The Physics of the Heart

John P. Wikswo

Heinz R. Pagels Memorial Lecture
Aspen Center for Physics
Aspen, Colorado

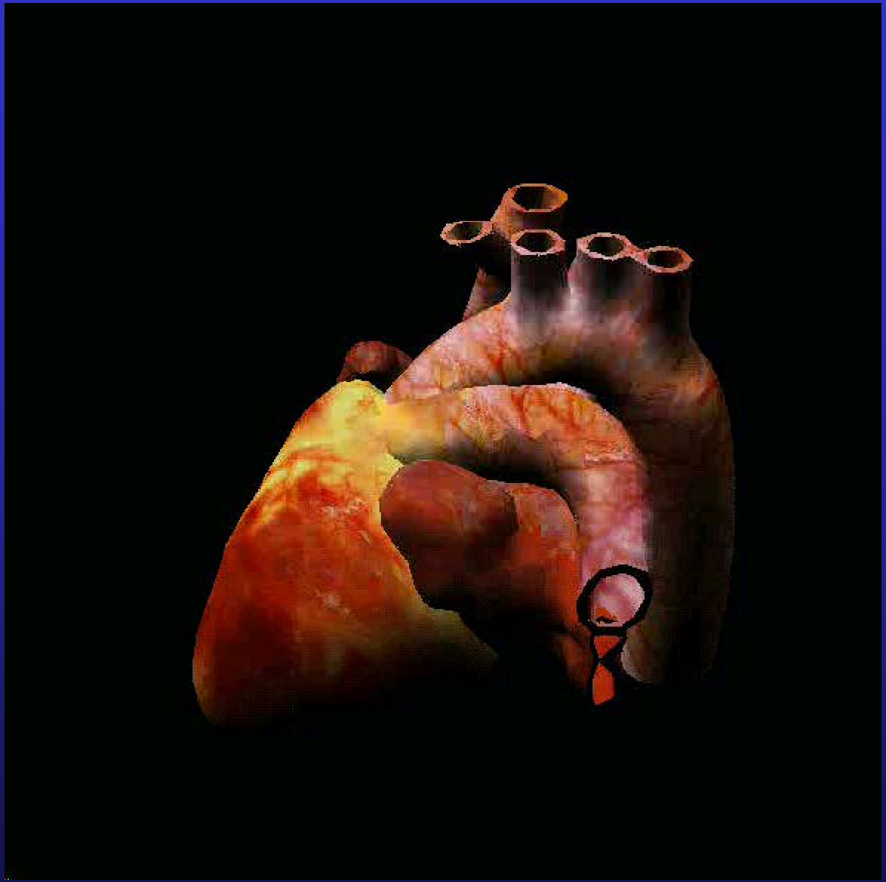
August 28, 2002

This talk is dedicated to the memory of
Heinz Pagels (1939-1988) and others whose contributions to science and society have been cut short by an untimely death.

Cardiac Inventory

Self, Family, Friends

- 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



Courtesy of Peter Hunter, Auckland

textured-heart-spin.mpg

CDC/ Statistics

National Vital Statistics Report,Vol.49,No.11,October 12,2001

Table C.Deaths and percent of total deaths for the 10 leading causes of death:

United States, 1998 and 1999

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

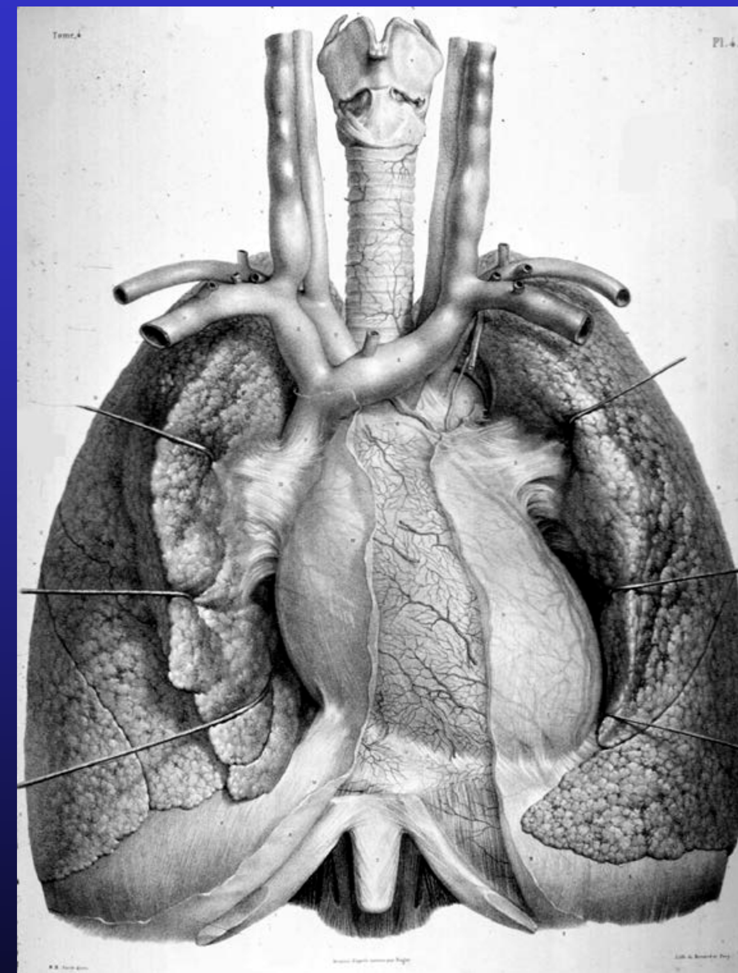
http://www.cdc.gov/nchs/products/pubs/pubd/nvsr/49/49-12.htm#49_11

Goals for This Talk

- To demonstrate, from the perspective of a physicist and engineer, the elegance of cardiac electrophysiology and biophysics
- To show how multiple spatial scales, complexity, and nonlinearity govern the behavior of the heart
- Answer questions about 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 <u>flying</u> tour of cardiac biophysics, …

with occasional stops…

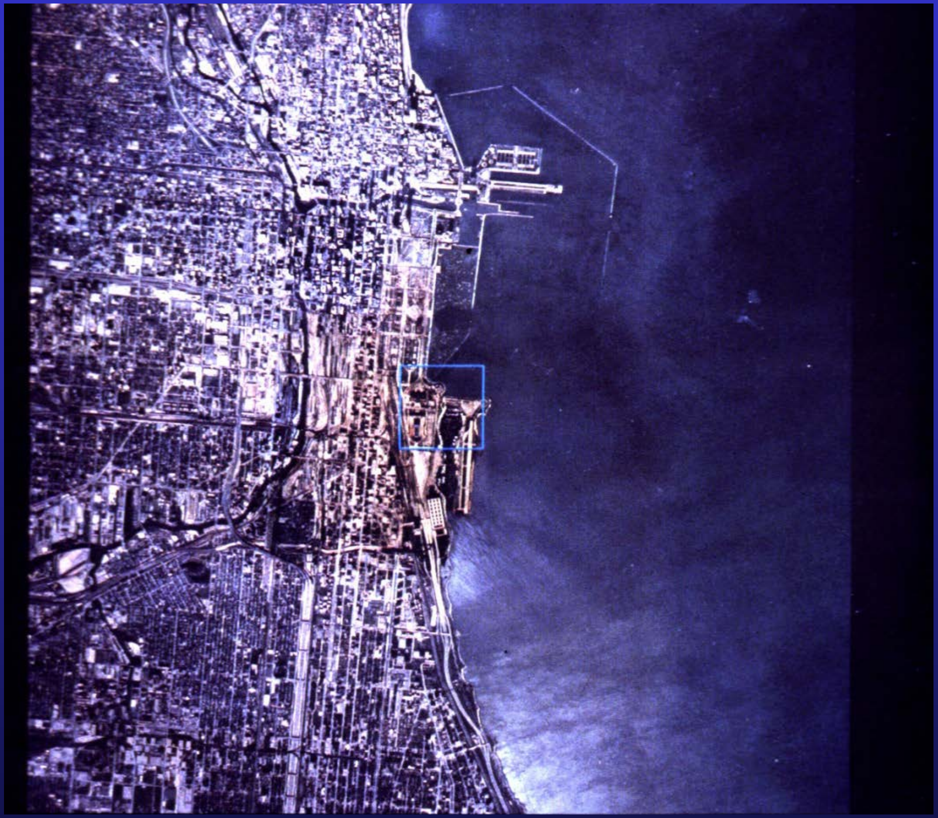
The Spatial Scales

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

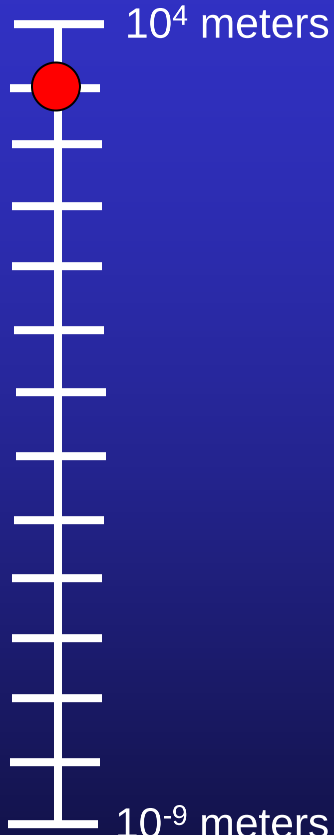
10^4 meters

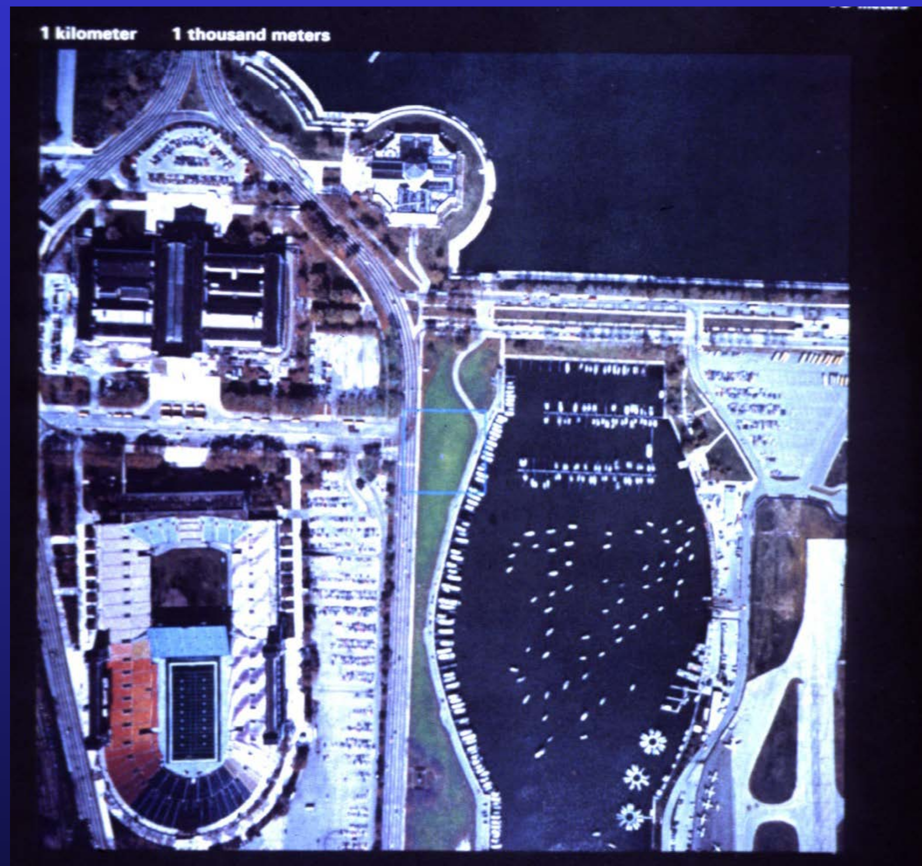
10^{-9} meters



From Powers of Ten by Philip Morrison

1 kilometer: Soldiers Field

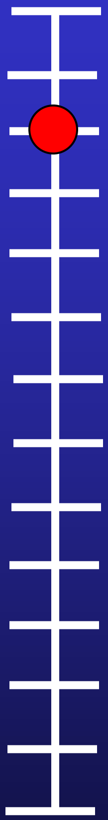




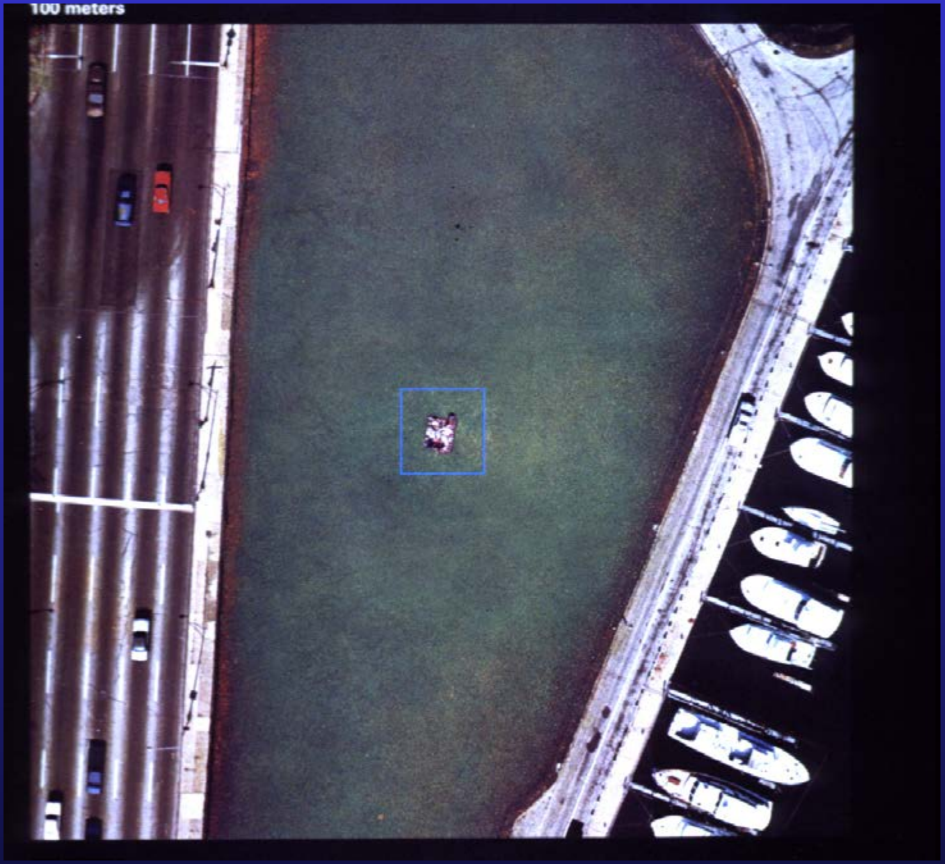
From Powers of Ten by Philip Morrison

100 meters: A park

10^4 meters

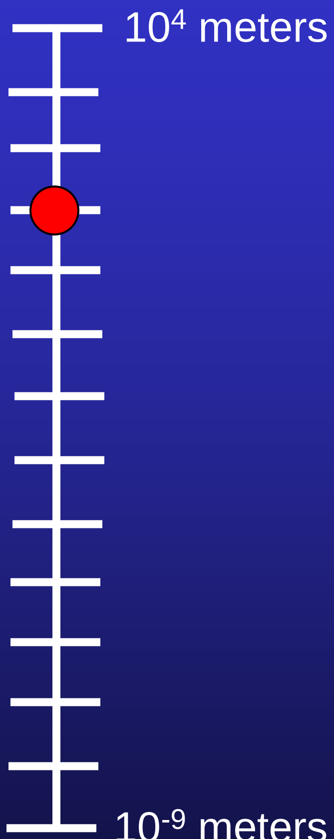


10^{-9} meters



From Powers of Ten by Philip Morrison

10 Meters: A picnic



From Powers of Ten by Philip Morrison

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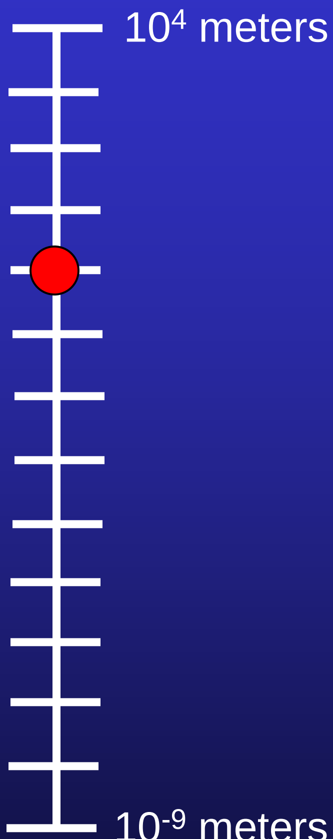
s01784

1 meter: A human

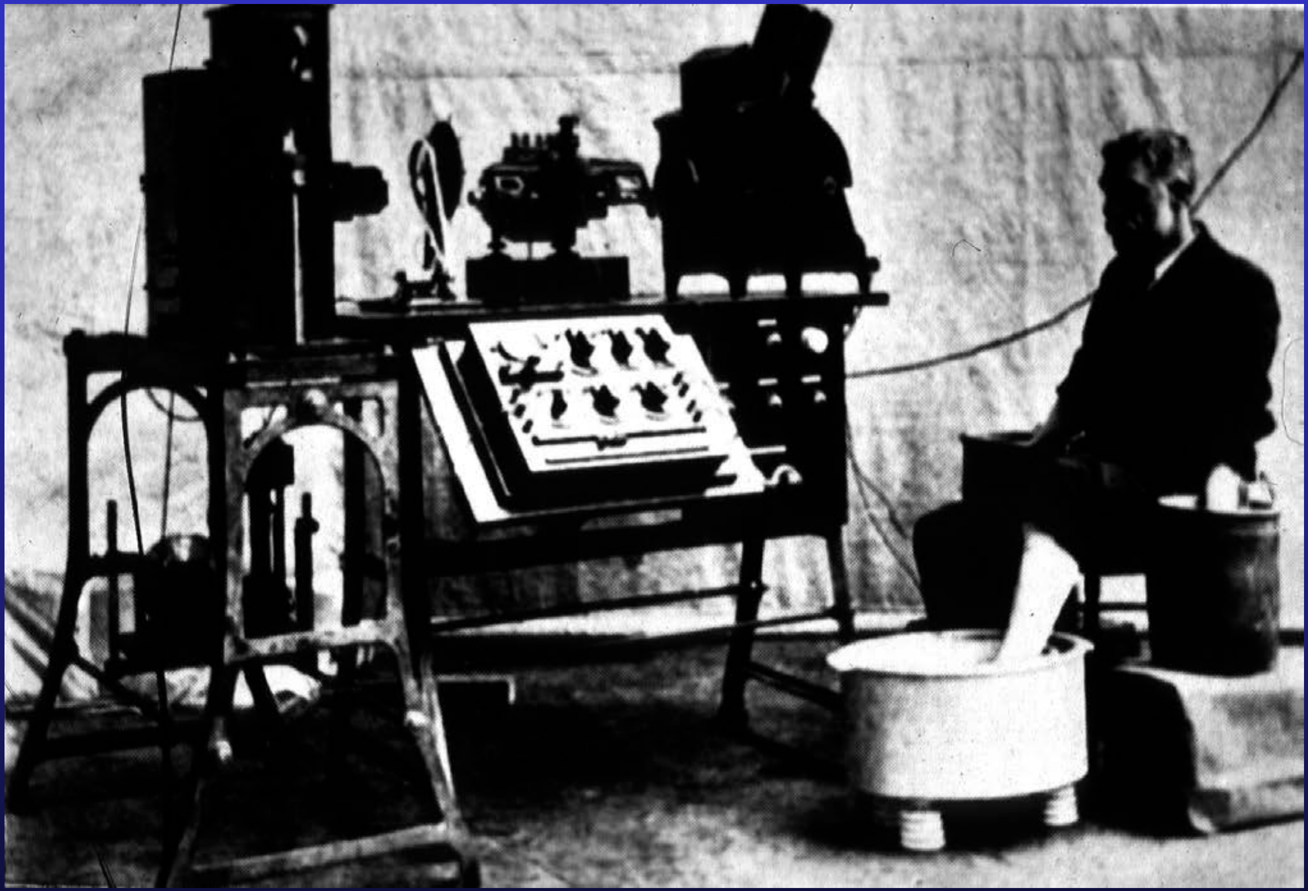


From <u>Powers of Ten</u> by Philip Morrison

1 meter

The First Clinical ECG Machine

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



1 meter

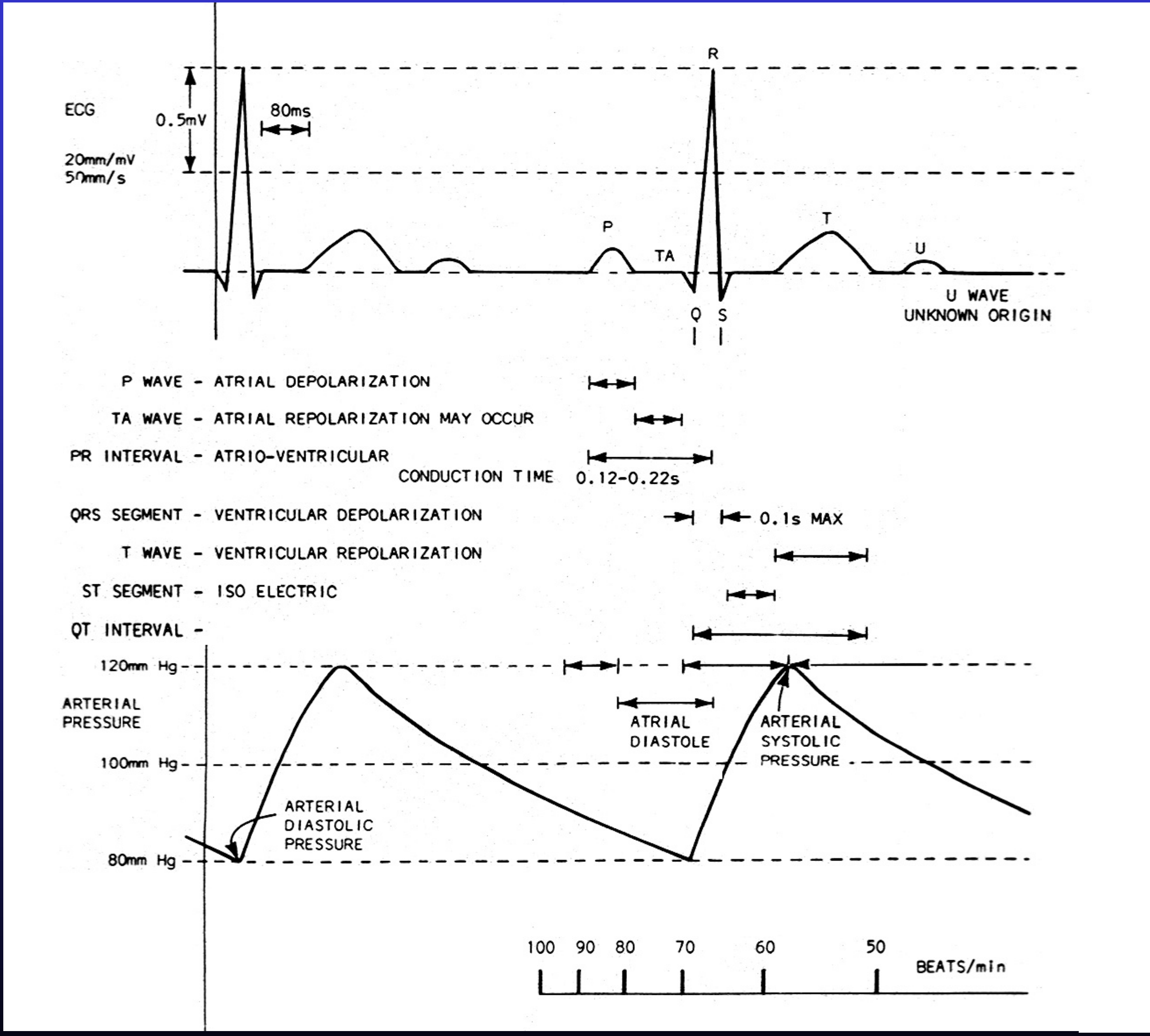
The First Clinical VMCG Machine

Vector Magnetocardiography
Stanford
~1974

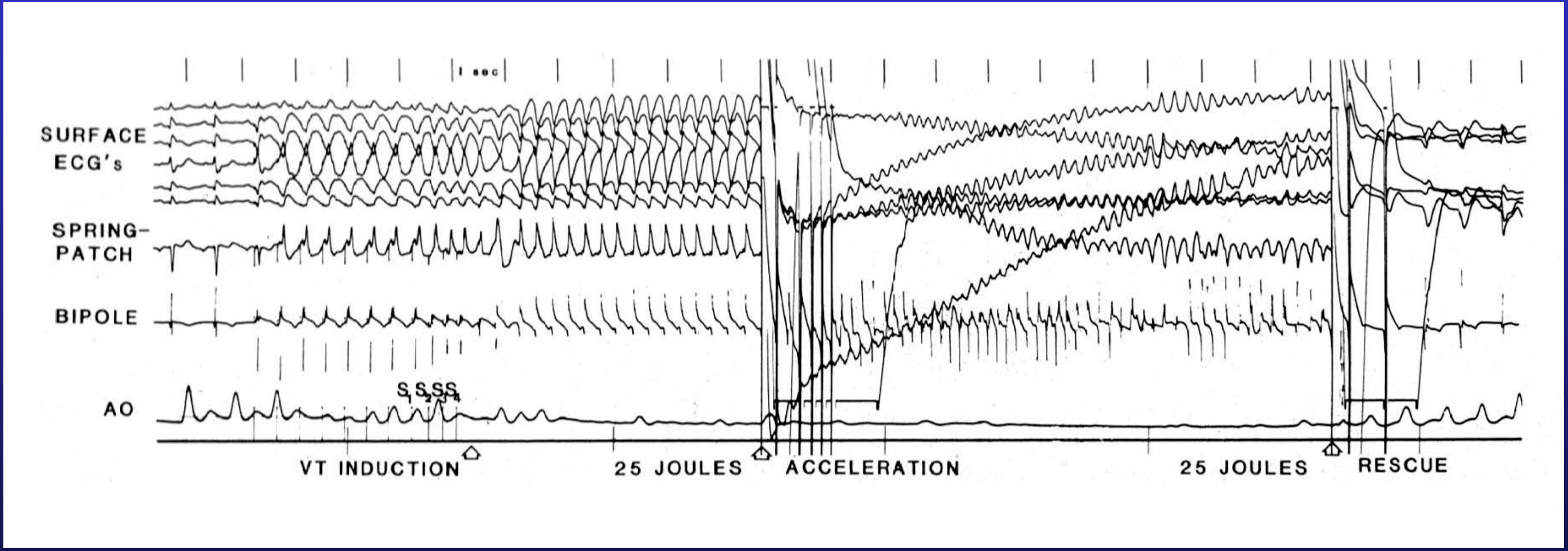
1 meter

The heart is an …

- electrically activated,
- mechanical pump



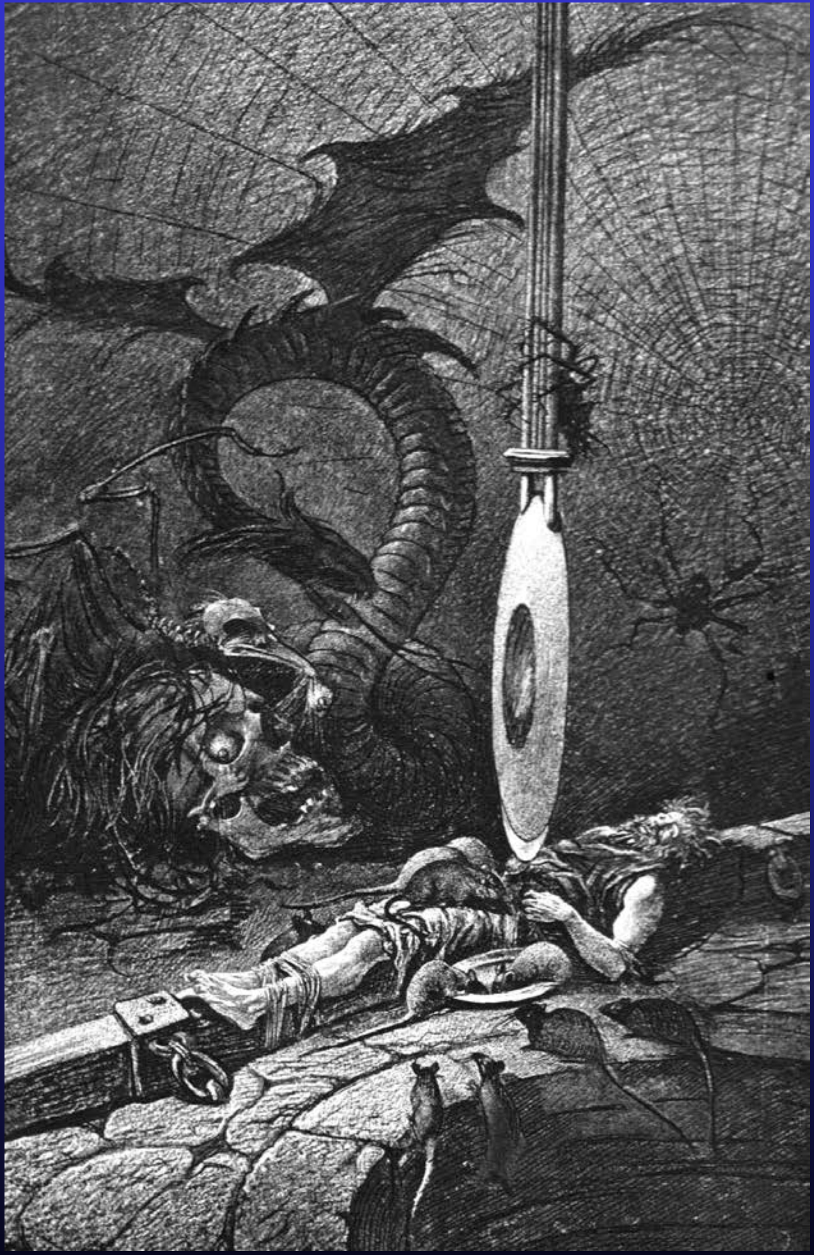
- …with a mean time-to-failure of approximately two billion cycles….



Courtesy of Debra Echt

Sinus rhythm, tachycardia, fibrillation and defibrillation

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



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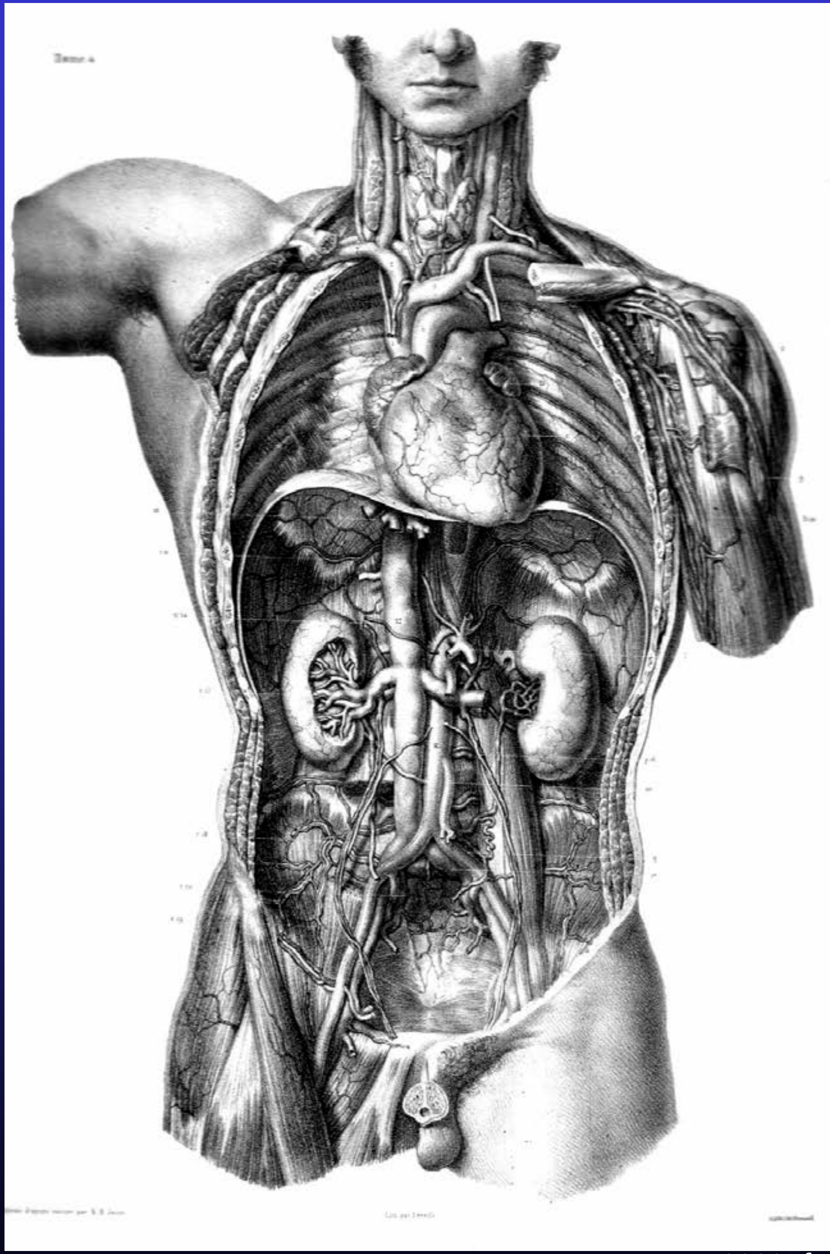
1 meter

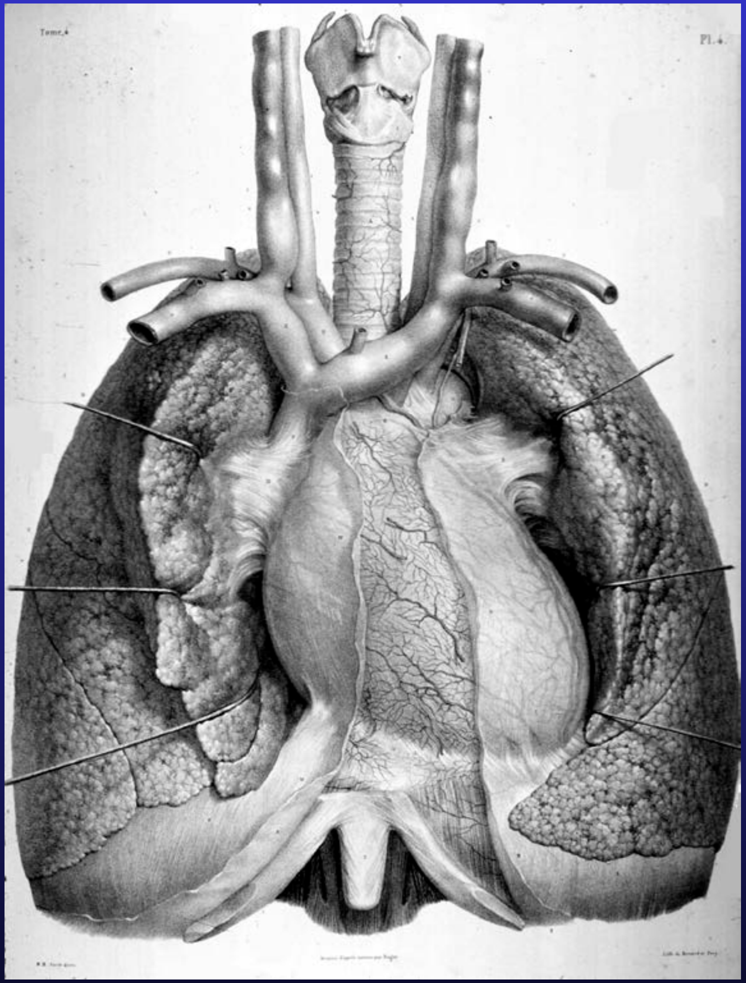
Et voilà, an uncomfortable gentleman from nineteenth century France



s00002f

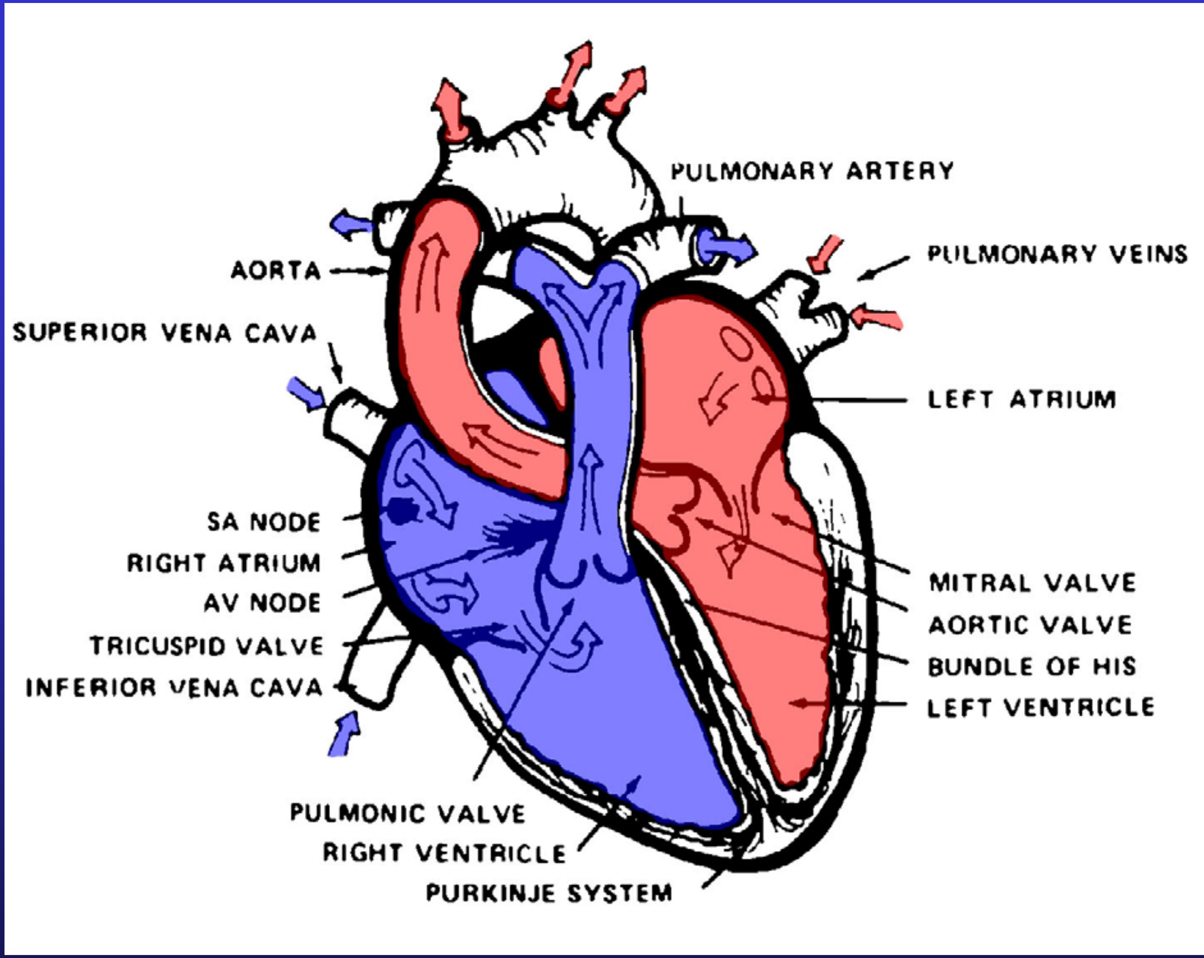
The Heart is a…

- 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.



The Heart is a…

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

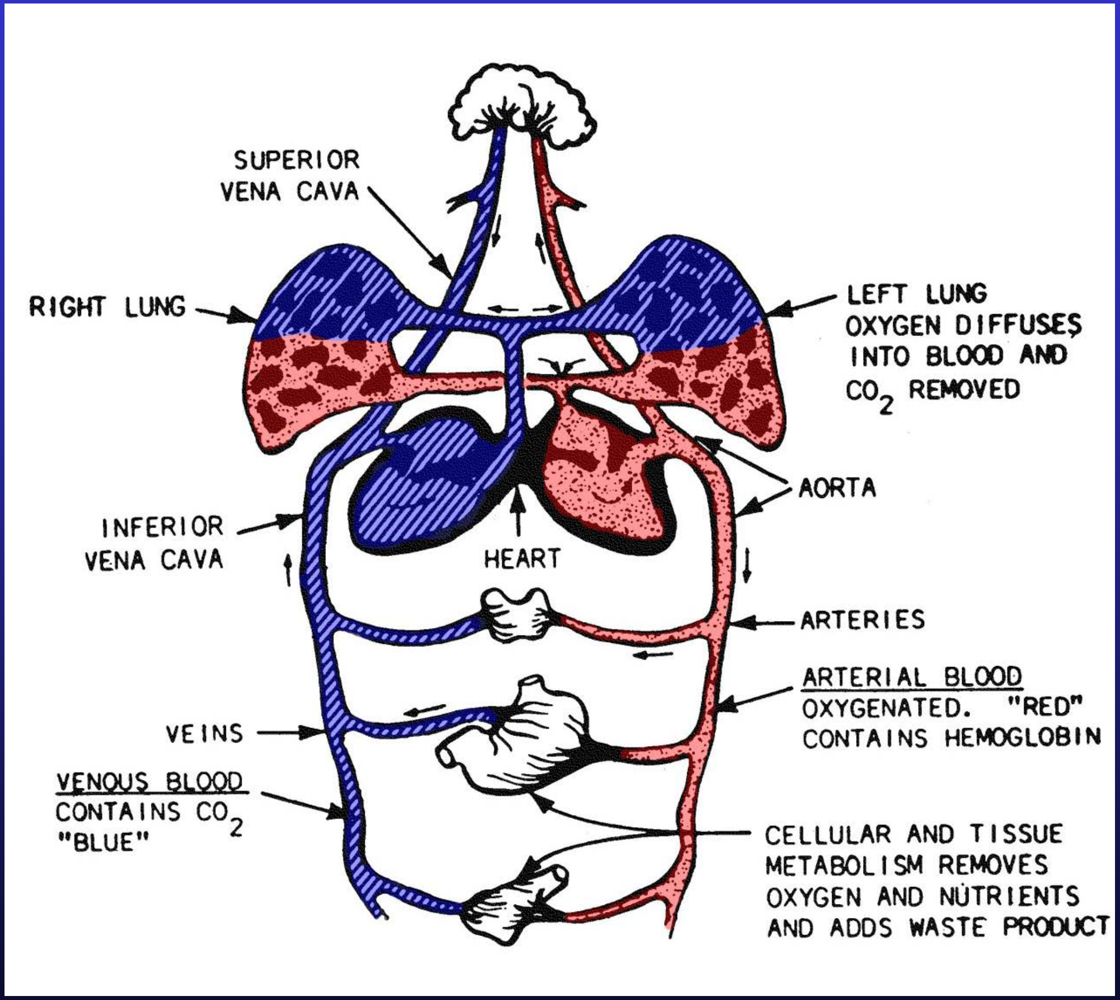


Courtesy of Peter Hunter, Auckland

textured-heart-beat.mpg

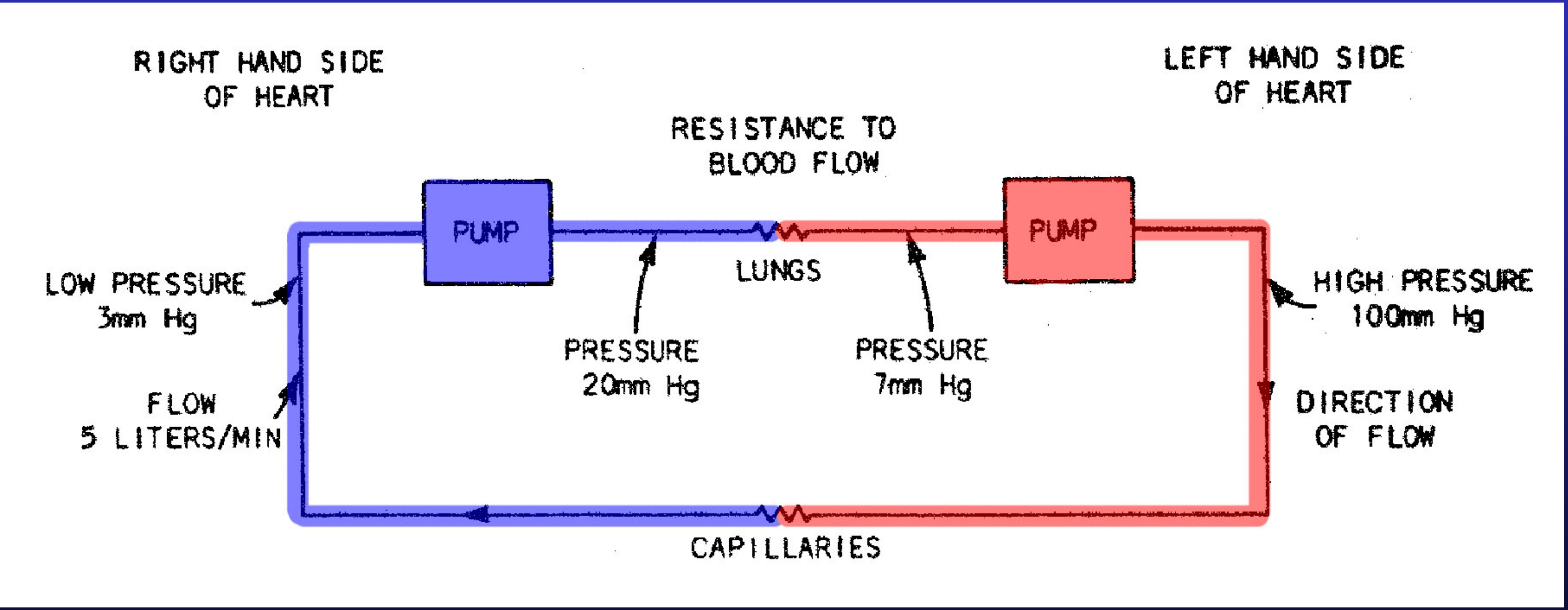
The Heart is…

- …..
- 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 …



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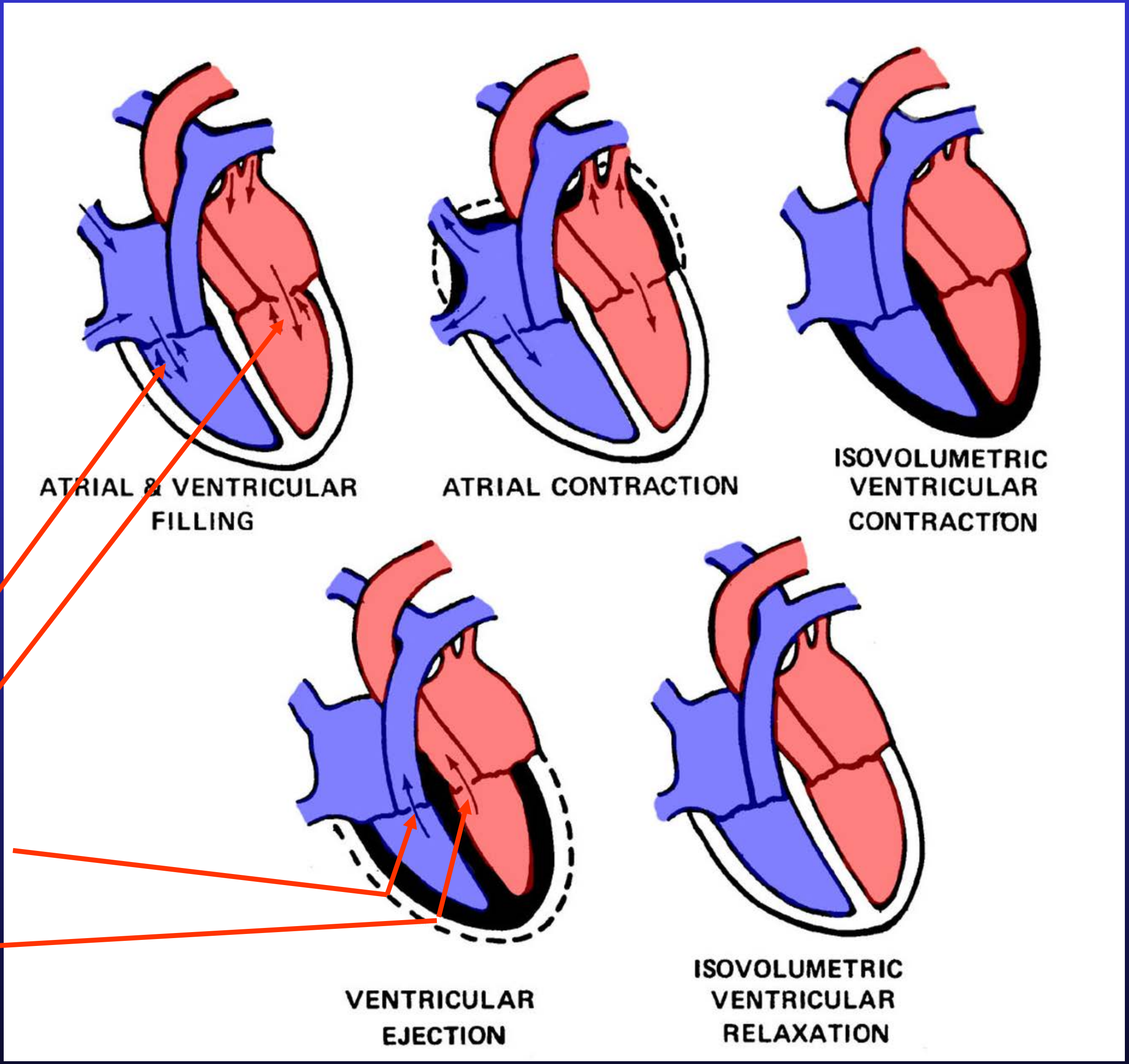
The Cardiac Cycle and Valves

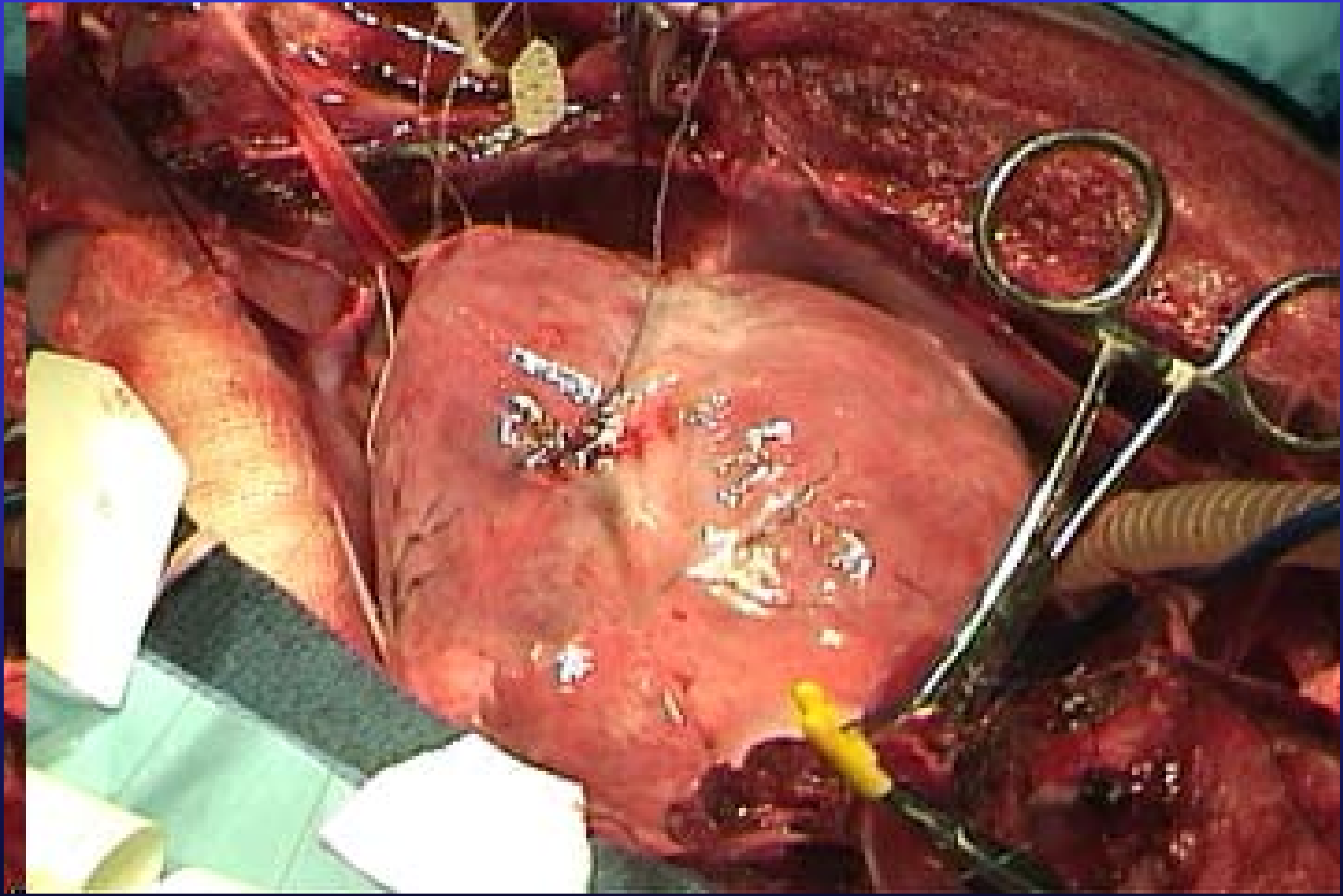
- •Tricuspid (R)
  Mitral (L)
- •Pulmonary (R)
  Aortic (L)



-- Warning --
Visual Discretion Required

- The following slide shows in living technicolor a beating pig heart
- If you are faint of heart or stomach, please close your eyes until further notice

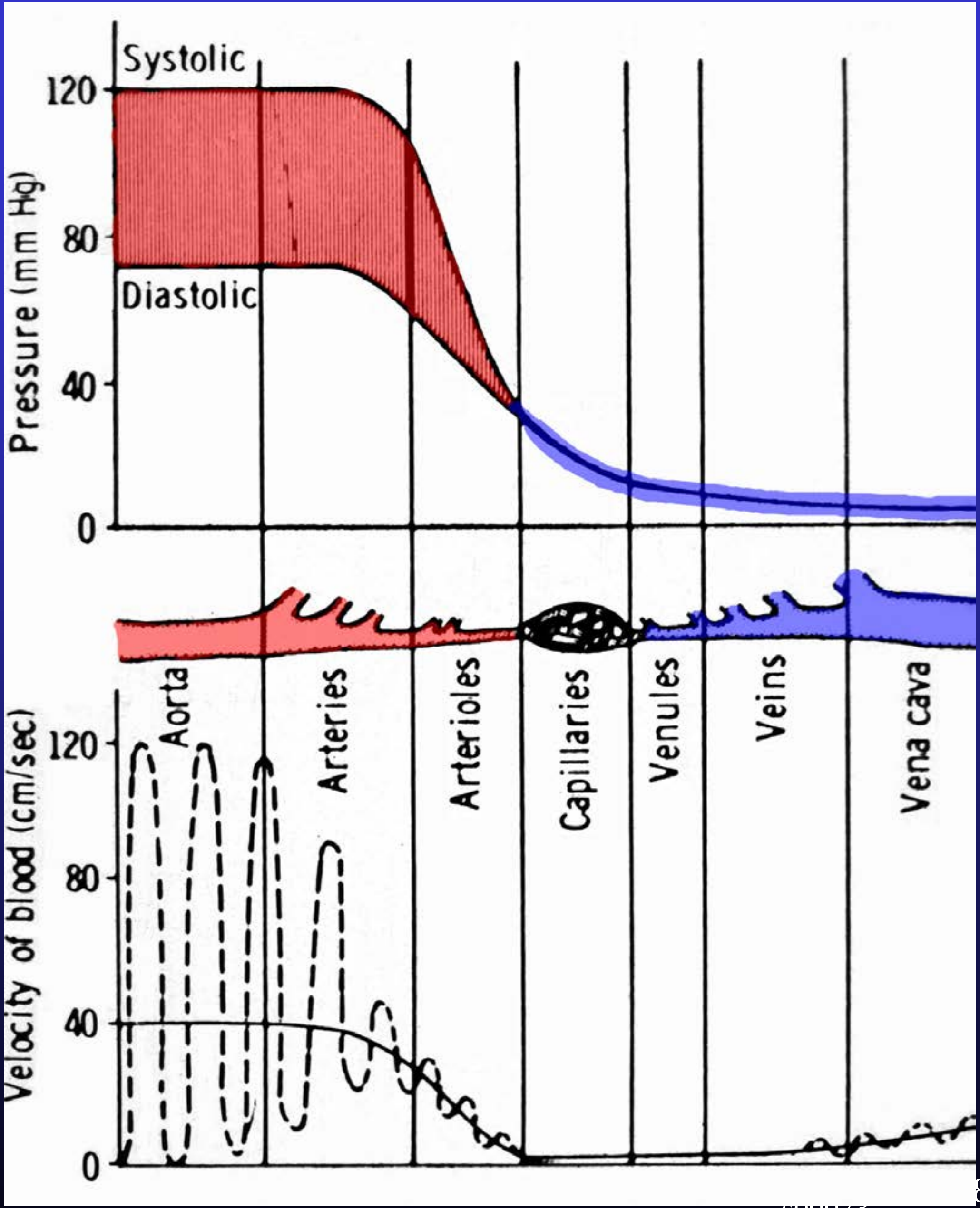
The Normal Heart Beat



Courtesy of Rick Gray and CRML, U. Alabama Birmingham

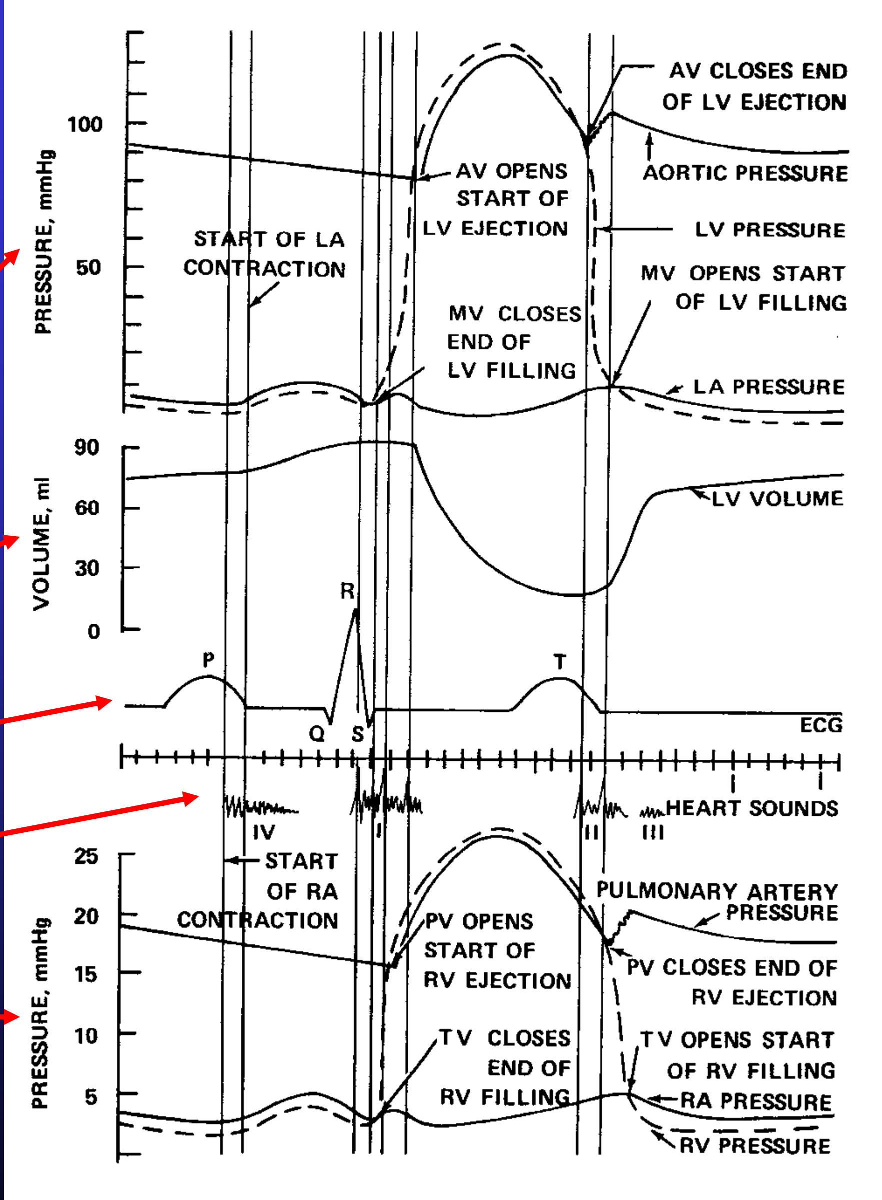
Peripheral Circulation

- 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



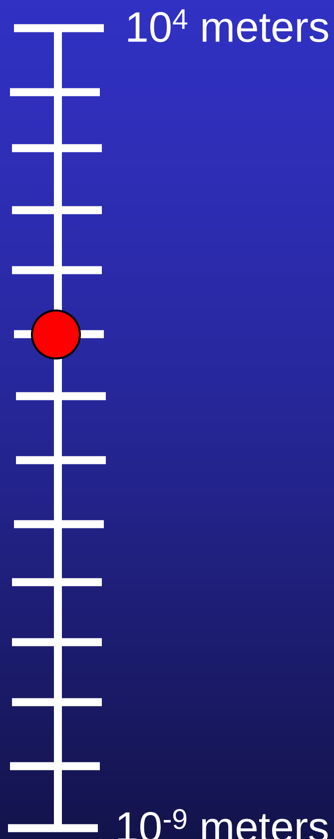
The Cardiac Cycle

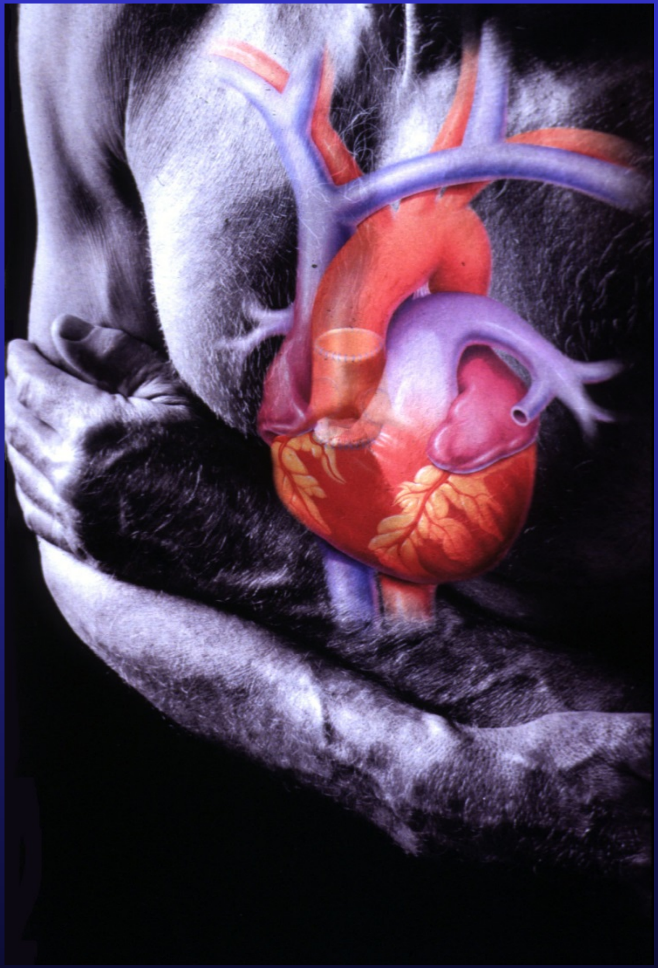
- Left pressures
- LV volume
- ECG
- Heart sounds
- Right pressures



Onward, inward….

10 centimeters: The human heart

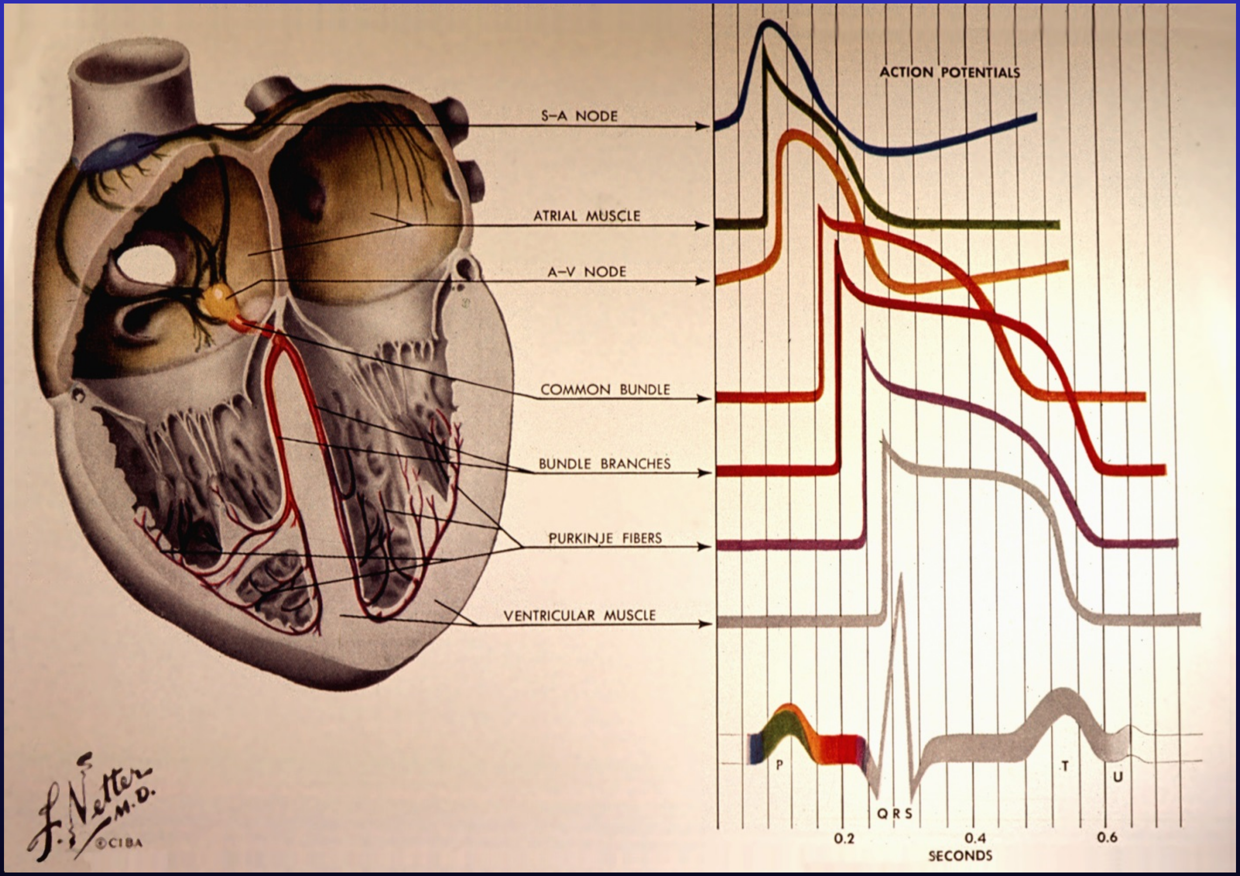


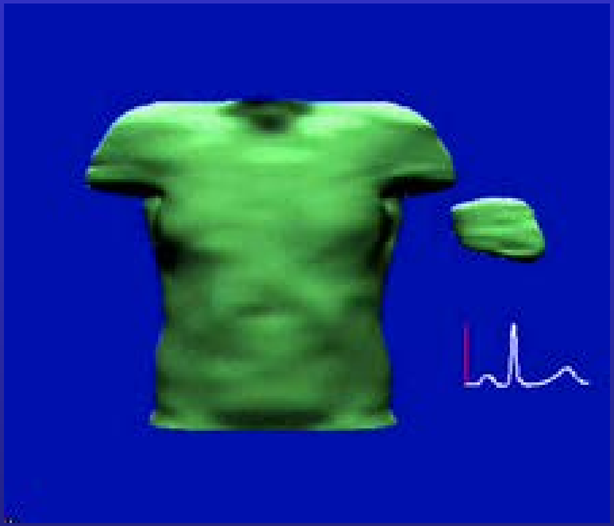


Medtronics

The heart is … 10 centimeters

electrically activated …





Courtesy of Peter Hunter, Auckland

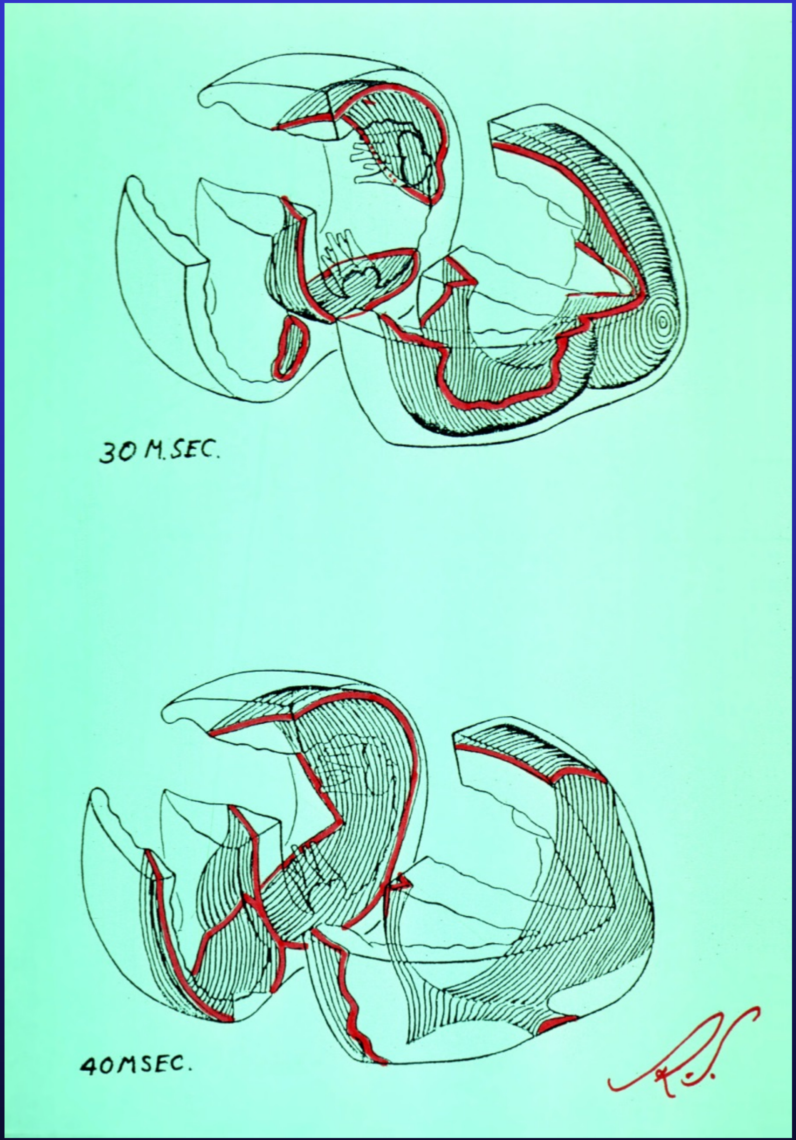
normalbsm.mpg

From: The Ciba Collection of Medical Illustrations: Heart, F. H. Netter, 1978

The cardiac depolarization wave front

10 centimeters

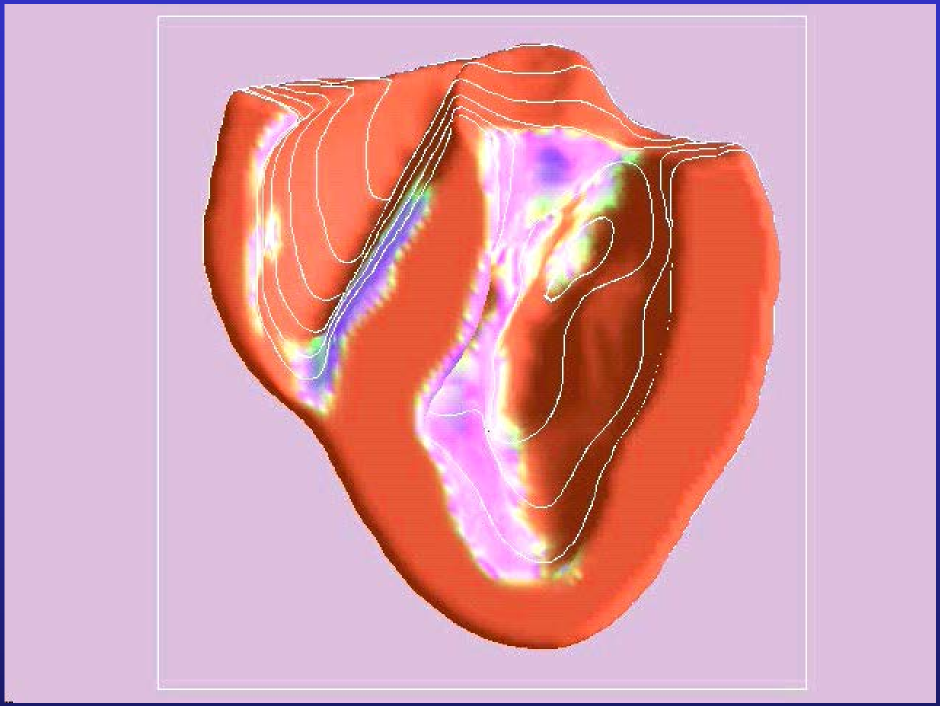
- Activated cells collectively form a sheet that is a moving 3-dimensional battery
- 1 mm thick
- Moving at ~1 m/sec

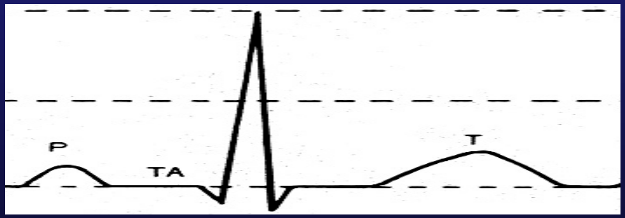


Courtesy of Ron Selvester

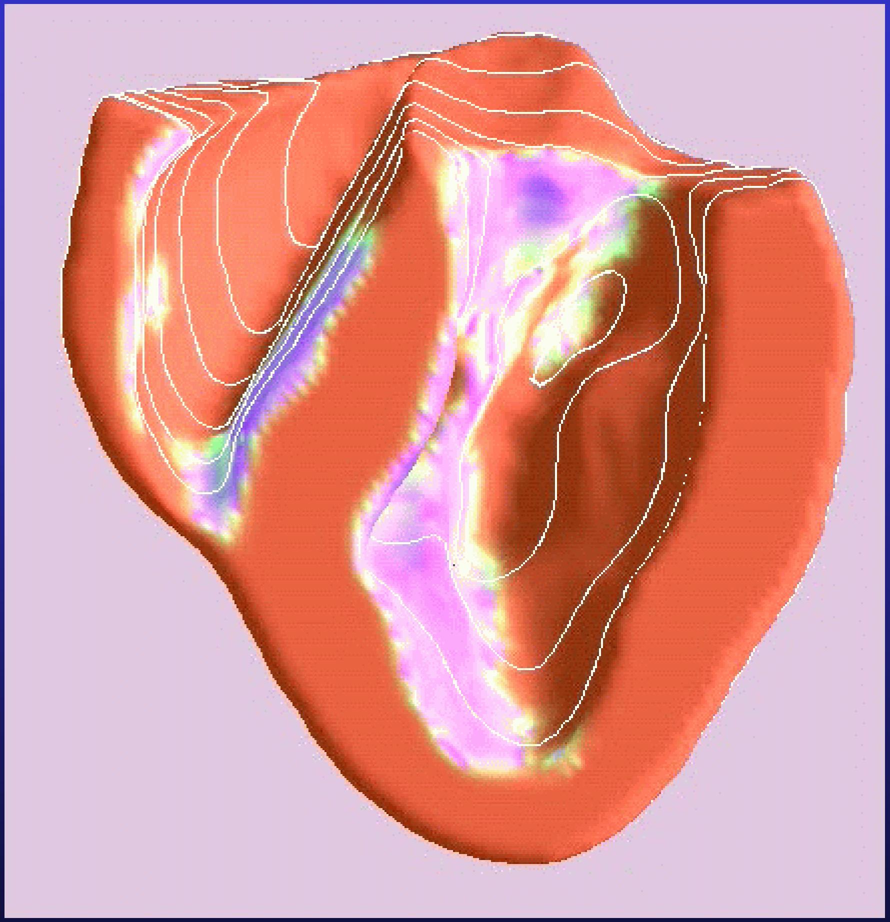
The cardiac depolarization wave front

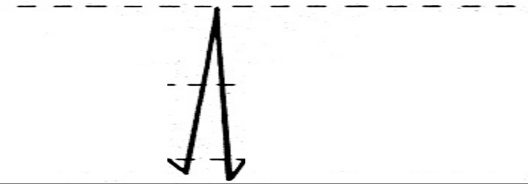
- The entire cardiac cycle





Depolarization only



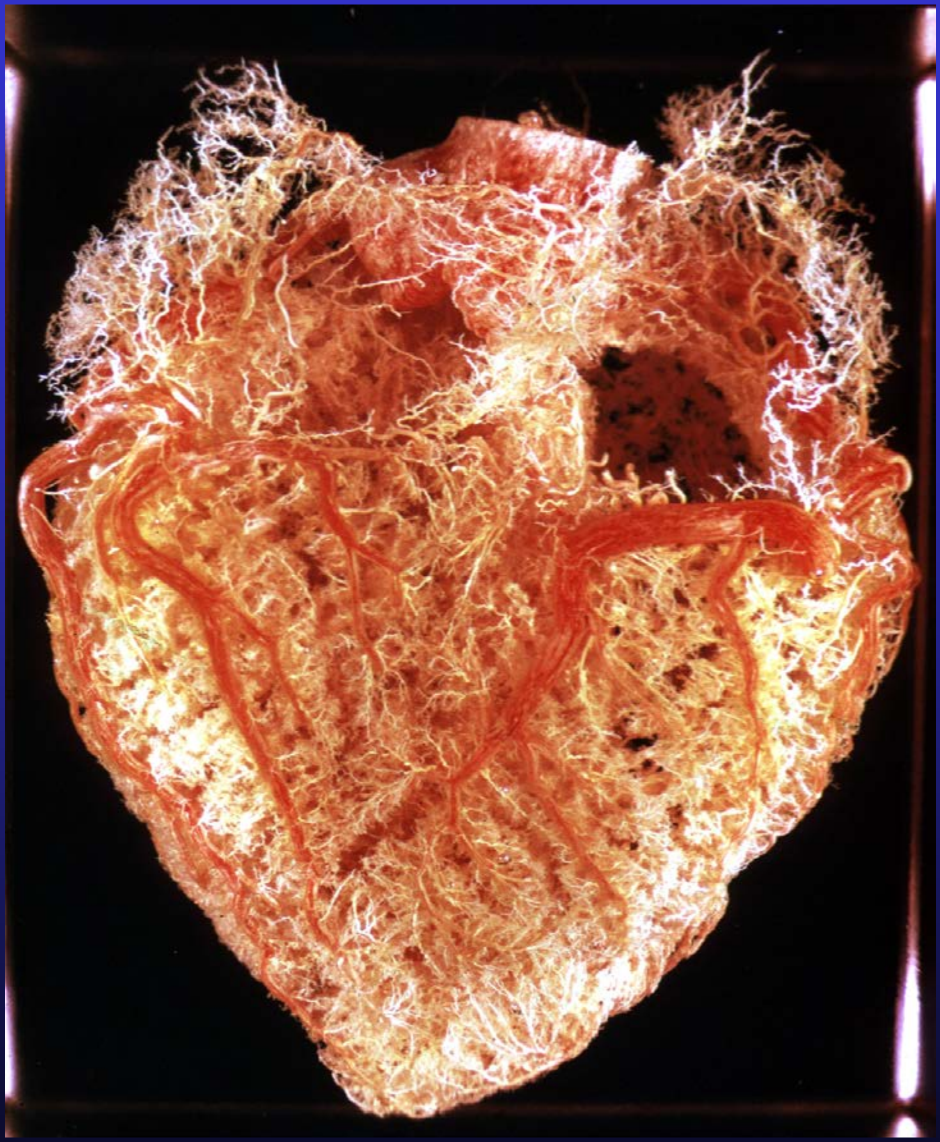


HLR2.MPG heartactivation2.MPG

Courtesy of Rubin Aliev

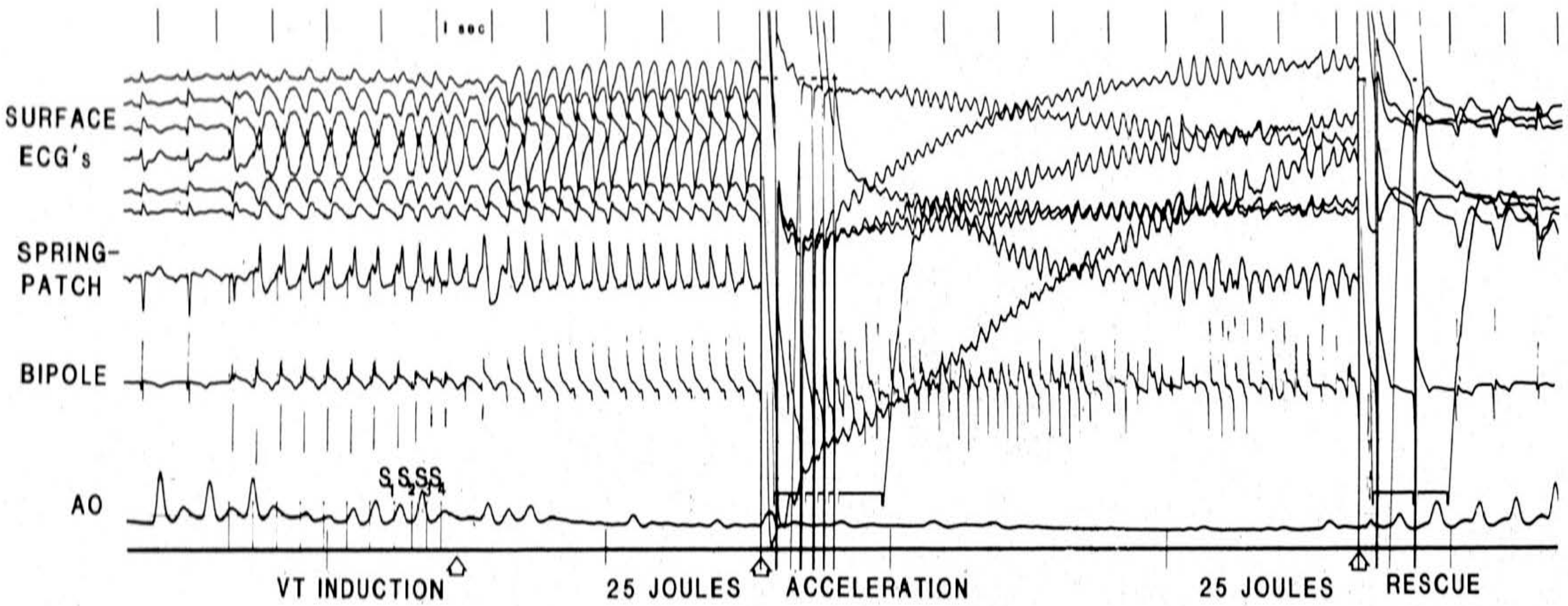
The Coronary Arteries

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



Courtesy of Jaakko Malmivuo

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

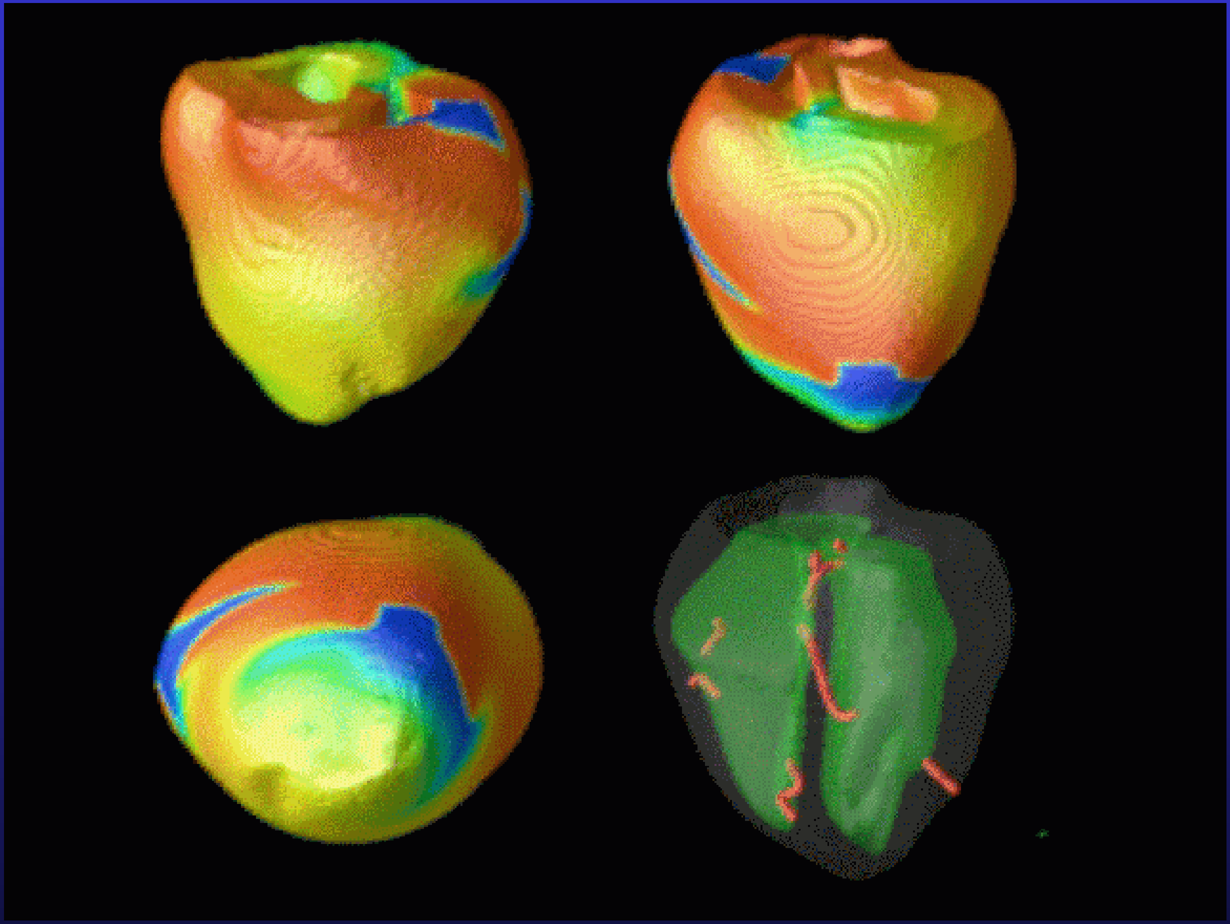


Courtesy of Debra Echt

Normal **Tachycardia** **Fibrillation** **Defibrillation**

The Fibrillating Heart

Anterior Posterior



Apex Posterior

(Transparent)

Movies courtesy of Flavio Fenton and Elizabeth Cherry

cytodLL.avi

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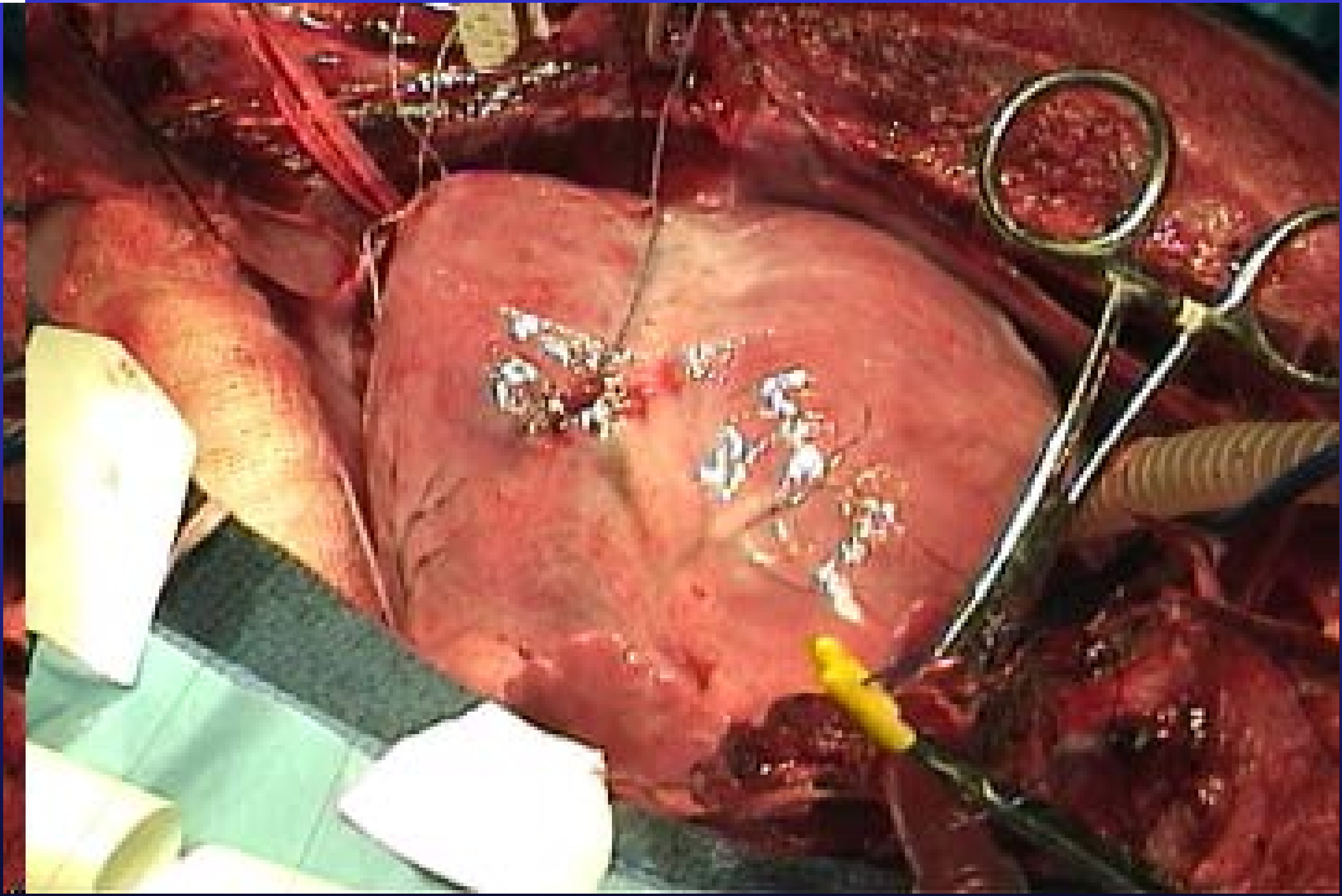
Induction of Fibrillation



Courtesy of Rick Gray and CRML, U. Alabama Birmingham

SwineSinusVF.mov

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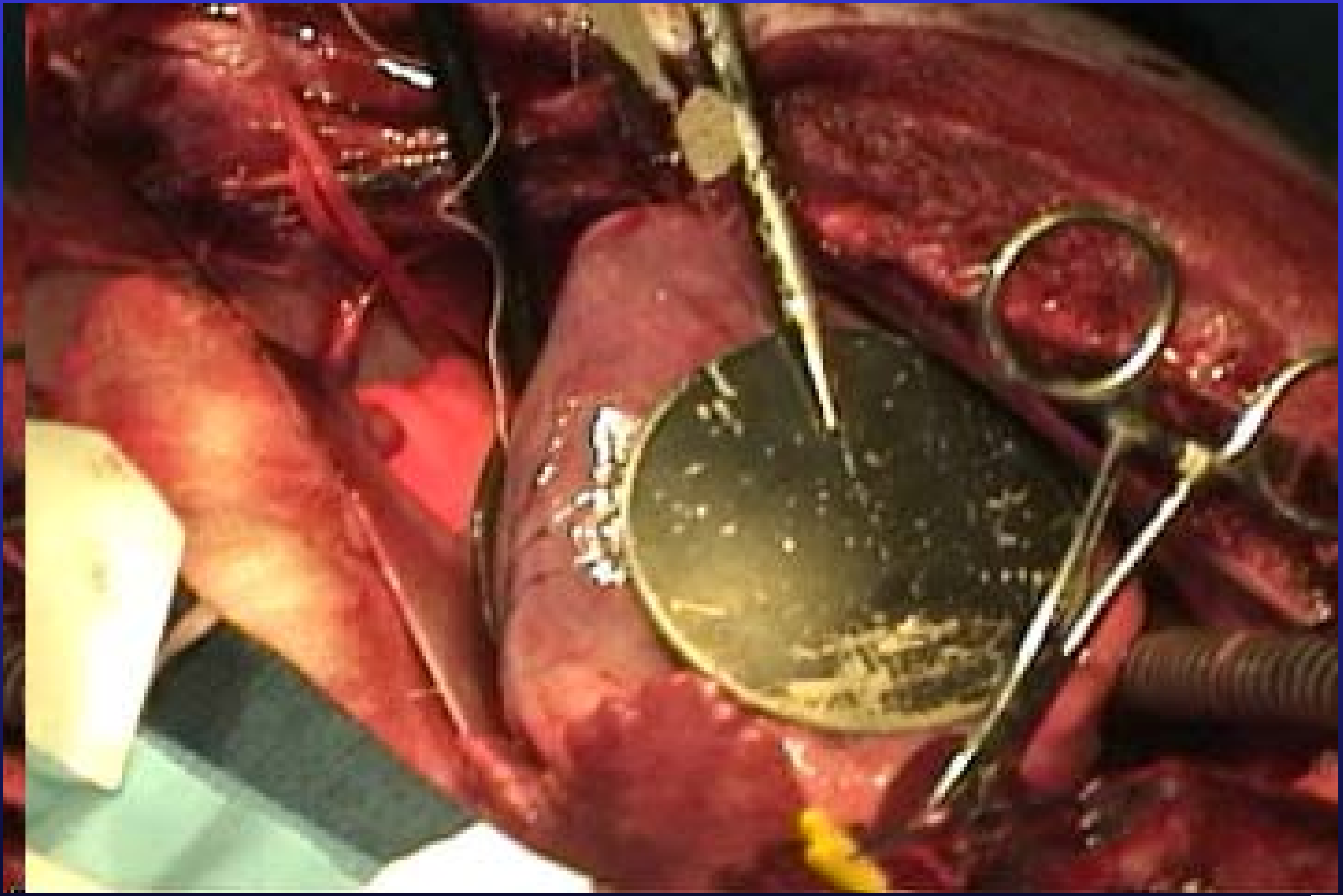
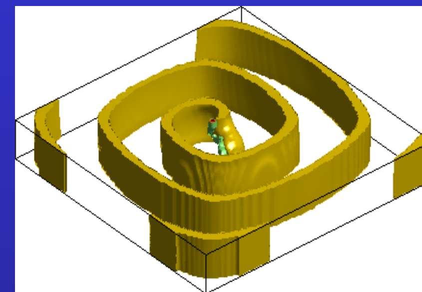
Termination of Fibrillation

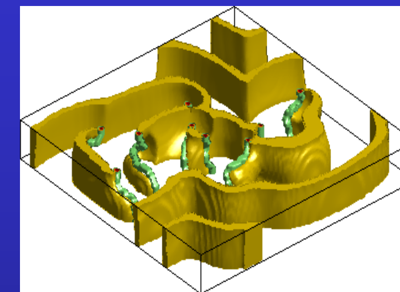


Courtesy of Rick Gray and CRML, U. Alabama Birmingham

SwineVFShockSinus.mov

Spiral and Scroll Waves in Nature



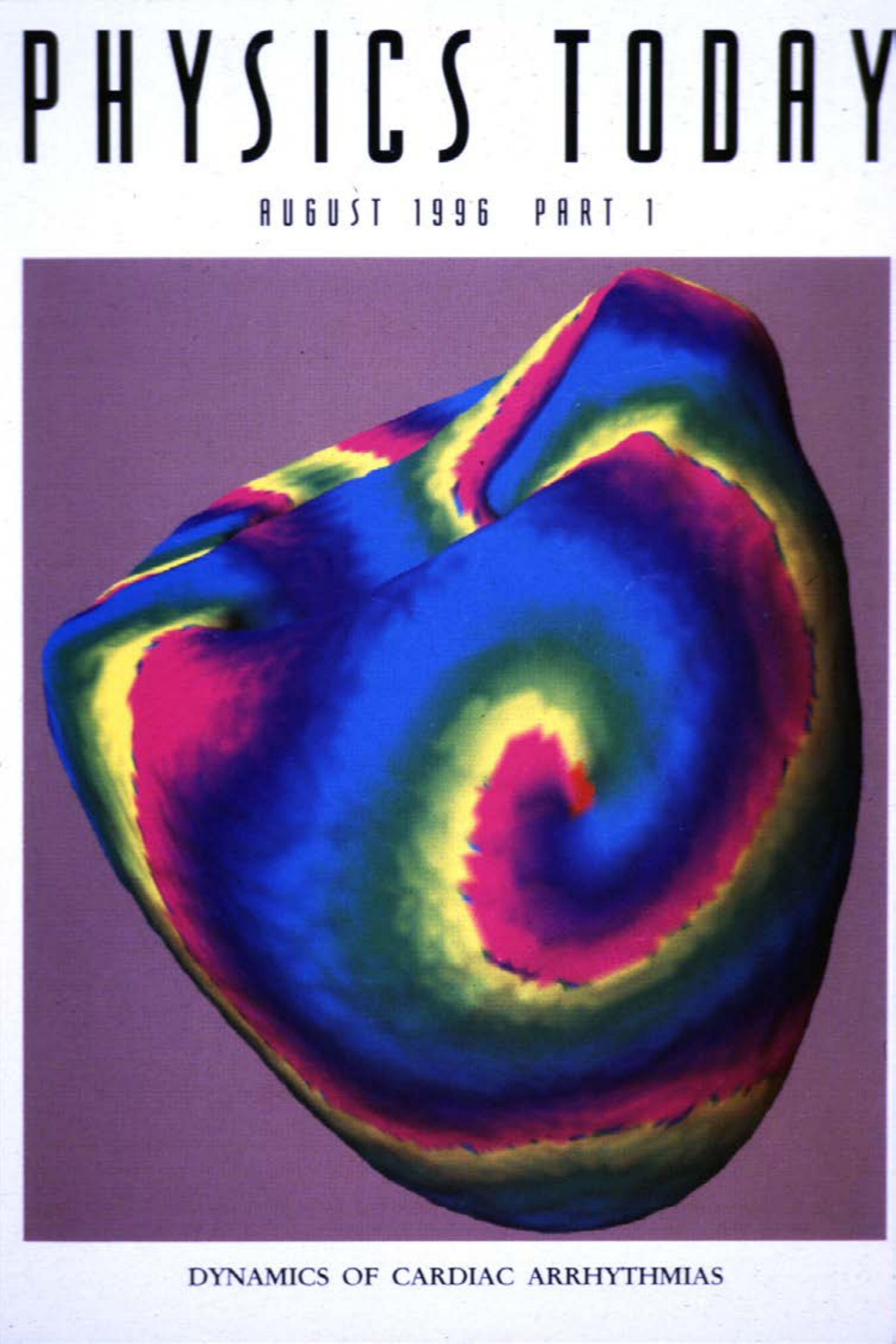


- A generic property of excitable (non-lineary) media
- Have been shown to occur in
  - Circulating waves of bioelectric activity in cardiac and retinal tissue
  - Autocatalytic chemical reactions, such as Belousov-Zhabotinsky reaction (BZ)
  - cAMP waves in slime mold *Dictyostelium discoideum*
  - Intracellular calcium release in oocytes
  - Oxidation of CO on crystal surfaces in ultrahigh vacuum conditions
  - In animal cortex
- Cardiac fibrillation involves multiple scroll waves in 3-D

Courtesy of Mark Bray

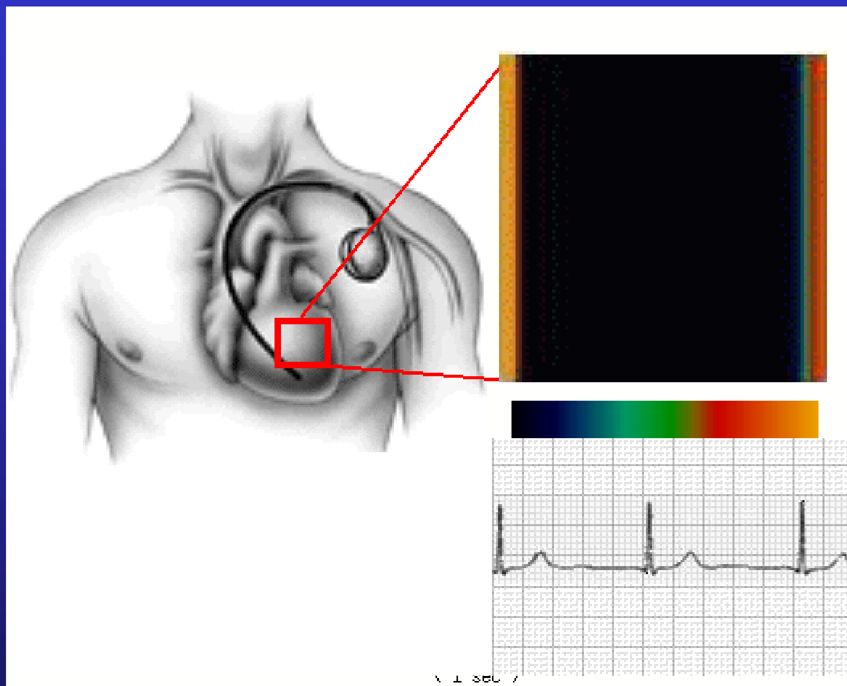
10 centimeters

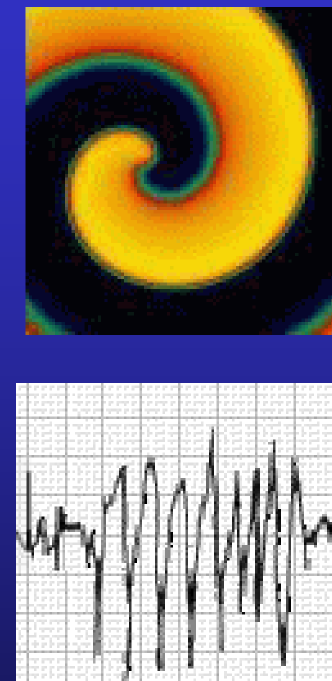
Cardiac fibrillation occurs at the spatial scale of the entire heart, and involves multiple, interacting spiral and/or scroll waves!

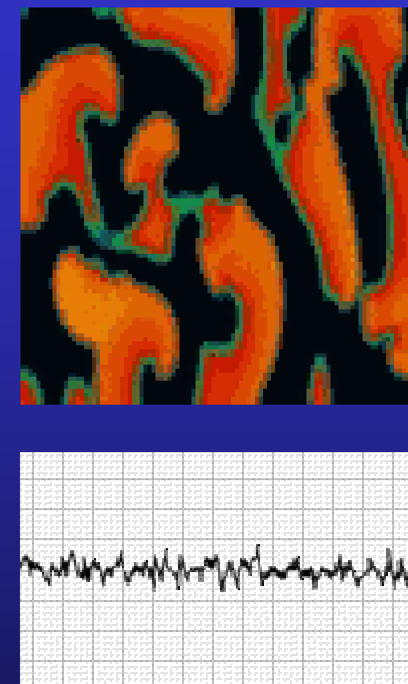


Leon Glass, Montreal

Transition from Normal Rhythm to Ventricular Tachycardia to Ventricular Fibrillation







A. Karma, *Chaos* 4 (3): 461-472, 1994

Normal Rhythm

VT

VF

Single spiral wave = Tachycardia

Multiple spiral waves = Fibrillation = SCD

Movies Courtesy of Flavio Fenton

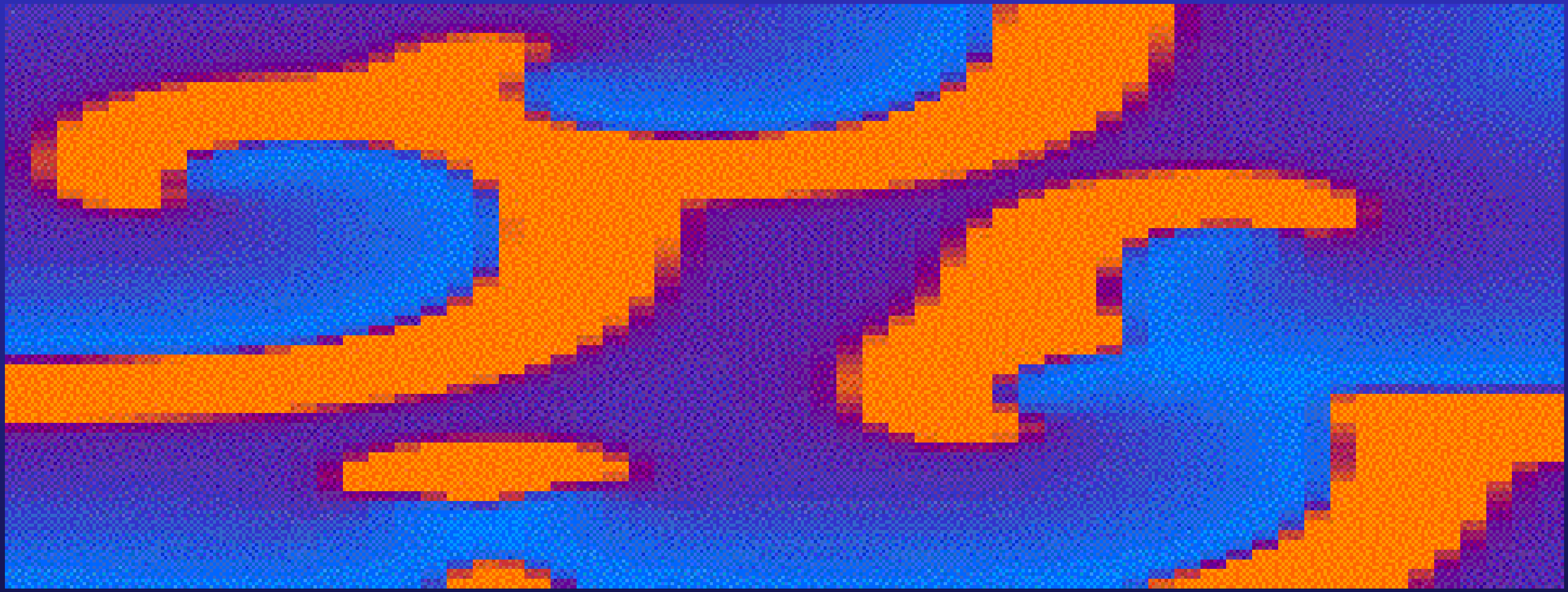
SA.avi

SBB.avi

scclong.avi

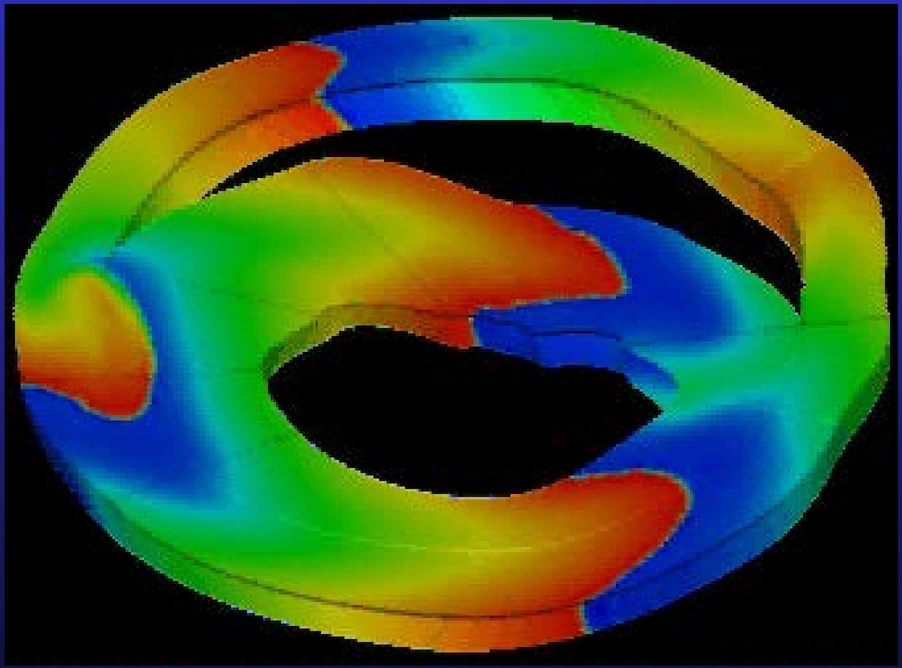
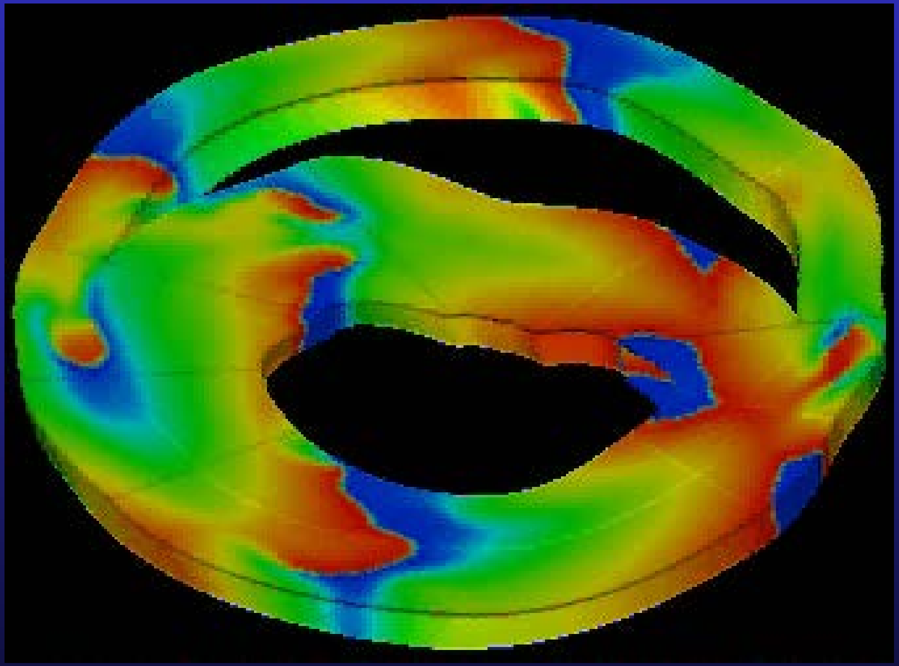
How do you defibrillate the heart?

- The Neils Otani Cyber Cardiologist



cybercardiologist_short.htm

Success vs. Failure?

Successful Defibrillation	Unsuccessful Defibrillation
	

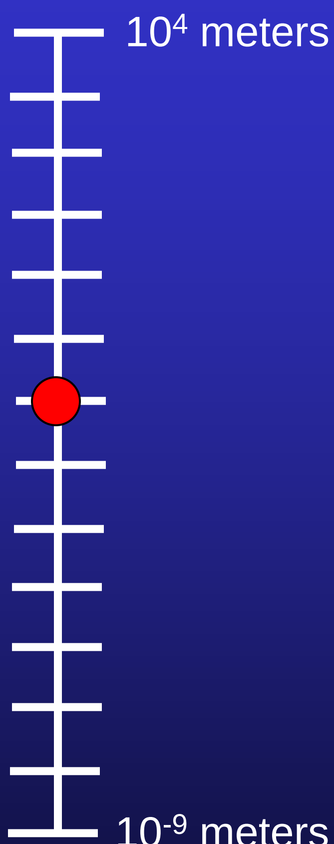
Natalia Trayanova

775single.avi

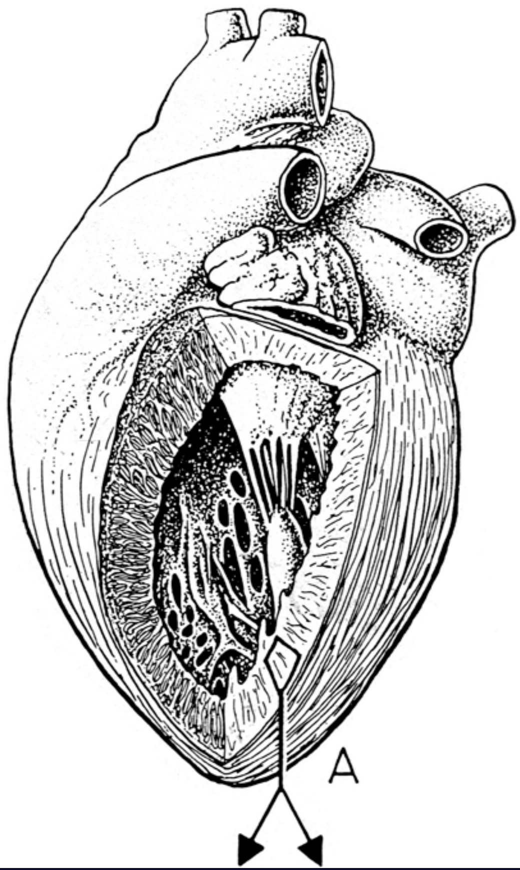
775multiple.avi

Onward, inward….

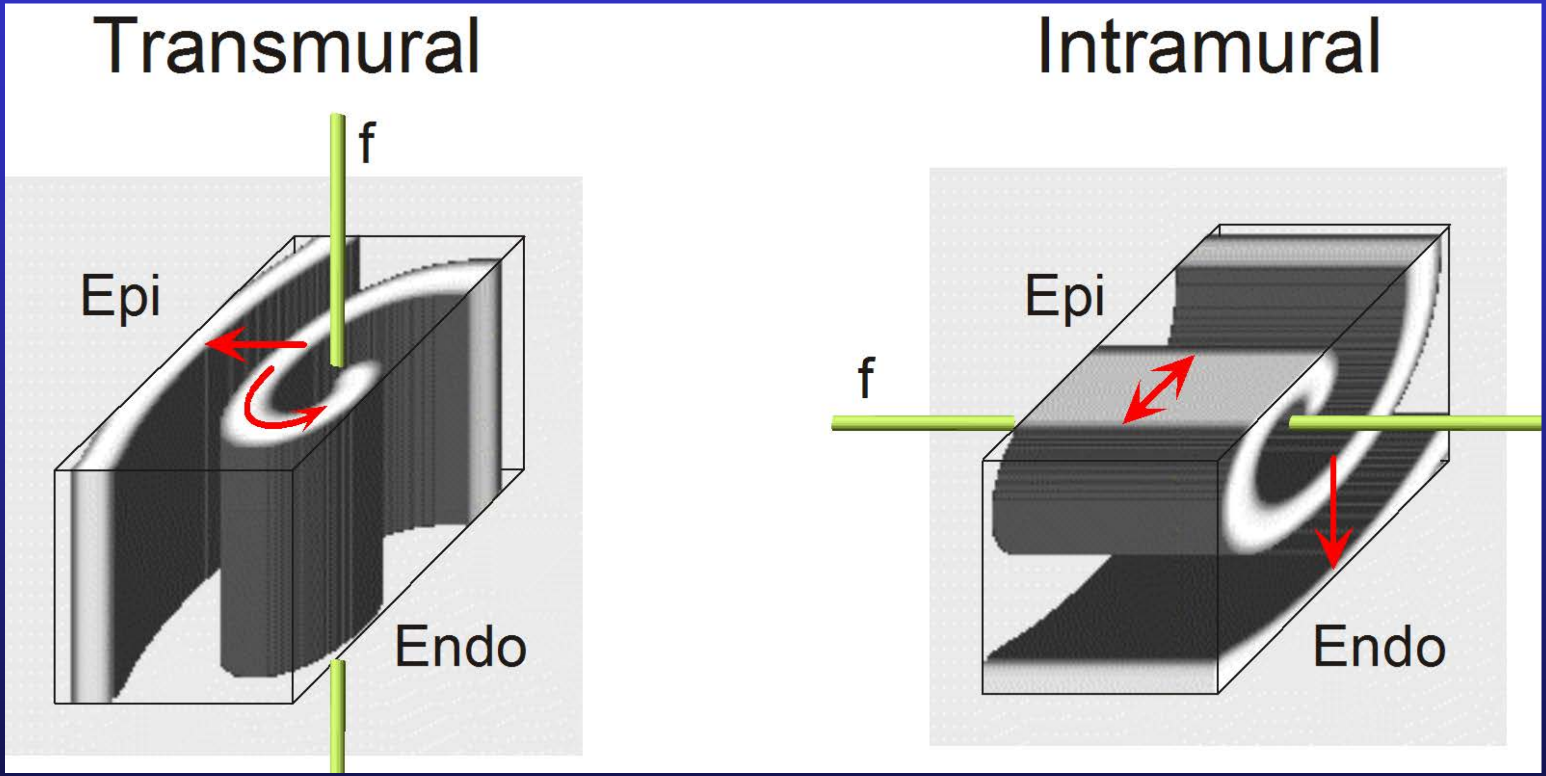
1 centimeter: The left ventricular wall



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



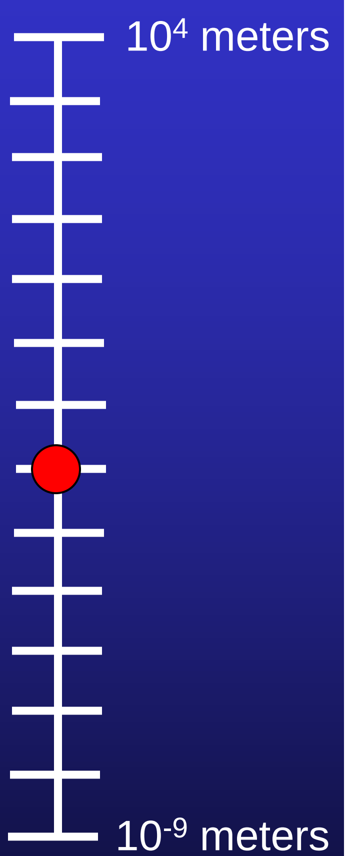
Transmural versus intramural scroll waves in reentrant arrhythmias and fibrillation

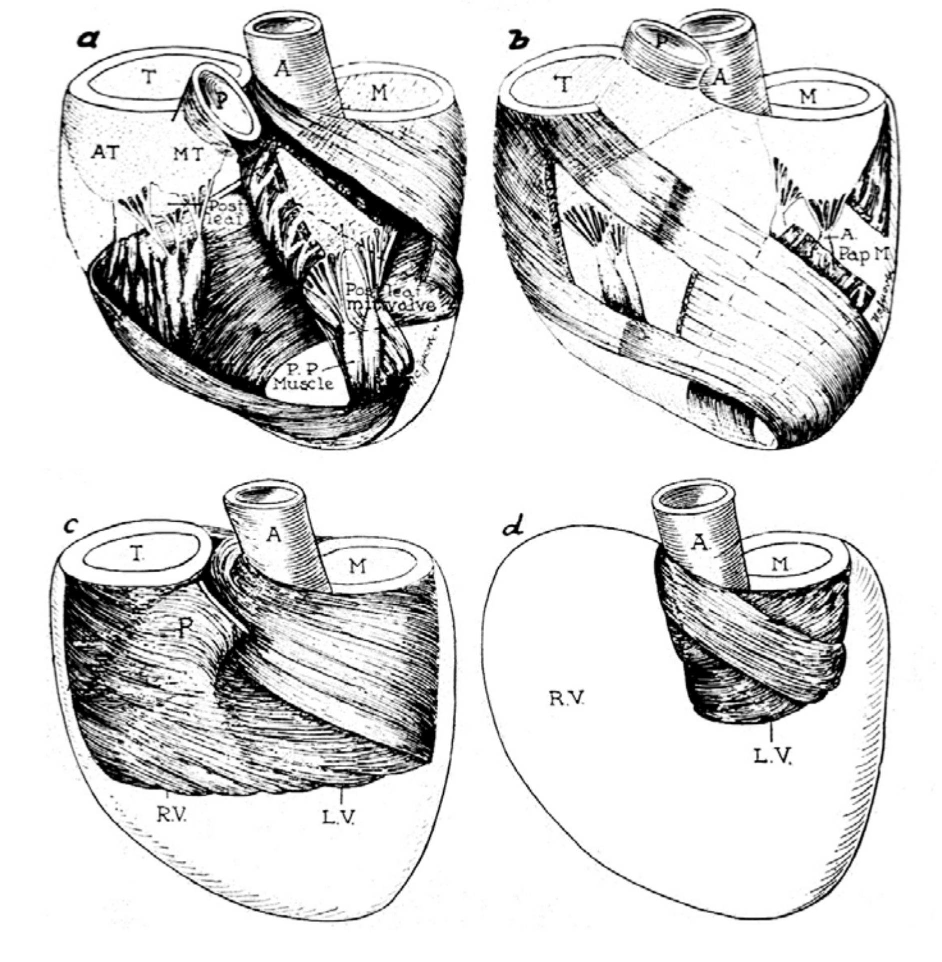


- Transmural waves can exist in 2-D (thin) or 3-D (thick)
- Intramural waves require ~1 cm wall thickness

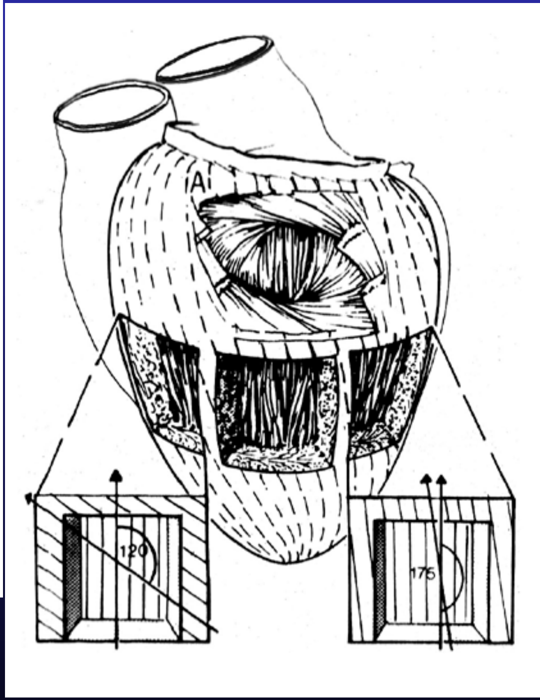
Courtesy of Arkady Pertsov, Syracuse

1 millimeter: Cardiac fiber sheets





s00397

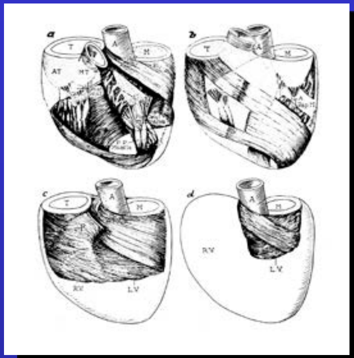


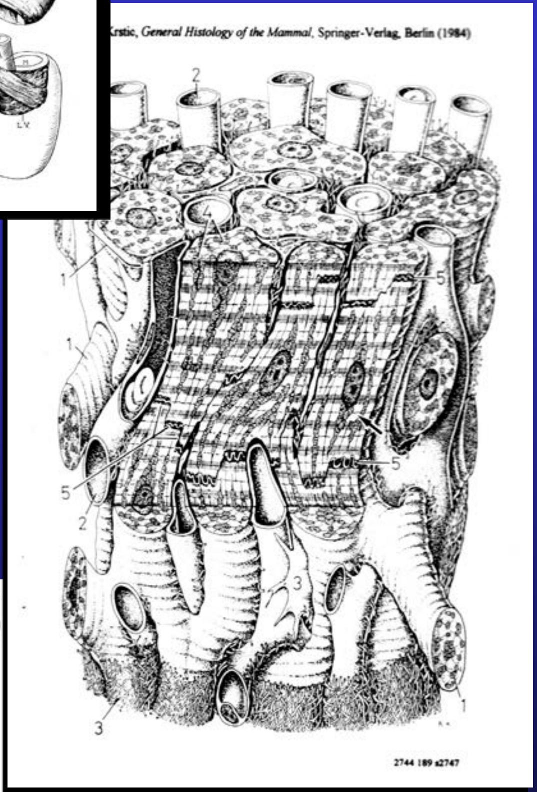
S00703

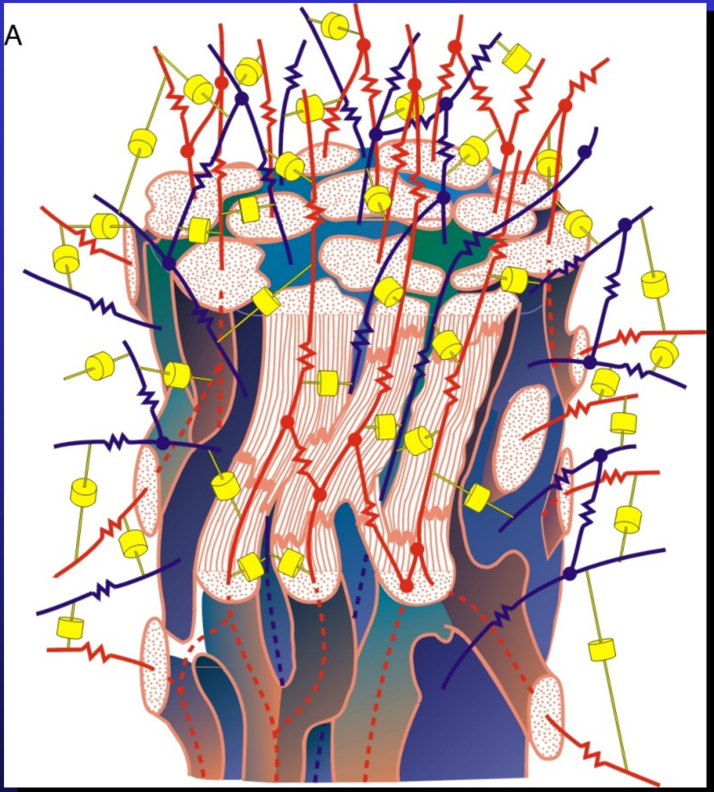
s02734

1 millimeter

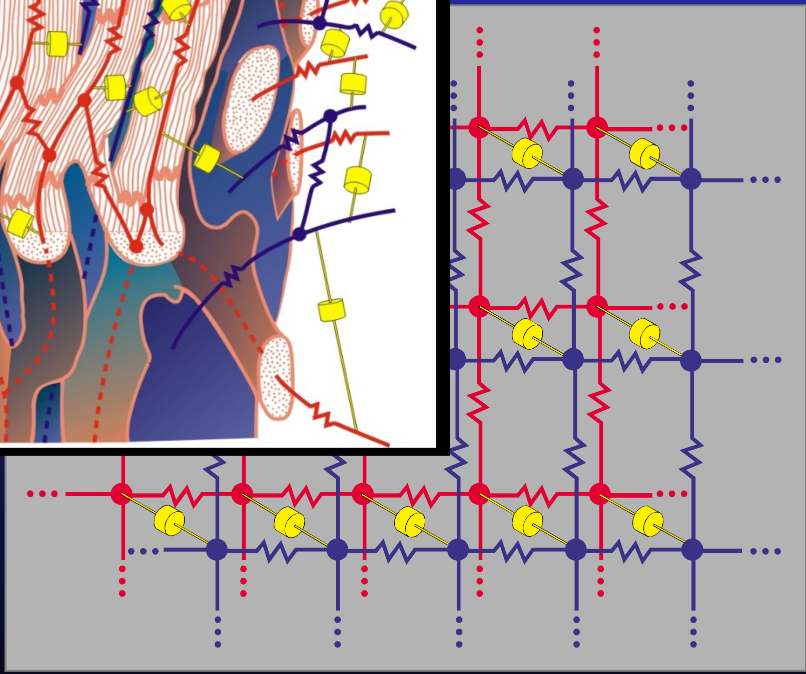
The cardiac syncytium: A three-dimensional non-linear anisotropic bidomain

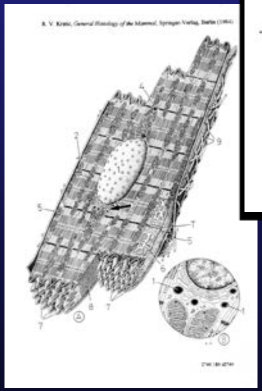






3-D
vs.
2-D





It's the anisotropy….

2-D Bidomain Equations

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

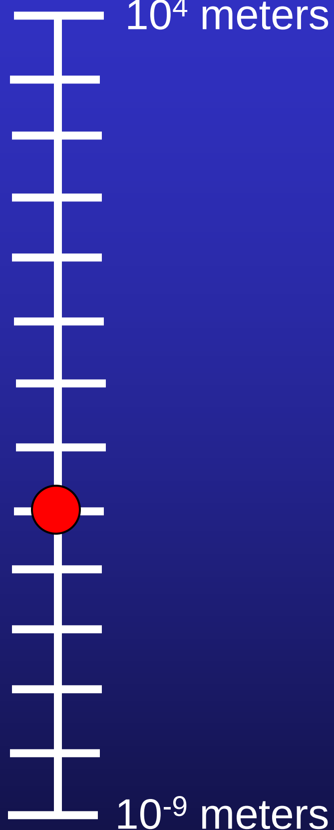
$$C_m \frac{\partial V_m}{\partial t} = -J_{ion} - \frac{1}{\beta} \nabla \bullet \tilde{g}_e \nabla V_e \quad ,$$

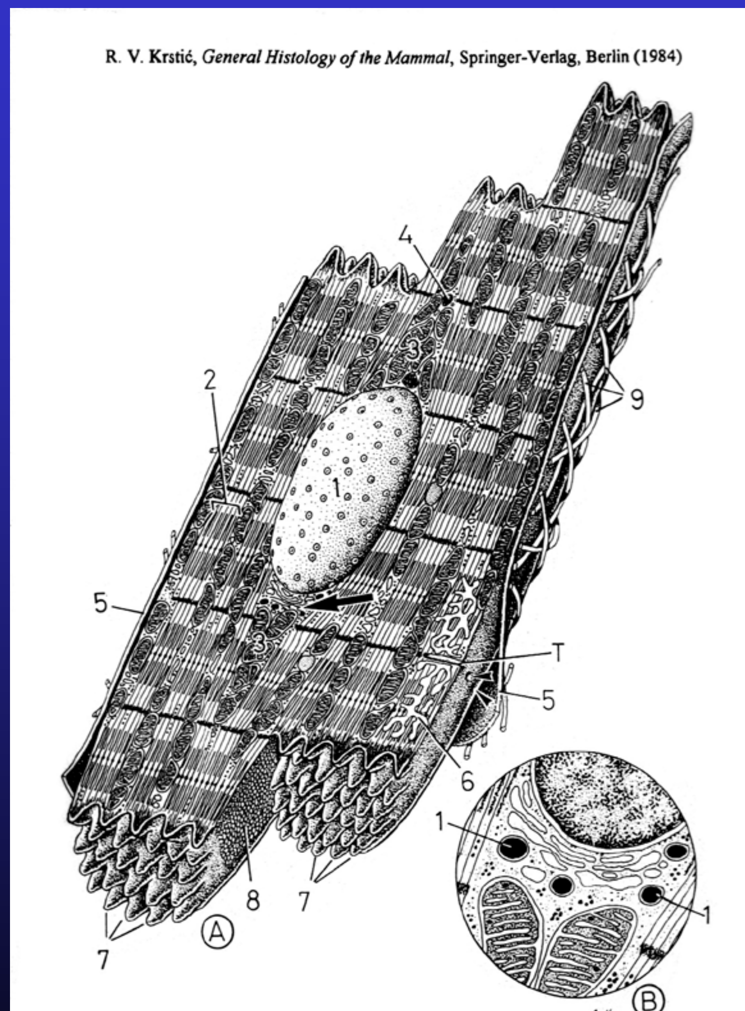
$$\nabla \bullet (\tilde{g}_i + \tilde{g}_e) \nabla V_e = -\nabla \bullet \tilde{g}_i \nabla V_m \, ,$$

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 ($0.3\ \mu m^{-1}$); 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].

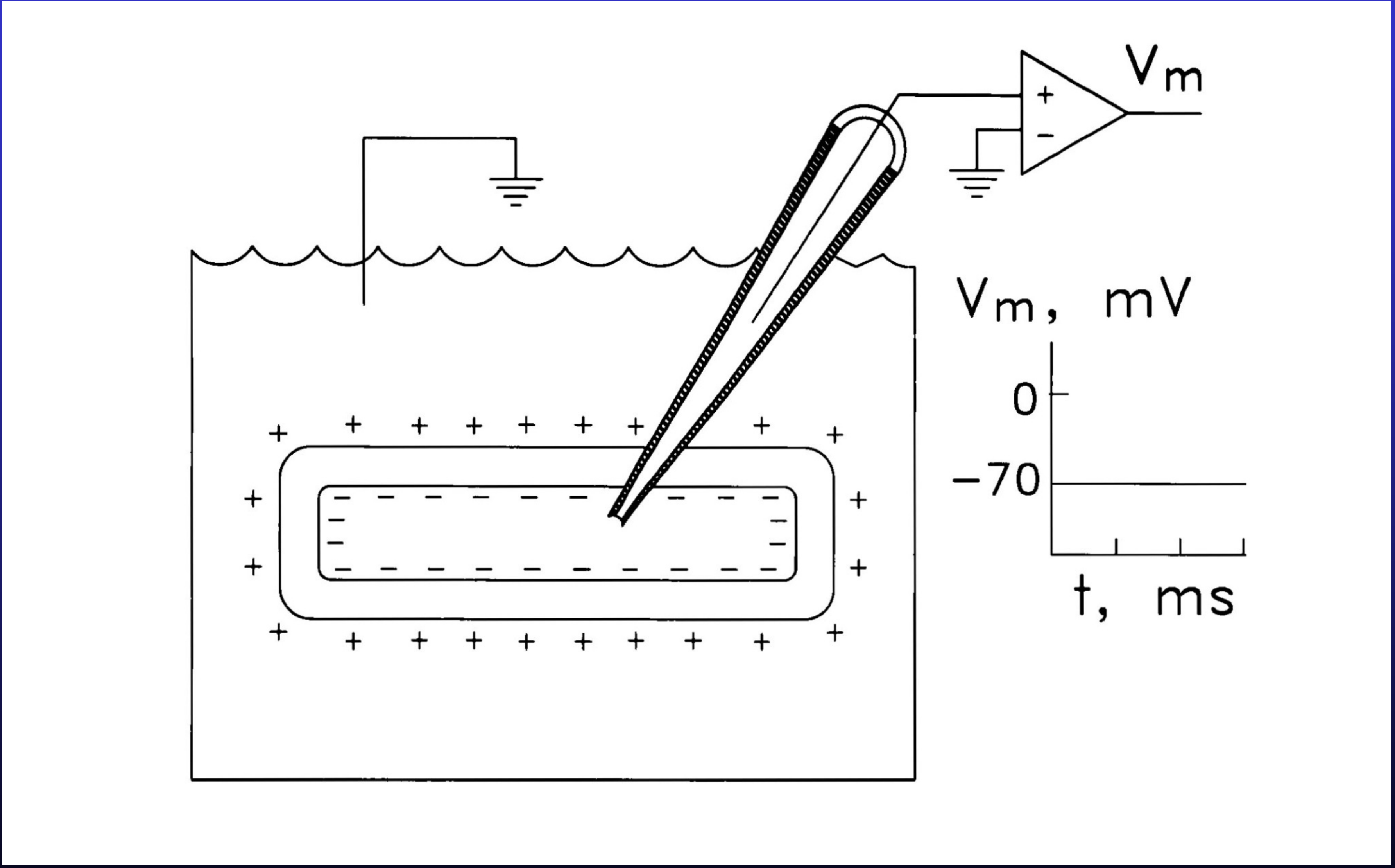
Onward, inward….

100 micrometers: Cardiac cell length

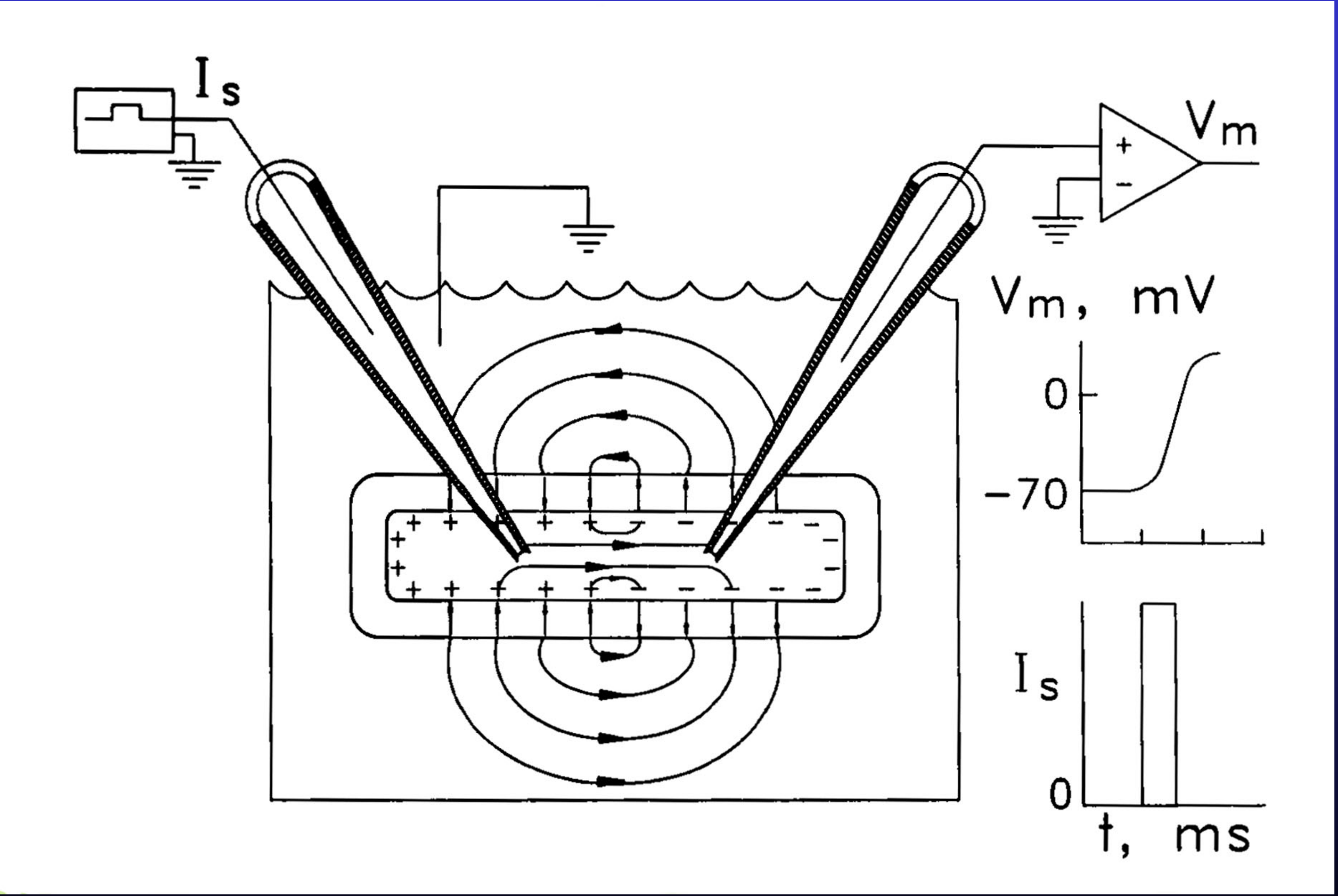




The resting cell and its transmembrane potential



The stimulated cell produces an action potential

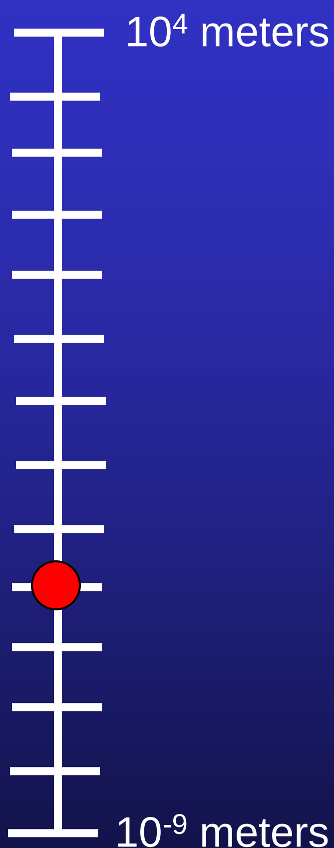


The cardiac cell membrane is …

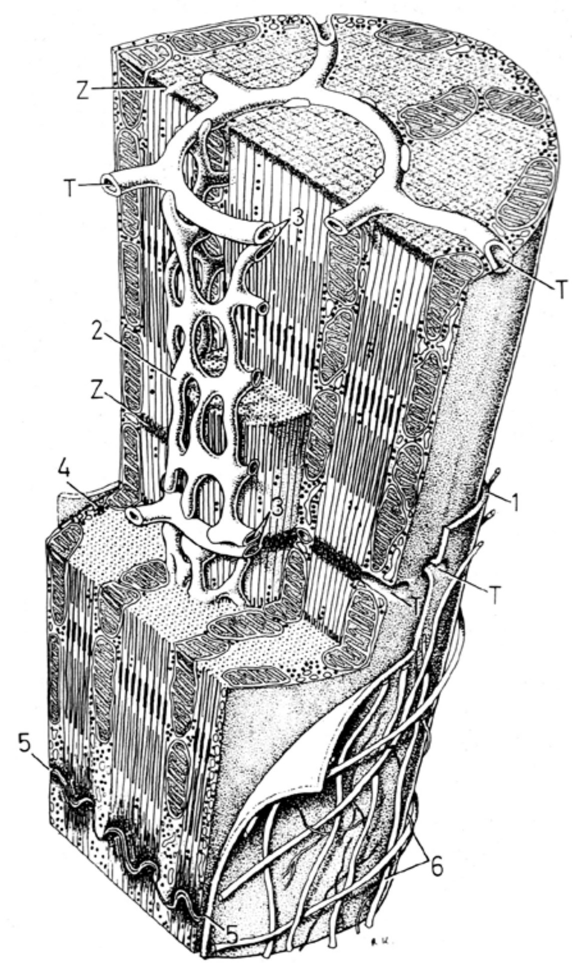
a planar accelerator that uses gradients of 10^7 volts per meter to accelerate heavy ions to energies of 70 meV.

Onward, inward….

10 micrometers: Cardiac cell diameter

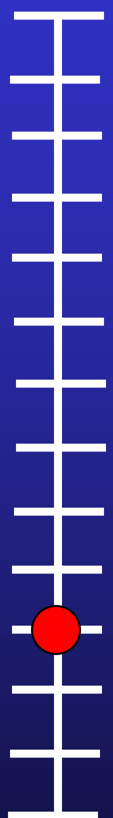


R. V. Krstić, *General Histology of the Mammal*, Springer-Verlag, Berlin (1984)

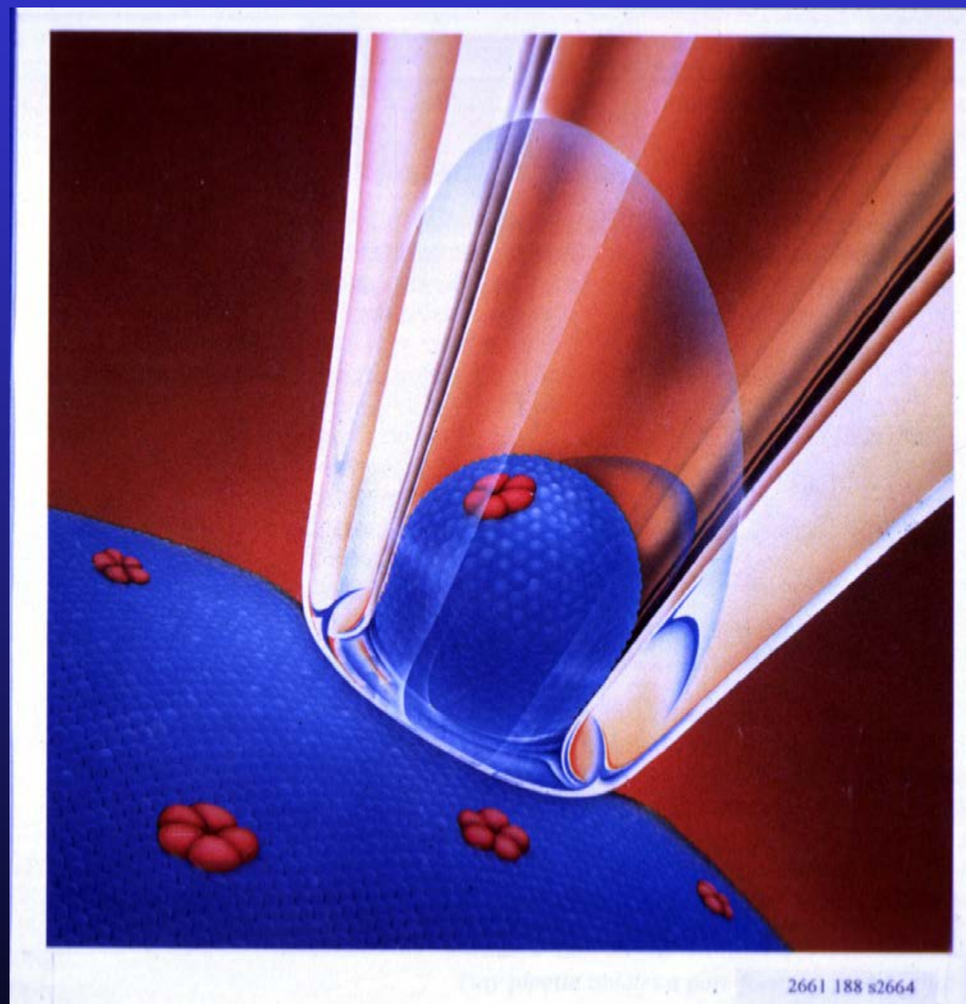


1 micrometer: Glass micropipette bore

10^4 meters

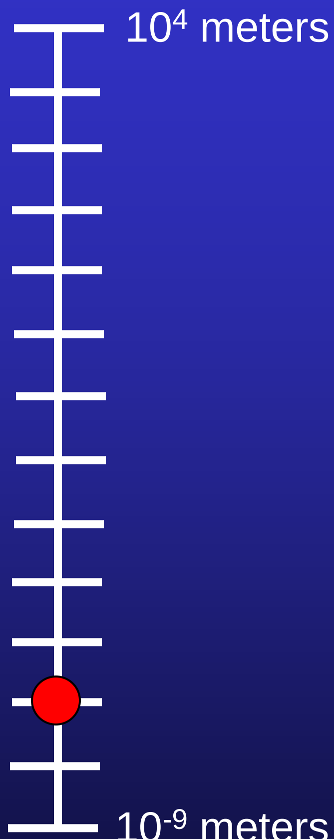


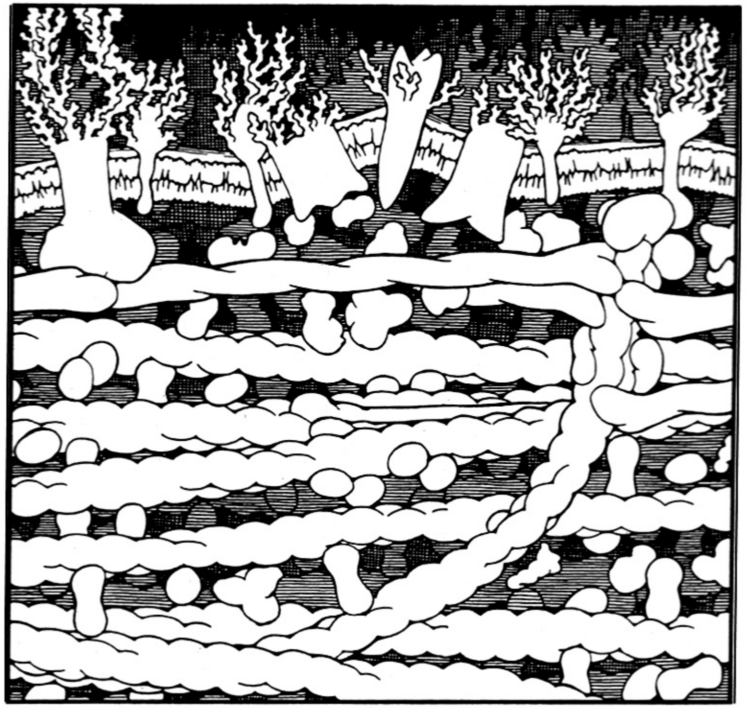
10^{-9} meters



Scientific American

100 nanometers: Molecular machinery





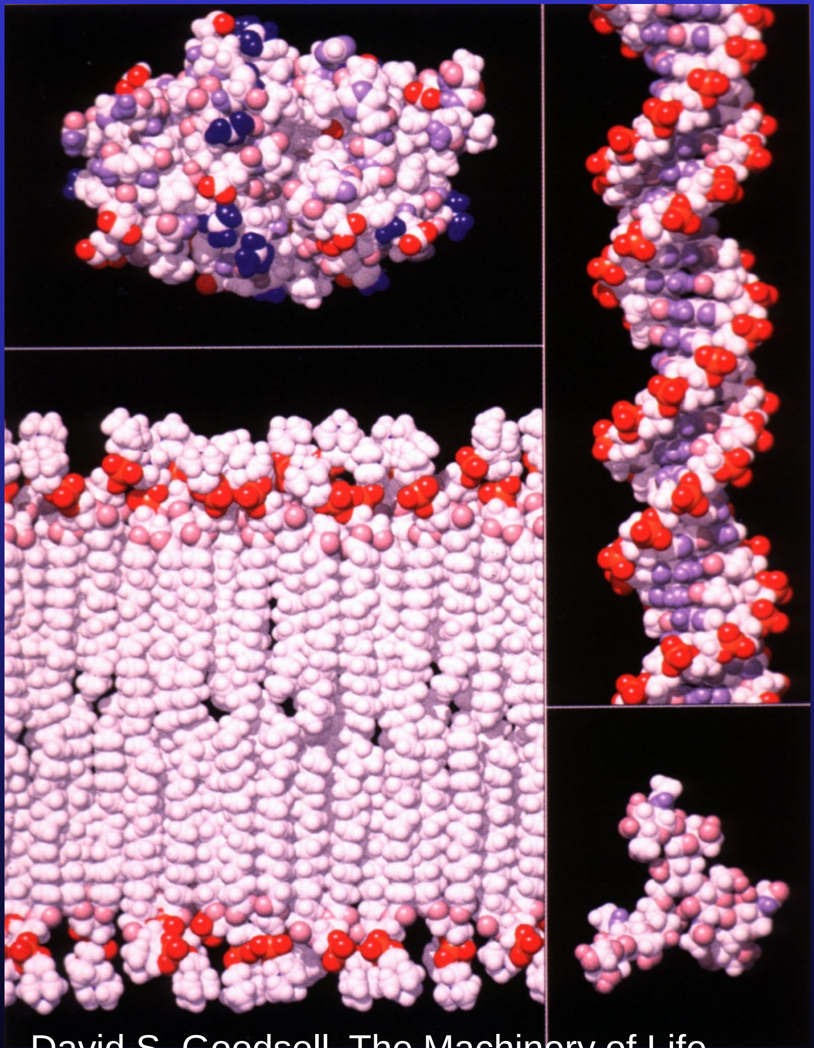
From: *The Machinery of Life*, D.S. Goodsell (Springer-Verlag, New York, 1992)

TL110P10 J188 S4116

10 nanometers: DNA and biomolecules

10^4 meters

10^{-9} meters



Protein

Nucleic Acid

Lipid

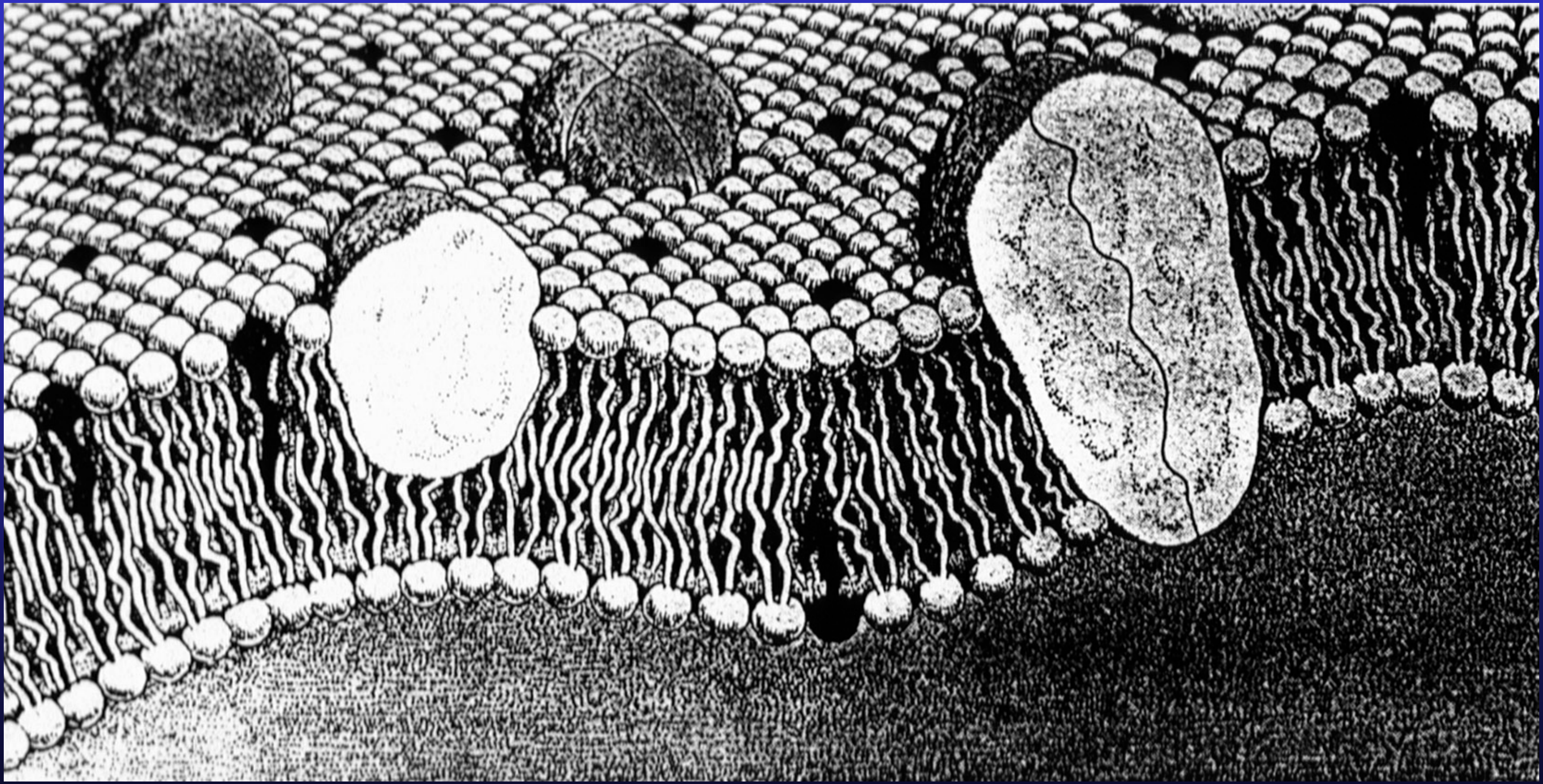
Polysaccharide

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

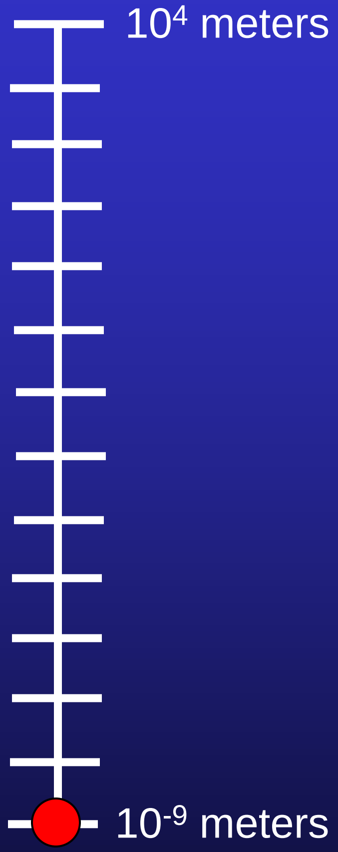
s02739

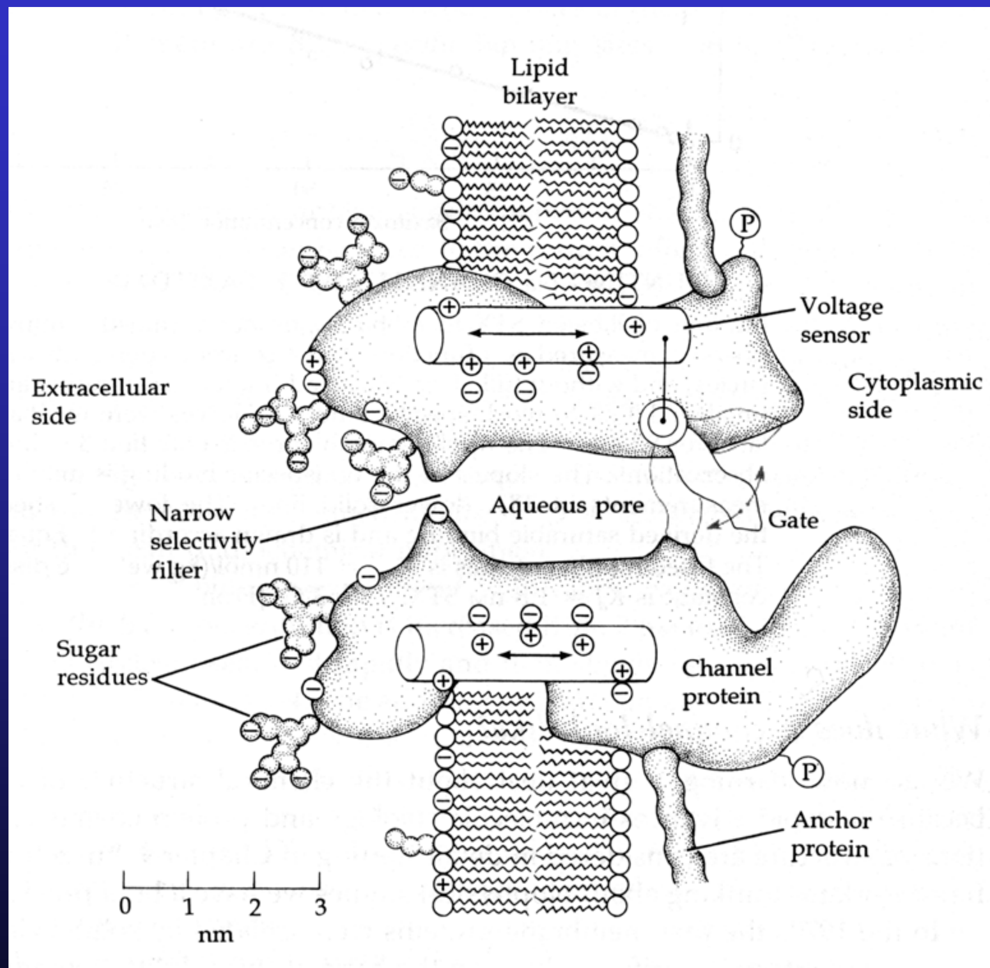
s04081

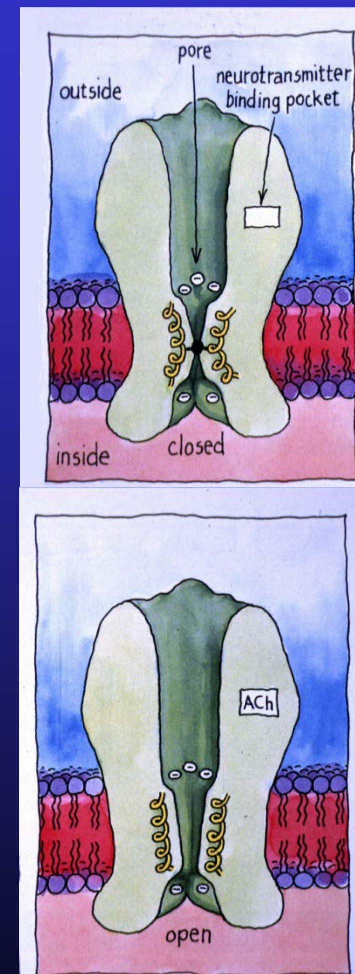
10 nanometers: Cell membrane thickness



1 nanometer: Pore in a gated ion channel



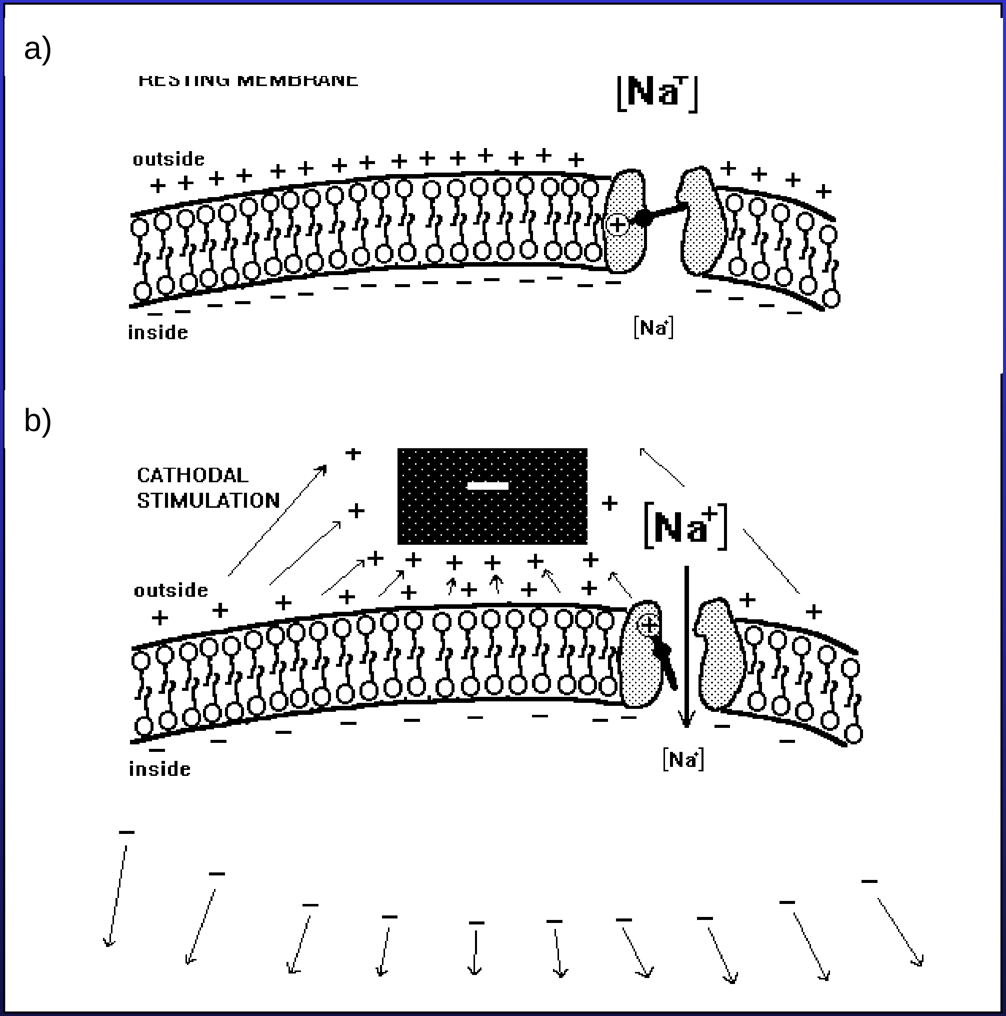


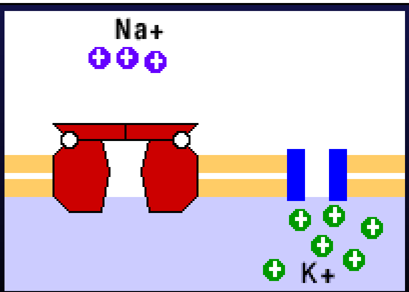


From Ionic Channels of Excitable Membranes, B. Hille, 1992

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





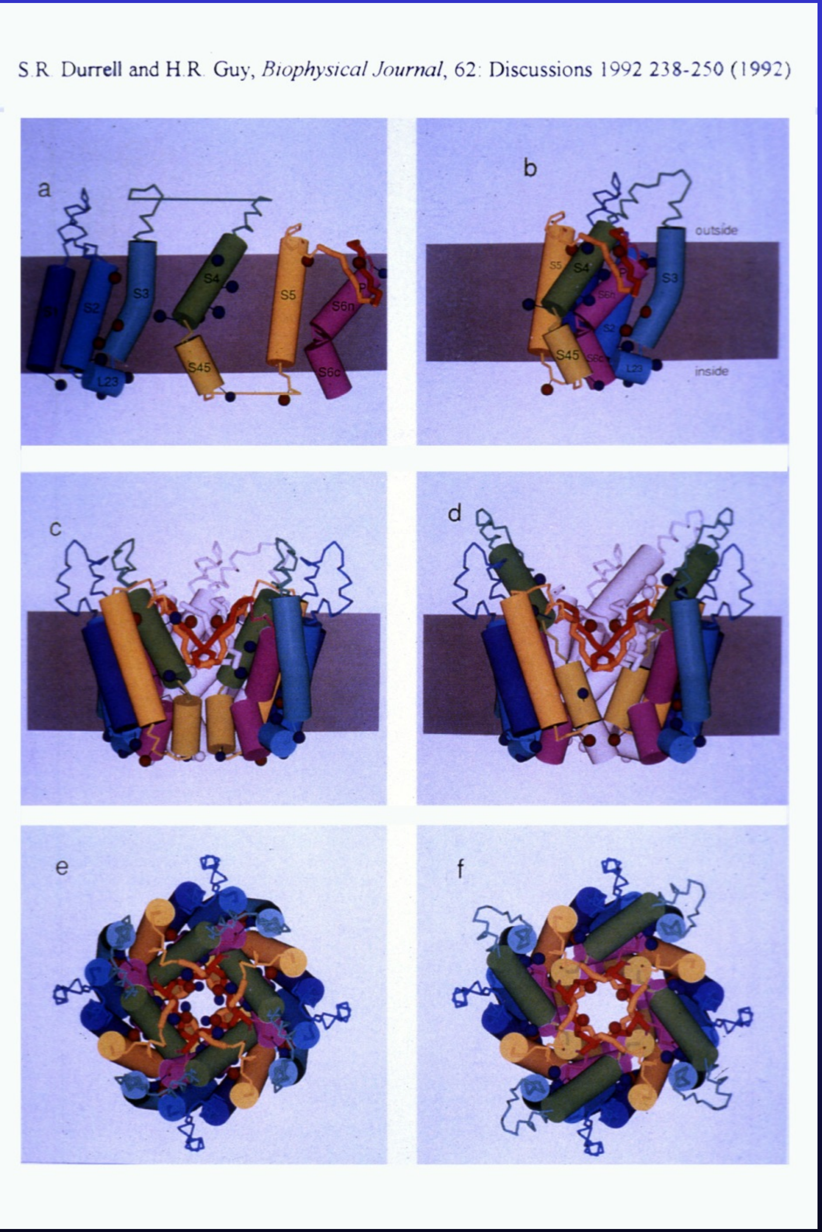
Outside of cell

Animation by Flavio Fenton

Inside of cell

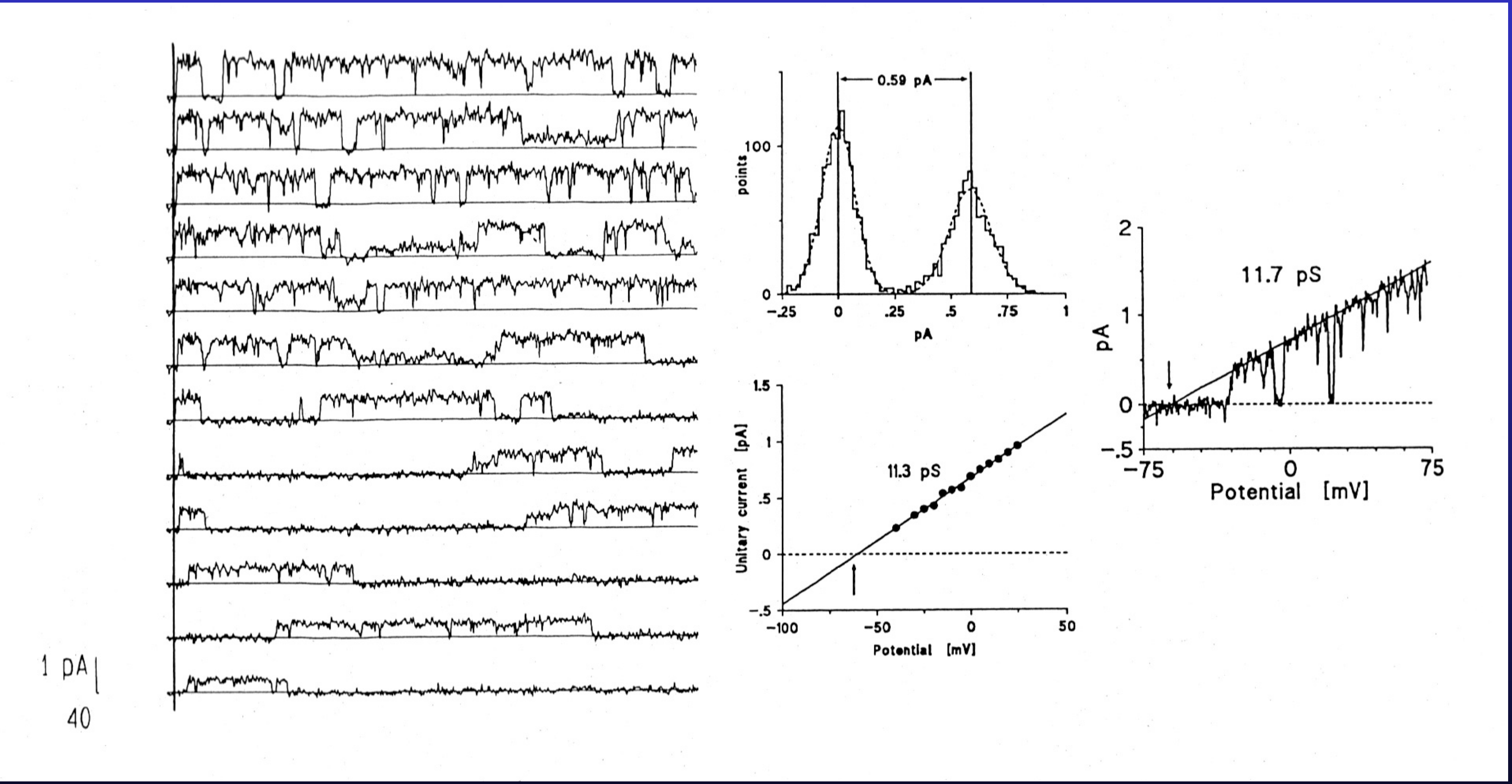
1 nanometer

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



1 nanometer

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

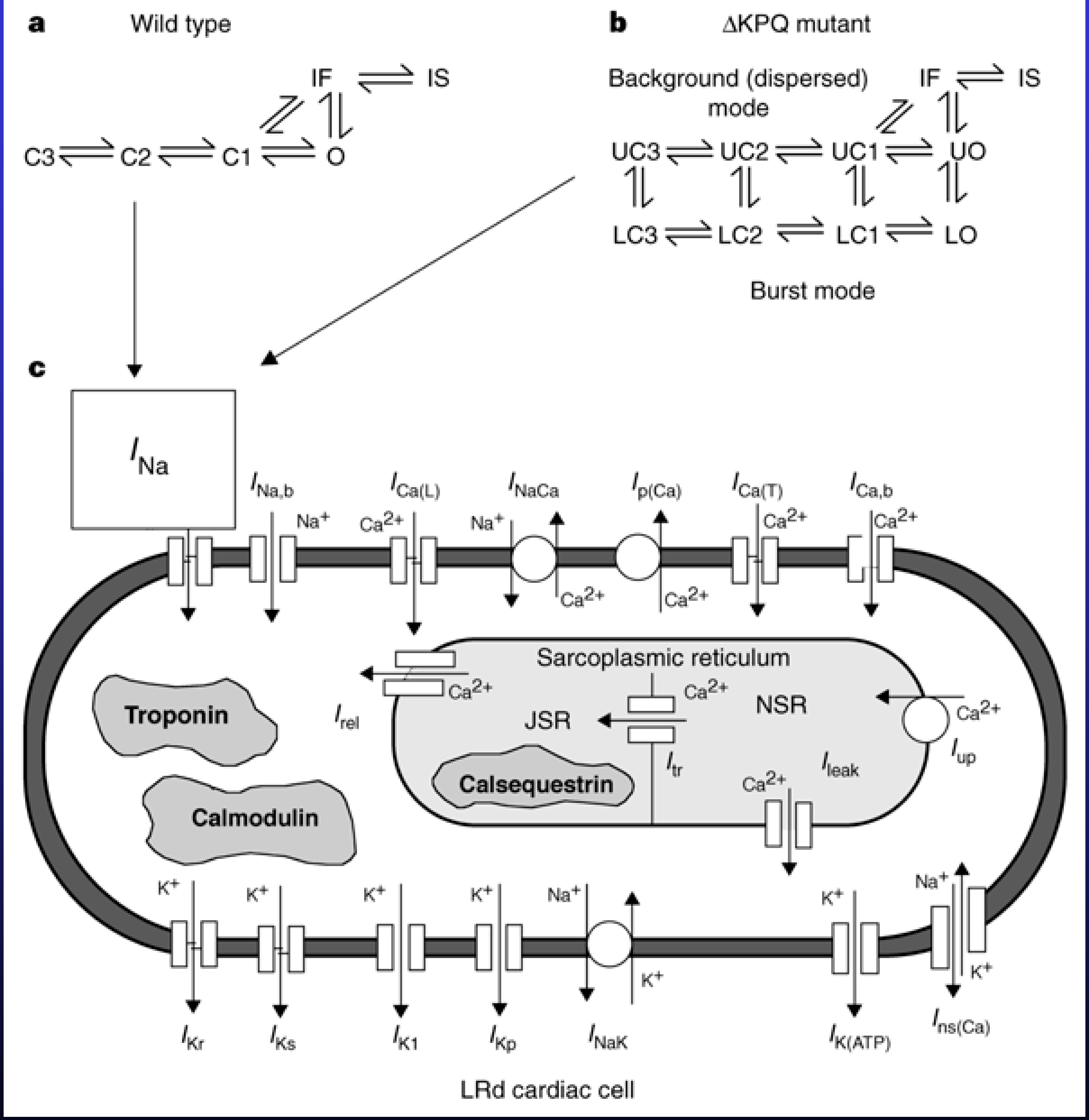


R Wilders and HJ Jongsma, Biophysical J, 65: 2601-2613 (1993)

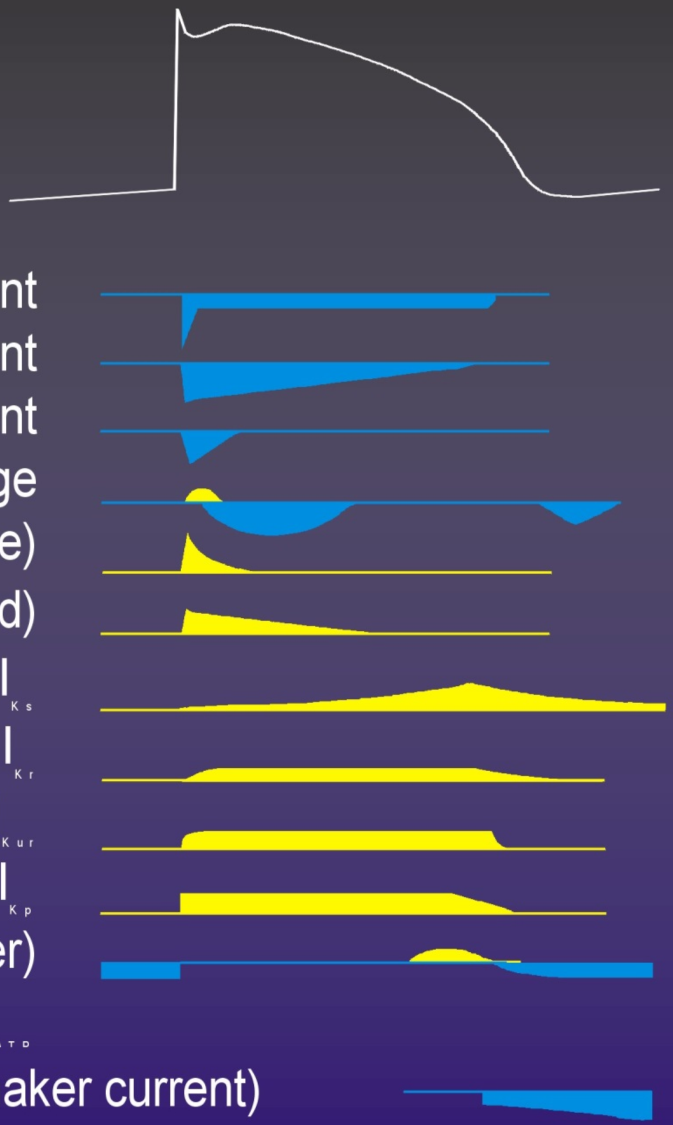
s02661

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.



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

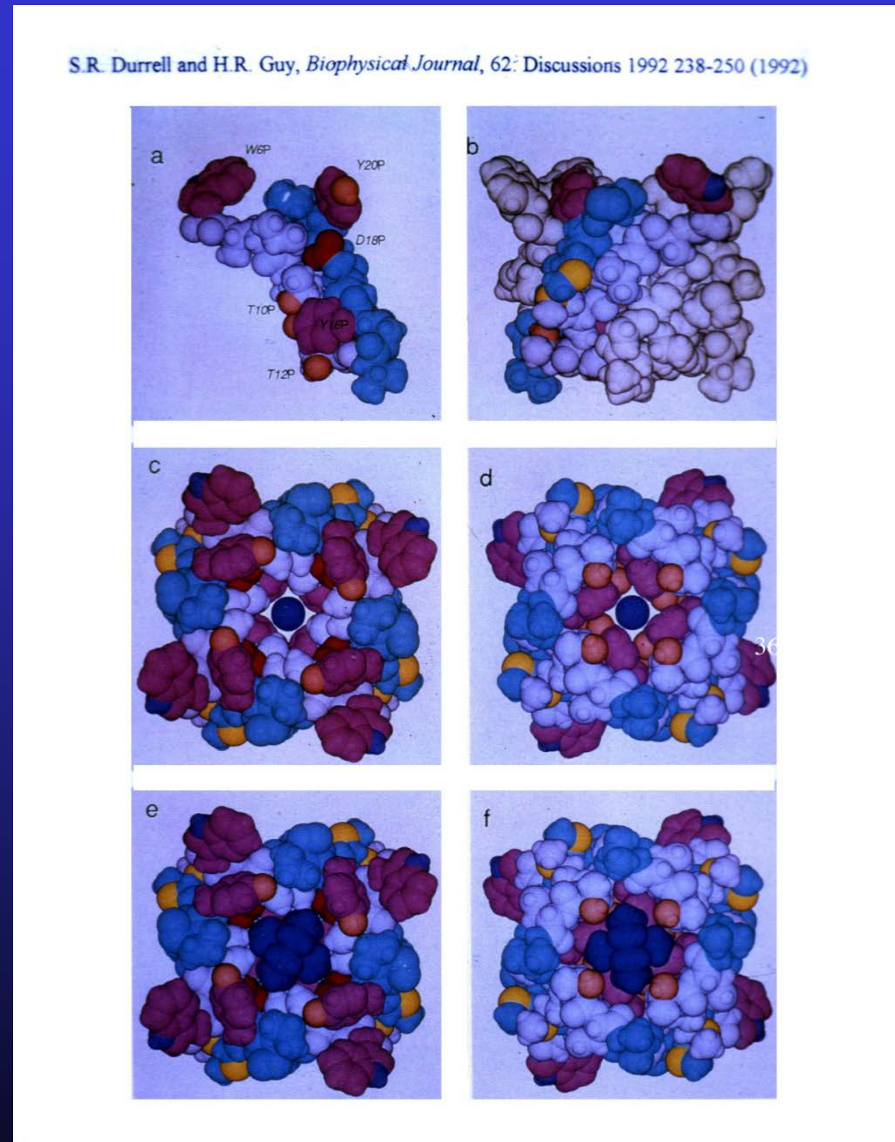
*+sub-units

Courtesy of Dan Roden

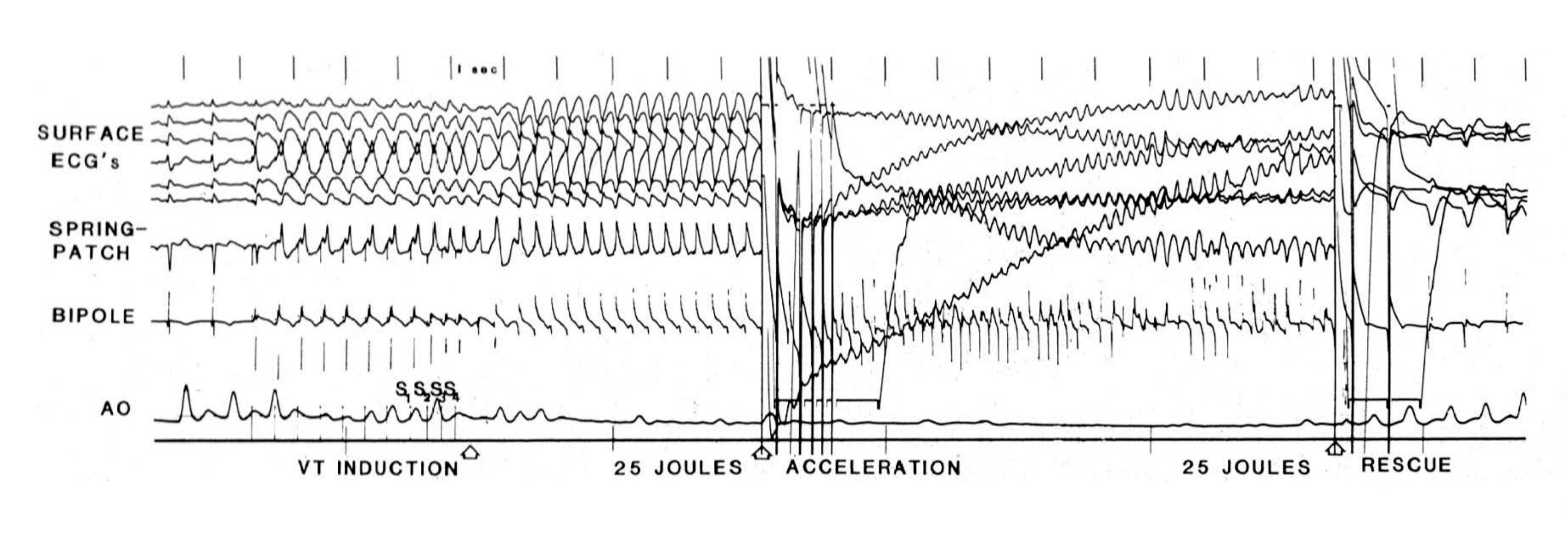
1 nanometer

See which drugs block the channel

We're there…



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

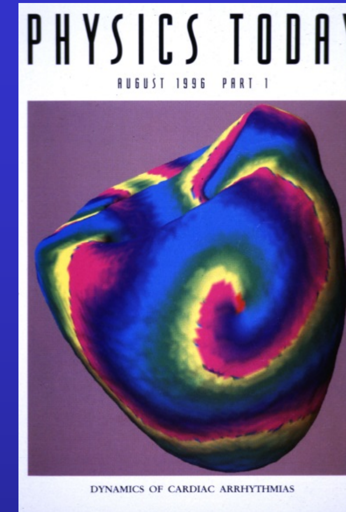


Courtesy of Debra Echt

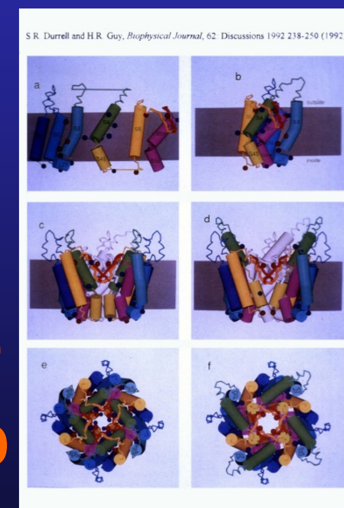
The Spatial Scales

• 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

The Challenges of Cardiac Fibrillation Research



- Cardiac fibrillation occurs at the spatial scale of the <u>entire</u> heart!
- Ion-channels a billion times smaller determine how the heart beats and responds to antiarhythmic drugs
- How do you relate the kinetics of single ion channels and their drug responses to fibrillation and the electrocardiogram?



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

- 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 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
- 1 einstein = 1 mole of photons;
- 1 leibnitz = 1 mole of PDEs ~ 1 etaFLOPS-year

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

Complexity & Nonlinearity

- "Science has explored the microcosmos and the macrocosmos; we have a good lay of the land. The great unexplored frontier is complexity. Complex systems include the body and its organs, especially the brain, the economy, population and evolutionary systems, animal behavior, large molecules -- all complicated things."
- "Life is nonlinear, and so is just about everything else of interest. The human mastery of the nonlinear regime will open a vast new realm of existence."

The Dreams of Reason: The Computer and the Rise of the Sciences of Complexity, Heinz. R. Pagels, 1988

Meanwhile …

- Exercise regularly
- Maintain your proper weight
- Don’t smoke
- Control your blood pressure
- Follow a balanced diet
- For more detailed advice, check with the American Heart Association

http://www.americanheart.org

Are there any questions?

? ? ? ? ?

2002 Heart and Stroke Statistical Update

American Heart Association

- 61,800,000 Americans have one or more types of cardiovascular disease (CVD) according to current estimates.[1] Of these, 29,700,000 are male and 32,100,000 are female. 24,750,000 are estimated to be age 65 and older.
  - High blood pressure— 50,000,000
  - Coronary heart disease — 12,600,000
  - Myocardial infarction — 7,500,000
  - Angina pectoris — 6,400,000
  - Stroke — 4,600,000
  - Congenital cardiovascular defects — 1,000,000
  - Congestive heart failure — 4,790,000.
- 1 in 5 males and females has some form of cardiovascular disease.
- If all forms of major CVD were eliminated, life expectancy would rise by almost 7 years. If all forms of cancer were eliminated, the gain would be 3 years.
- The probability at birth of eventually dying from major CV diseases is 47 percent, and the chance of dying from cancer is 22 percent. Additional probabilities are 3 percent for accidents, 2 percent for diabetes and 0.7 percent for HIV.

http://www.americanheart.org

2002 Heart and Stroke Statistical Update

American Heart Association

- Coronary heart disease (CHD) caused 529,659 deaths in the United States in 1999 — about 1 of every 5 deaths
- CHD is the single largest killer of American males and females.
- About every 29 seconds an American will suffer a coronary event, and about every minute someone will die from one.
- This year an estimated 1,100,000 Americans will have a new or recurrent coronary attack (defined as myocardial infarction or fatal CHD). About 650,000 of these will be first attacks and 450,000 will be recurrent attacks
- Over 45 percent of the people who experience a coronary attack in a given year will die from it.
- About 250,000 people a year die of CHD without being hospitalized. Most of these are sudden deaths caused by cardiac arrest, usually resulting from ventricular fibrillation.
- The lifetime risk of developing CHD after age 40 is 49 percent for men and 32 percent for women.
- The incidence of CHD in women lags behind men by 10 years for total CHD and by 20 years for more serious clinical events such as MI and sudden death.
- CHD rates in women after menopause are 2-3 times those of women the same age before menopause.
- 50 percent of men and 63 percent of women who died suddenly of CHD had no previous symptoms of this disease.

http://www.americanheart.org

Department of Physics and Astronomy
http://www.vanderbilt.edu/lsp
http://www.physics.vanderbilt.edu

Department of Biomedical Engineering
http://www.bme.vanderbilt.edu/

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)