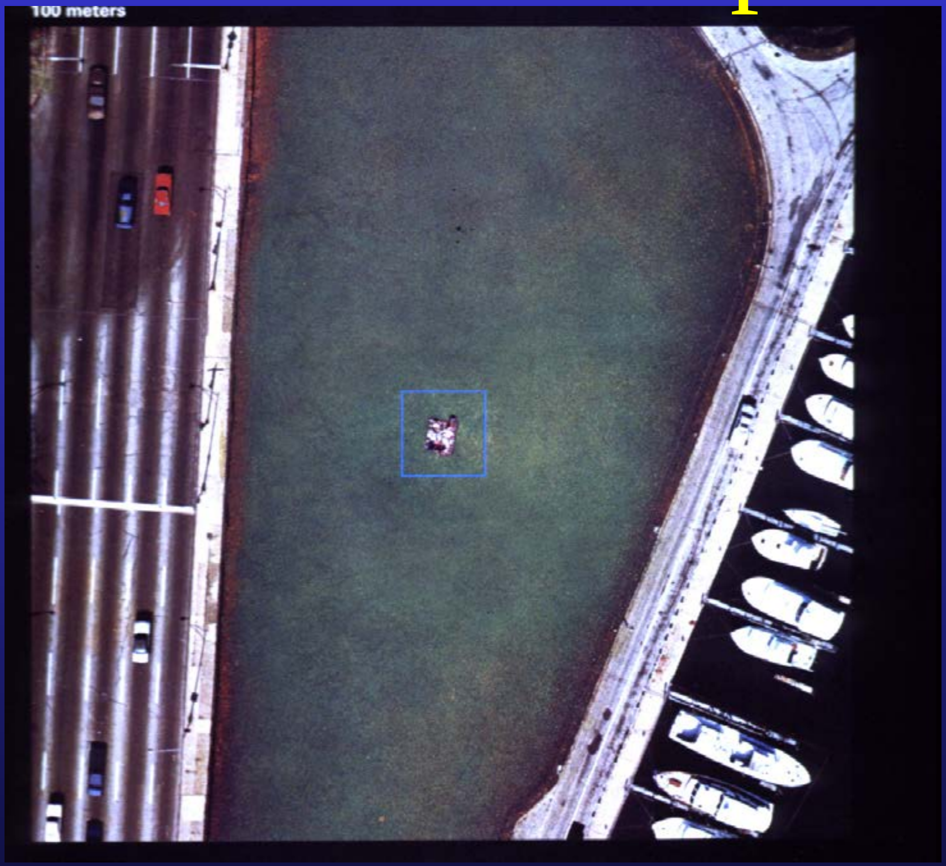
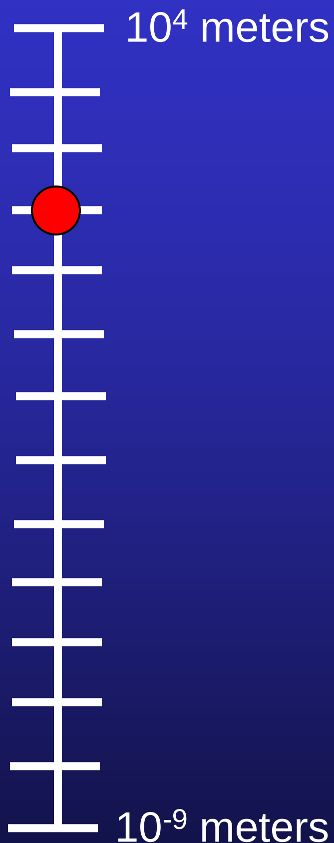
100 meters: A park





From Powers of Ten by Philip Morrison

10 Meters: A picnic



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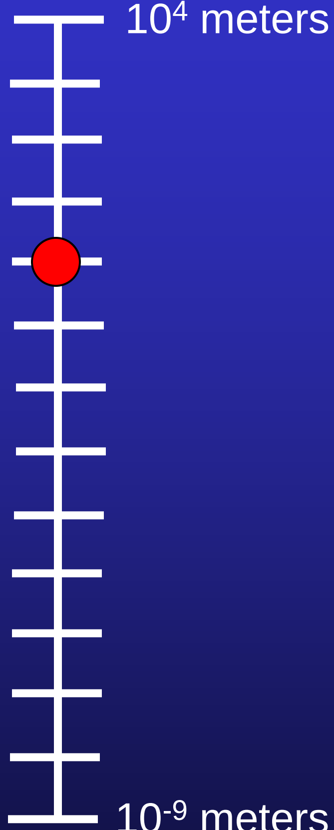
1 meter: A human



From Powers of Ten by Philip Morrison

s02731

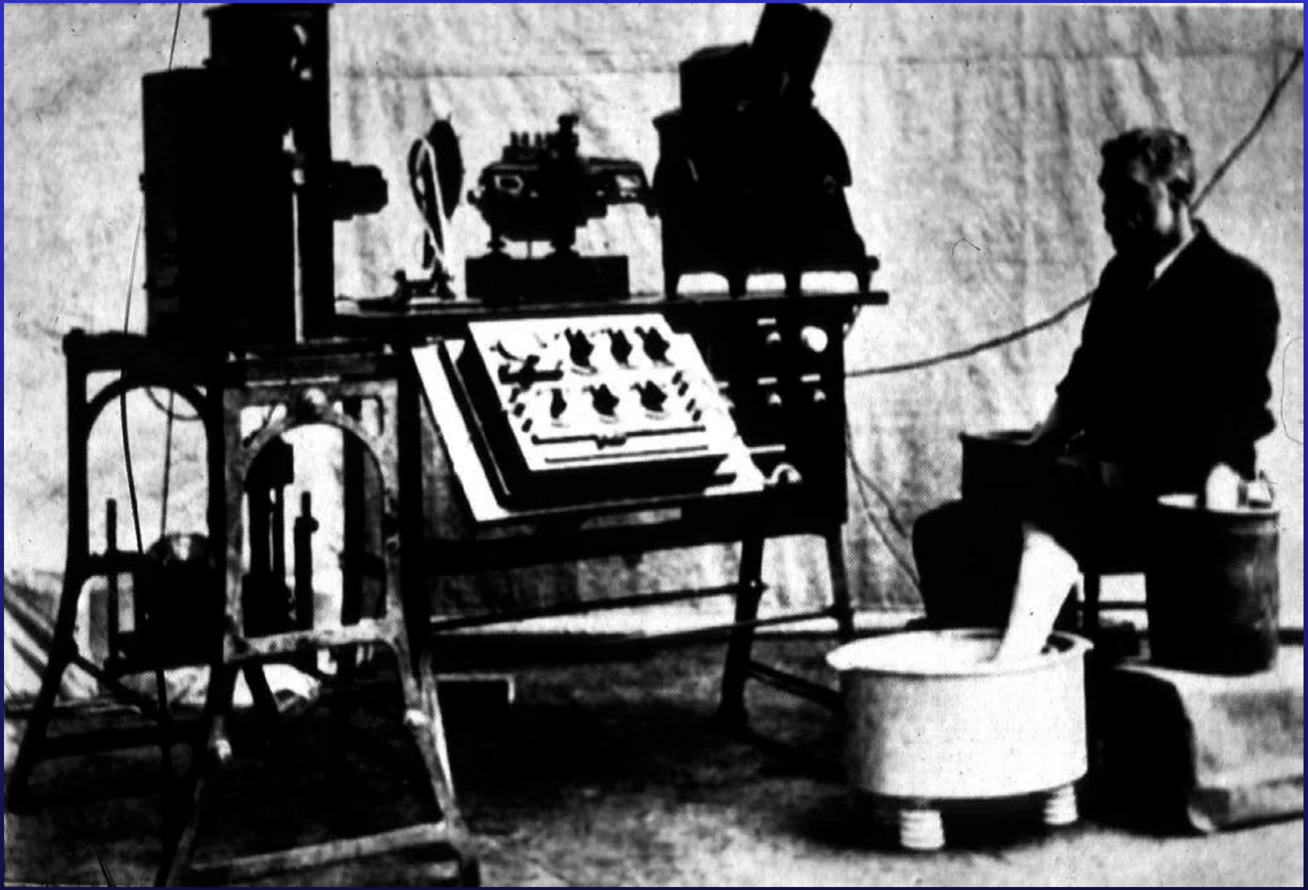
s01783

1 meter

VIBRE

The First Clinical ECG Machine

- Arc lamp
- String galvanometer
- Chopper
- Falling-plate camera
- H_2SO_4-filled bucket electrodes



1 meter

VI∫BRE

The First Clinical VMCG Machine

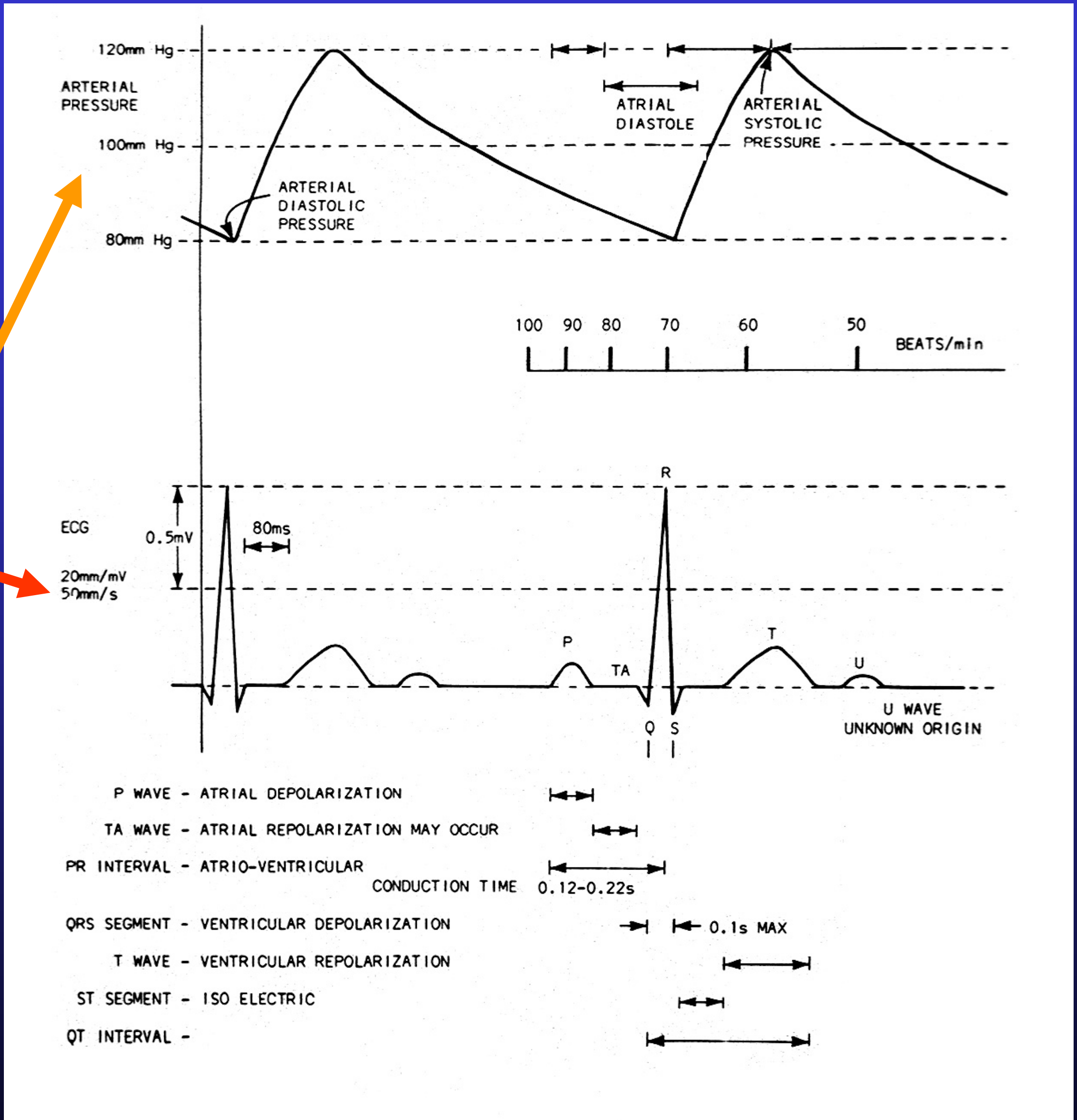
Vector Magnetocardiography
Stanford
~1974

1 meter

VI∫BRE

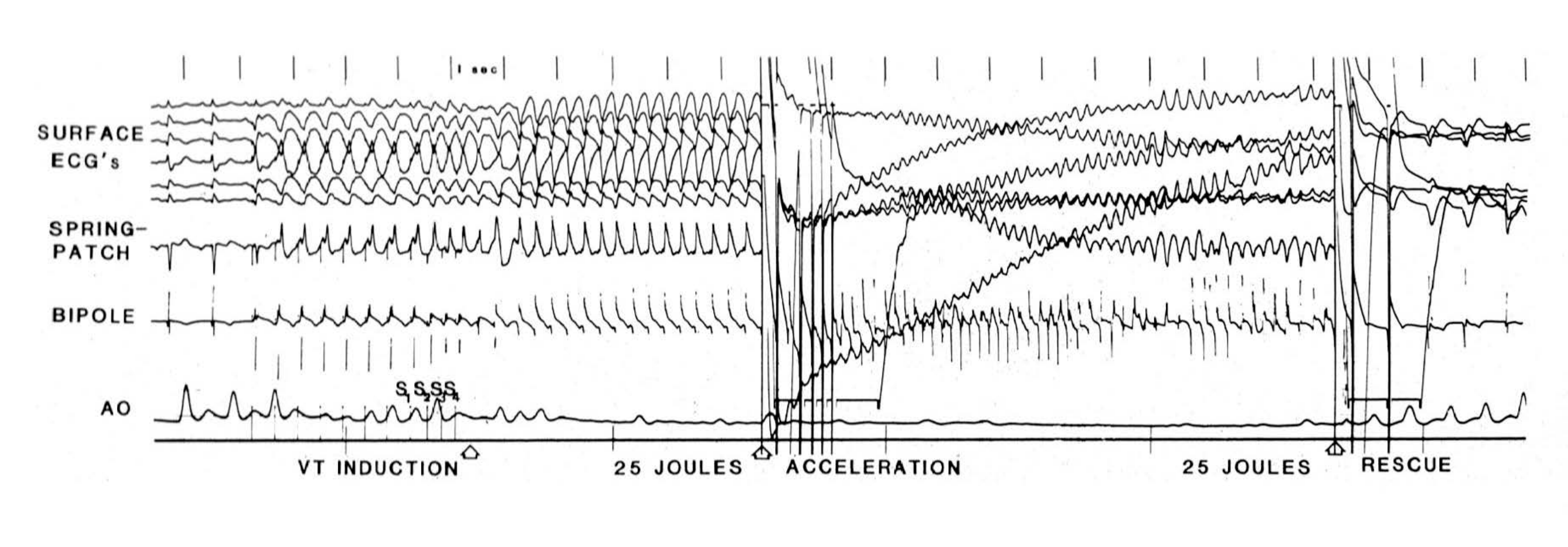
The Heart is an …

- Electrically activated,
- Mechanical pump



1 meter

- …with a mean time-to-failure of approximately two billion cycles….



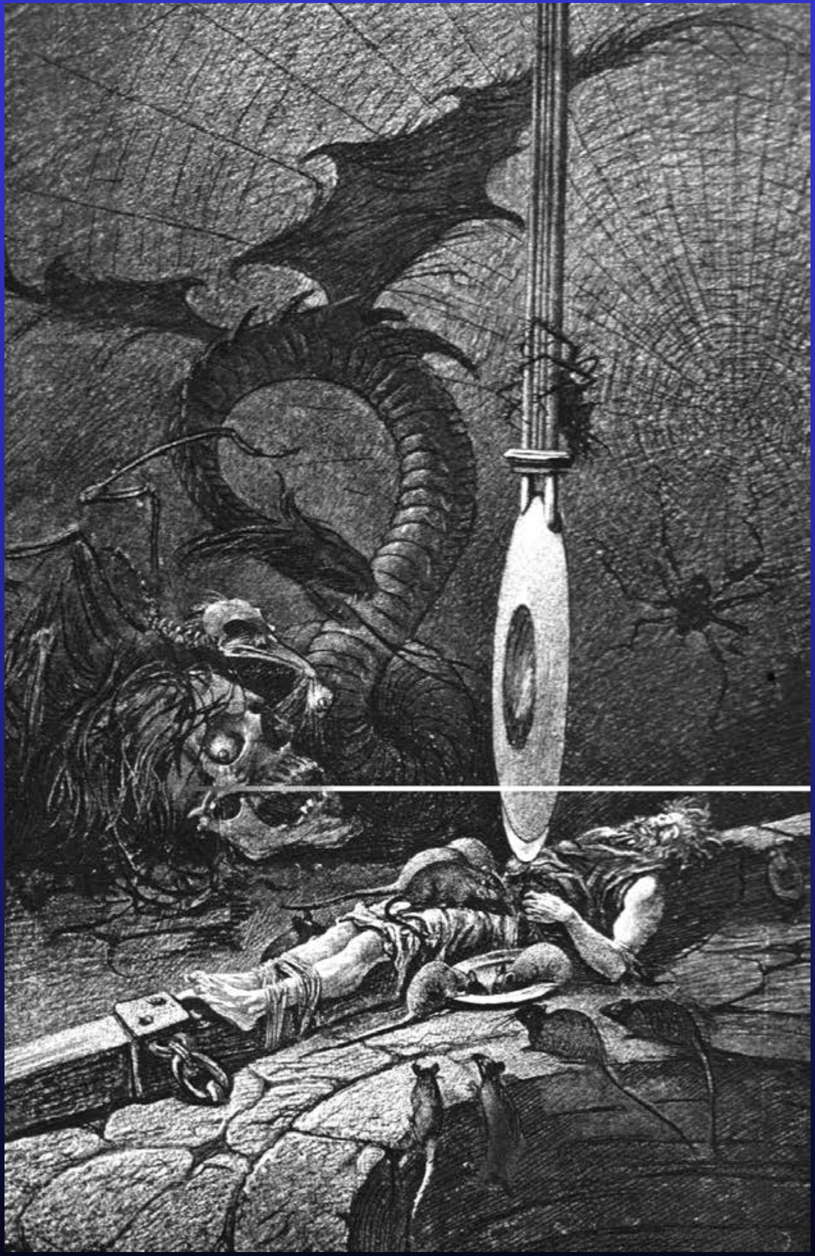
Courtesy of Debra Echt

Sinus rhythm, tachycardia, fibrillation and defibrillation

1 meter

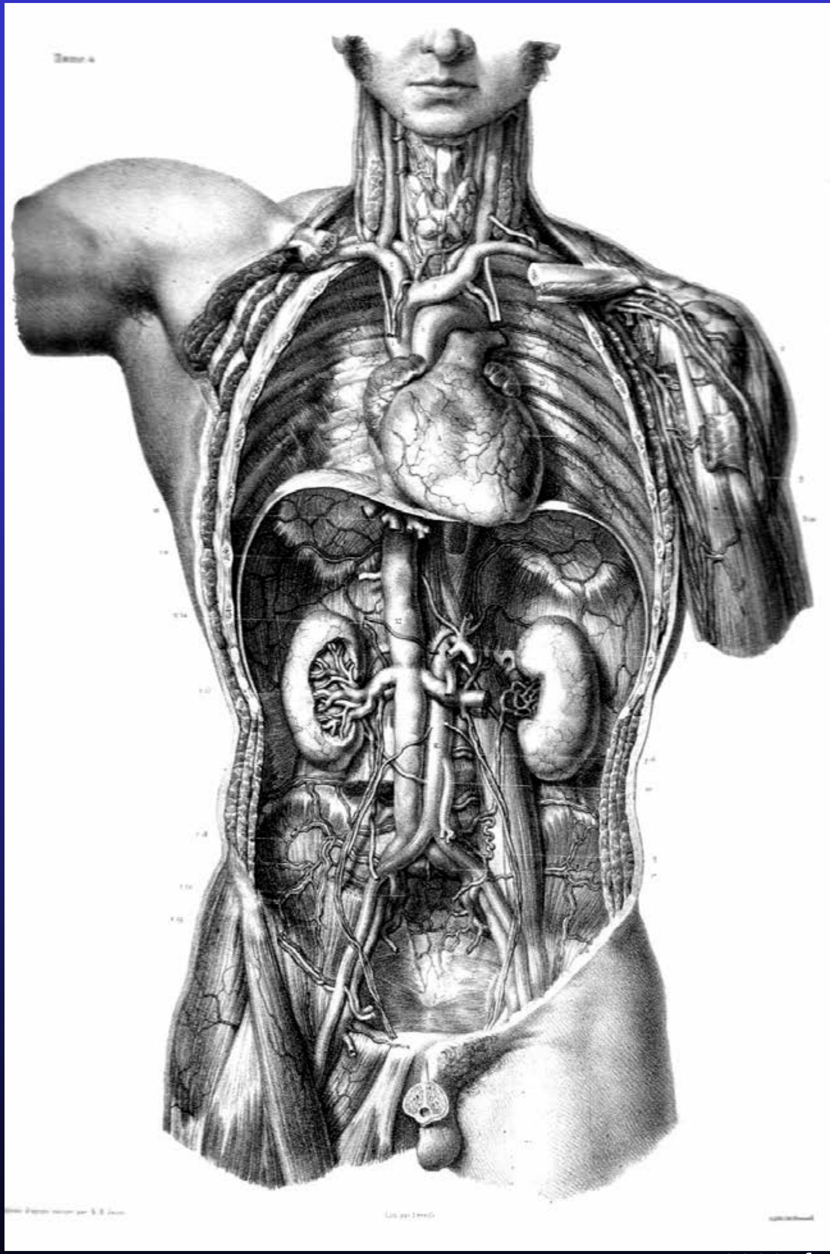
VIIBRE

…to go to smaller scales, we must make a small incision…



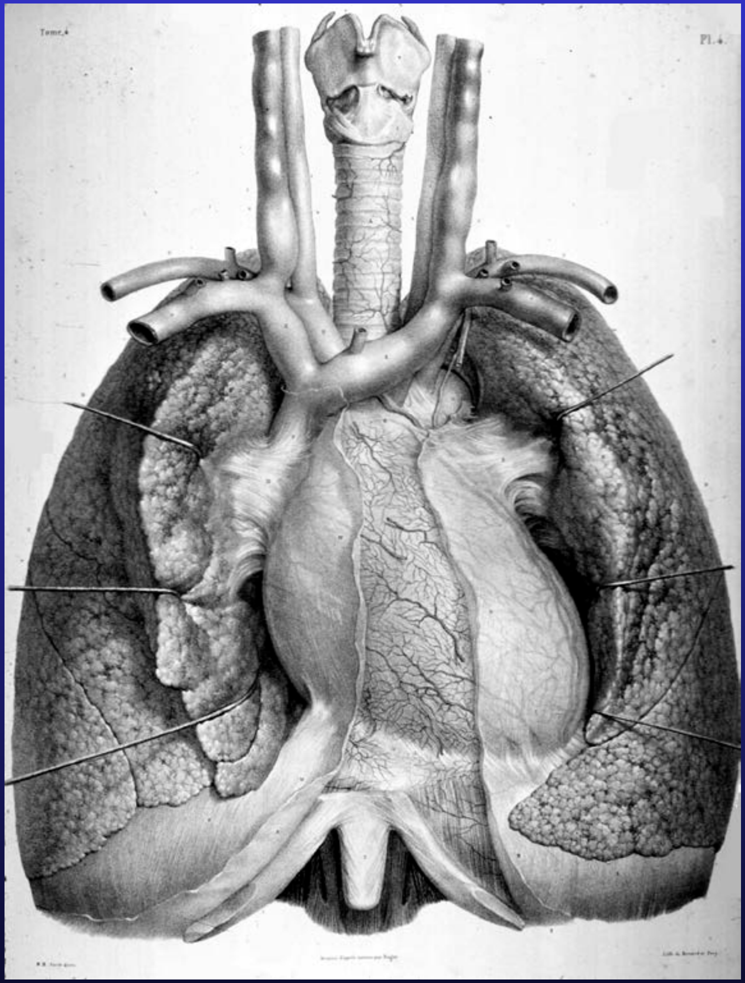
1 meter

Et voilà, an uncomfortable gentleman from nineteenth century France



The Heart is a…

- Biochemically powered,
- Electrically activated,
- Pressure- and volume-regulated,
- Two-stage,
- Tandem,
- Series-connected,
- Mechanical pump
- With a mean time-to-failure of approximately two billion cycles.



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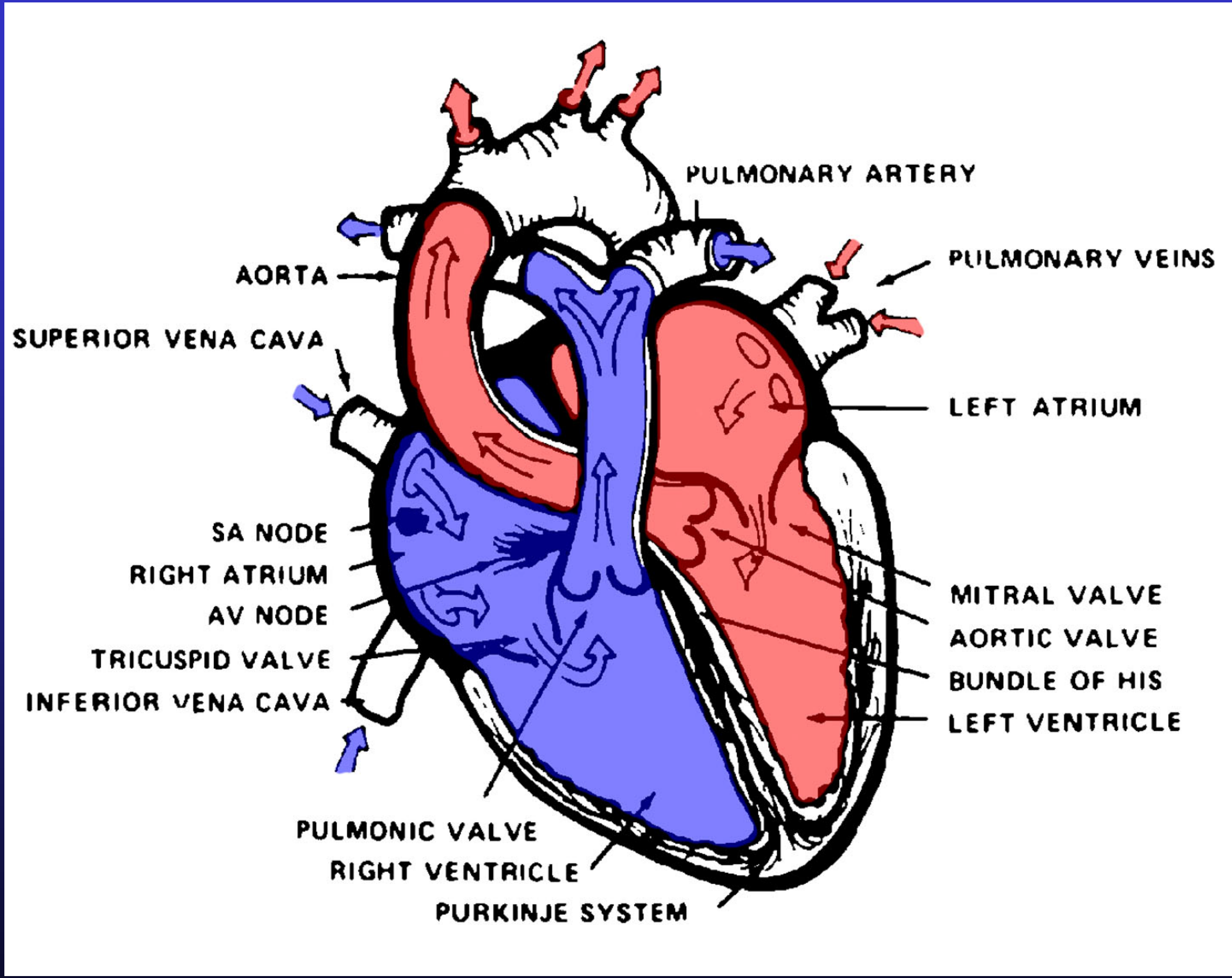
VIBRE

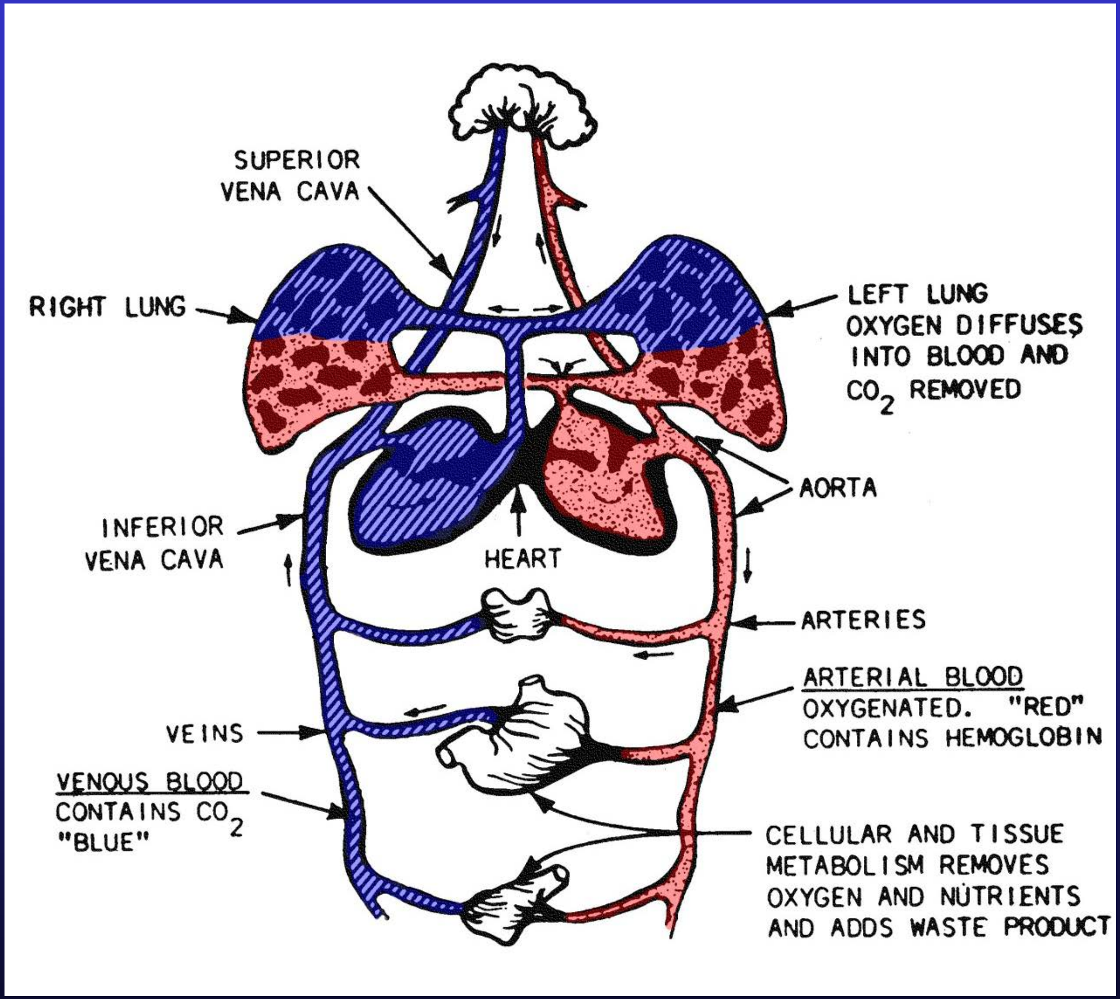
The Heart is a…

- …
- Two-stage,
- Tandem,
- ….
- Mechanical pump
- …..



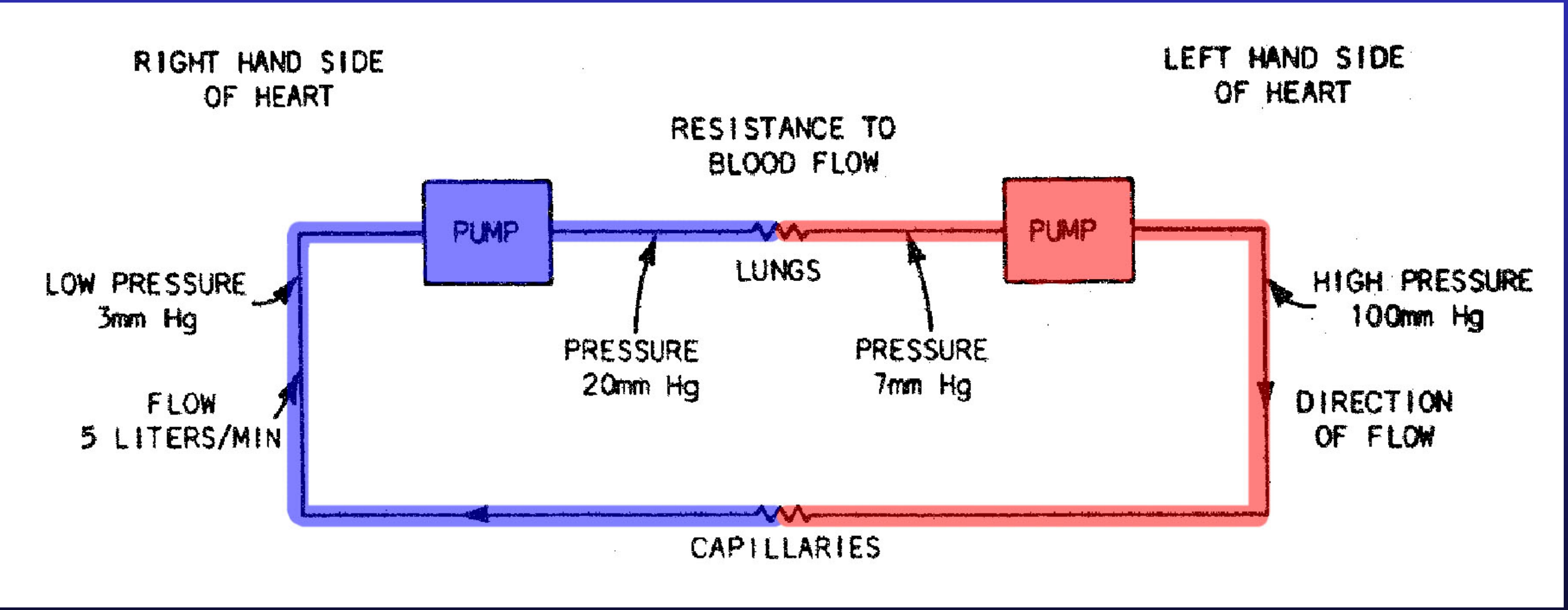
The Heart is…

- …..
- Pressure- and volume-regulated,
- Two-stage,
- Tandem,
- Series-connected,
- Mechanical pump
- …



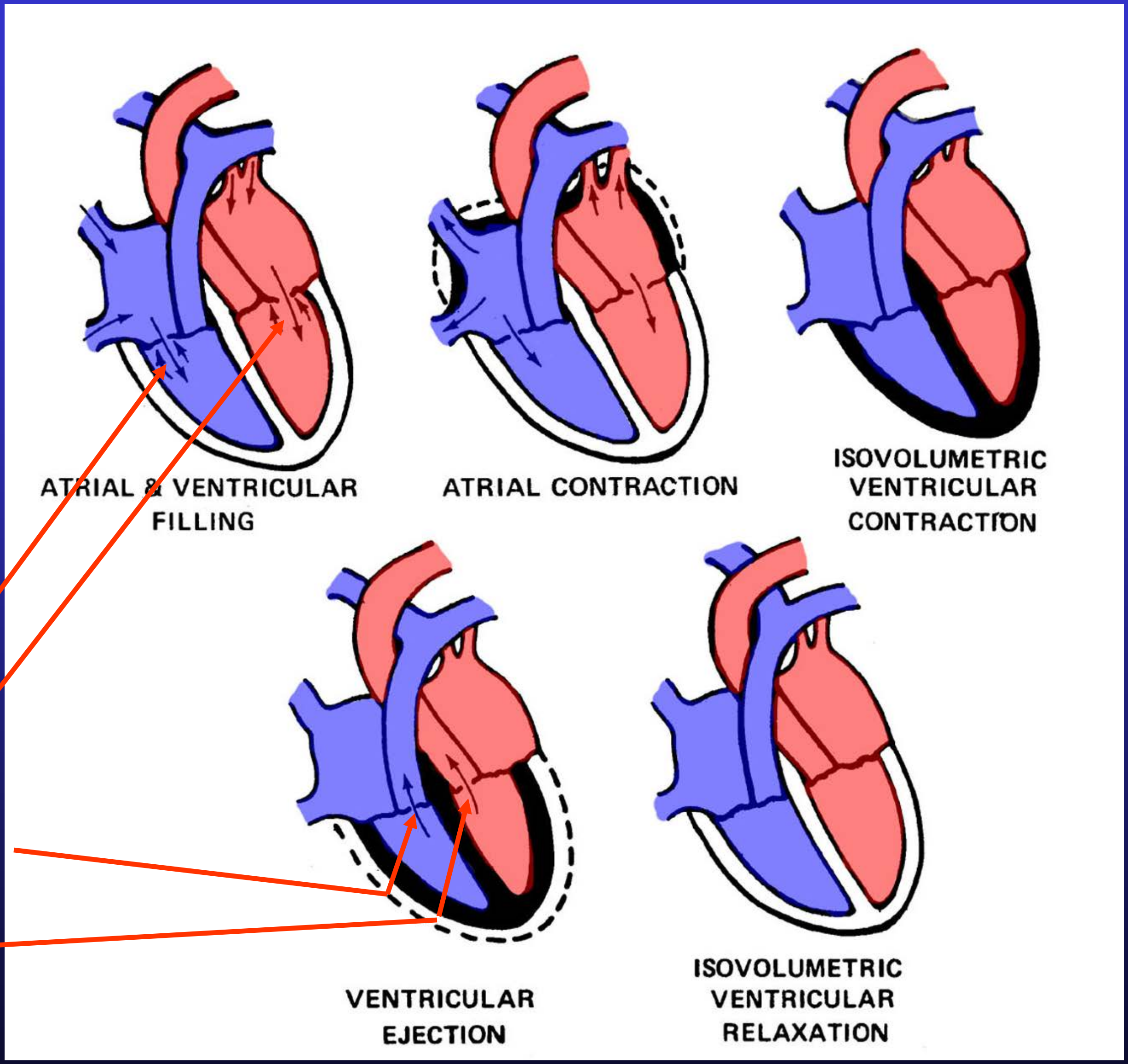
The Heart is a…

… Pressure- and volume-regulated, two-stage, ***series-connected***, tandem, mechanical pump …



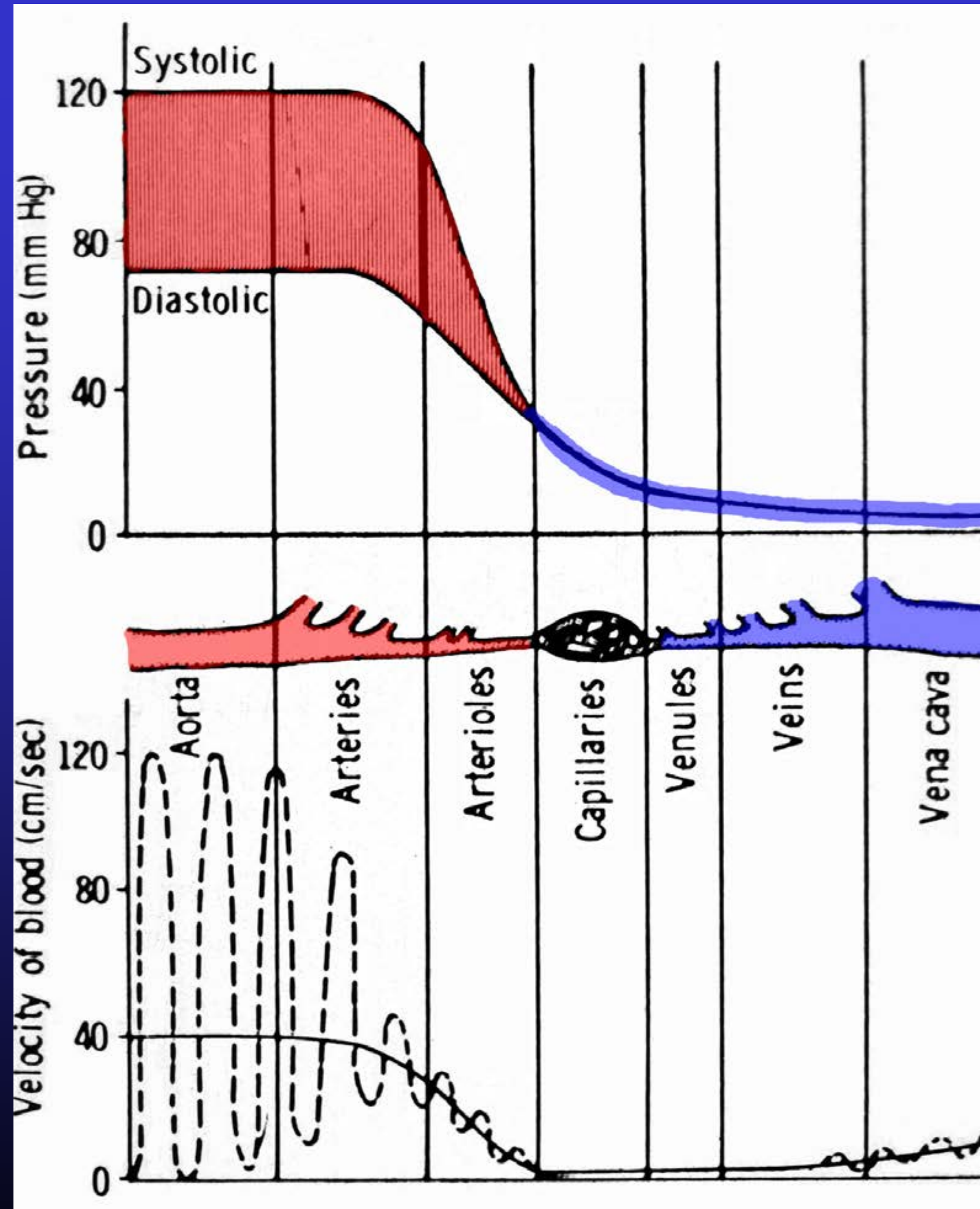
The Cardiac Cycle and Valves

- Tricuspid (R)
  Mitral (L)
- Pulmonary (R)
  Aortic (L)



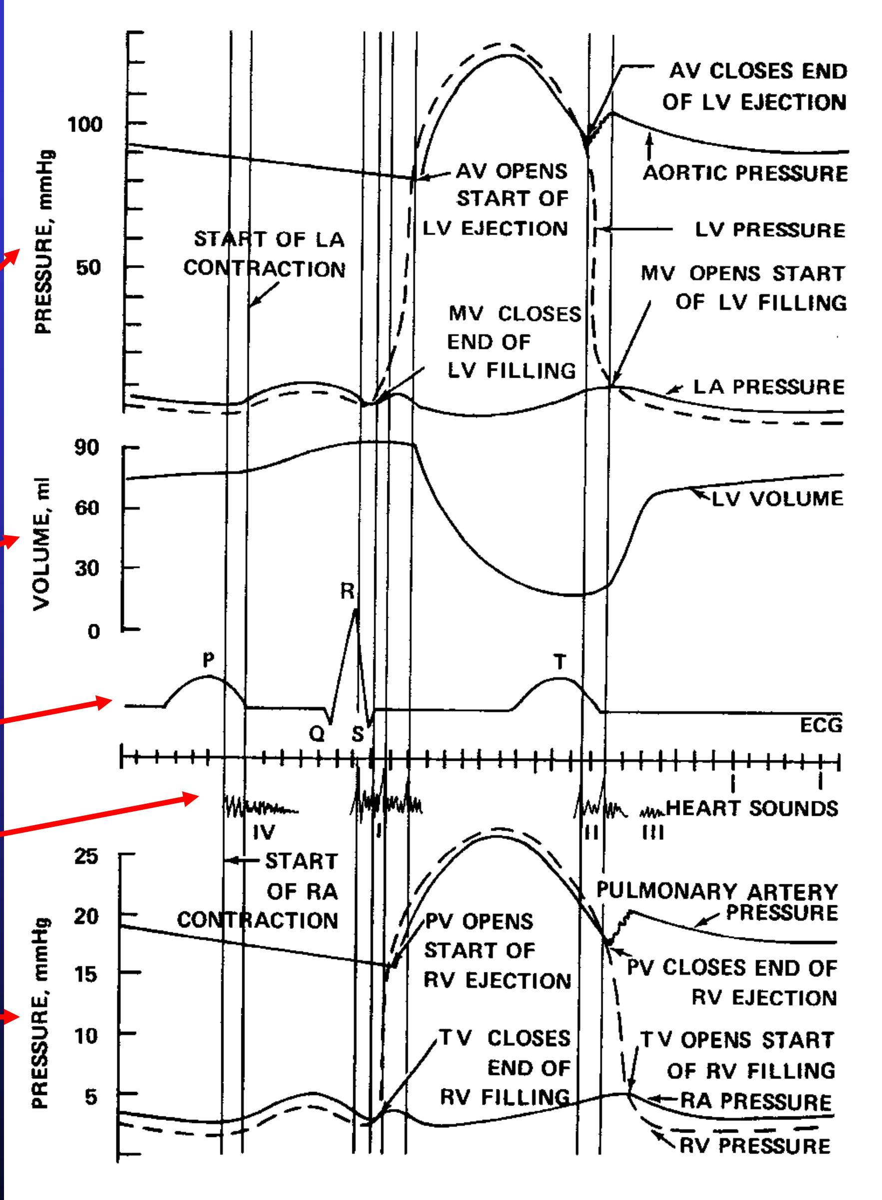
Peripheral Circulation

- Pressure fluctuations
  - Systolic 120 mm Hg
  - Diastolic 70 mm Hg
- Velocity ~1 m/s
  - Oscillating in arteries
  - Steady in capillaries
  - Most of the pressure drop occurs in the arterioles to control peripheral resistance



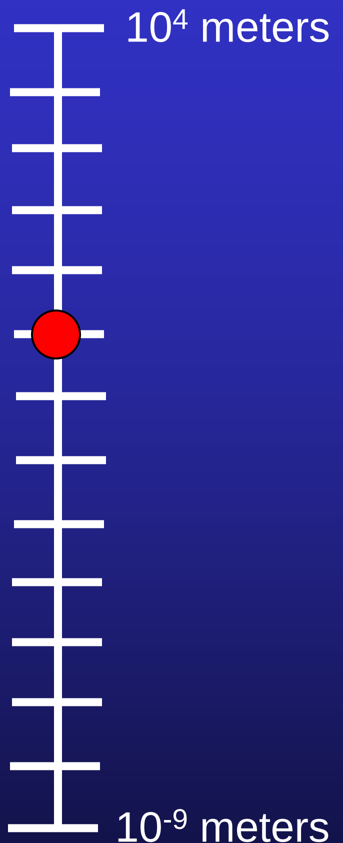
The Cardiac Cycle

- Left pressures
- LV volume
- ECG
- Heart sounds
- Right pressures



Onward, inward….

10 centimeters: The human heart



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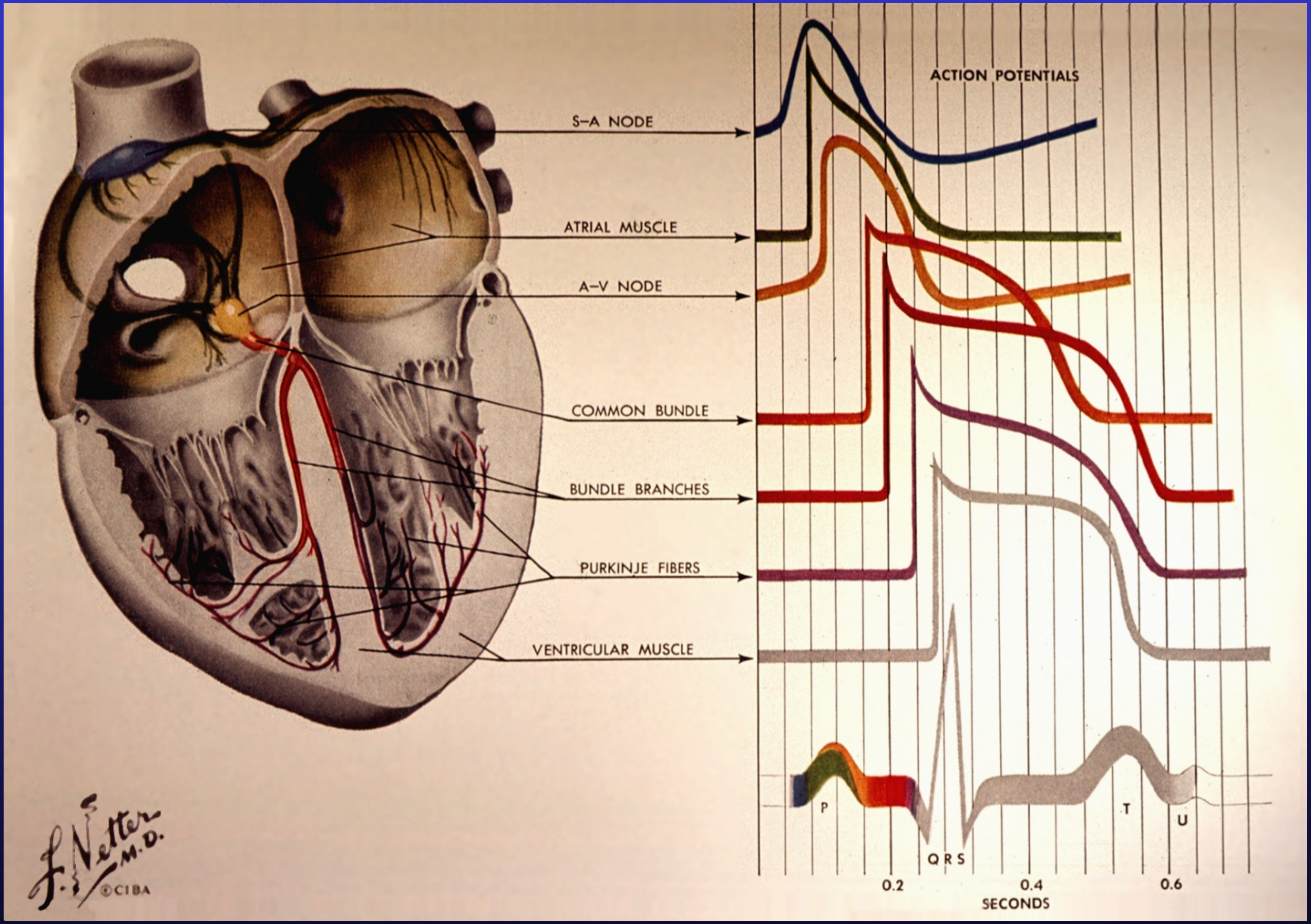
s04034

10 centimeters

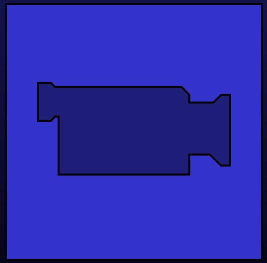
The heart is ... Electrically activated,



10 centimeters

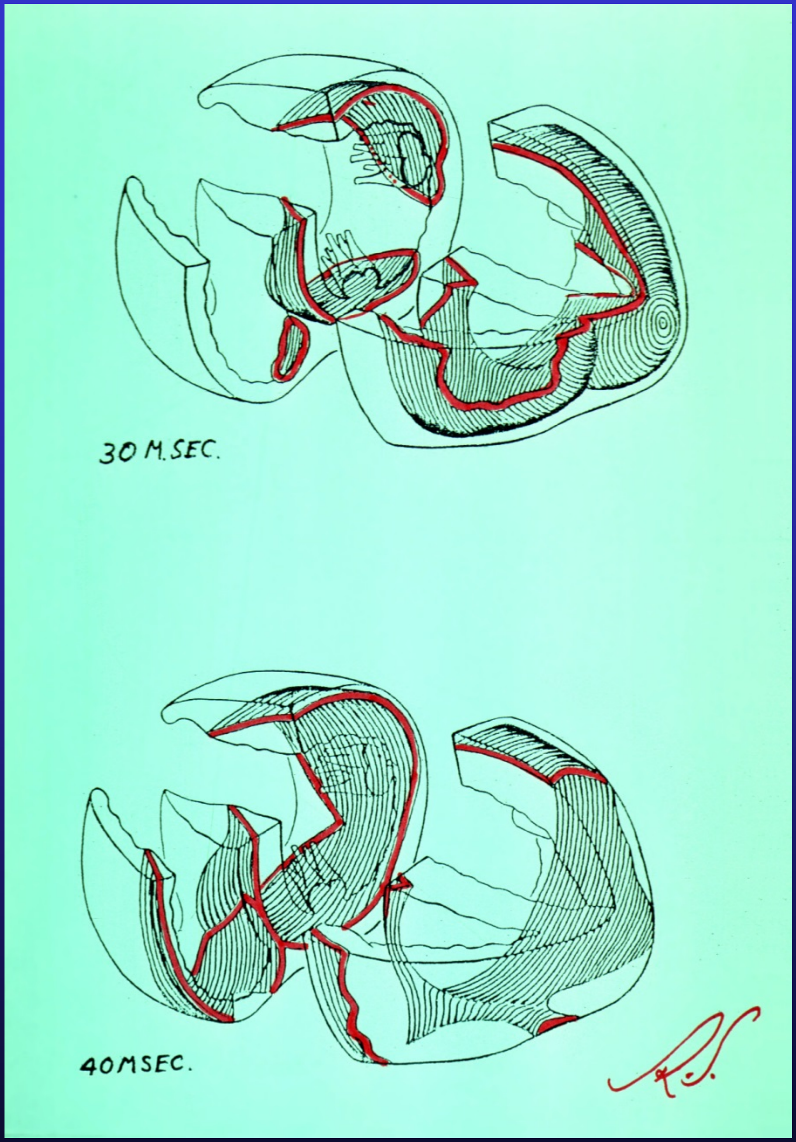
The cardiac depolarization wave front

- Activated cells collectively form a sheet that is a moving 3-dimensional battery
- 1 mm thick
- Moving at ~1 m/sec



Courtesy of Rubin Aliev

HLR2.mpg

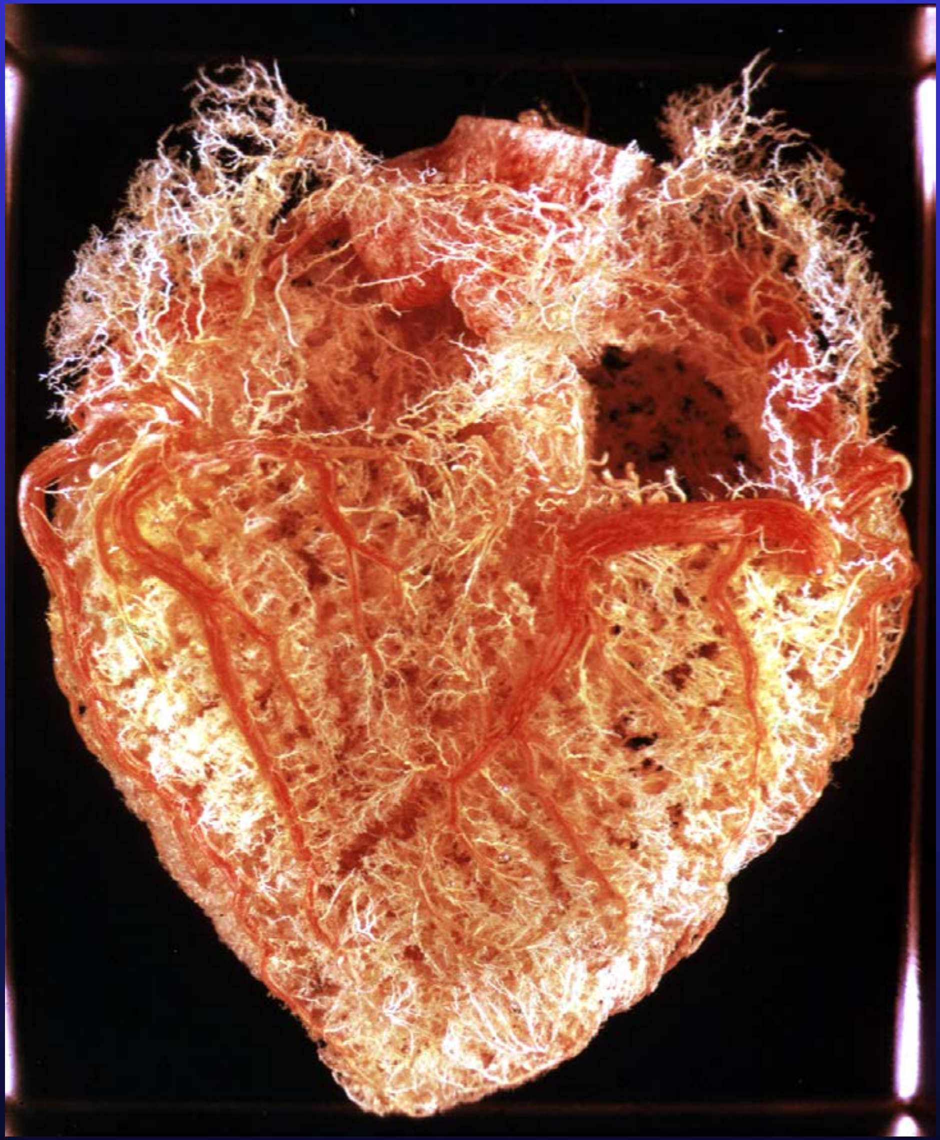


Courtesy of Ron Selvester

10 centimeters

The Coronary Arteries

- ….
- With a mean time-to-failure of approximately two billion cycles.



Courtesy of Jaakko Malmivuo

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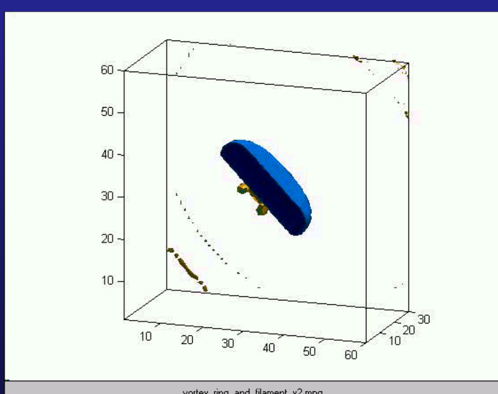
10 centimeters

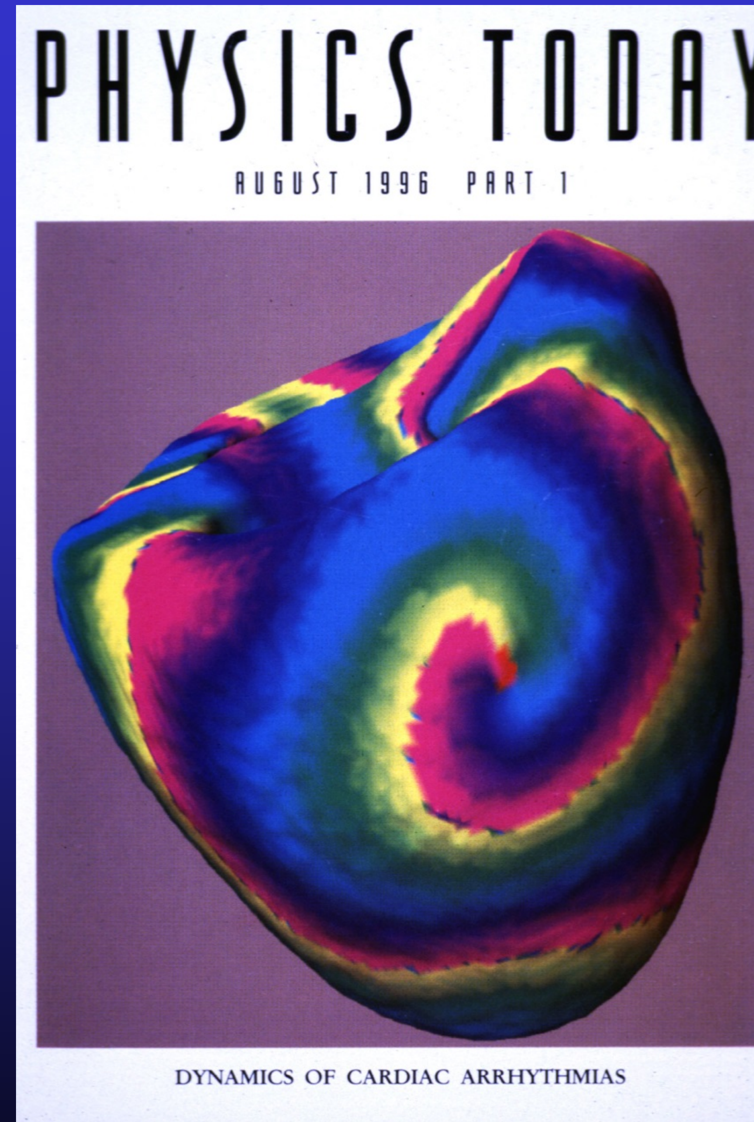
Cardiac fibrillation occurs at the spatial scale of the entire heart!



Spiral wave reentry during ventricular tachycardia

Courtesy of Mark Bray

vortex_ring_and_filament_v2.mpg



Leon Glass, Montreal

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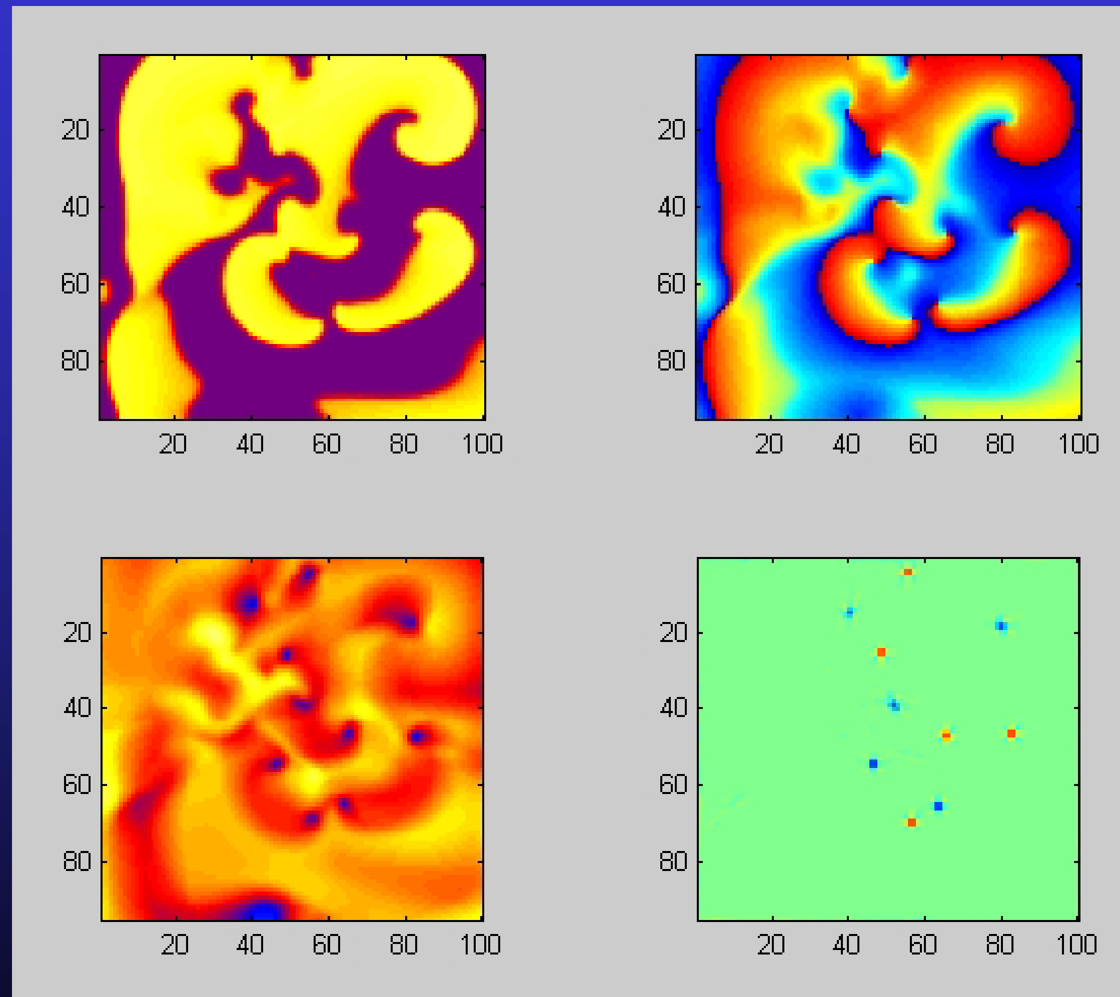
Simulated Fibrillation

V_m Phase

Variance Curl

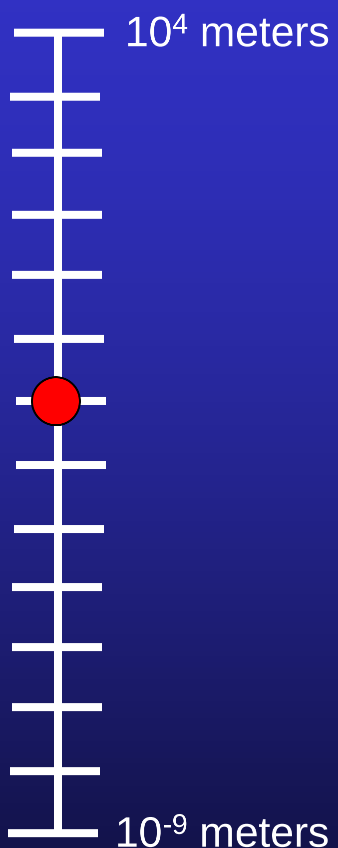


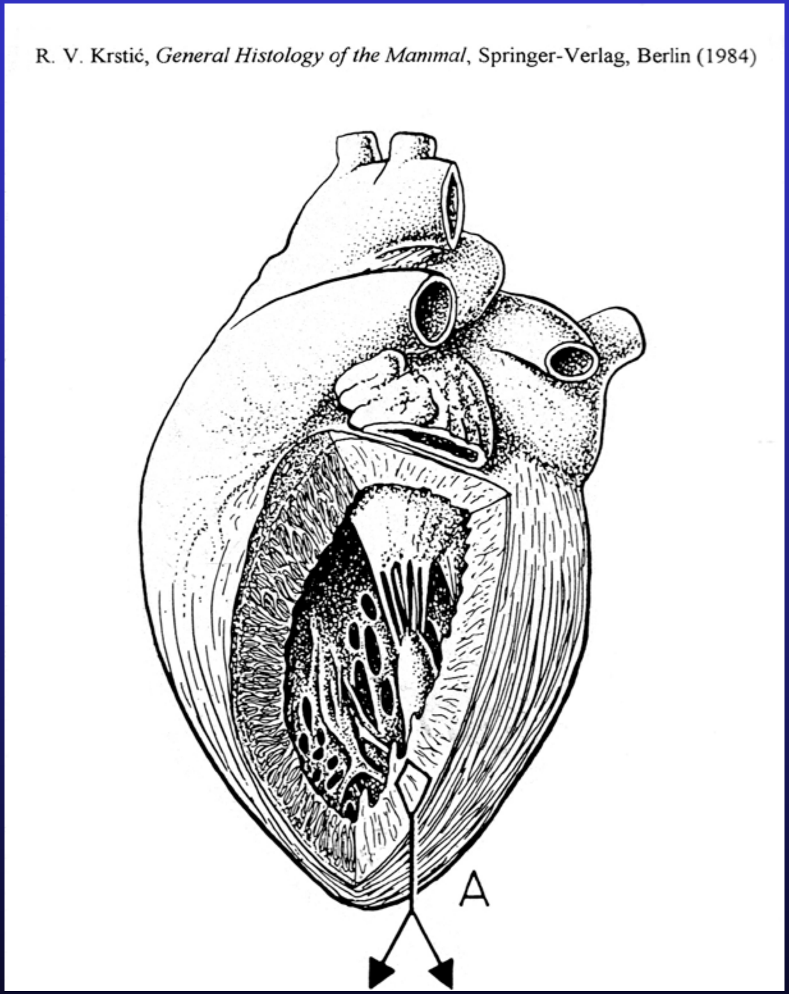
Vm_Var_Phase_Curl.mp4

Courtesy of Mark Bray and Rubin Aliev

Onward, inward….

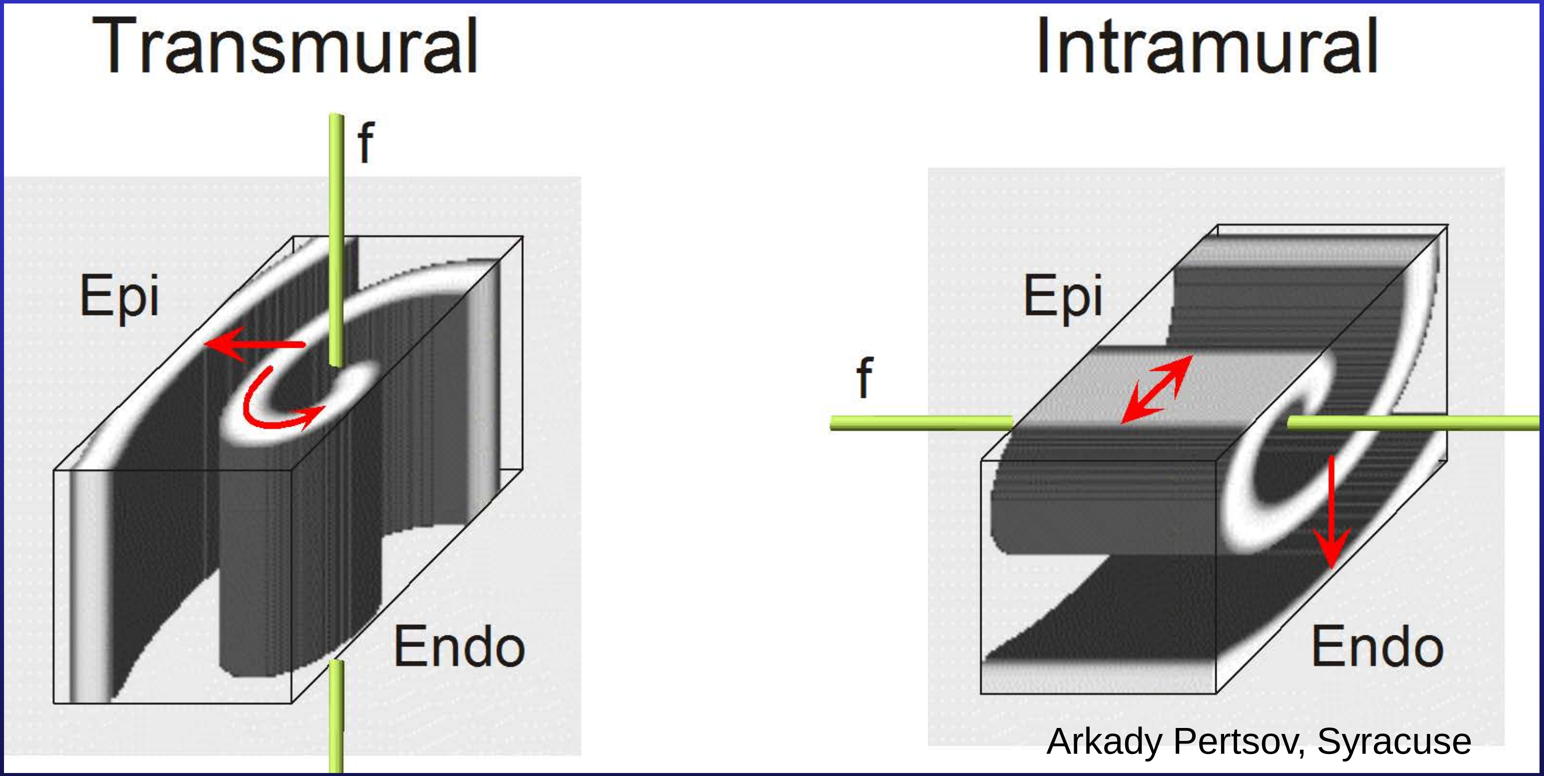
1 centimeter: The left ventricular wall





1 centimeter

Transmural versus intramural scroll waves in reentrant arrhythmias and fibrillation



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

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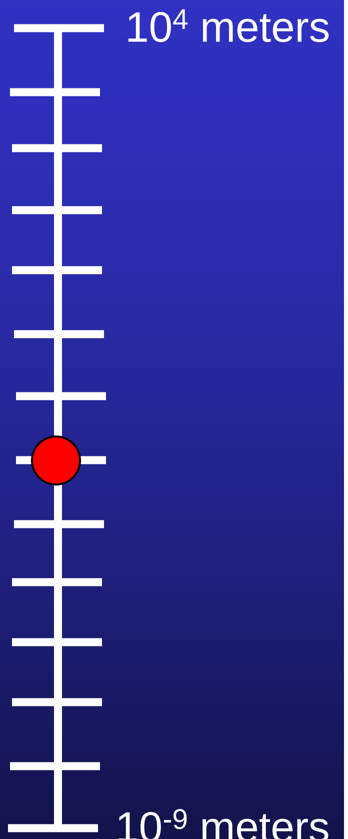
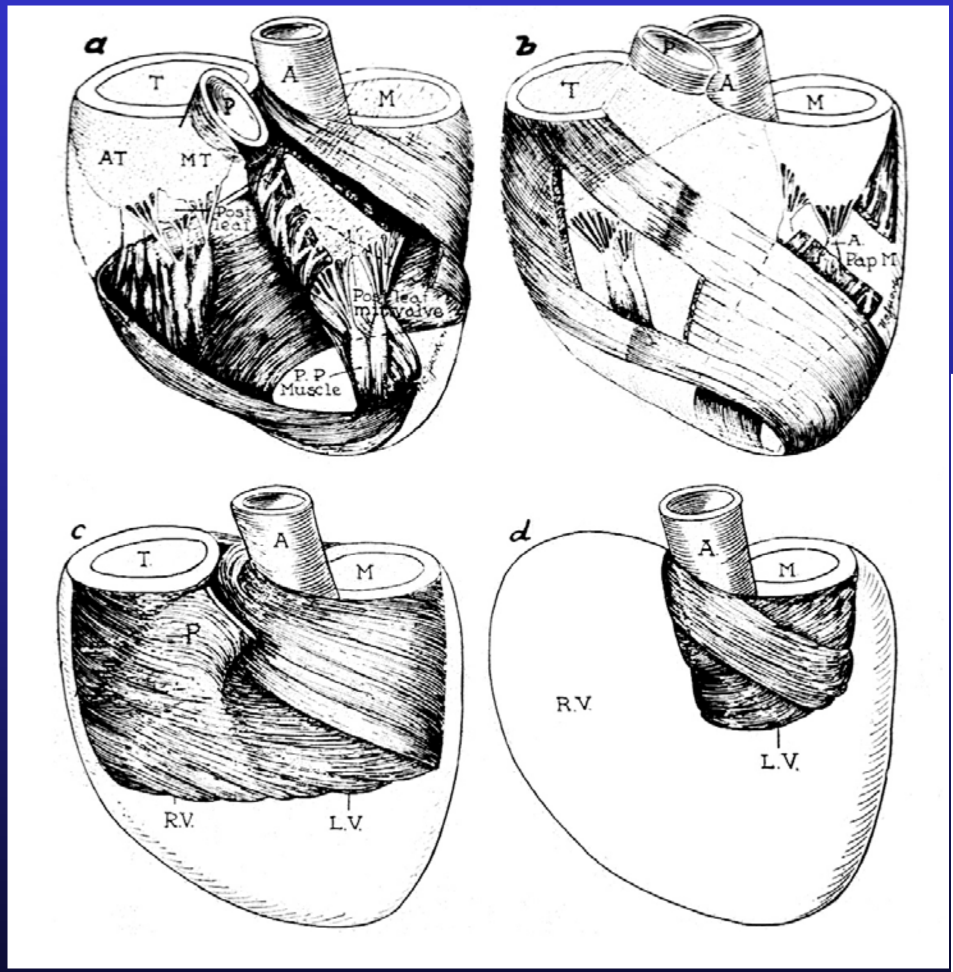
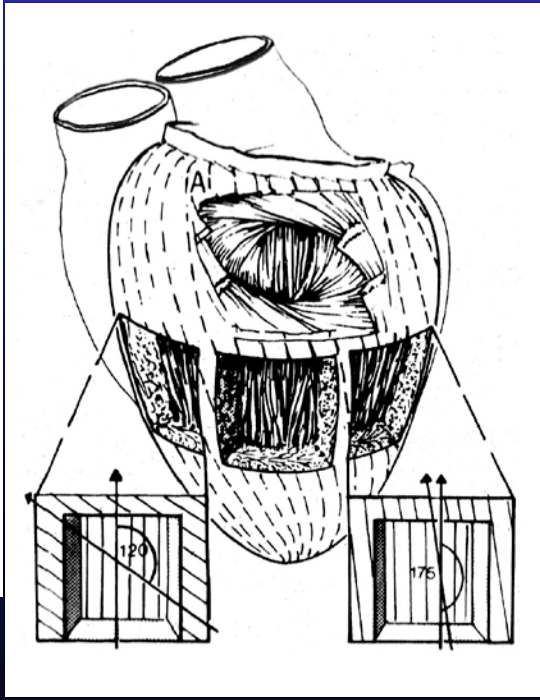
1 millimeter: Cardiac fiber sheets





s00397

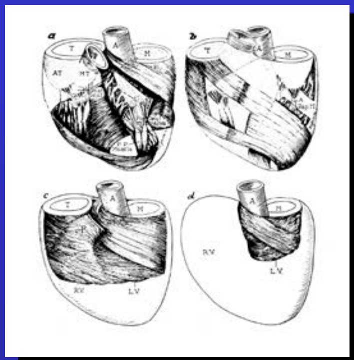


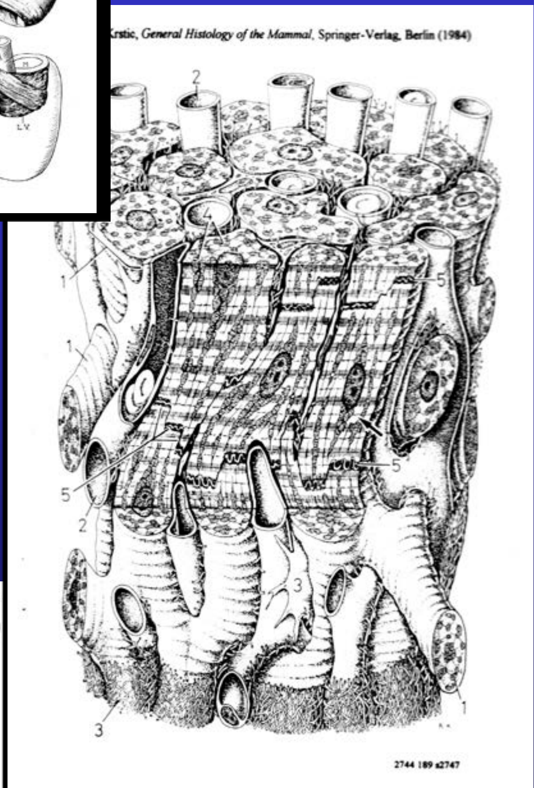
S00703

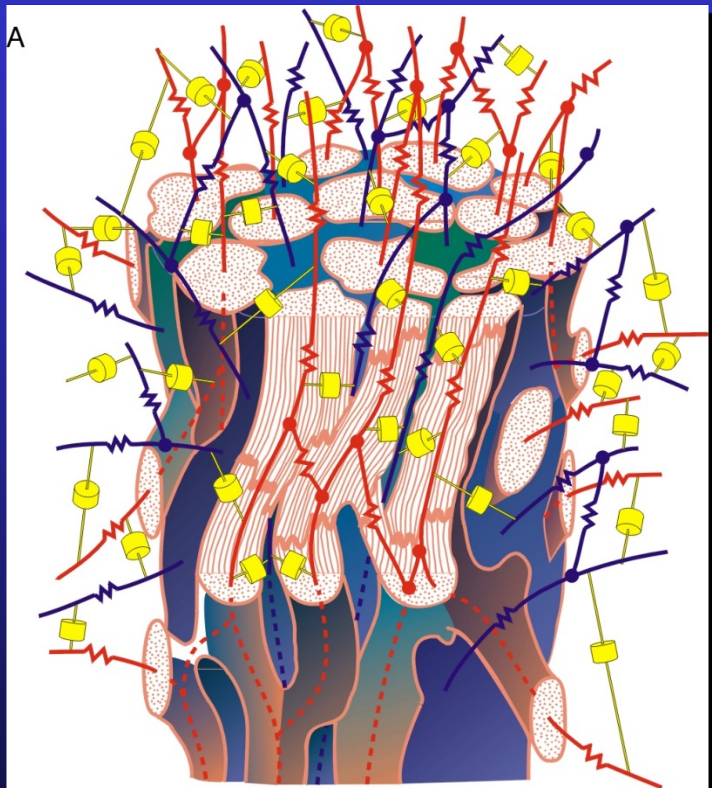
s02734

1 millimeter

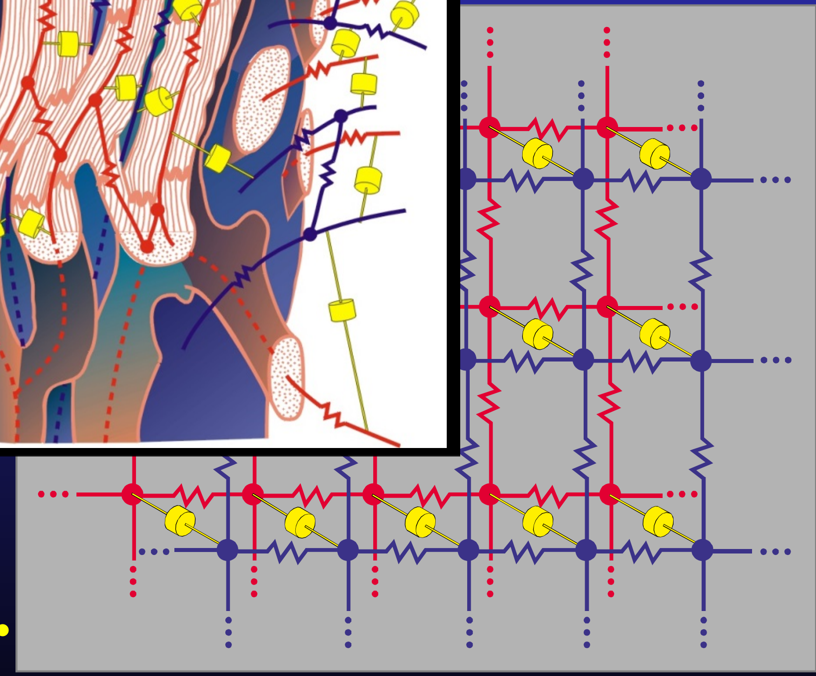
The cardiac syncytium: A three-dimensional non-linear anisotropic bidomain

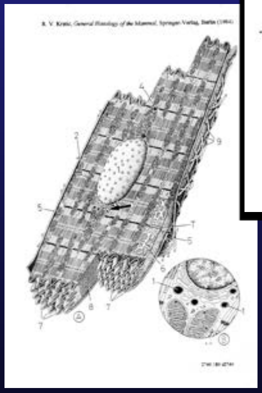






3-D
vs.
2-D





It's the anisotropy….

2-D Bidomain Equations

- Homogenized
- Coupled V_m & V_e
- Nonlinear reaction-diffusion equation
- Boundary value equation

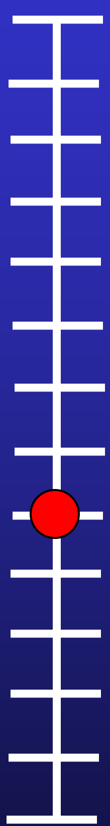
$$C_m \frac{\partial V_m}{\partial t} = -J_{ion} - \frac{1}{\beta} \nabla \bullet \tilde{g}_e \nabla V_e \quad ,$$

$$\nabla \bullet \left(\tilde{g}_i + \tilde{g}_e \right) \nabla V_e = -\nabla \bullet \tilde{g}_i \nabla V_m \, ,$$

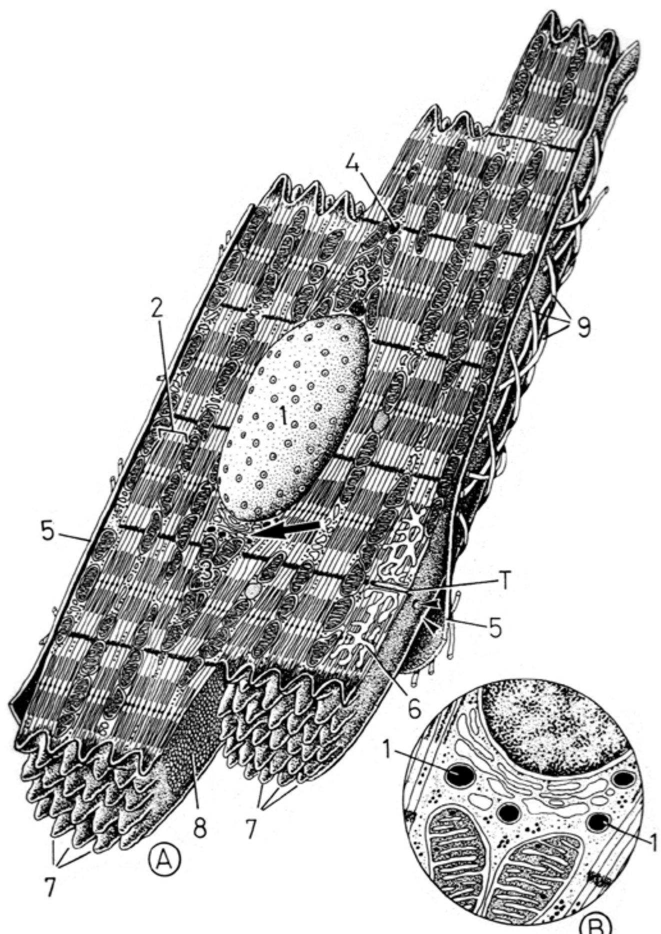
where $\tilde{g}_i$ and $\tilde{g}_e$ are the intracellular and extracellular conductivity tensors; β is the ratio of membrane surface area to tissue volume (0.3 μm^{-1}); C_m is the membrane capacitance per unit area (0.01 F/m^2); and J_{ion} is the membrane current per unit area, determined by the Beeler-Reuter model[9].

Onward, inward….

100 micrometers: Cardiac cell length



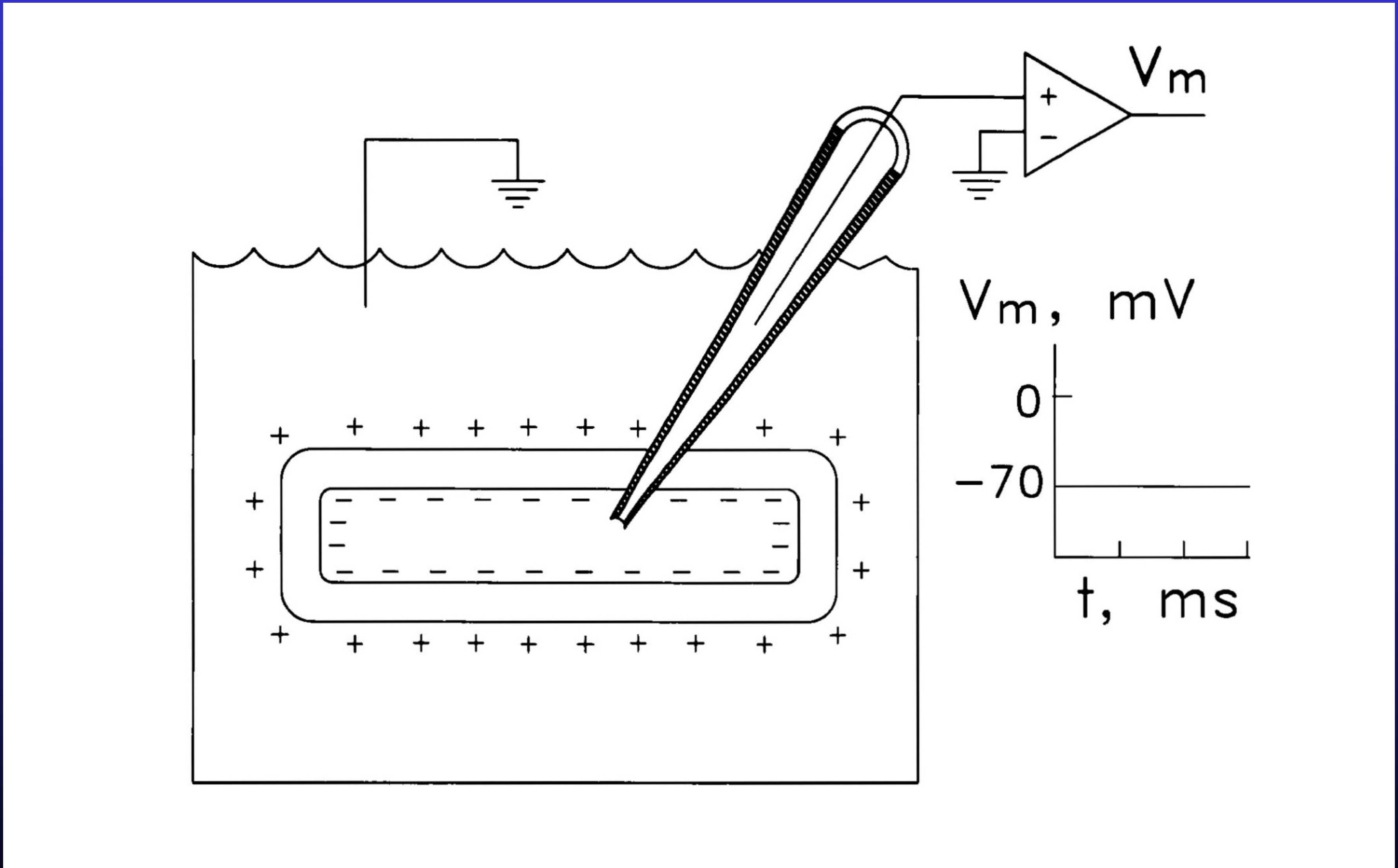
R. V. Krstić, *General Histology of the Mammal*, Springer-Verlag, Berlin (1984)



100 micrometers

VIBRE

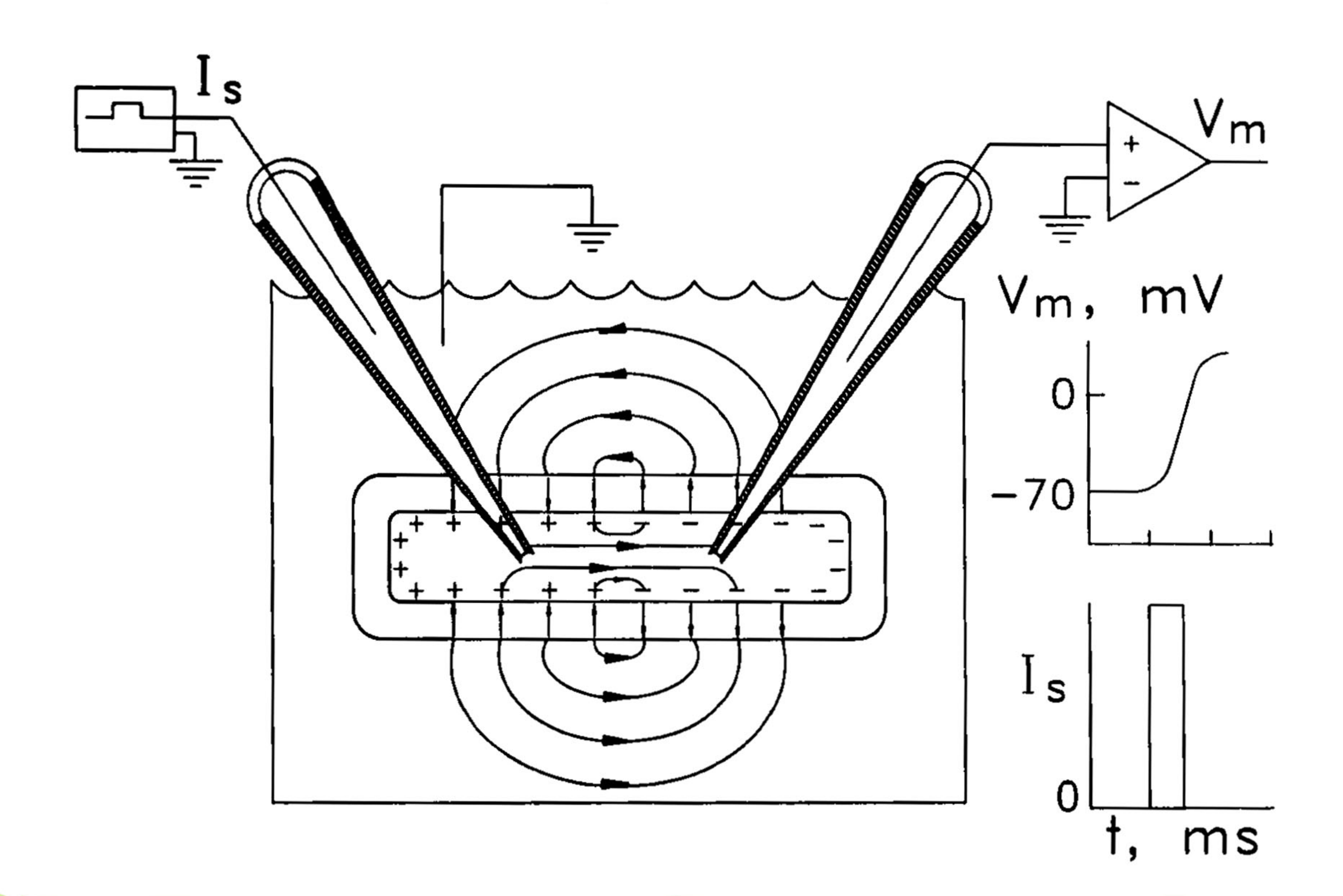
The resting cell and its transmembrane potential



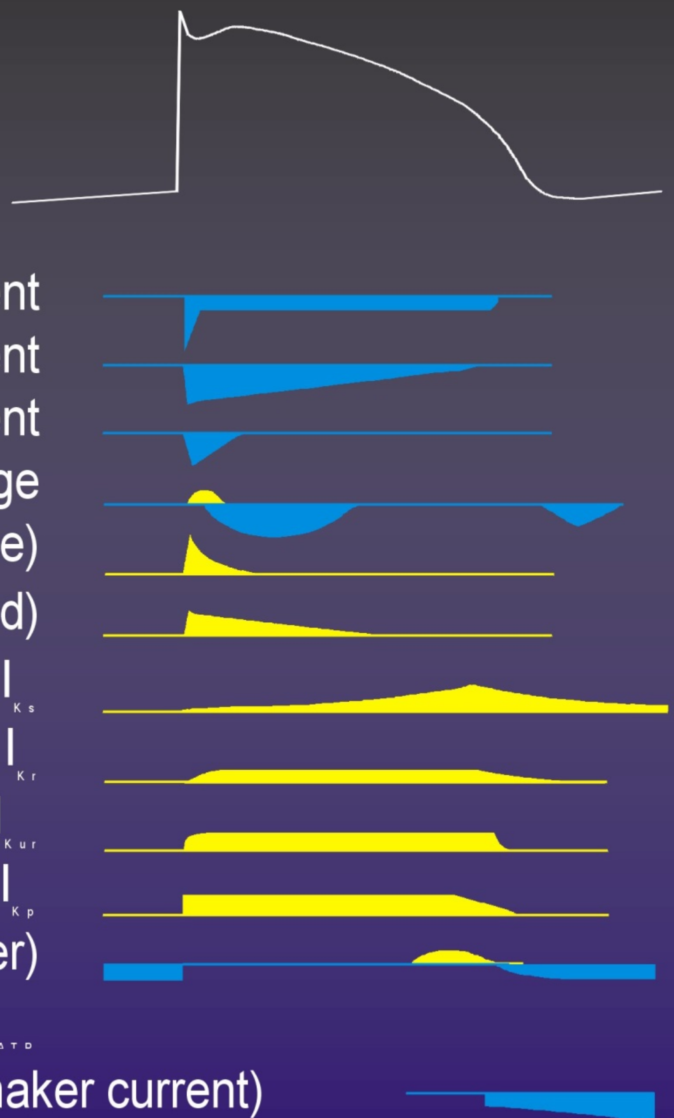
100 micrometers

VI∫BRE

The stimulated cell produces an action potential



Ion currents and ion channel clones



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
$I_{K\text{-}ACh}$; $I_{K\text{-}ATP}$	Kir3.1/3.4; Kir6.x/SUR
I_f (pacemaker current)	hCNG

*+sub-units

Courtesy of Dan Roden

The cardiac cell membrane is …

a planar accelerator that uses gradients of 10^7 volts per meter to accelerate heavy ions to energies of 70 meV.

Onward, inward….

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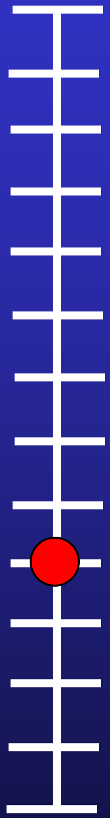
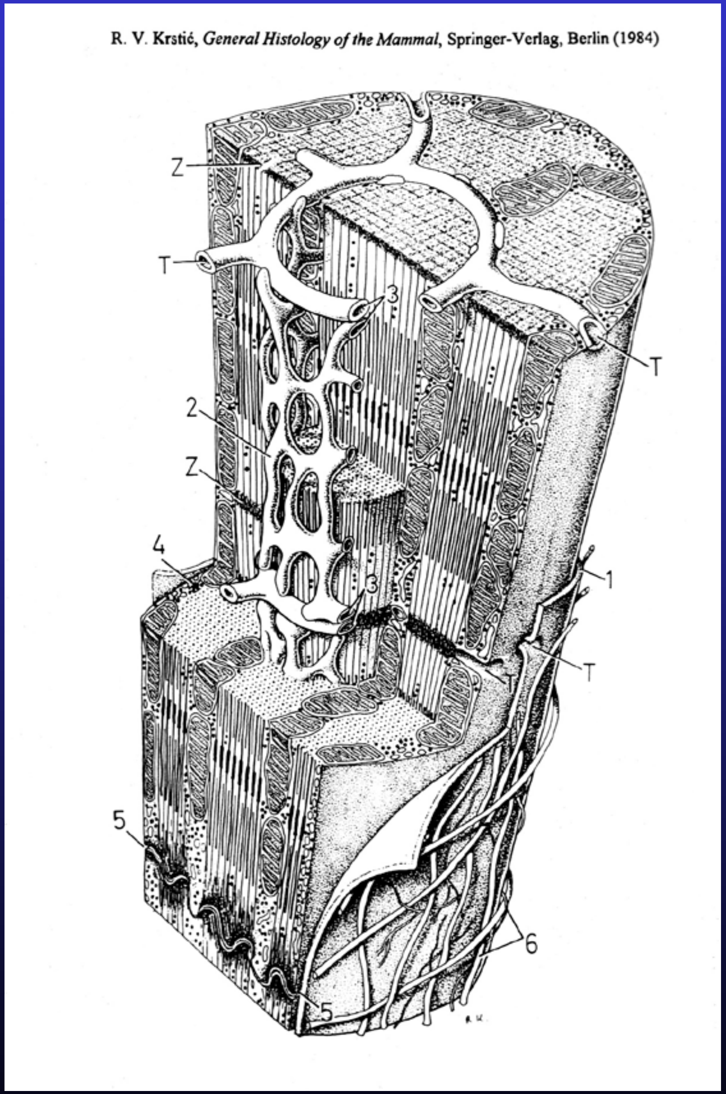
10 micrometers: Cardiac cell diameter

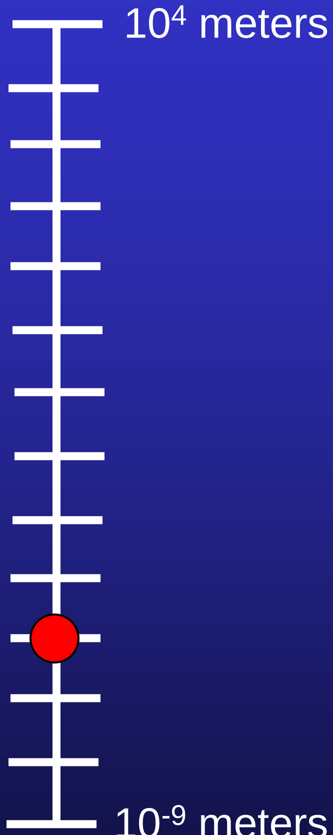


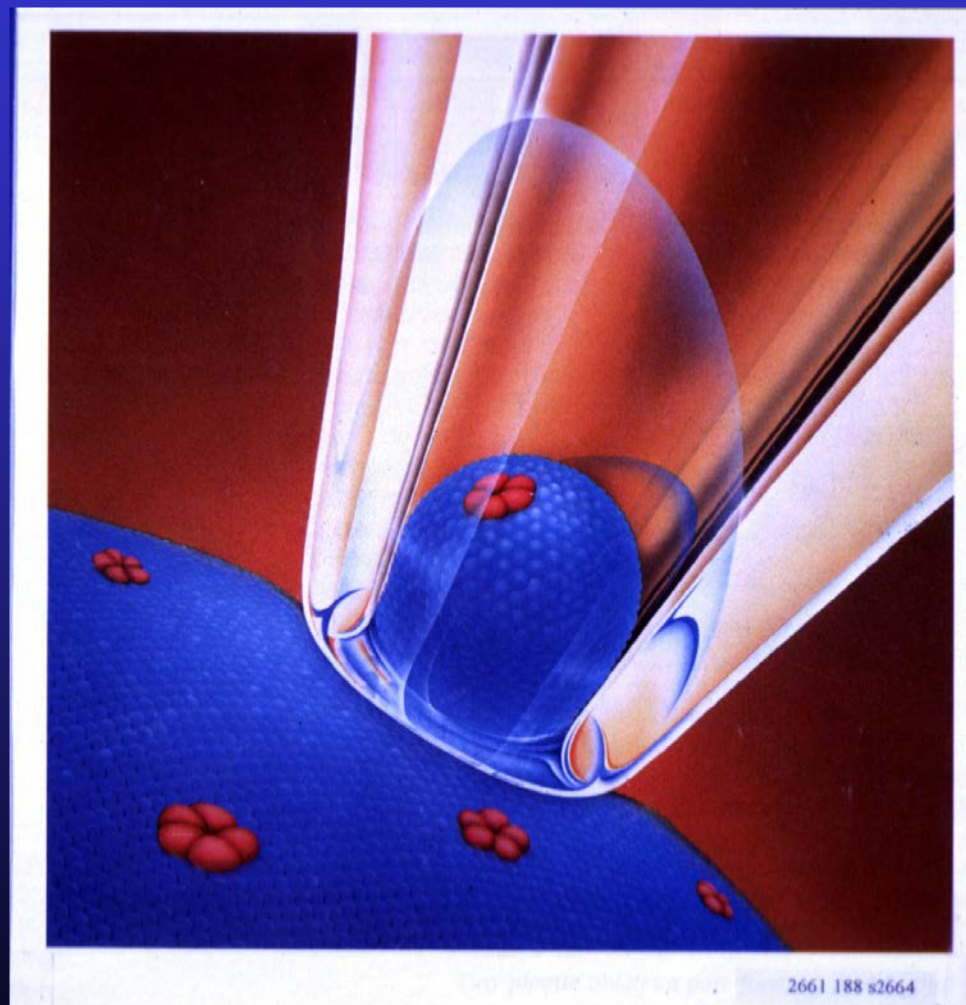


s02736

s02750

1 micrometer: Glass micropipette bore





Scientific American

s02737

s02664

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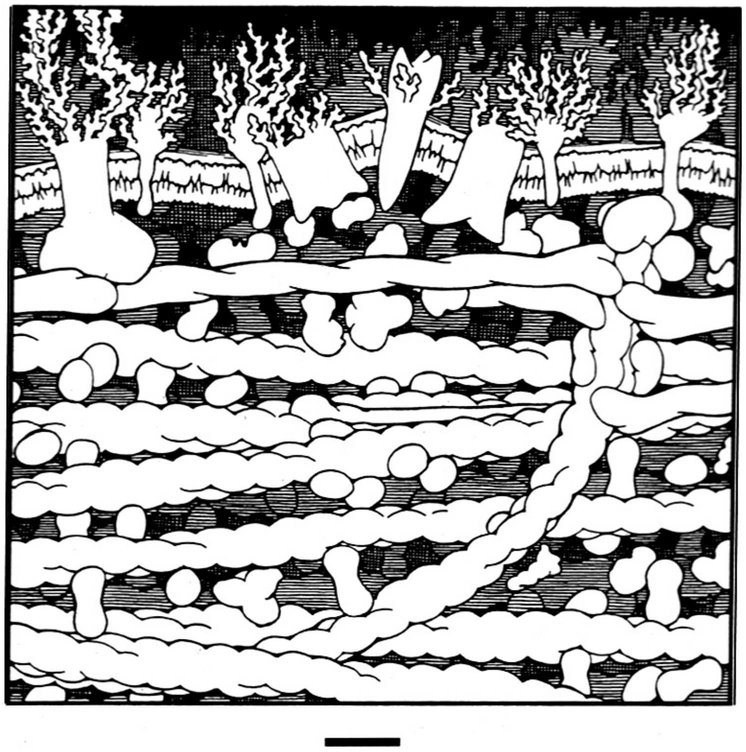
100 nanometers: Molecular machinery

10^4 meters

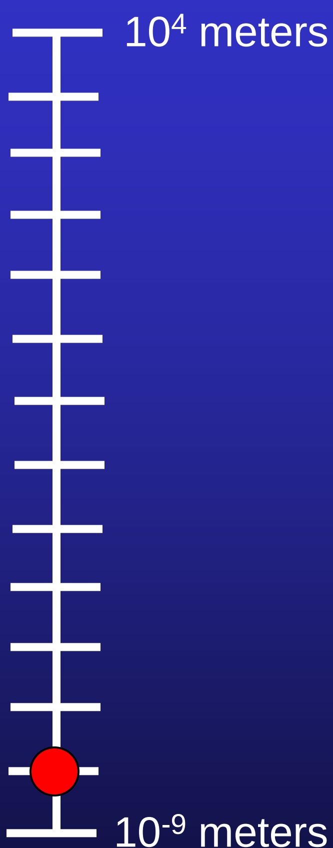
10^{-9} meters

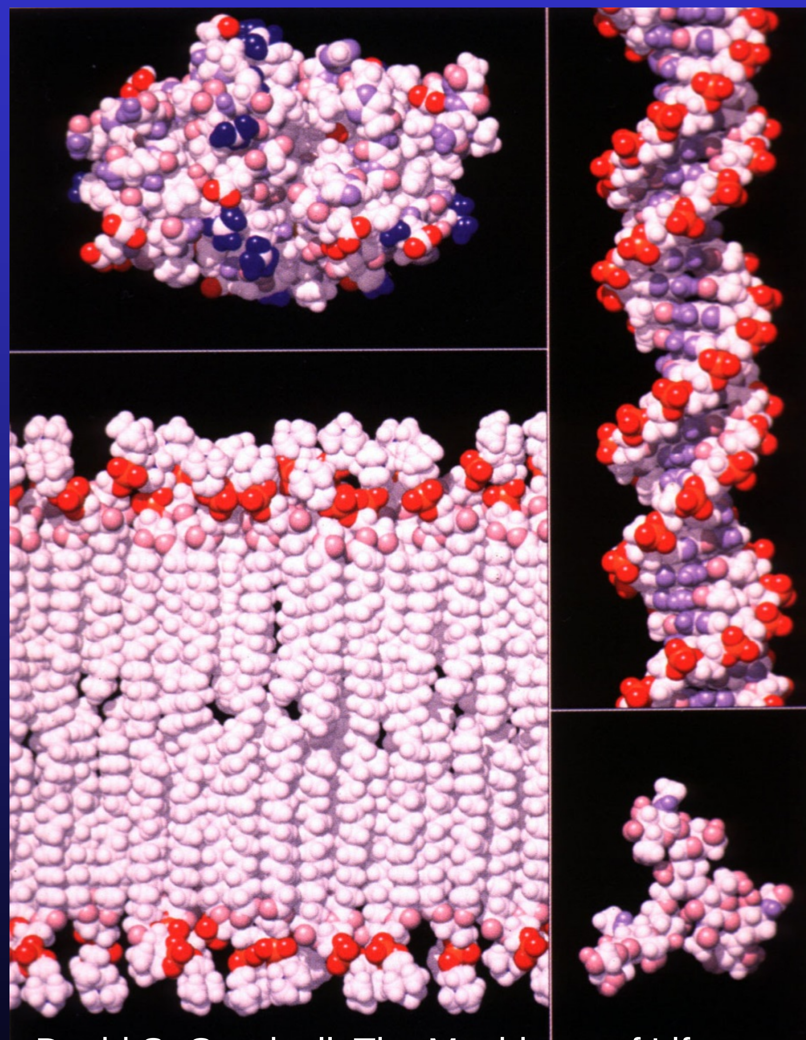


From: *The Machinery of Life*, D.S. Goodsell (Springer-Verlag, New York, 1992)

TL110P10 J188 S4116

10 nanometers: DNA and biomolecules





Protein

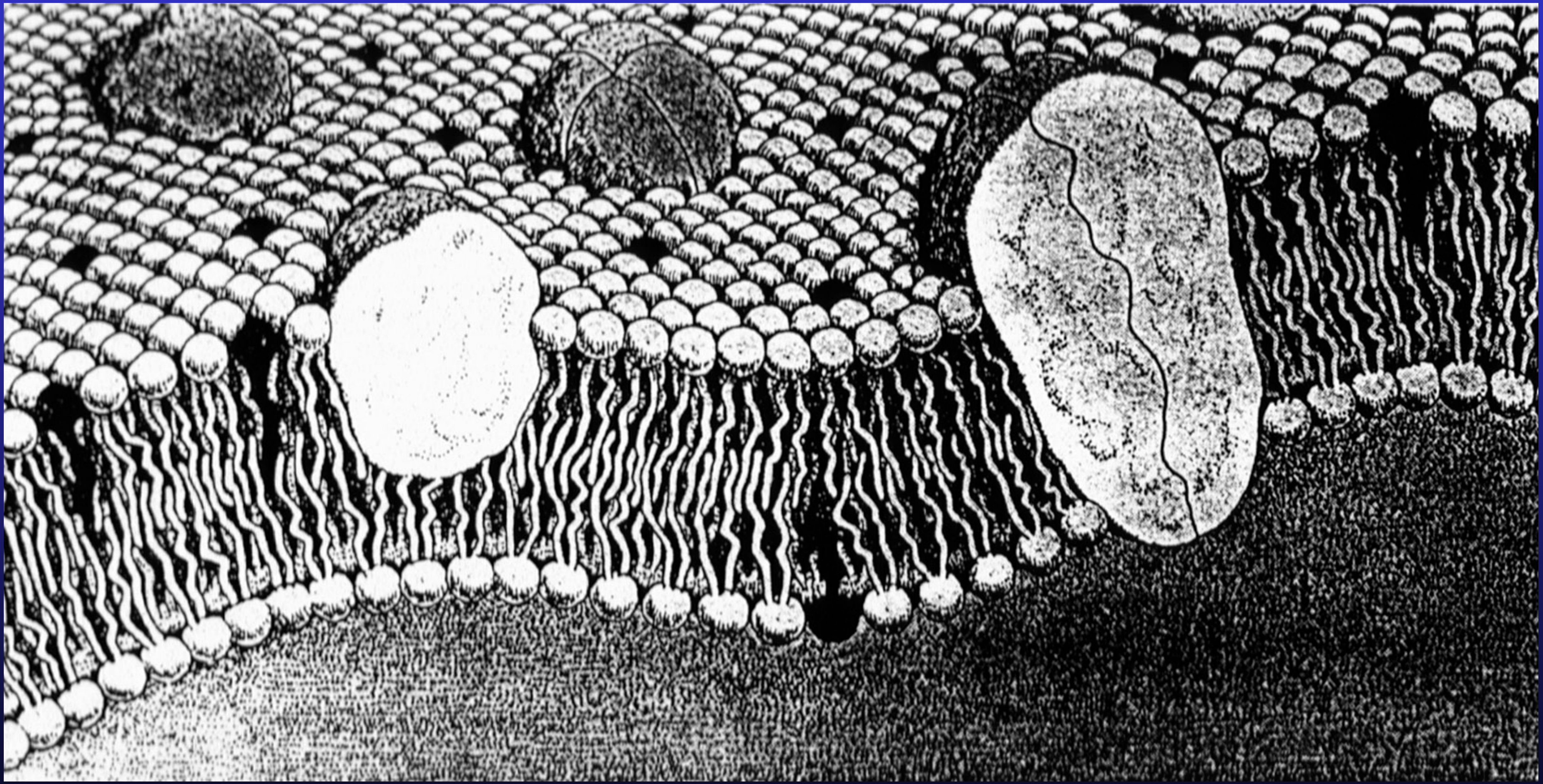
Nucleic Acid

Lipid

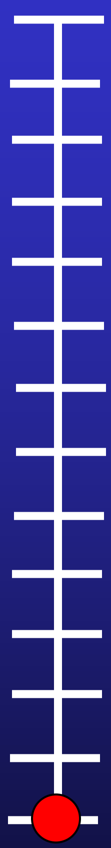
Polysaccharide

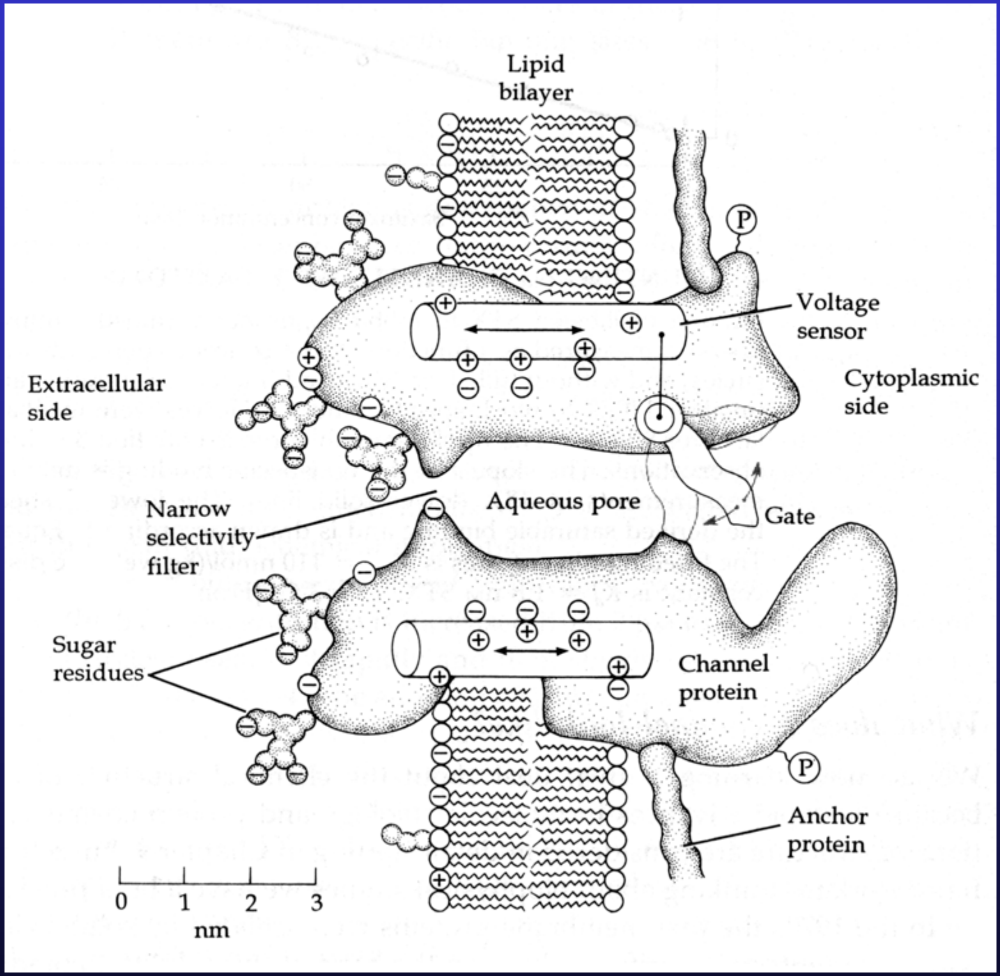
David S. Goodsell, The Machinery of Life, Springer-Verlag, 1993

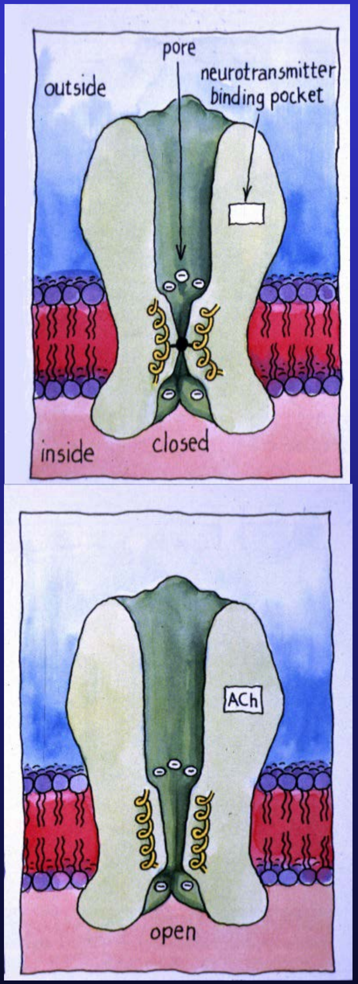
10 nanometers: Cell membrane thickness



1 nanometer: Pore in a gated ion channel







s02740

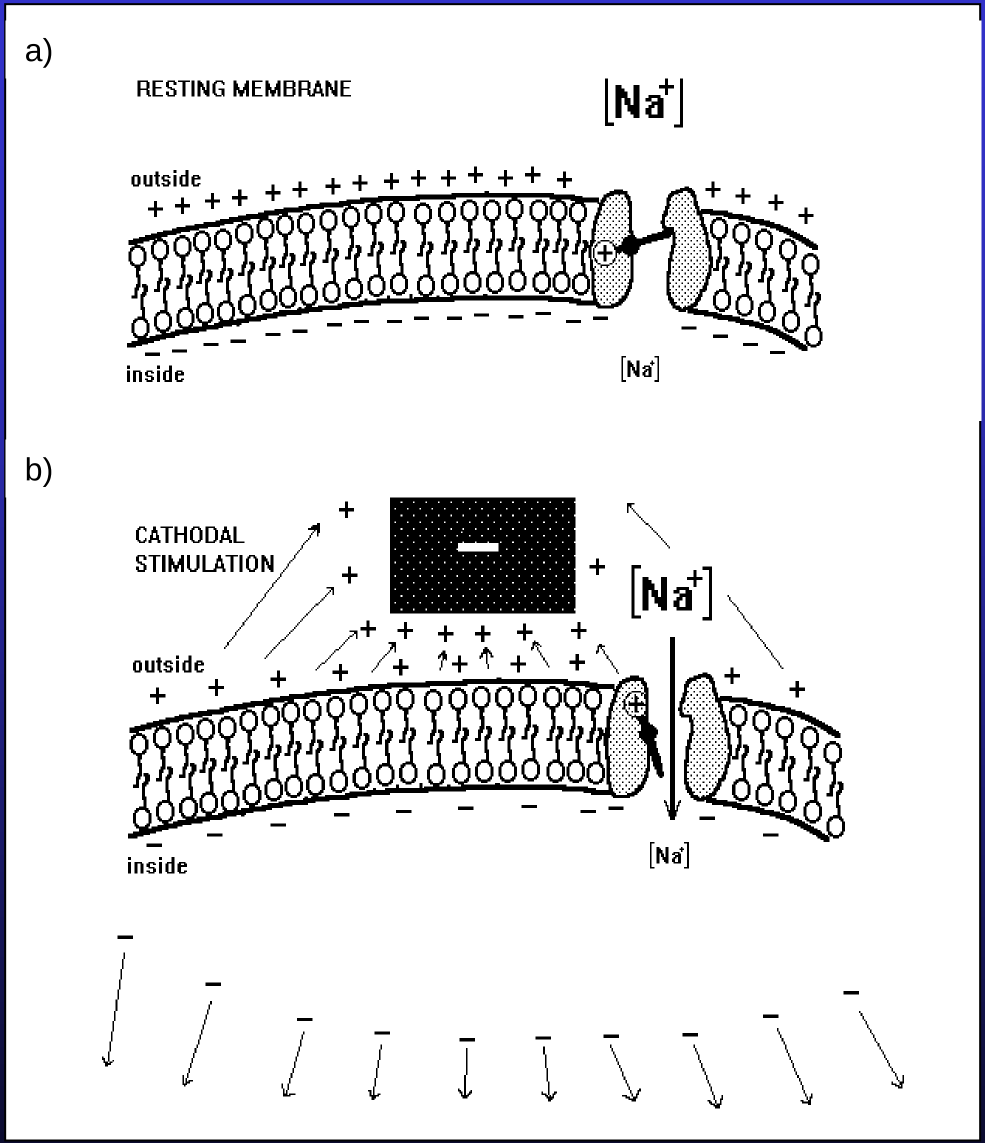
s04138

1 nanometer

The voltage-gated ion channel

- Ion channel contains an electric field sensor

  (~10^7 V/m)
- An external electrode switches conductance to a specific ion
- The ultimate nanodevice

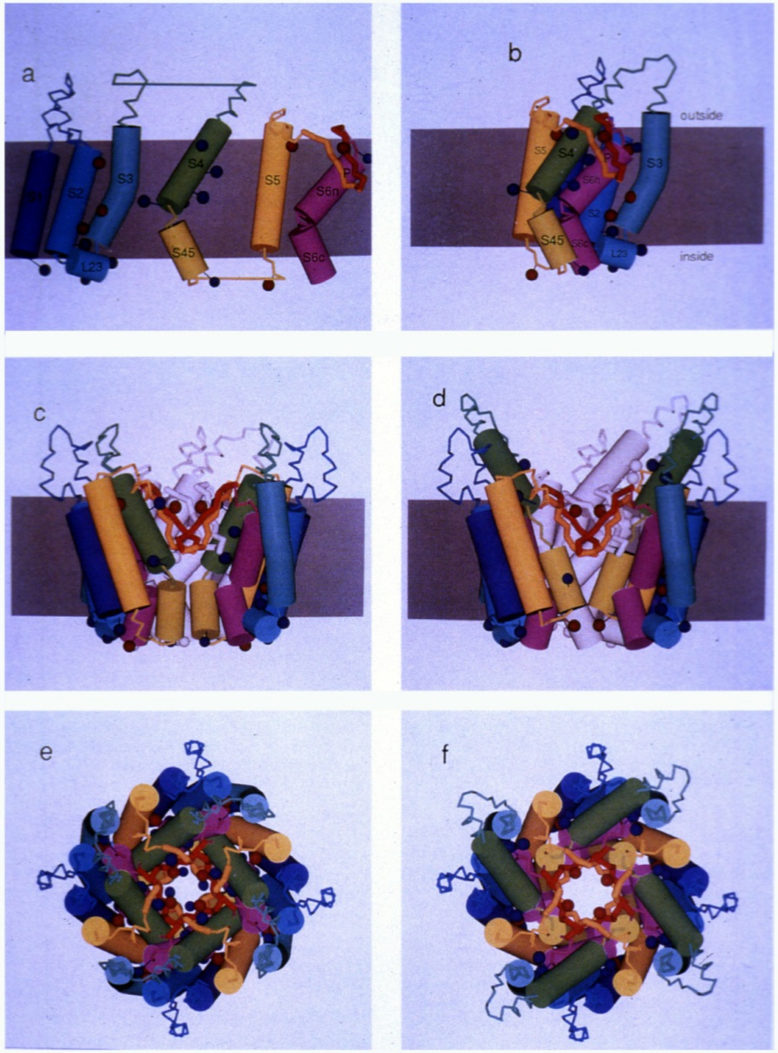


1 nanometer

VI∫BRE

The channel diameter, and ability to conduct ions, depends upon voltage or ligand binding

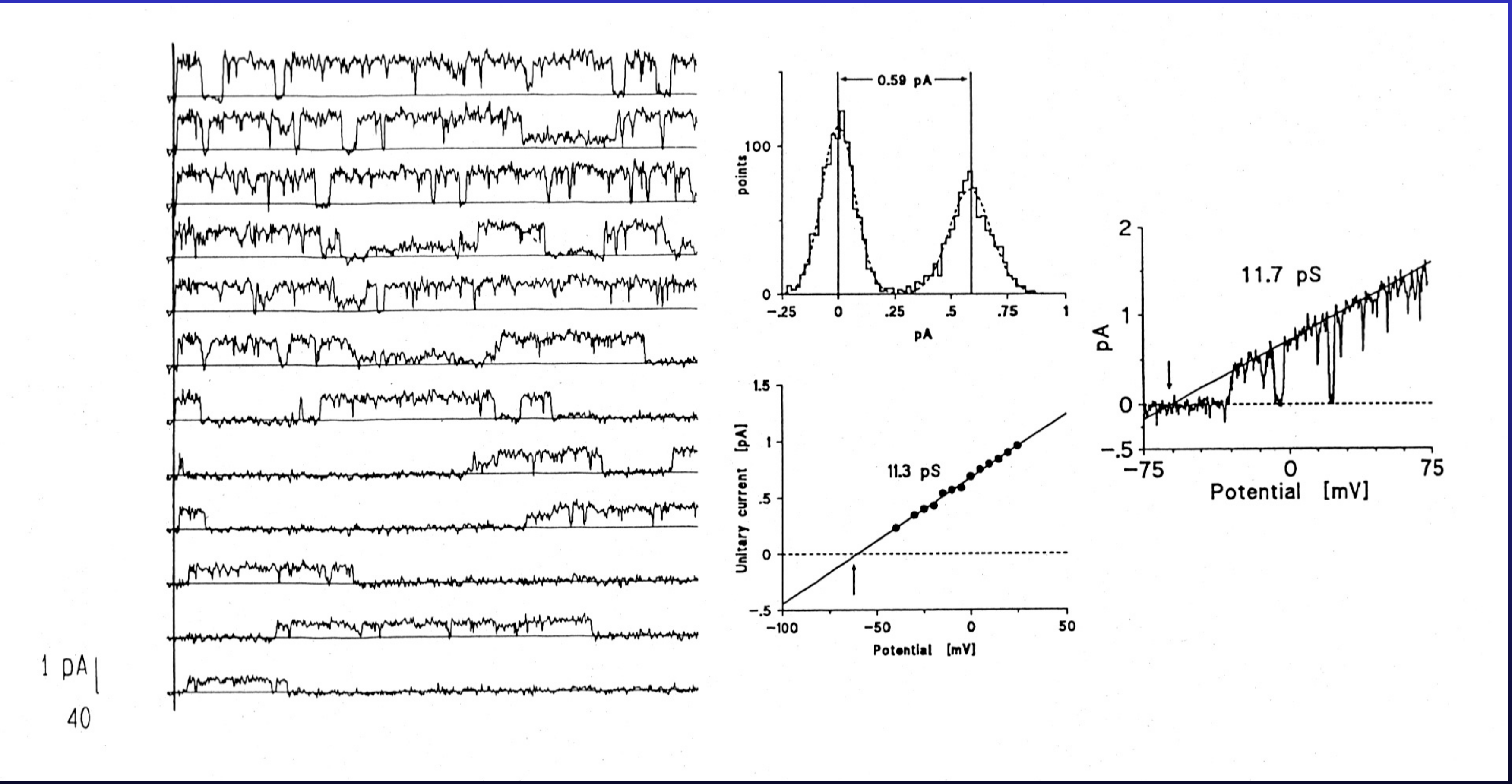
S.R. Durrell and H.R. Guy, *Biophysical Journal*, 62: Discussions 1992 238-250 (1992)



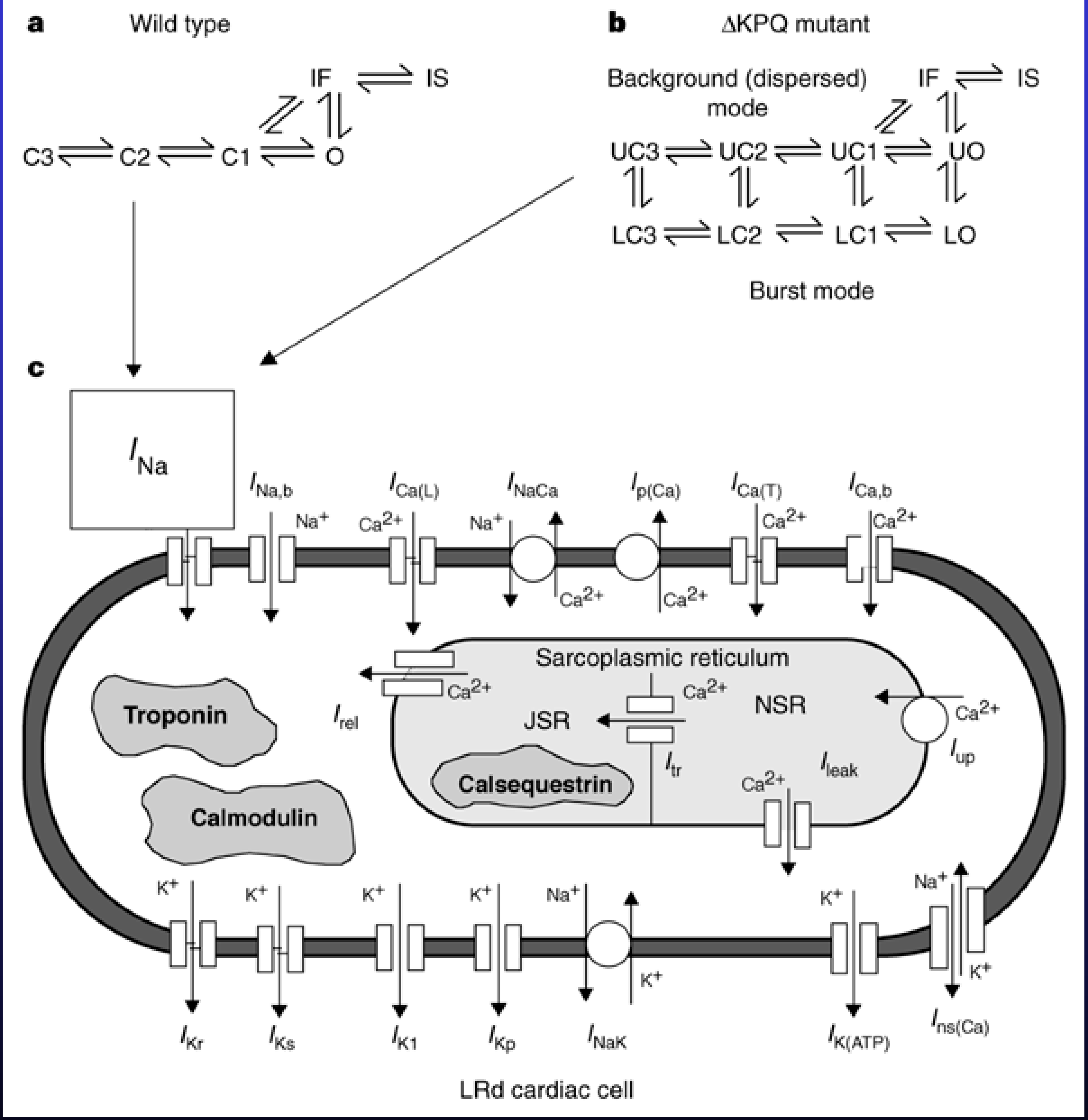
1 nanometer

VIʃBRE

Transmembrane ion channels have a time- and voltage-dependent conductance

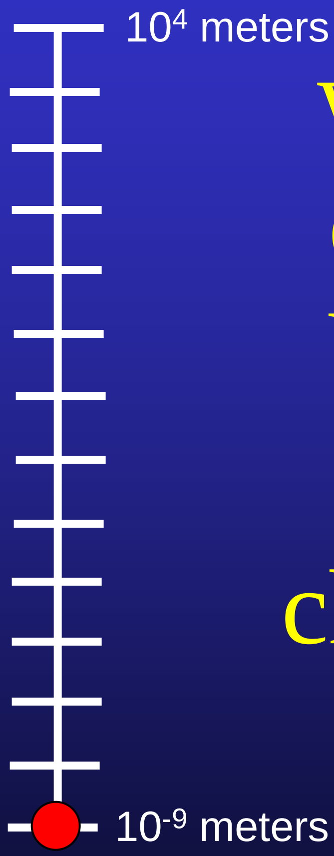


Cell Models with Gated Ion Channels



Clancy, C. E. and Y. Rudy. Linking a genetic defect to its cellularphenotype in a cardiac arrhythmia. Nature 400 (6744) 566-569, 1999.

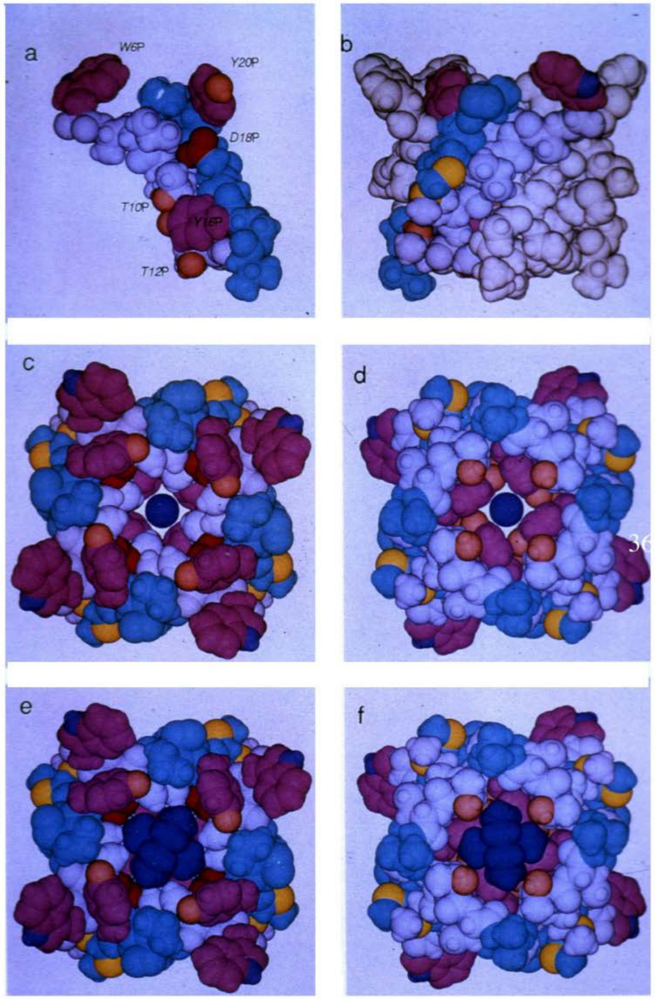
1 nanometer



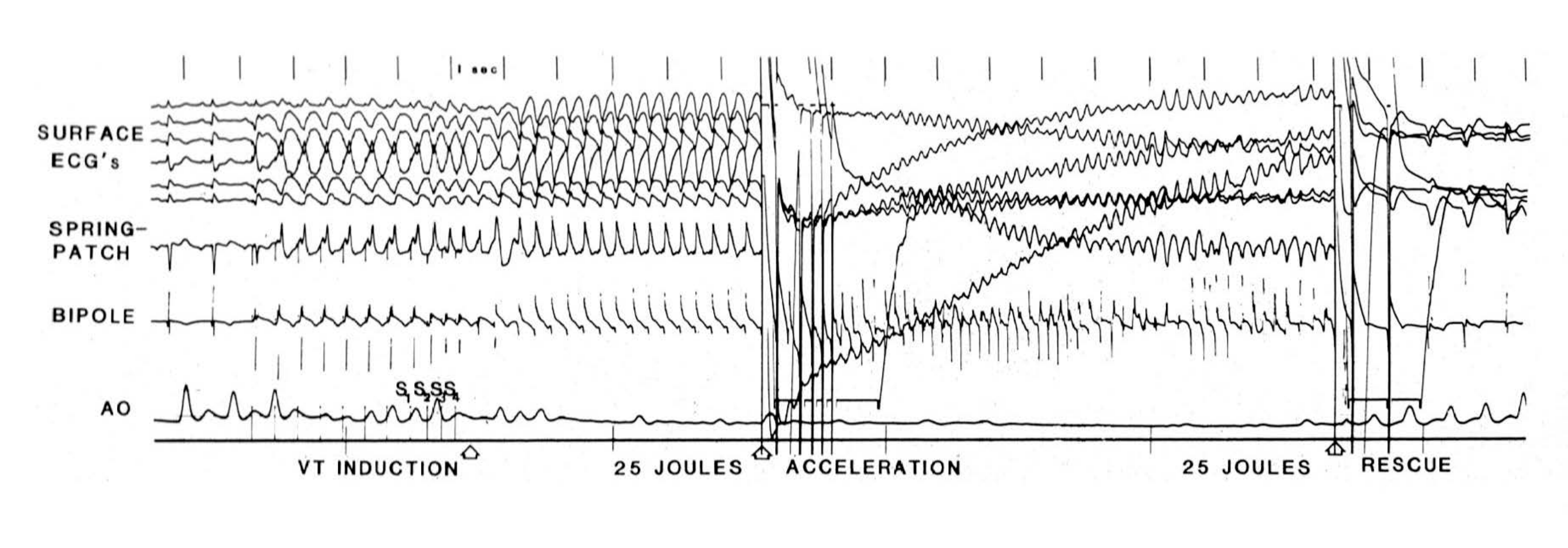
See which drugs block the channel

We’re there…

S.R. Durrell and H.R. Guy, *Biophysical Journal*, 62: Discussions 1992 238-250 (1992)



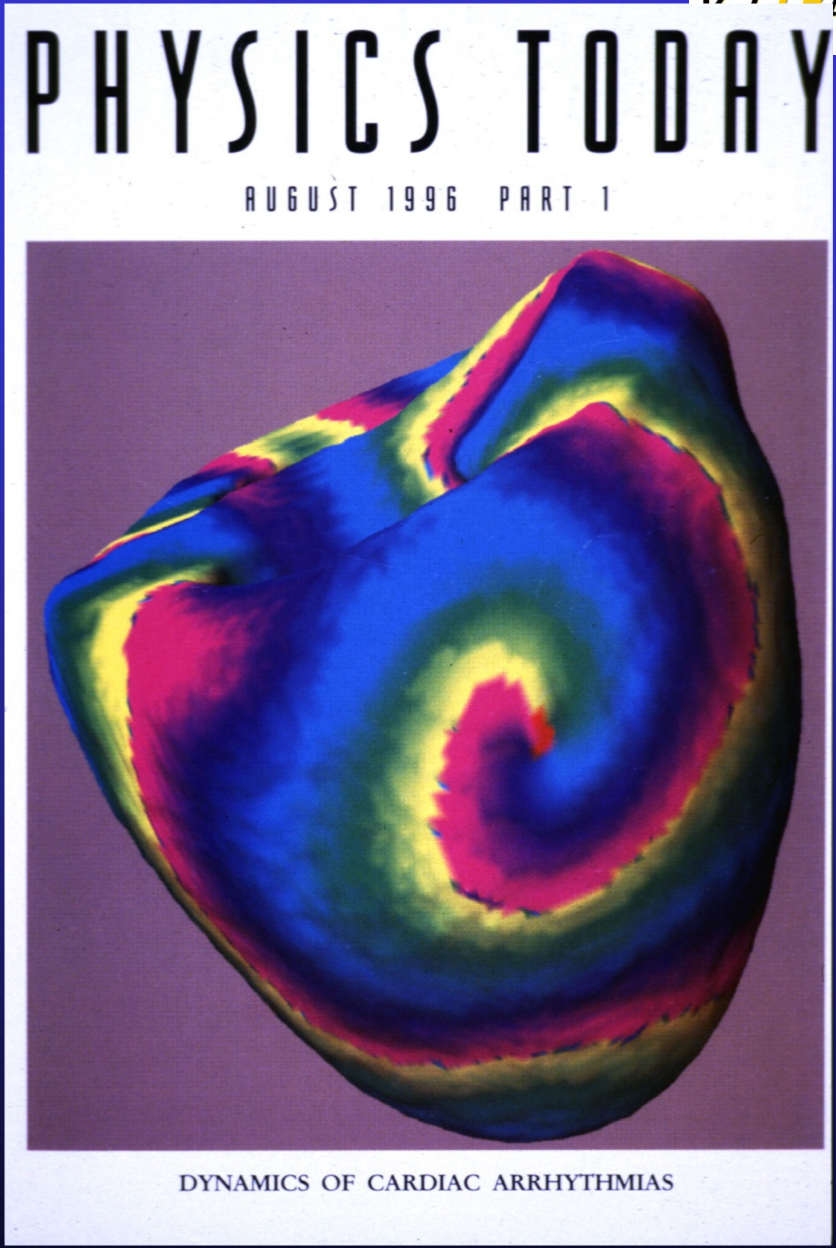
But my goal is to understand how drugs and electrical shocks affect fibrillation and defibrillation…



Courtesy of Debra Echt

Cardiac fibrillation occurs at the spatial scale of the entire heart!

Leon Glass



The Ultimate Forward Problem: Compute, from first principles, the behavior of the heart

- An ion channel: 10 nm ~ 1 channel/mm^2
- Cardiac cell: 150 mm x 15 mm x 15 mm

  500 to 30,000 channels per cell depending upon cell type
- The heart: 10 cm

  4 x 10^9 cells

  2 x 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 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

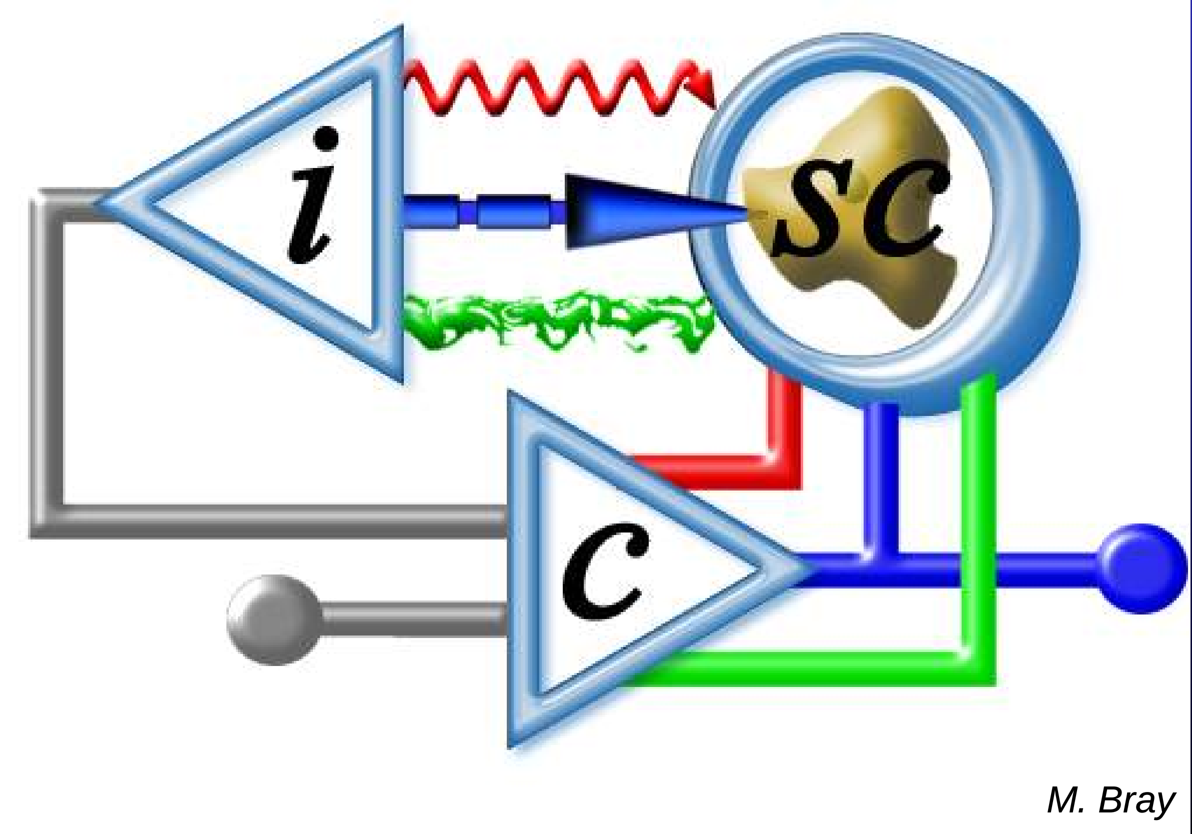
Cherry, Greenside, Henriquez PRL 2/7/00: Whole-heart, minimal adaptive mesh LR1 estimated 10^{-5} real time with a 533 MHz DEC a, 70x increase with a 100-parallel computer.

Solutions to the *Ultimate Forward Problem*

- Develop 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
  - Physiological determination of eikonal equations
- An isolated rabbit heart
  - Massively parallel analog computer
  - Solves ~10^{17} equations/second at $30/hour
  - Requires improved programming techniques
  - Requires improved readout of the answer
- *I*nstrument and *C*ontrol the *S*ingle *C*ell
  - The cell is an excellent analog computer
  - Learn how to program it

VIIBRE

Instrumenting and Controlling

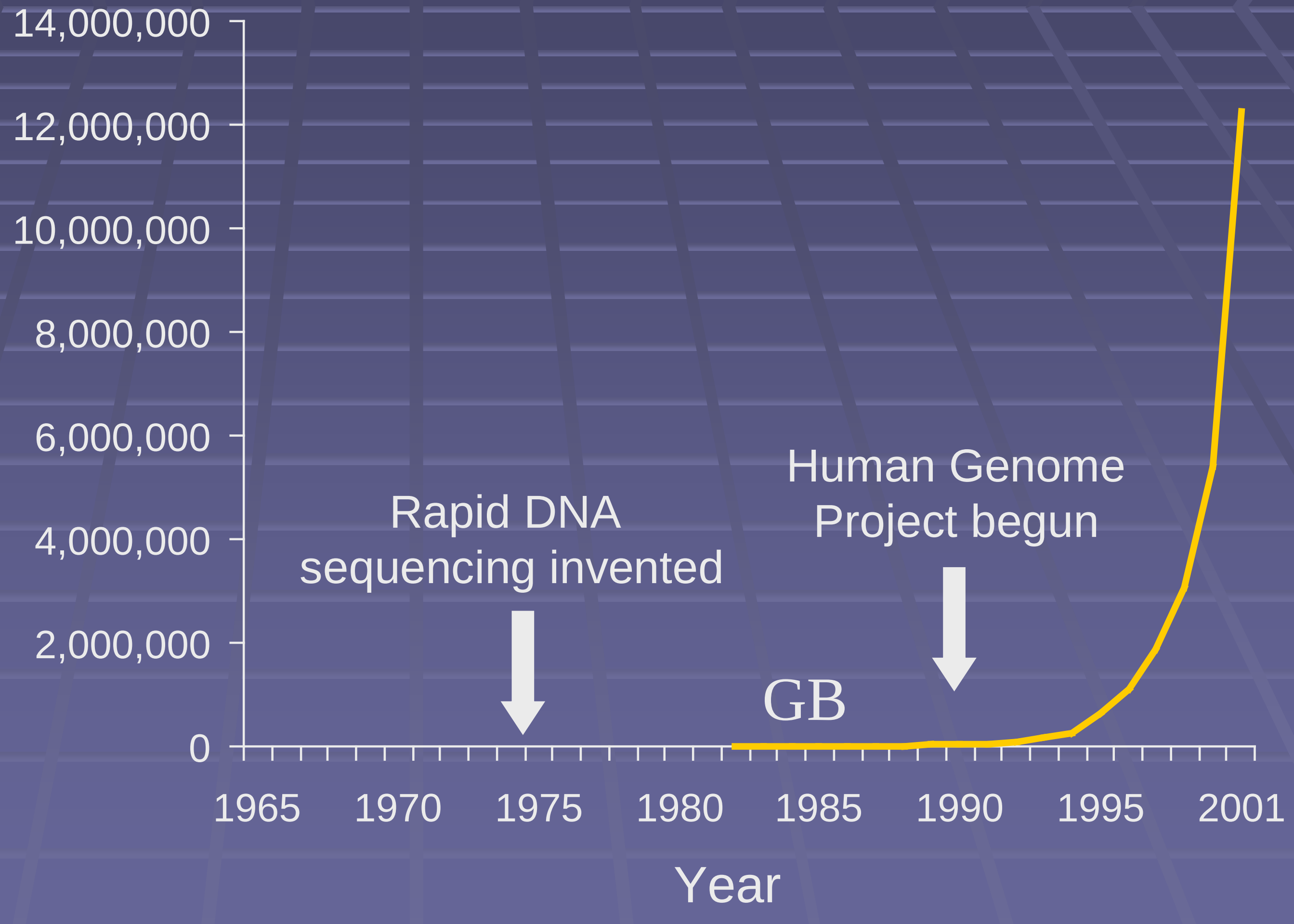


The Single Cell

The rate at which DNA sequences began accumulating was exponential

~13 million sequence entries in GenBank

Nearly 13 billion bases from ~50,000 species



Courtesy of Mark Boguski

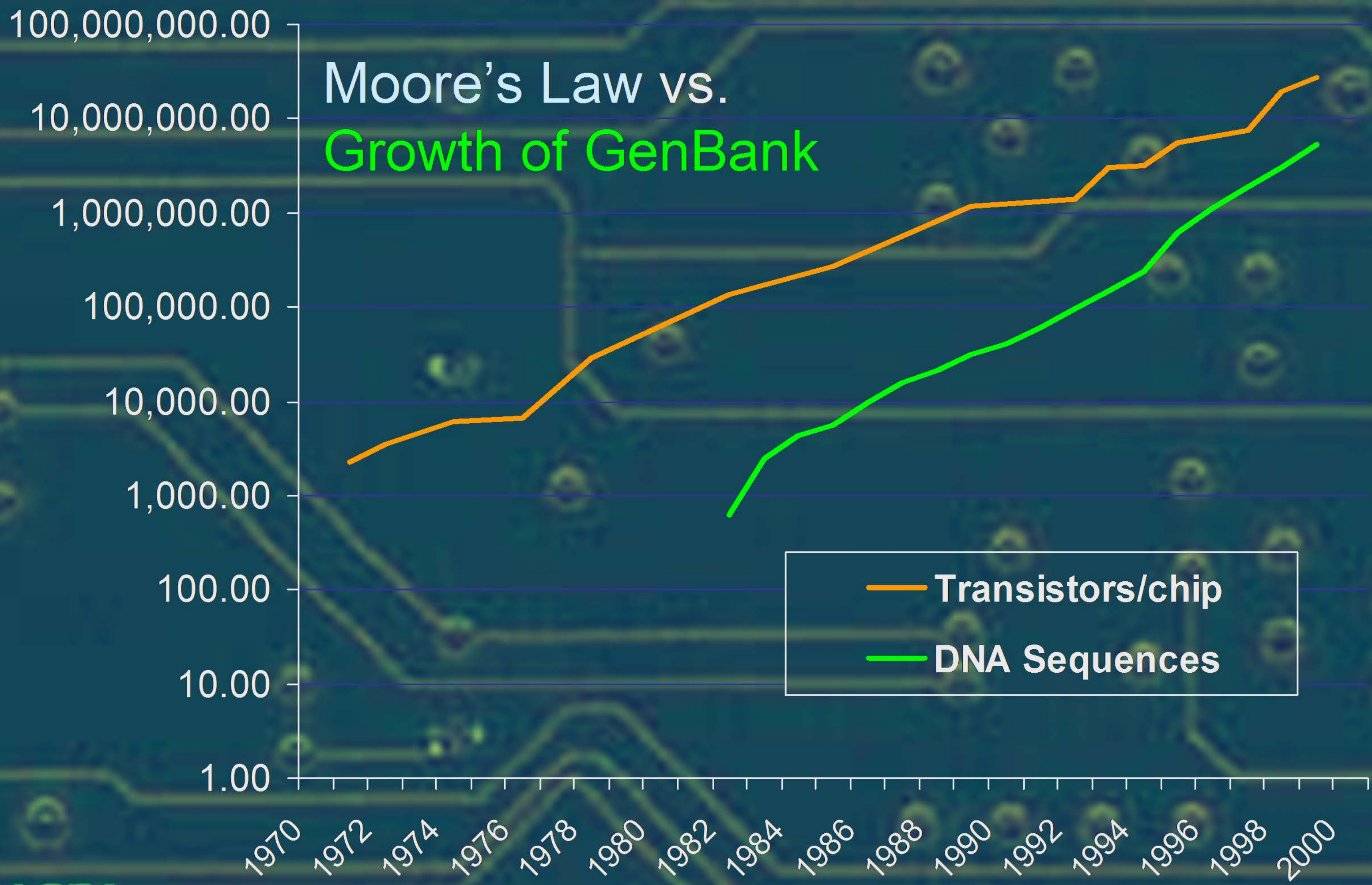
"Anticipated advances in computer speed will be unable to keep up with the growing [DNA] sequence databases and the demand for homology searches of the data."

Charles DeLisi, 1988
U.S. Department of Energy

NCBI

Courtesy of Mark Boguski

Luckily, DeLisi's dire prediction has not (yet) come true



Courtesy of Mark Boguski

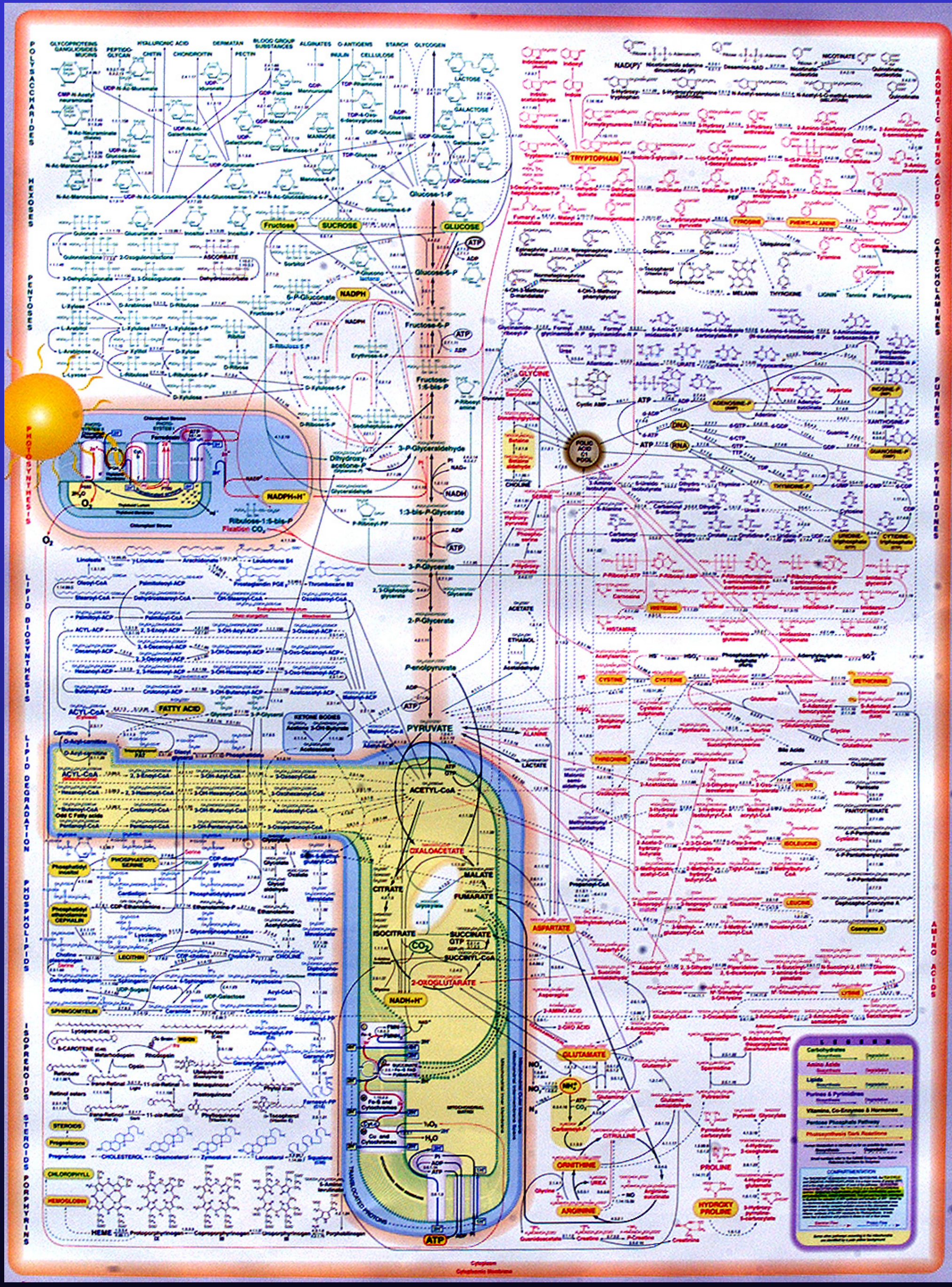
NCBI

Progress in Biology

- Genomics
  - Structural genomics
- Proteomics
  - Structural proteomics
  - Functional proteomics
- What's next?
  - Complexity and cellular biophysics in the post-genomic, post-proteomic era

Postgenomic Integrative/Systems Physiology/Biology

- Specify concentrations and
- Rate constants
- Add gene expression,
- Protein interactions, and
- Signaling pathways
- Include intracellular spatial distributions, diffusion, and transport
- … and **calculate** how the cell behaves in response to a toxin



The Catch

- Modeling of a single mammalian cell may require 100,000 variables and equations
- Cell-cell interactions are critical to system function
- 10^9 interacting cells in some organs
- The data don't yet exist to drive the models
- Hence we need to experiment…

The Challenge

- Develop the tools and techniques for integrative, post-genomic **cellular** biophysics
  - Genes
  - Proteins
  - Metabolic and signaling pathways
  - **Models**
  - **Instruments**
  - **Wide-bandwidth dynamic control theory for cellular systems**

The Problem

- Existing chemical and metabolic sensors and actuators are too slow to track biochemical events at the cellular level
- Metabolic control is today possible only at the animal and organ level: metabolic clamp
- Post-genomic physiology needs cellular metabolic control

Possible Approaches

- A biological cell or molecule inserted into a microinstrument, *e.g.*, a single-cell spectrophotometer or a whole-cell patch clamp
- A nanoinstrument inserted into the cell/molecule, e.g., caged ATP
- Combine the two approaches to form an integrated, closed-loop bio/nano/micro system

Why Fast?

- Wide measurement bandwidth, *i.e.*, good response to high frequencies, is required to track cellular events
- Stable control requires high bandwidth

VIIBRE

How do we go fast?

- Small size yields decreased mixing times for mass and heat transfer
  - Oxygen diffusion time is
    - 1 ms @ 1 μm
    - 100 ms @ 10 μm
    - 10 s @ 100 μm
    - 1,000 s @ 1 mm
- Fast, small, and many by moving from microliters to nanoliters!

LIVING STATE PHYSICS GROUP

DEPARTMENT OF PHYSICS AND ASTRONOMY, VANDERBILT UNIVERSITY

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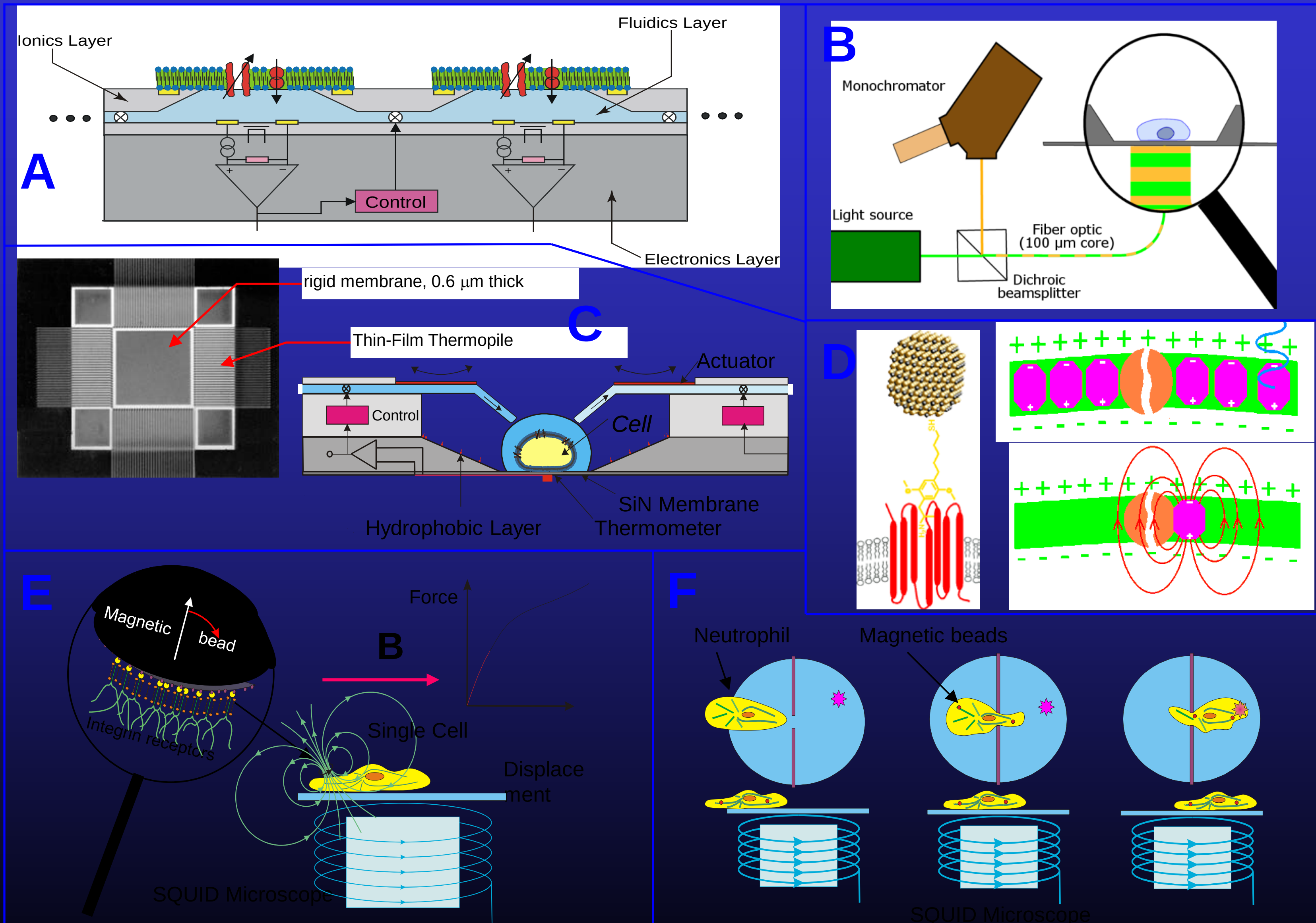

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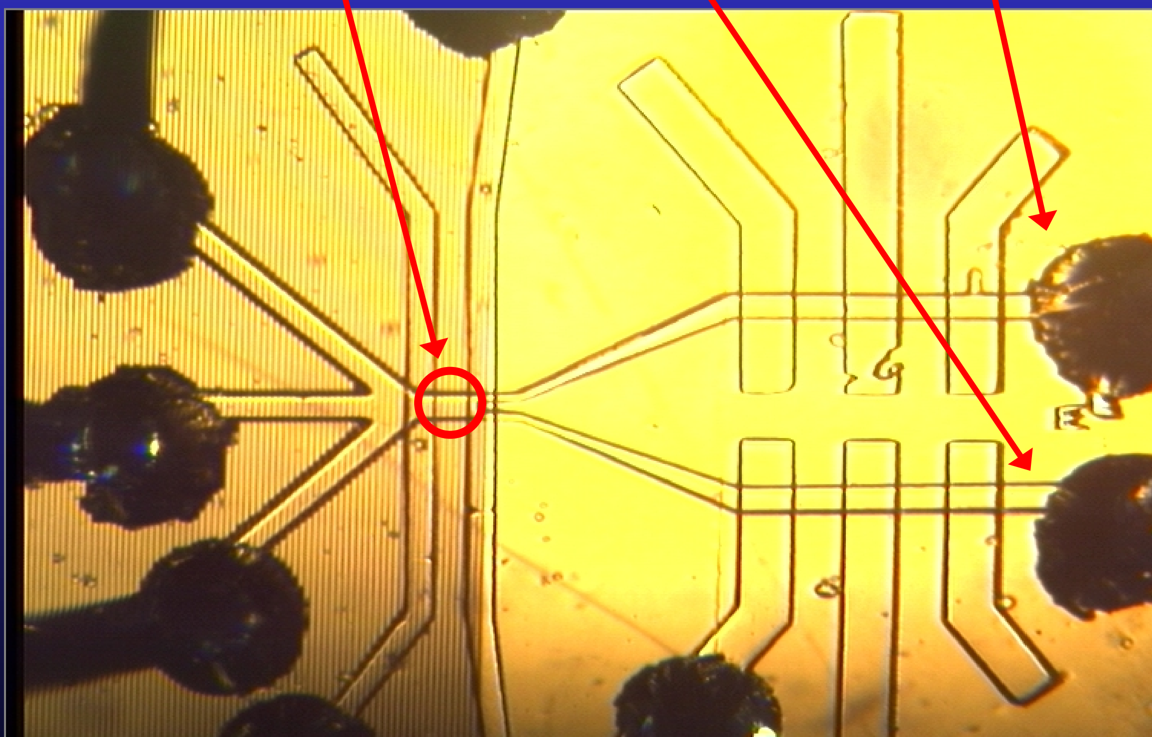
Living Hepatocyte in Prototype Vanderbilt PDMS NanoPhysiometer

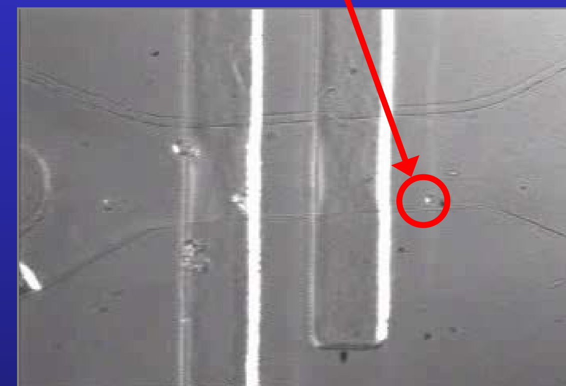
Active volume

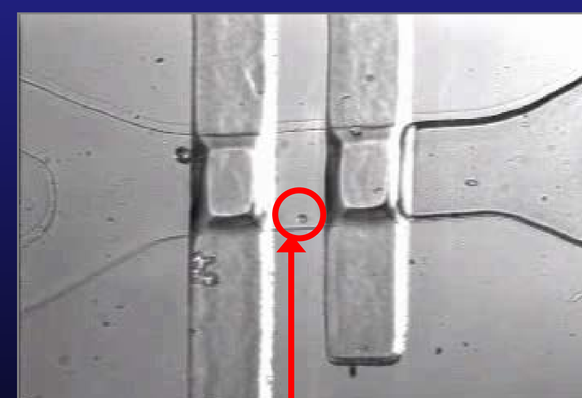
Inflow

Outflow

Load cell







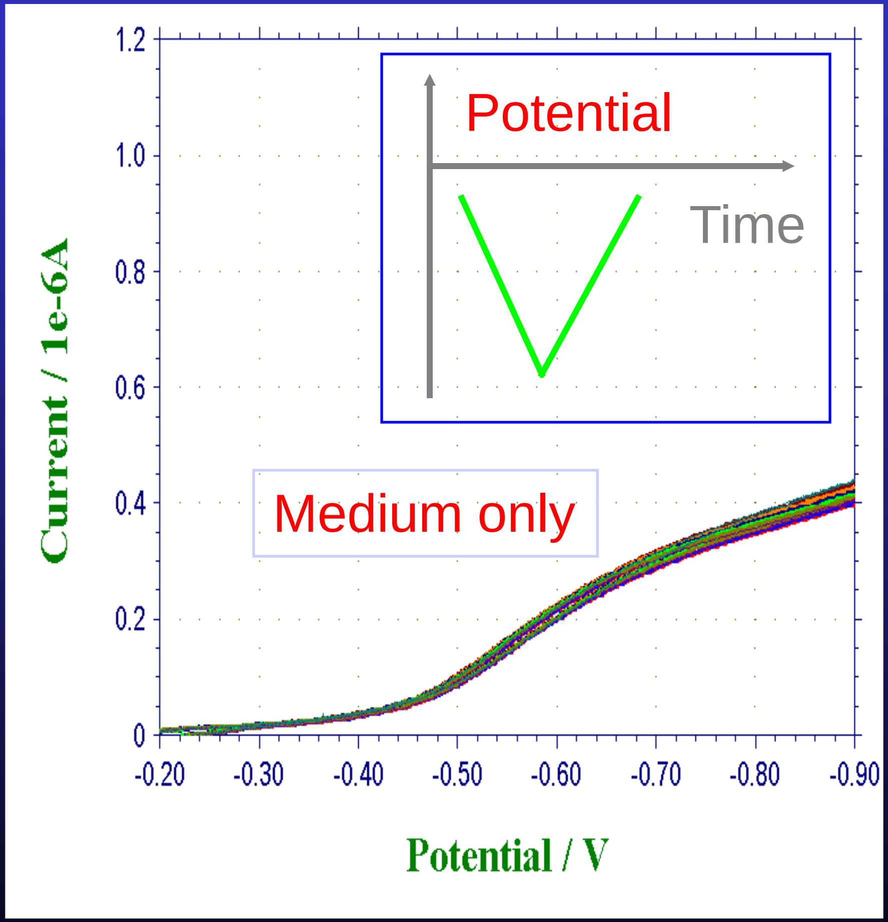
Trap cell

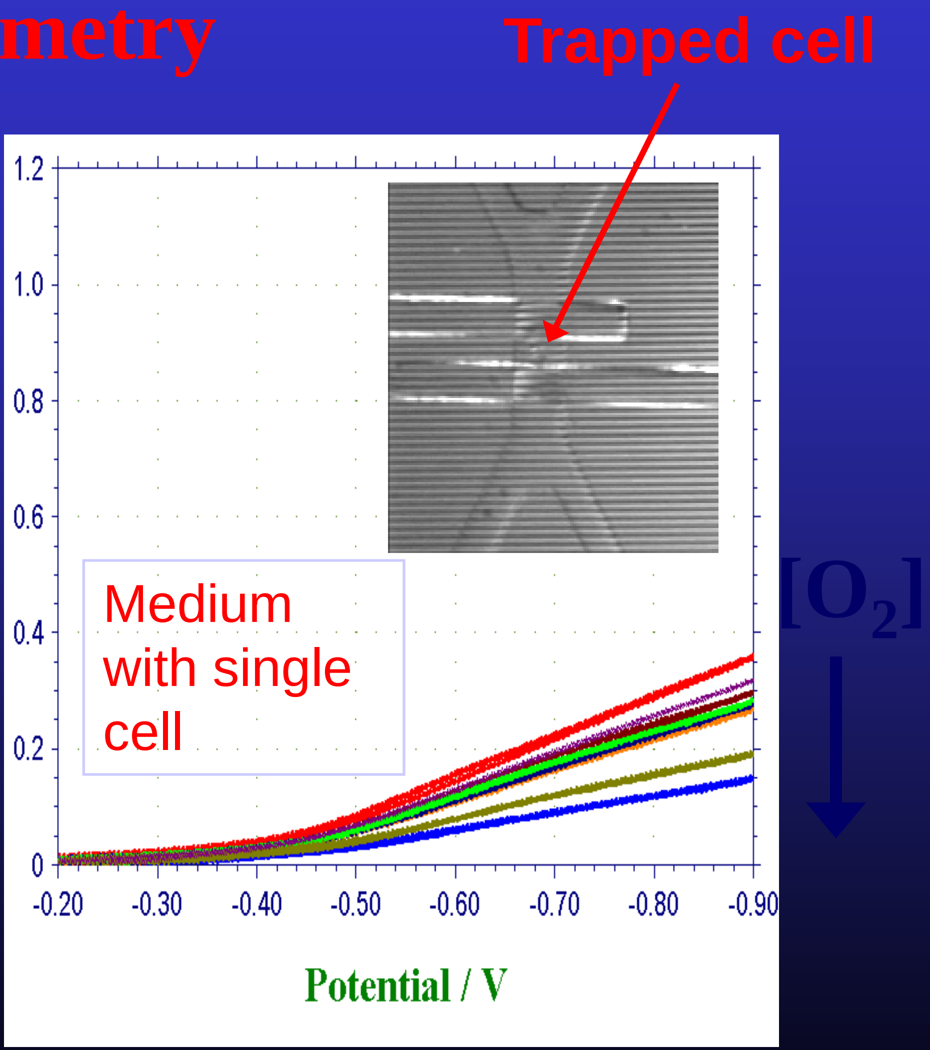
Werdich and Baudenbacher

Cell_in_Chamber2.mpg

1valve1a.m1v

Oxygen Measurement with Linear Sweep Voltammetry





LIVING STAT… PHYSICS GRO…
DEPARTMENT OF PHY… ASTRONOMY, VANDER…

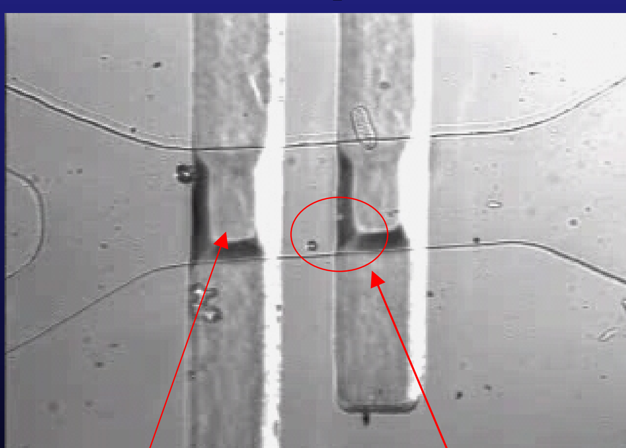
Single Cell Respiration: Preliminary Data

a) **Electrode O_2 consumption**

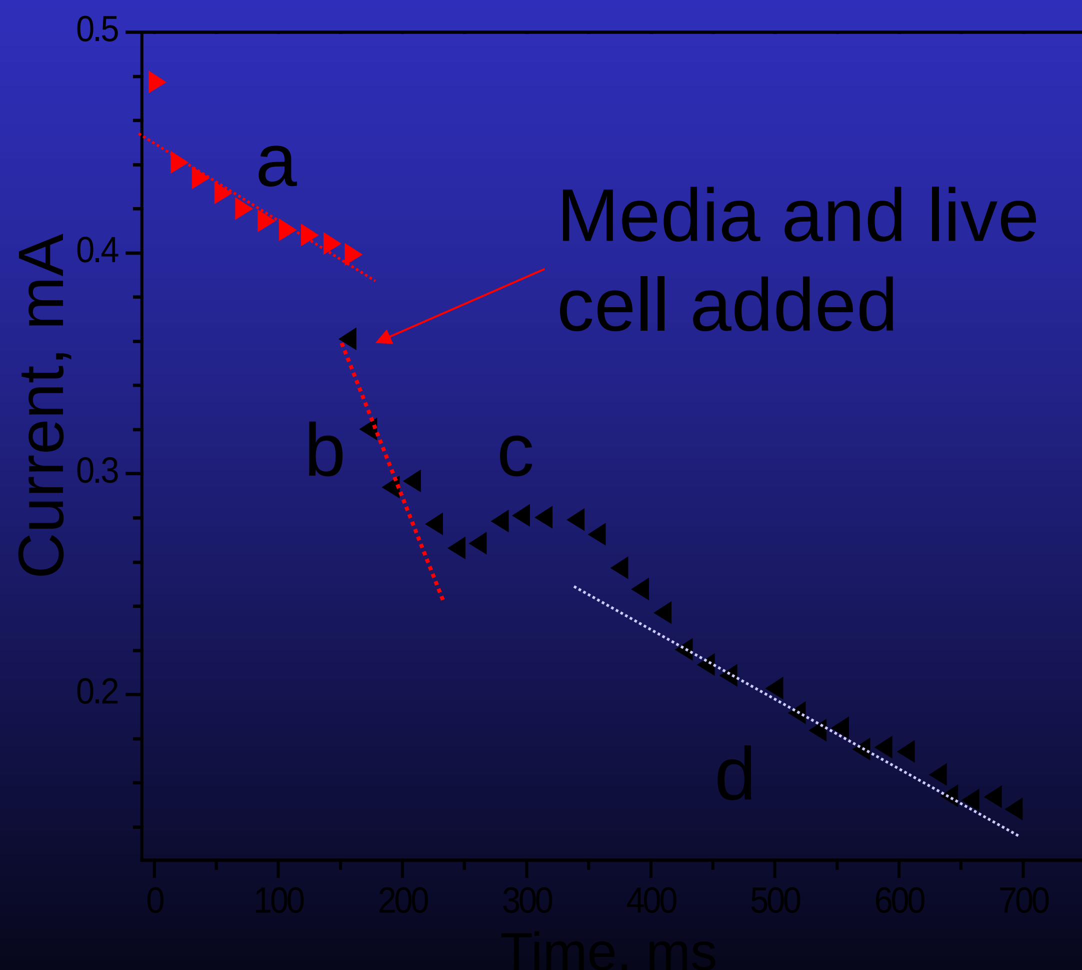
b) **Electrode + cell**

c) **Cell death??**

d) **Electrode O_2 consumption**



Valve Hepatocyte



The Future

- High-bandwidth, high resolution electromagnetic imaging and modelling
- Multiphasic, high bandwidth cellular microinstrumentation
  - Single cardiac myocyte sensing and control
  - Measurements of the dynamics of cardiac metabolism
  - Drug development for infarct damage control

Acknowledgements - ICSC

- Robert Balcarcel, Chemical Engineering
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- Ales Prokop, Chemical Engineering
- Mark Stremler, Mechanical Engineering
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- Elizabeth Dworska, Biomedical Engineering
- Yuansheng Yang, Chemical Engineering
- Eugeni Koslov, Chemical Engineering
- David Schaefer, Mechanical Engineering
- Steven (Zhijun) Yu, Mechanical Engineering
- Chung Cao, SBCCOM ECBC

Acknowledgements - Heart

- Rashi Abbas – Detection of make & break stimulation
- Franz Baudenbacher – SQUID measurements
- Mark Bray – Singularity dynamics and phase resetting
- Rubin Aliev – Cardiac modeling and non-linear dynamics
- Rick Gray – Phase encoding & singularity detection
- Brad Roth – Prediction of four modes of make & break stimulation; quatrefoil reentry
- Marc Lin – Development of imaging system, detection of quatrefoil reentry and make-break stimulation
- Marcella Woods – Response to field stimulation

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http://www.bme.vanderbilt.edu/

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Vanderbilt Institute for Integrative Biosystems Research and Education (VIIBRE)
http://www.vanderbilt.edu/viibre (coming soon)