The Abdus Salam
International Centre for Theoretical Physics

United Nations Educational, Scientific and Cultural Organization

International Atomic Energy Agency

Summer School on

Design and Control of Self-Organization in Physical, Chemical, and Biological Systems

25 July to 5 August, 2005

Miramare-Trieste, Italy

1668/2

Dynamics and Control of Cardiac Arrhythmias

Leon Glass
McGill University, Quebec - Canada

Strada Costiera 11, 34014 Trieste, Italy - Tel. +39 040 2240 111; Fax +39 040 224 163 - sci_info@ictp.it, www.ictp.it

Dynamics and Control of Cardiac Arrhythmias

Leon Glass

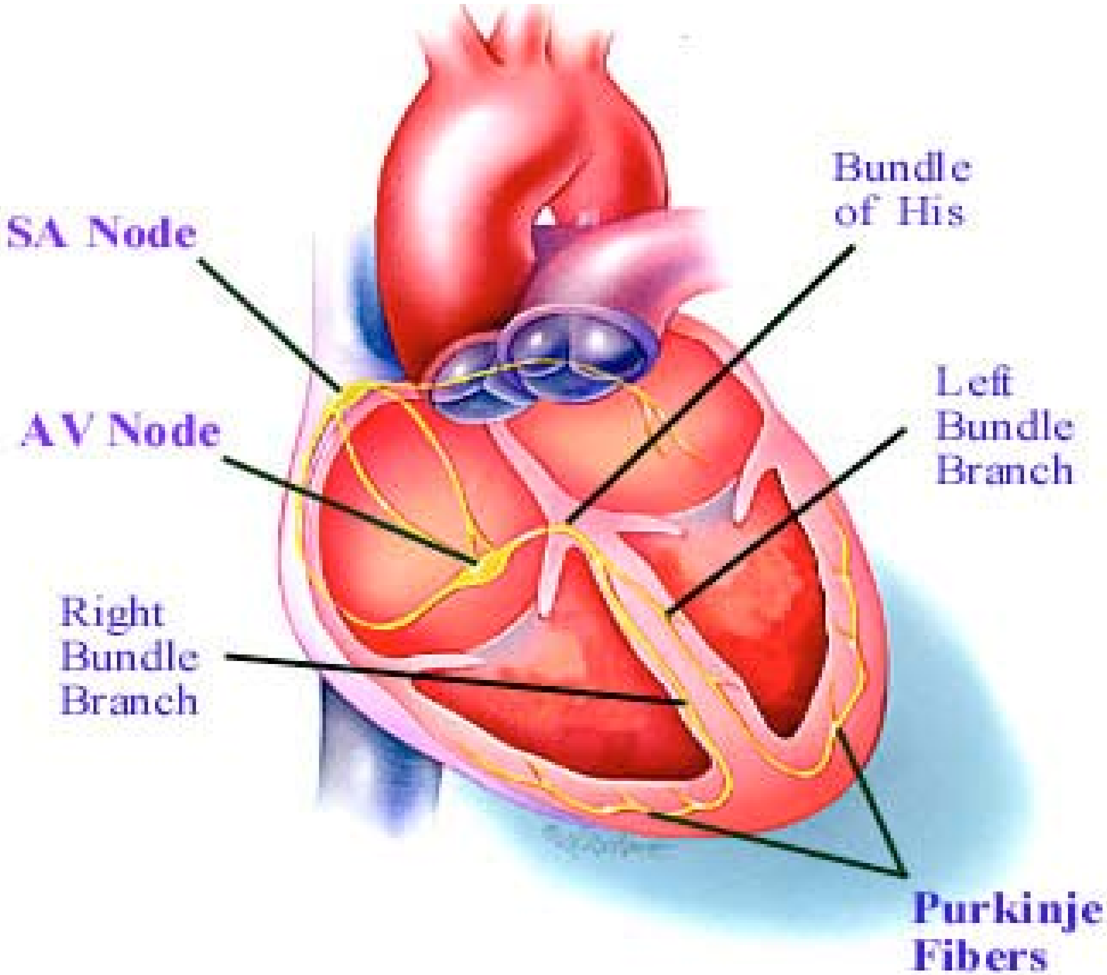
Isadore Rosenfeld Chair in Cardiology, McGill University, Montreal, Quebec

Outline

- Dynamics: Paroxysmal rhythms
- Dynamics: Resetting oscillations
- Dynamics: Excitation in a ring
- Dynamics: Universal organization dynamics in excitable media
- Control: Better diagnosis of arrhythmia
- Control: Stimulation to control arrhythmia

BIG PROBLEM TO ASK ME: IF YOU UNDERSTAND CARDIAC PHYSIOLOGY SO WELL, WHY CAN'T YOU FIGURE OUT BETTER WAYS TO TREAT CARDIAC ARRHYTHMIAS IN PATIENTS?

Conduction System of the Normal Heart



Complex ectopic beats precede polymorphic VT in a German Shepherd dog (provided by Dr. S. Moise, Cornell)

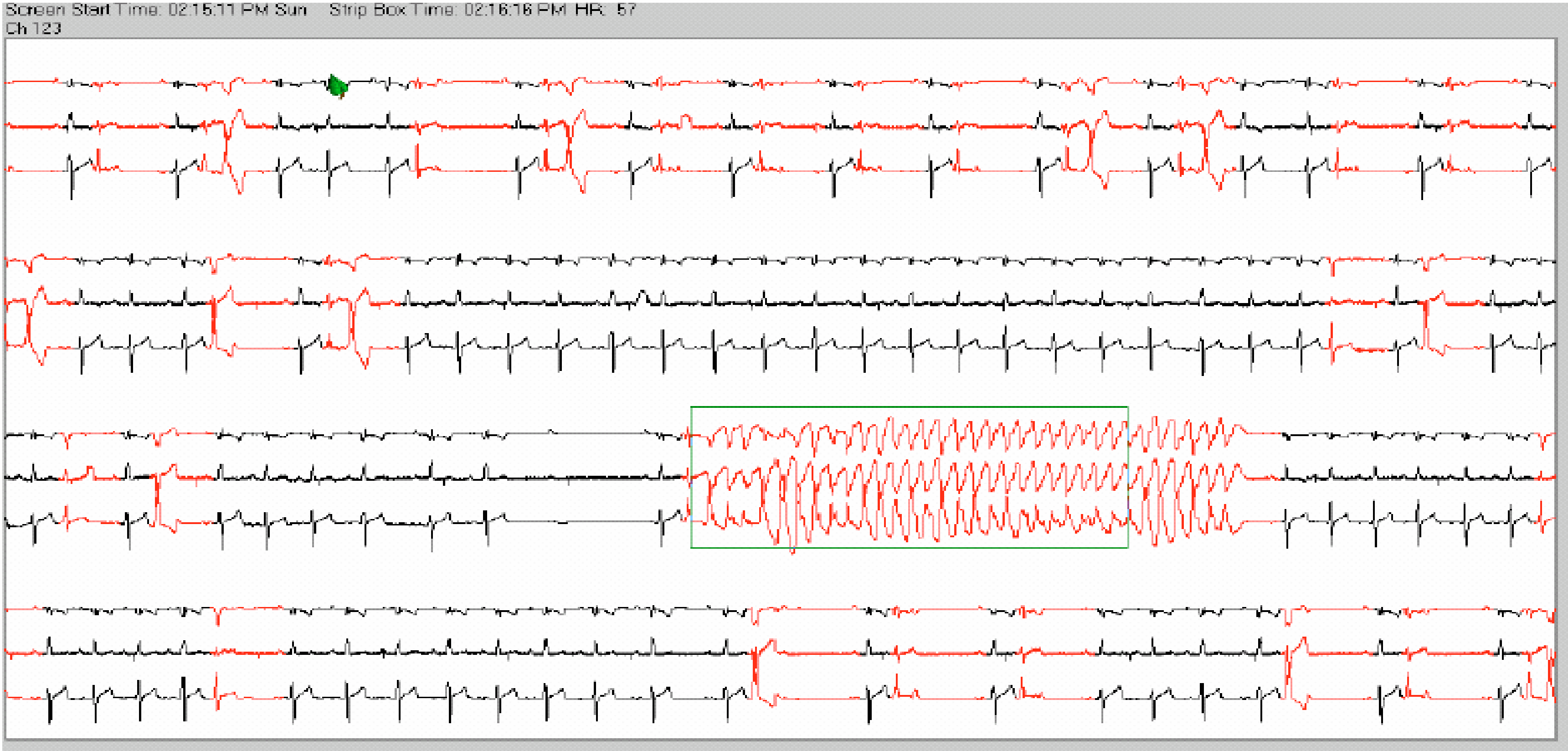
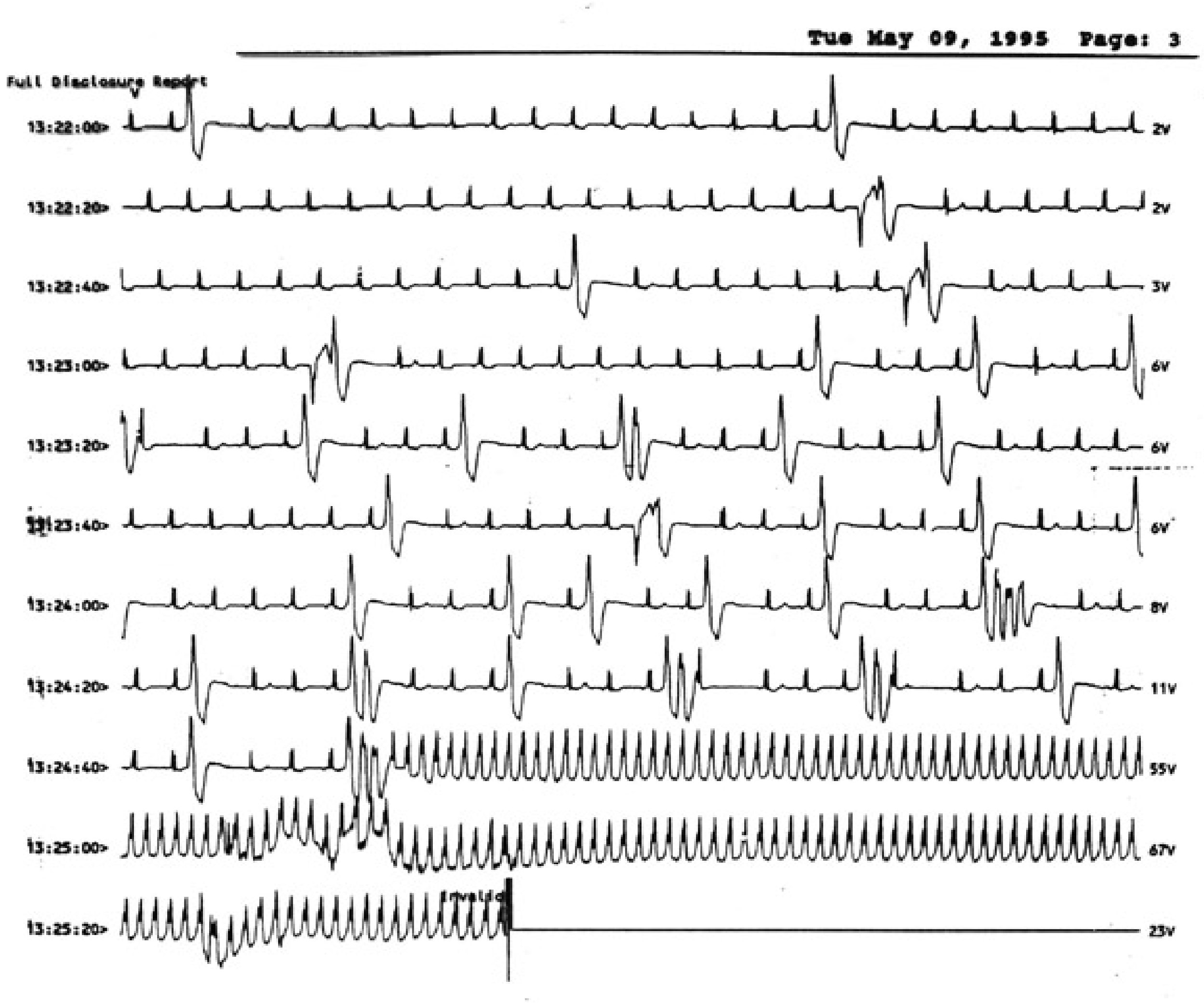


Figure 3. Excerpt of 24 hour ambulatory electrocardiographic recording from a 15-week-old female German shepherd with inherited ventricular arrhythmia syndrome. Three simultaneous leads are recorded as a continuous

Complex ventricular ectopic beats before cardiac arrest in the intensive care unit

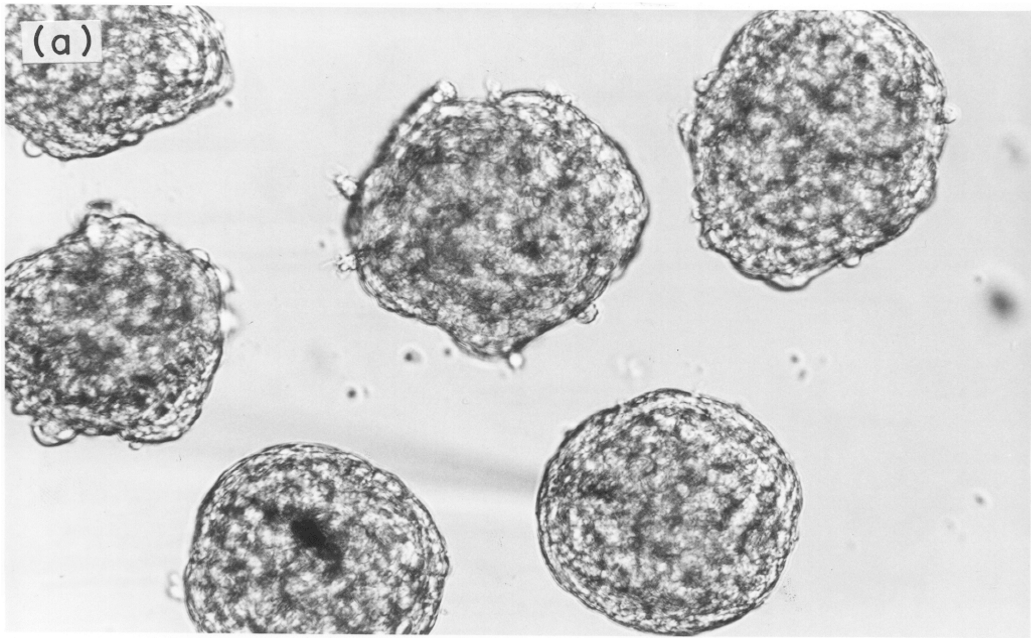


WE DO NOT KNOW EXACTLY WHAT IS HAPPENING IN THE HEART DURING THESE ARRHYTHMIAS

Physiological properties of real heart cells

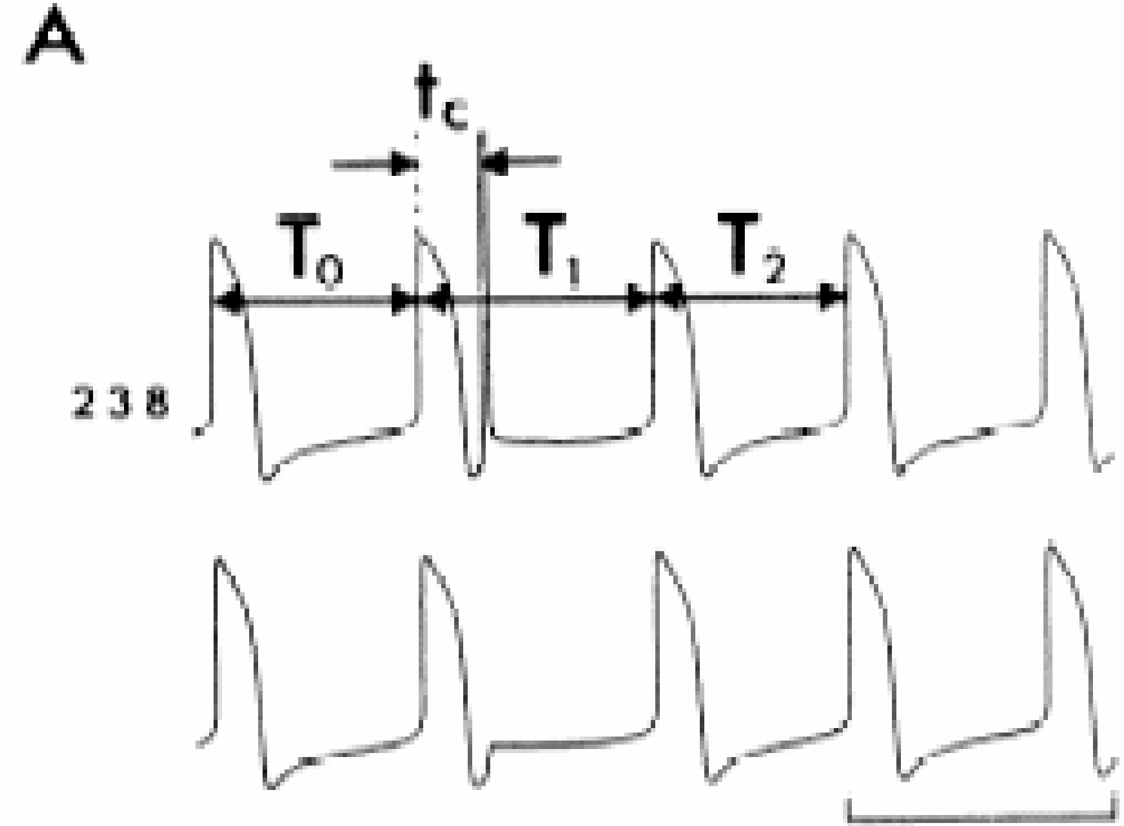
- Excitable
- Refractory time (depends on the history)
- Oscillatory (can be reset and entrained)
- Fatigue (less excitable following rapid stimulation – overdrive suppression)
- Heterogeneous

Model System – Embryonic chick heart tissue culture

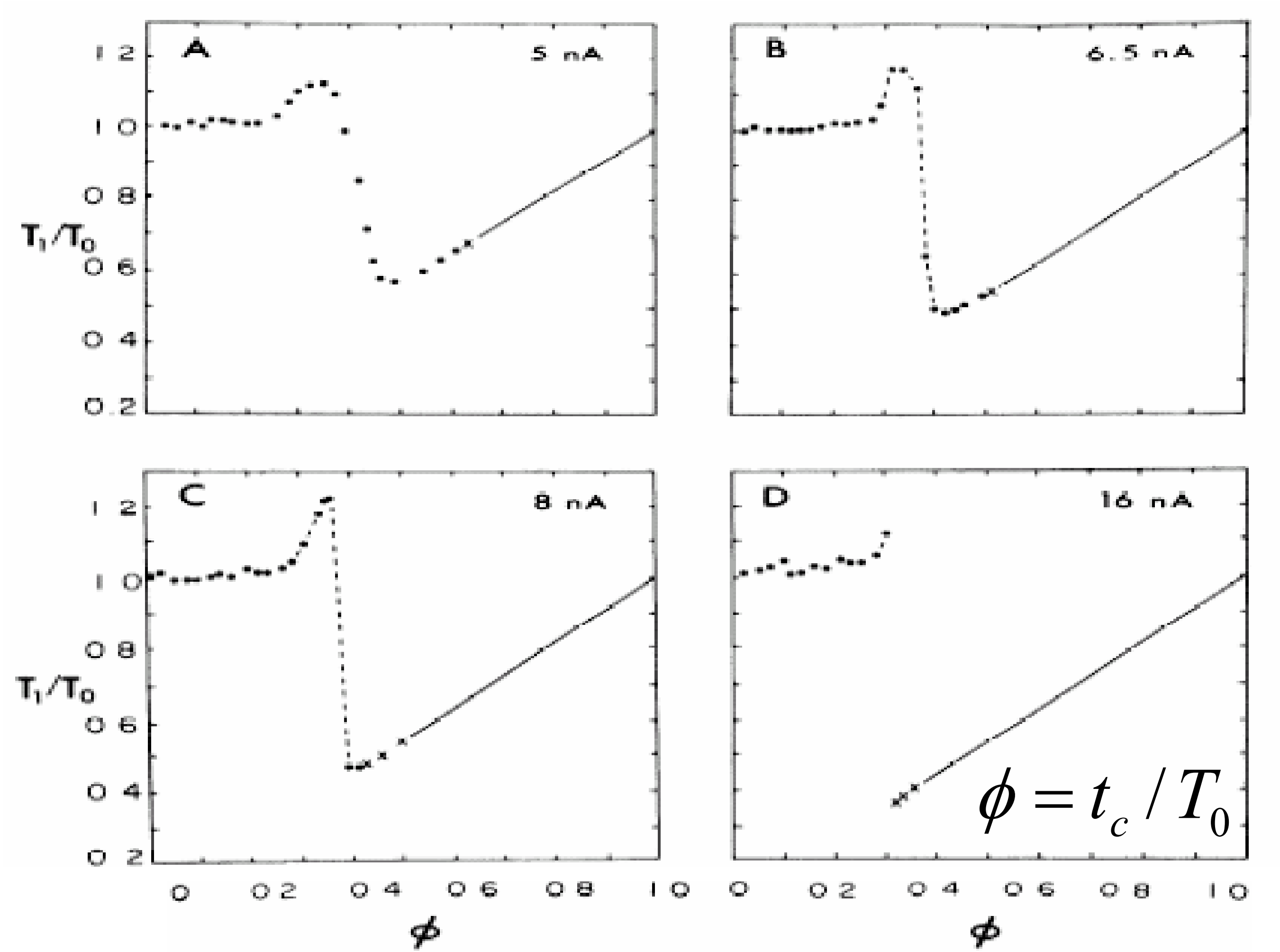


Thanks to Alvin Shrier my colleague and collaborator for over 20 years.

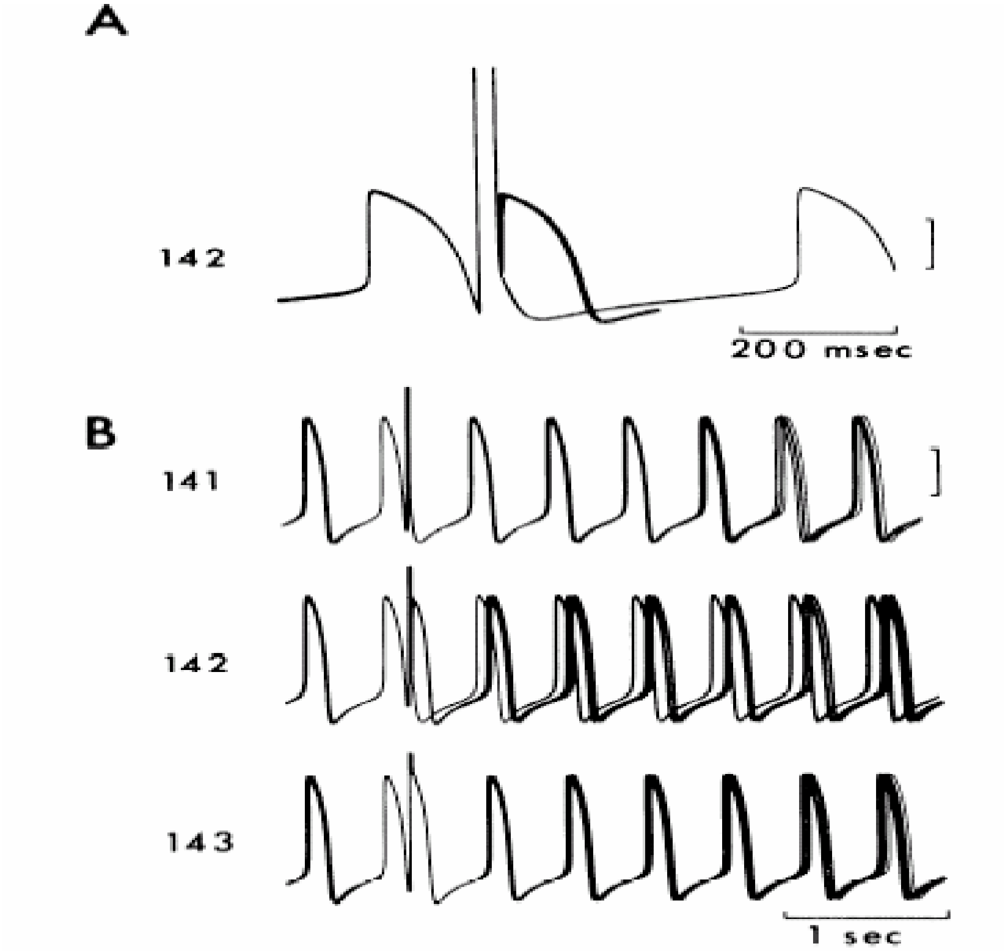
A Resetting Experiment



Perturbed Cycle Length Curves

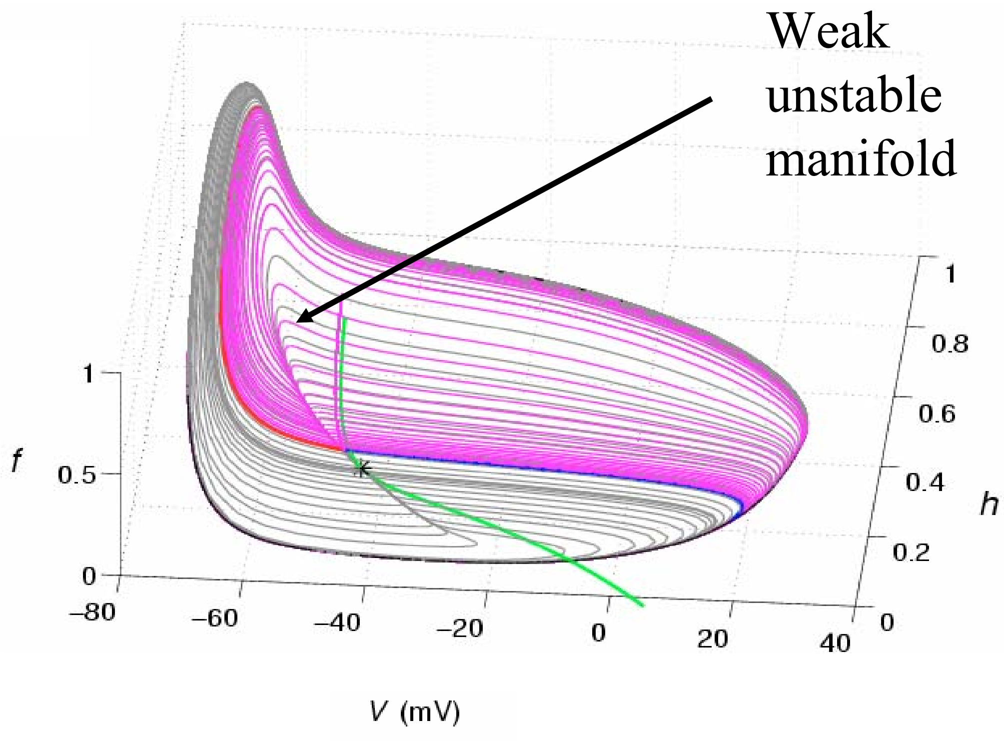


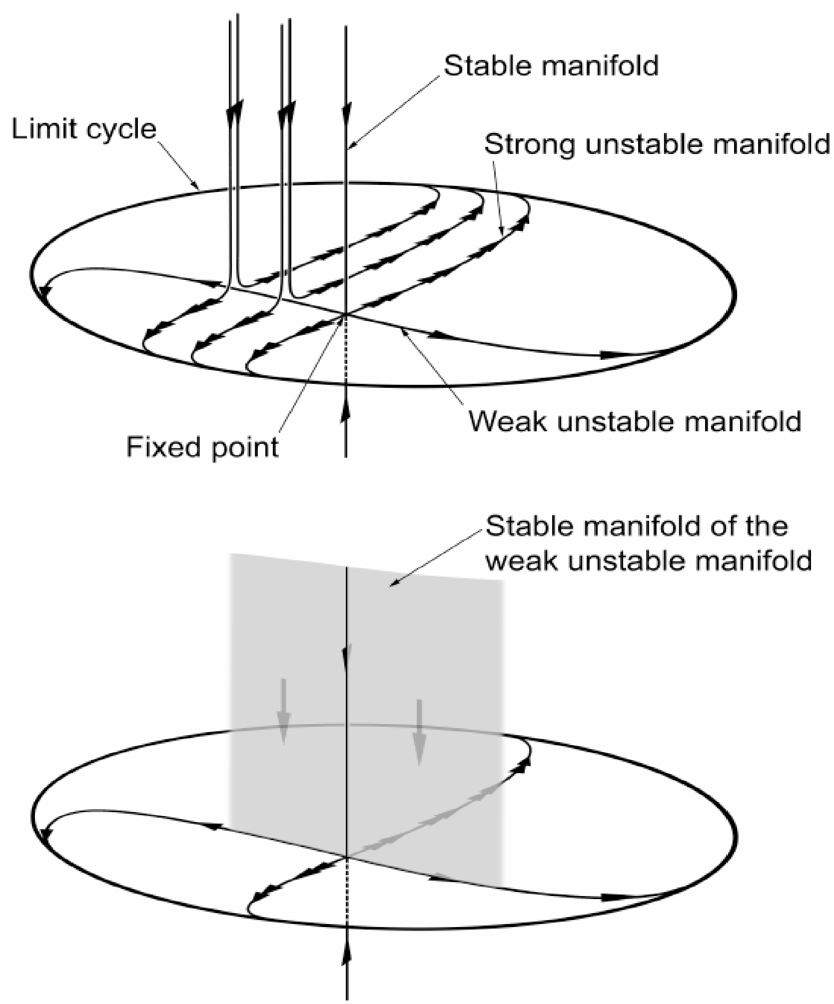
Puzzle: How can there be discontinuous resetting?



Guevara, Shrier, Glass (1986)

Answer: The phase-resetting in a HH-type model is continuous **BUT**

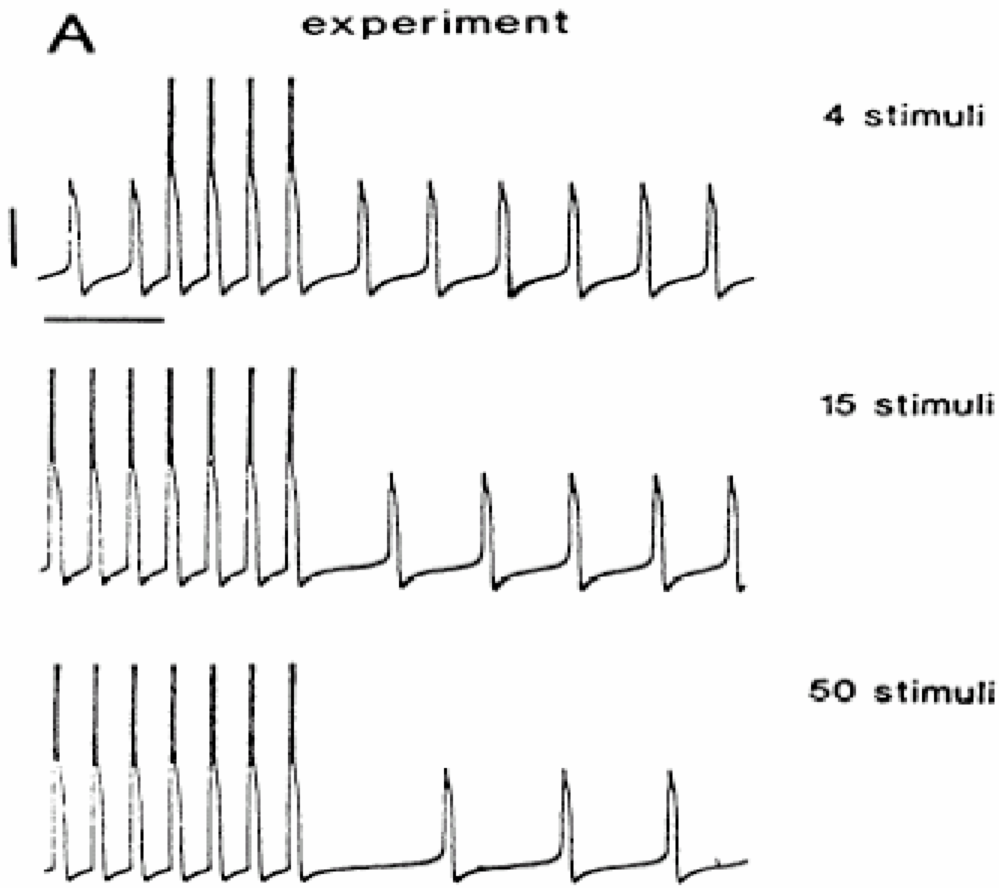




the stochastic opening of a single channel can lead to either an immediate action potential or a delayed action potential.

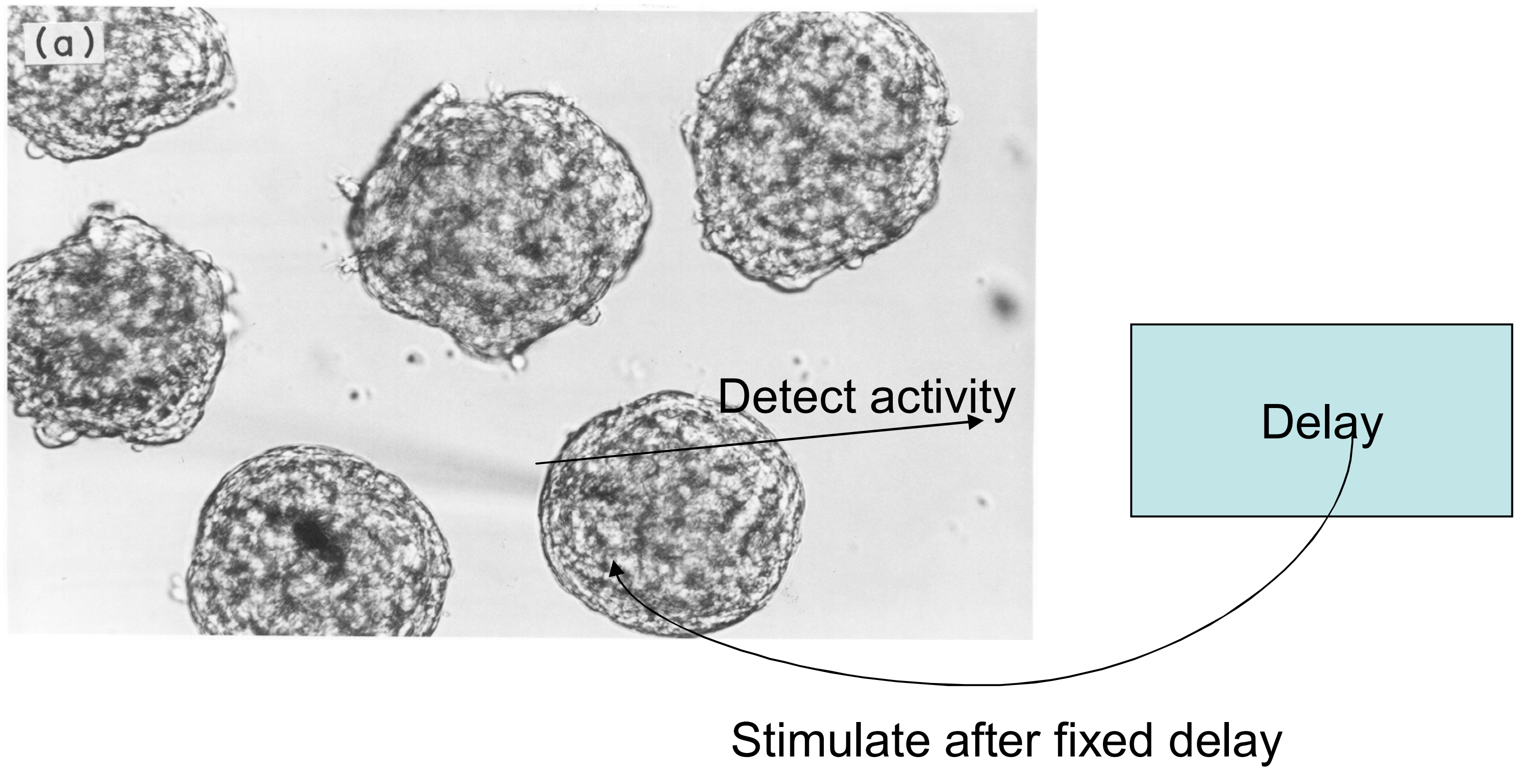
Krogh-Madsen, Glass, Doedel, Guevara (2004)

Rapid Stimulation Leads to a Slower Rhythm (Overdrive Suppression)

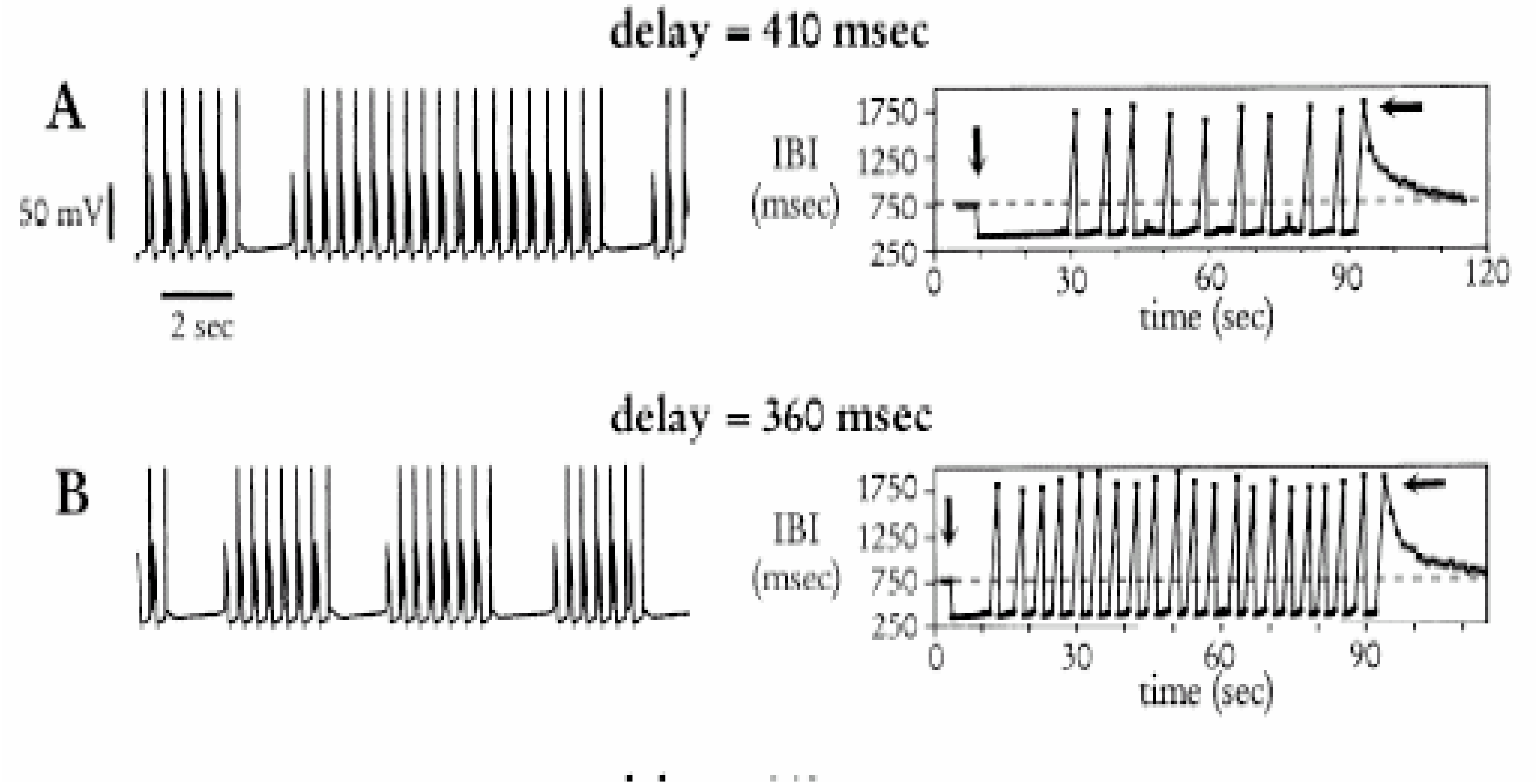


(Kunysz, Glass, Shrier 1995)

Fixed Delay Stimulation

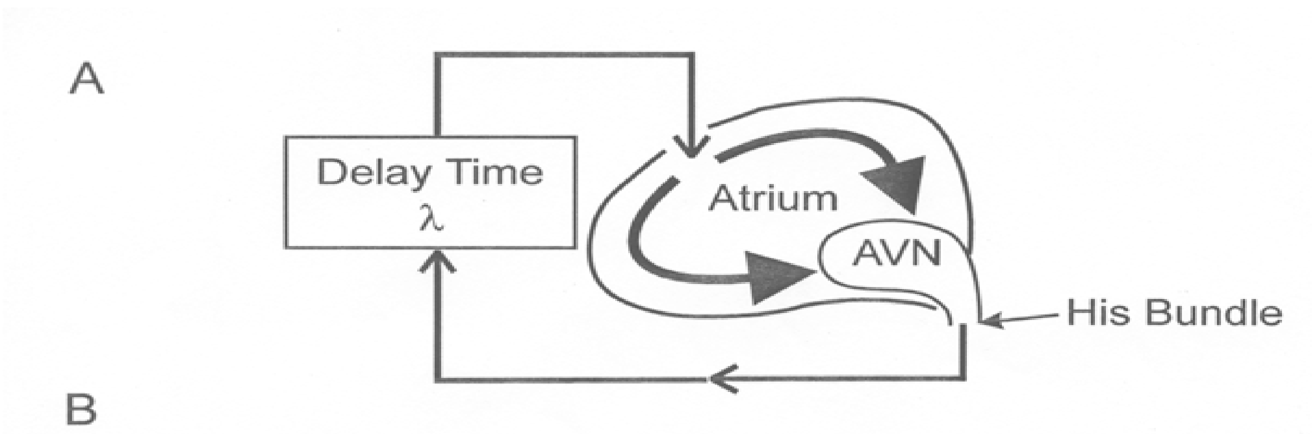


Fixed Delay Stimulation of Cardiac Aggregates Leads to Bursting



(Kunysz, Shrier, Glass 1997)

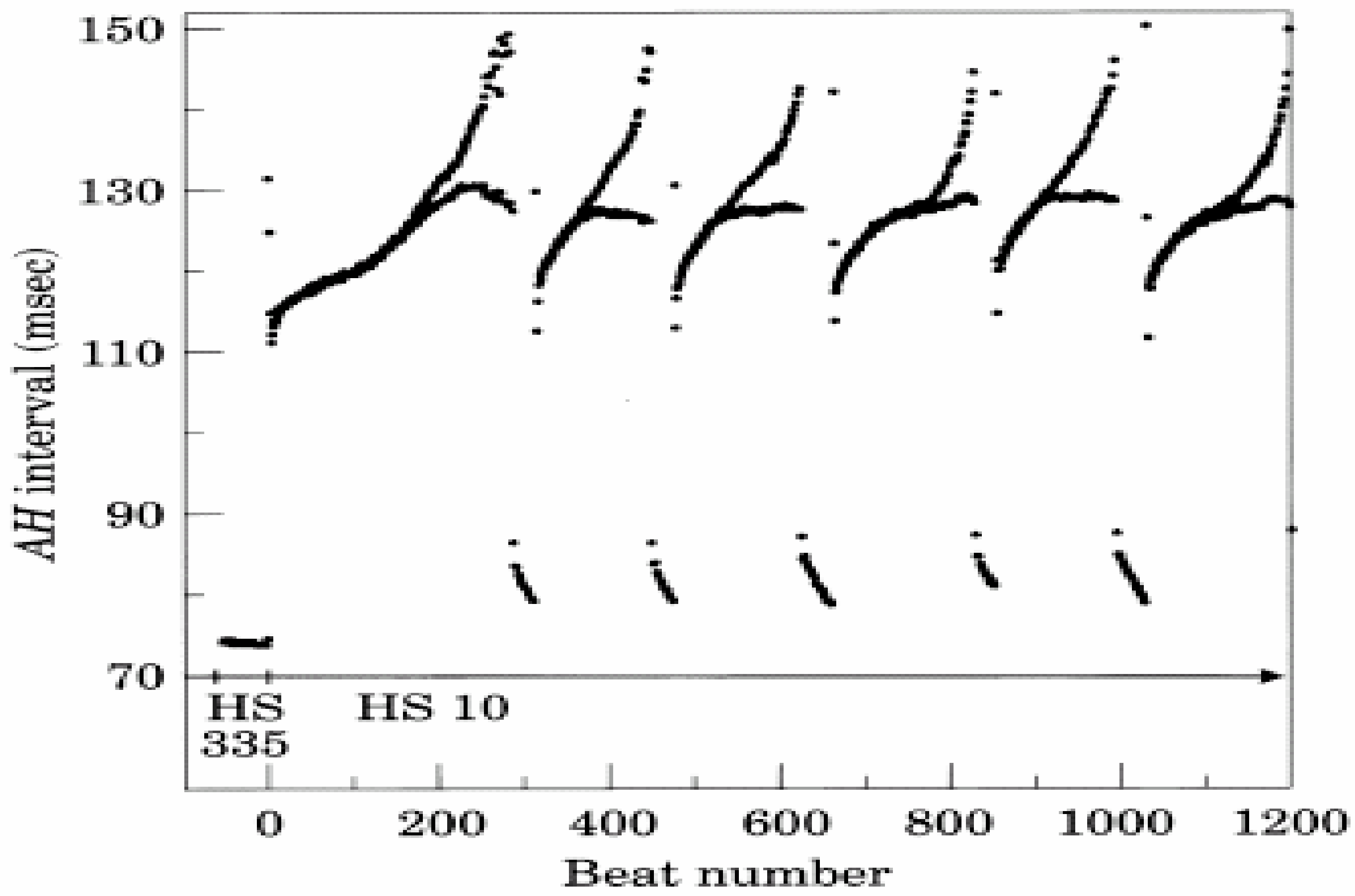
Cardiac Alternans in a Rabbit Heart in Vitro (1995)



Alternans and Period-doubling Bifurcations in Atrioventricular Nodal Conduction

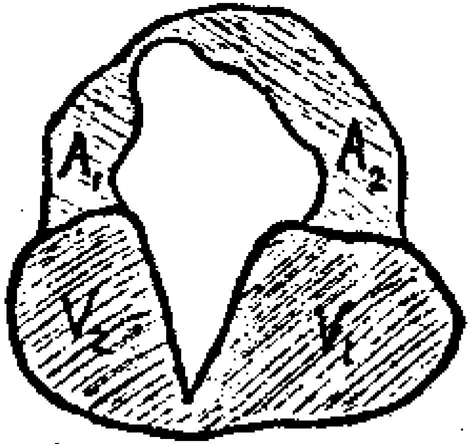
JIONG SUN,† FARID AMELLAL,‡ LEON GLASS,†§ AND JACQUES BILLETTE‡

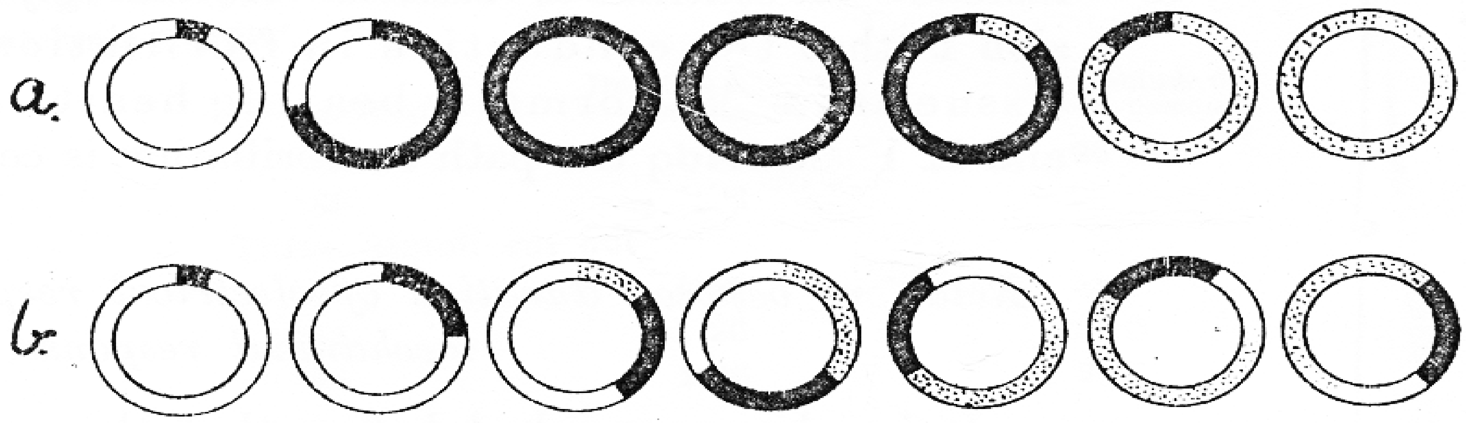
Bursting rhythms in reentrant rabbit preparation (1995)



(Model of tachycardia in WPW patients)

Anatomical Reentry

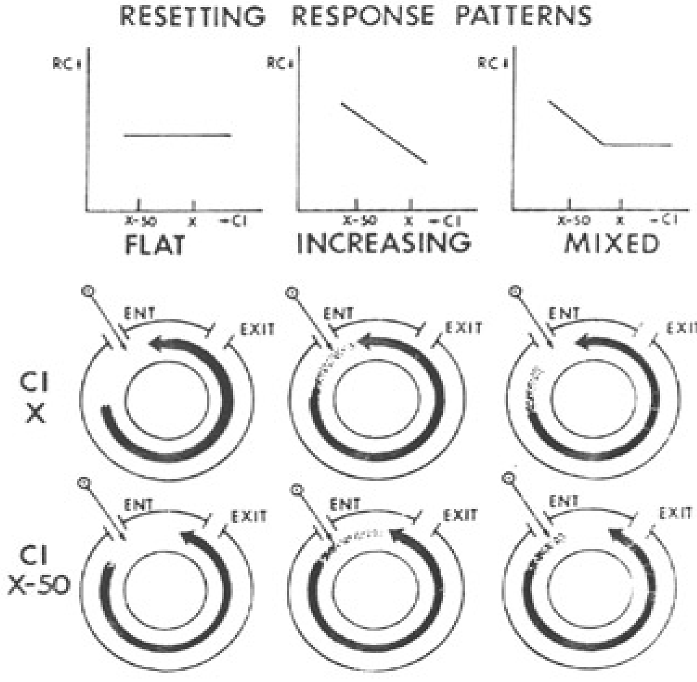




G. R. Mines (1913)

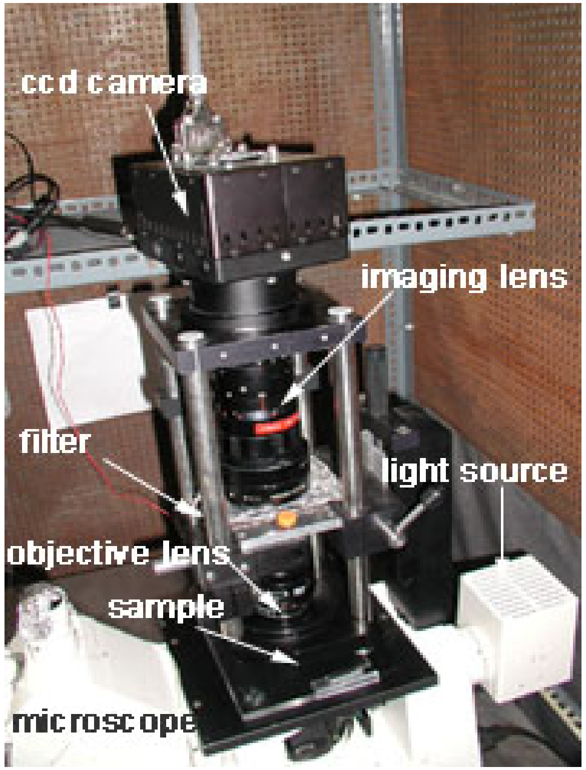
Resetting and Entrainment of Ventricular Tachycardia Associated with Infarction: *Clinical and Experimental Studies*

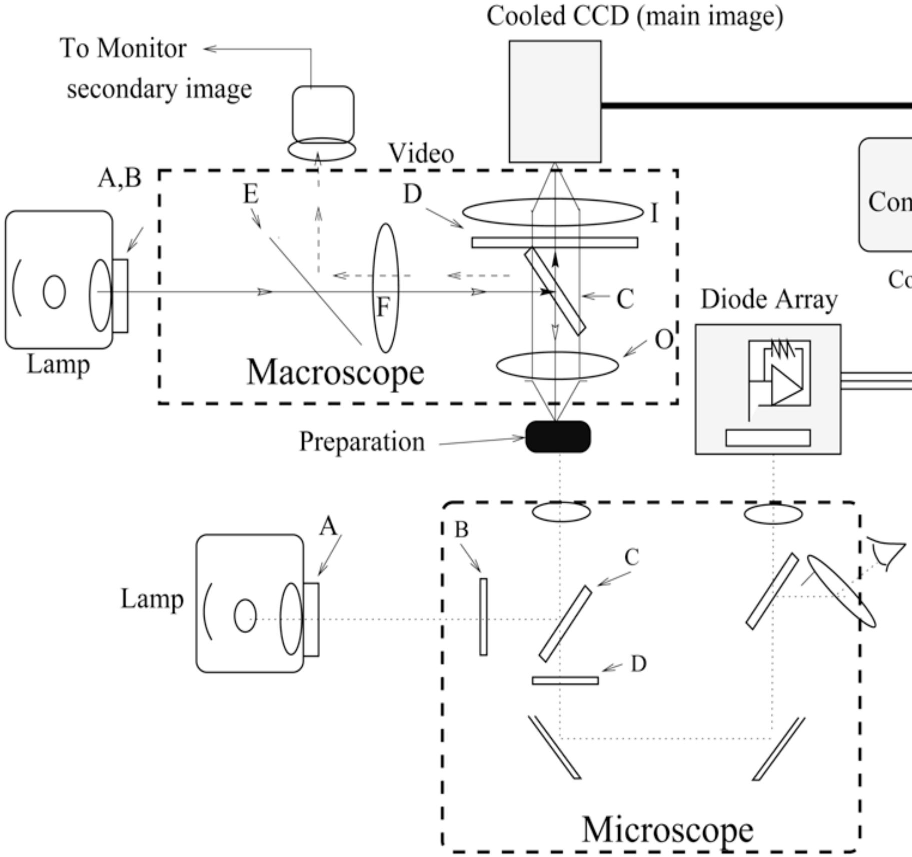
M. E. Josephson, D. Callans, J. M. Almendral, B. G. Hook, R. B. Kleiman



Macroscope for studying dynamics in tissue culture

(Gil Bub, Alvin Shrier, Yoshihiko Nagai, Katsumi Tateno)

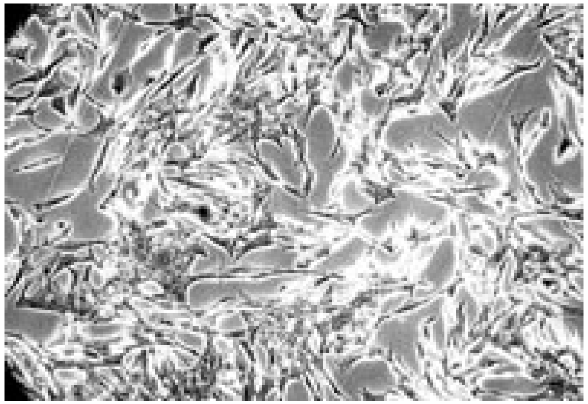




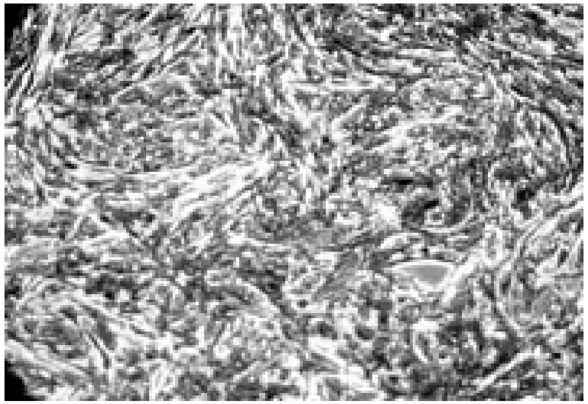
A) Heat Filter
B) Excitation Filter
C) Dichroic Mirror
D) Emmision filter
E) Beam Splitter
F) Illumination focus
O) Objective lens
I) Imaging lens

Cell Culture

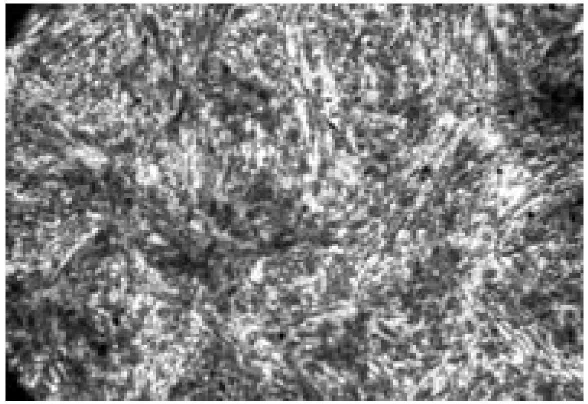
Incubate 30 White Leghorn eggs for 7 days.
Isolate ventricles.
Dissociate with DNAse and trypsin.
Add inactivating medium and filter.
Centrifuge and resuspend in maintenance media.
Plate at various densities.
Incubate for 1-2 days.
Load with dye, perform experiment.



$0.5x10^3$ /cm^2

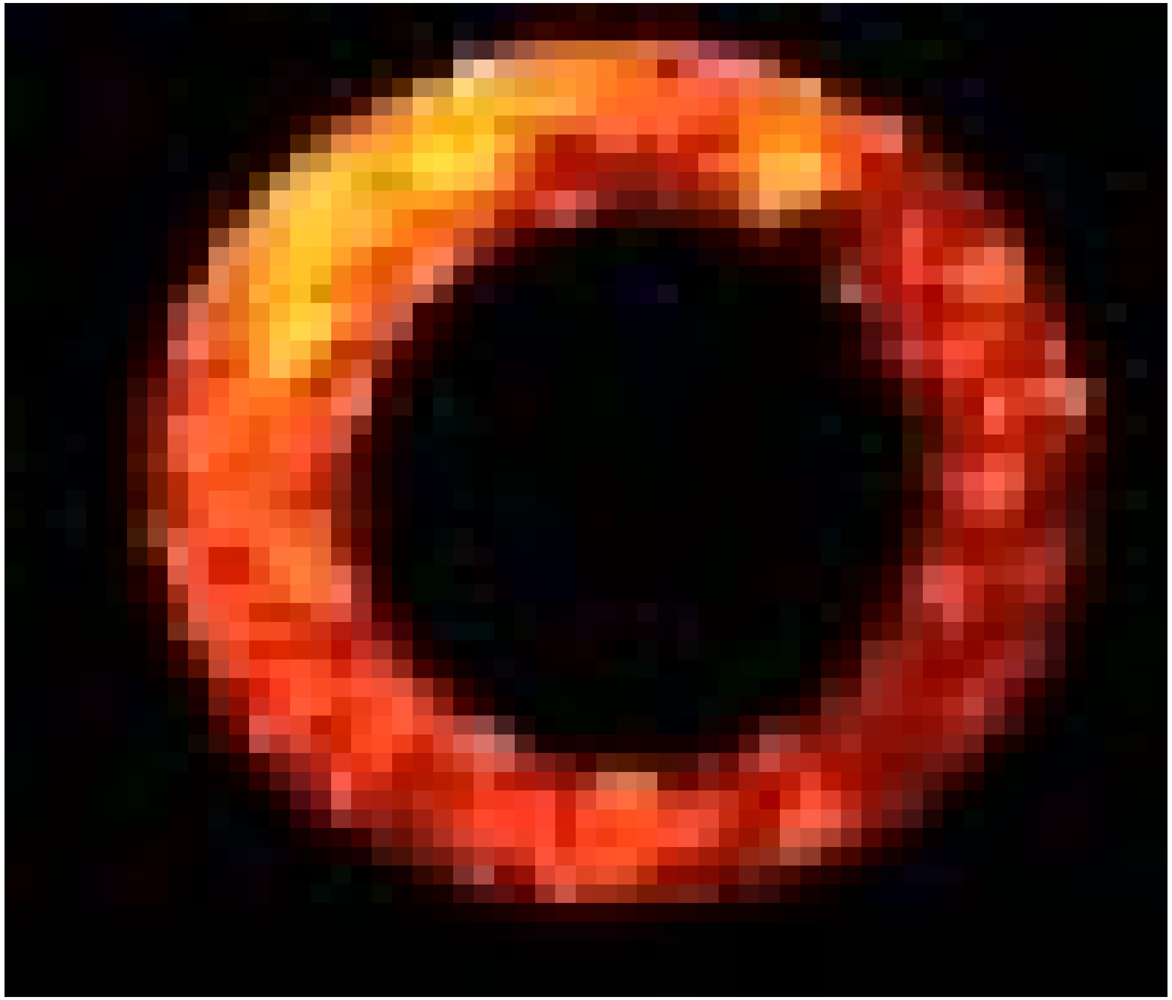


$1.0x10^3$ /cm^2



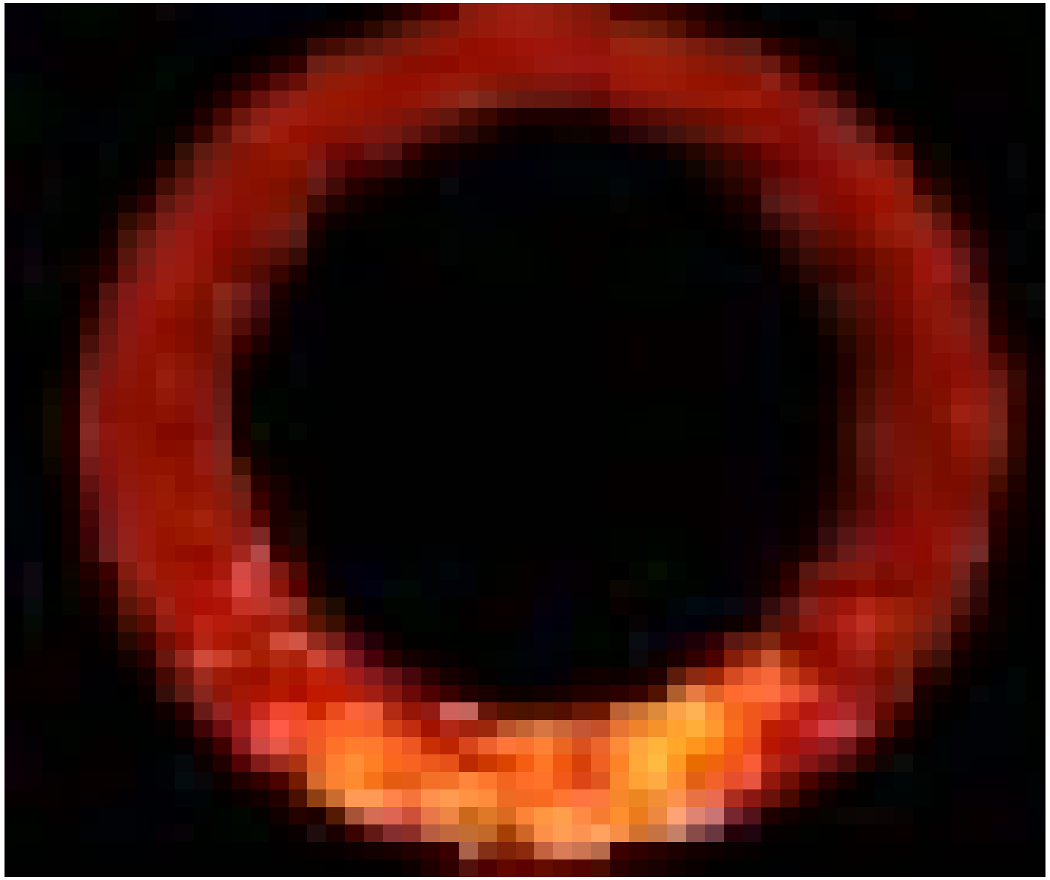
$2.0x10^3$ /cm^2

Dynamics in a Ring of Cardiac Cells

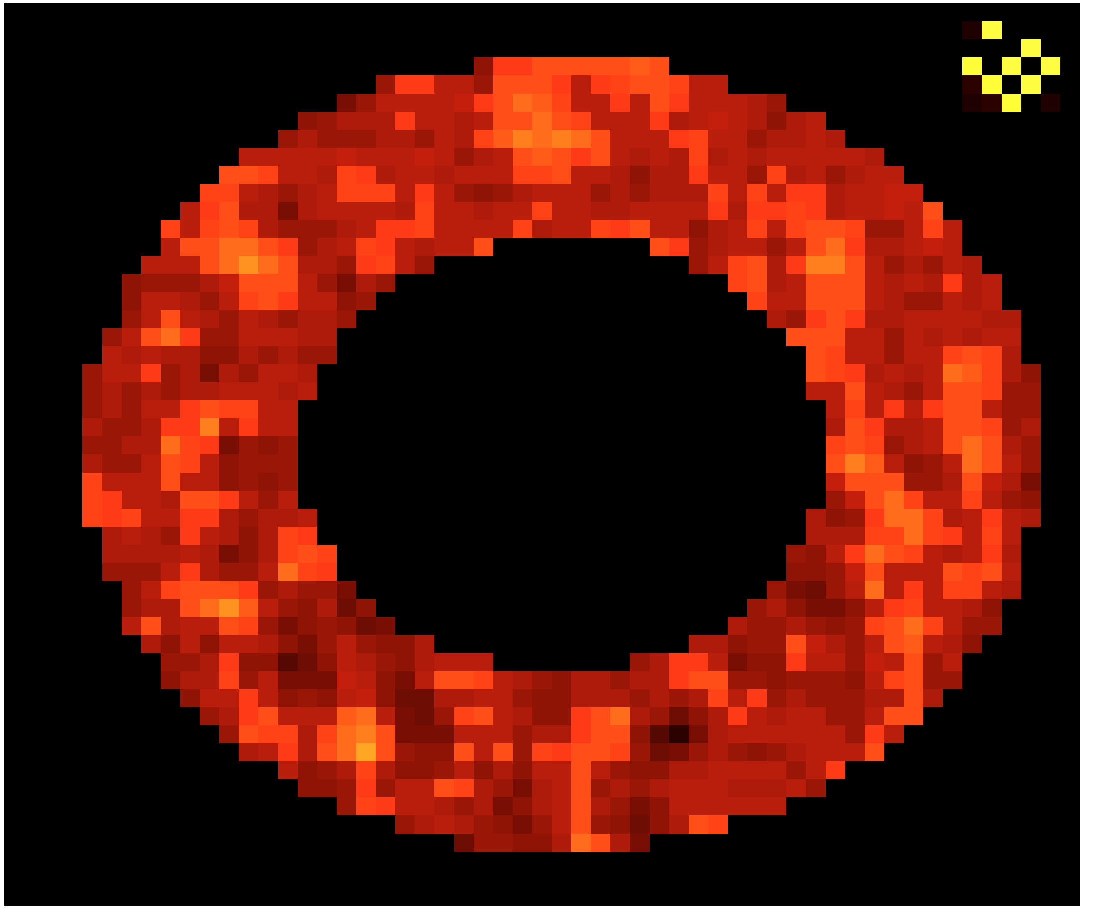


Pacemaker

Nagai, Gonzalez, Shrier, Glass, PRL (2000)



Reentry



Cardiac Ballet

FitzHugh-Nagumo Model of Propagation

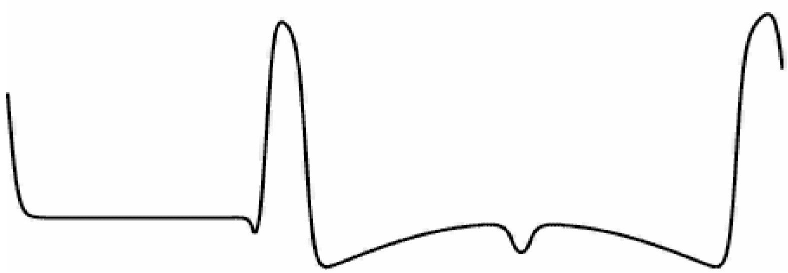
$$\frac{\partial v}{\partial t} = -(v+.1)(v-.9)(v-.039) - w + D\frac{\partial^2 v}{\partial r^2} + I,$$

$$\frac{\partial w}{\partial t} = (.005v - .01w + .0005)R(\zeta, v),$$

$$\frac{dz}{dt} = -\gamma_\alpha z + (\Delta z)\delta(t - t_{AP}),$$

$$\zeta(z) = \frac{.015}{z+1.},$$

$$R(\zeta, v) = \begin{cases} \frac{(1-\zeta)}{1+10e^{-10(v-.1)}} + \zeta, & \textbf{Pacemaker cells} \\ 1 & \textbf{Otherwise} \end{cases}$$



Dynamic Changes with Time in Culture

Time in Culture:

30h

39h

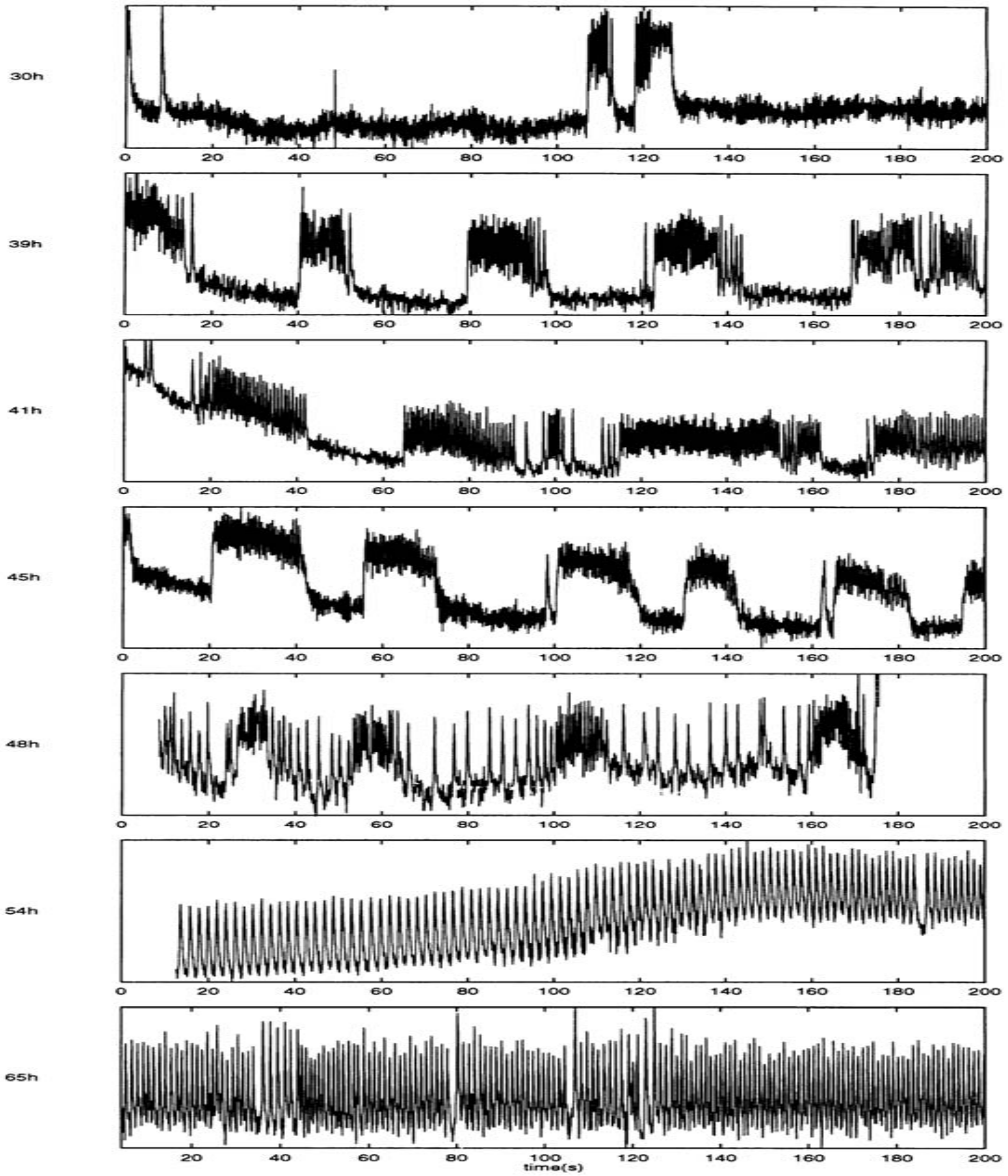
41h

45h

48h

54h

65h



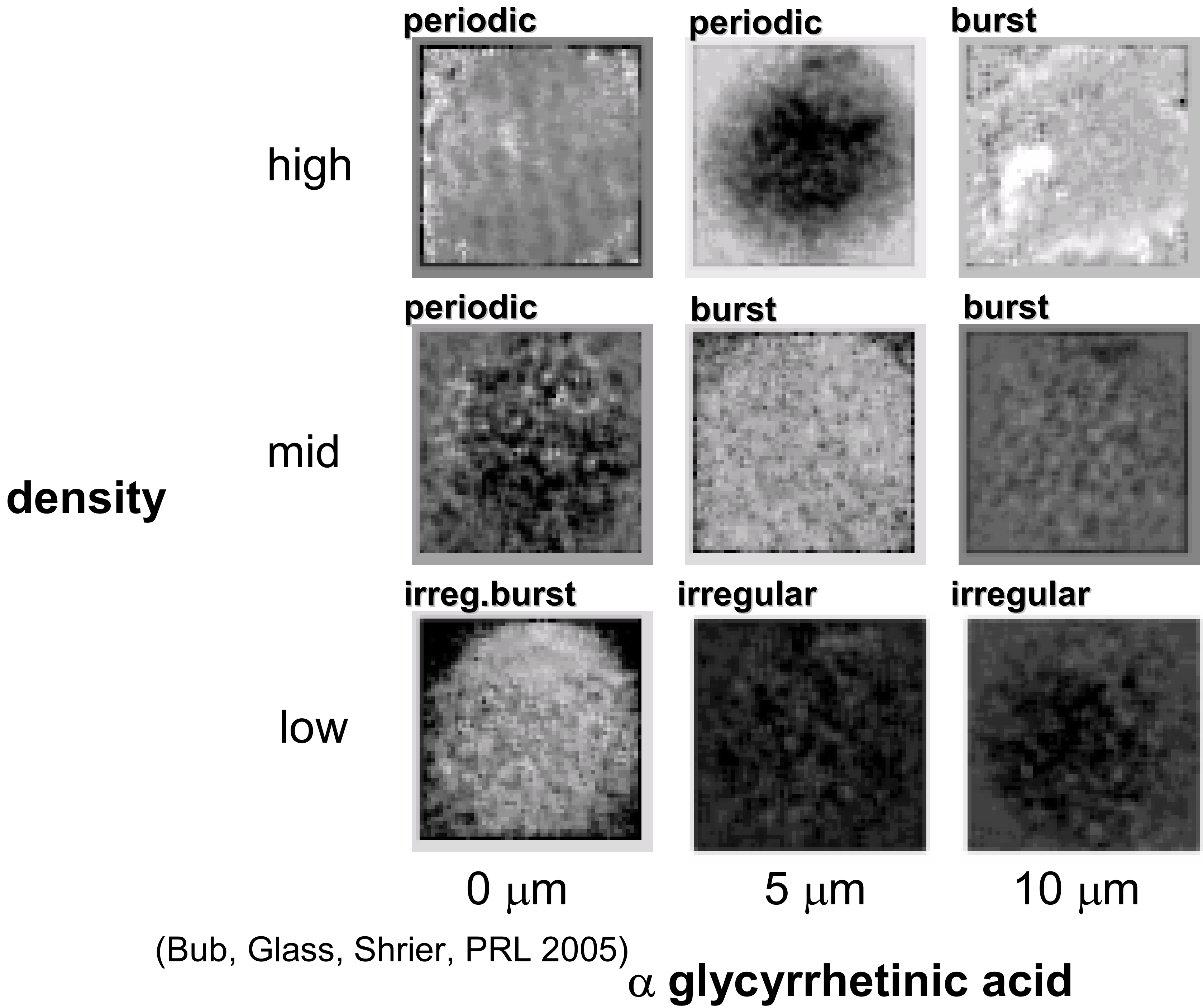
irregular activity

bursting spirals

stable spirals

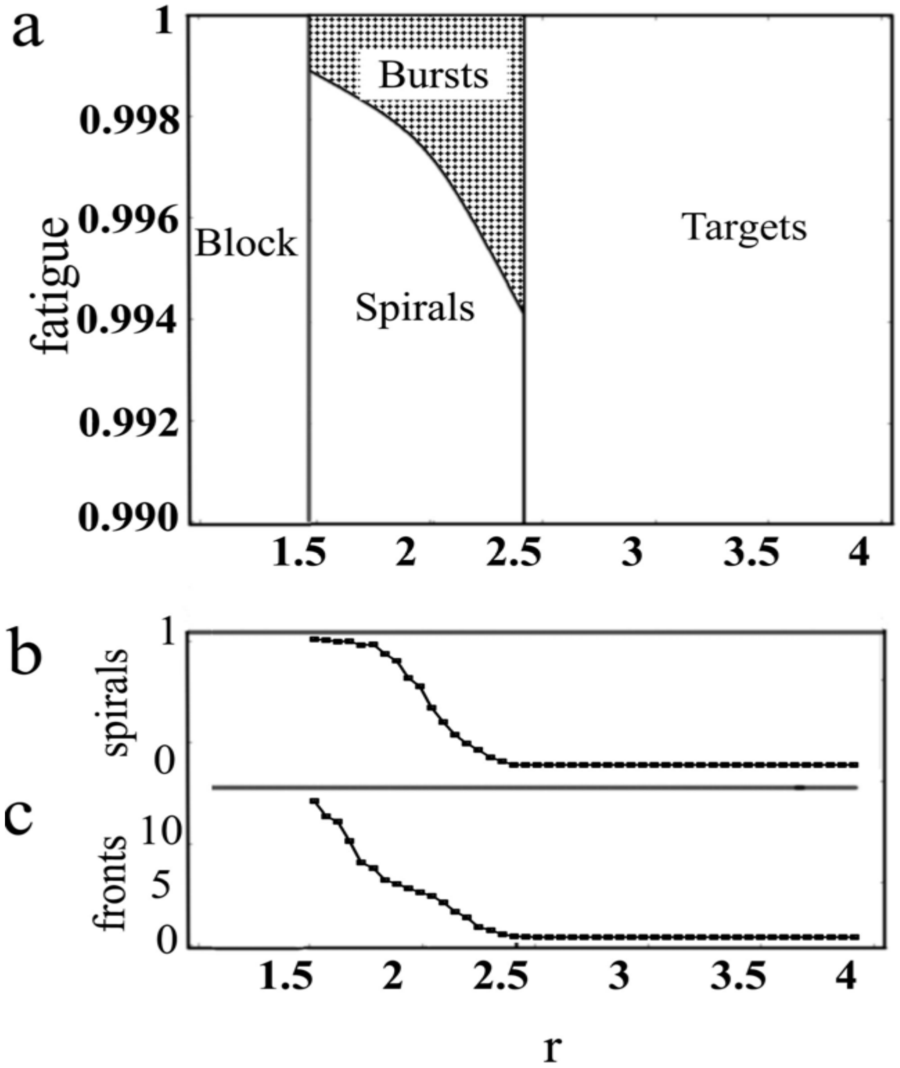
targets

(Bub, Tateno, Glass, Shrier JCE 2003)



periodic
periodic
burst
high
periodic
burst
burst
mid
density
irreg.burst
irregular
irregular
low
0 μm
5 μm
10 μm
(Bub, Glass, Shrier, PRL 2005)
α glycyrrhetinic acid

Universal organization: Fatigue vs Coupling

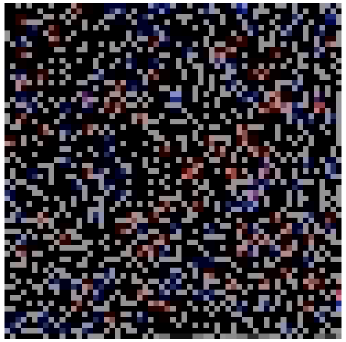


(Bub, Glass, Shrier, PRL 2005)

Simulating bursting dynamics as a function of connectivity

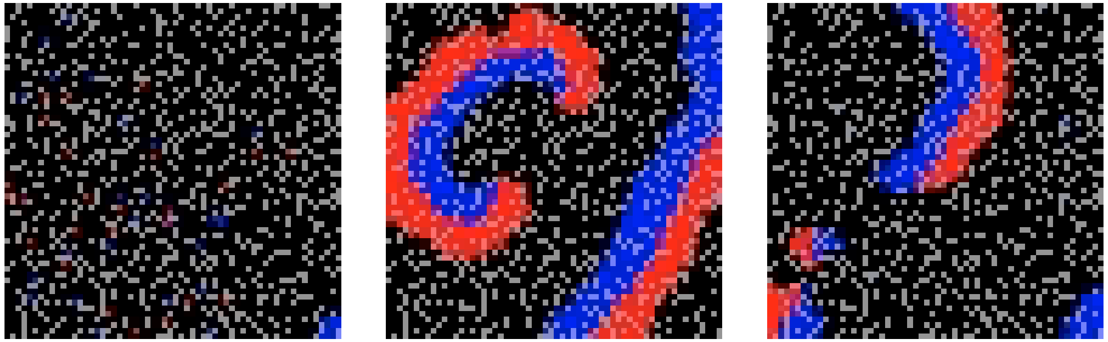
1)Add spontaneous activity by giving excitable cells a probability of firing.
2) Add fatigue by giving each cell a fatigue variable η where
 a) if the cell just became excited, $\eta_{i,j}(t+1) = \eta_{i,j}(t) + F$,
 b) Otherwise, $\eta_{i,j}(t+1) = \chi\eta_{i,j}(t)$, where $0<\chi<1$ (exponential decay)
Now a cell is activated if $\eta_{i,j} + \theta <$ active/inactive

R=3, θ=0.35



Target patterns ('periodic')

R=1.8, θ=0.35



bursting

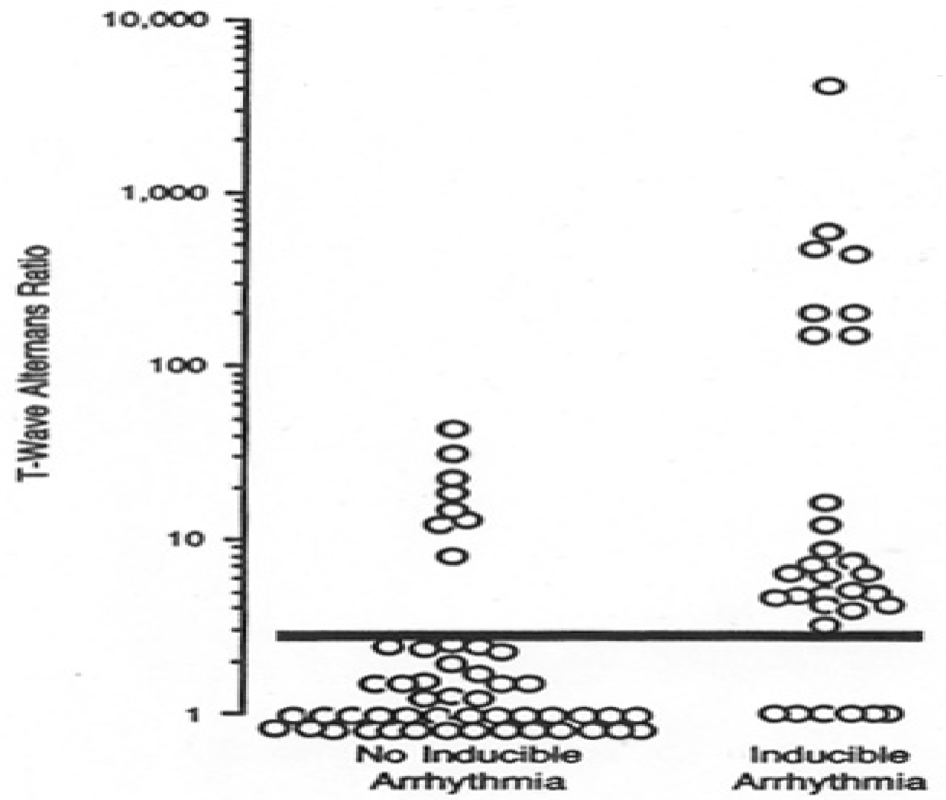
One mechanism for paroxysmal rhythms

- Initiation by reentry in heterogeneous excitable systems
- Termination as a result of “fatigue” – loss of excitability

Control: Use quantitative methods to better identify arrhythmia and assess the risk for sudden cardiac death

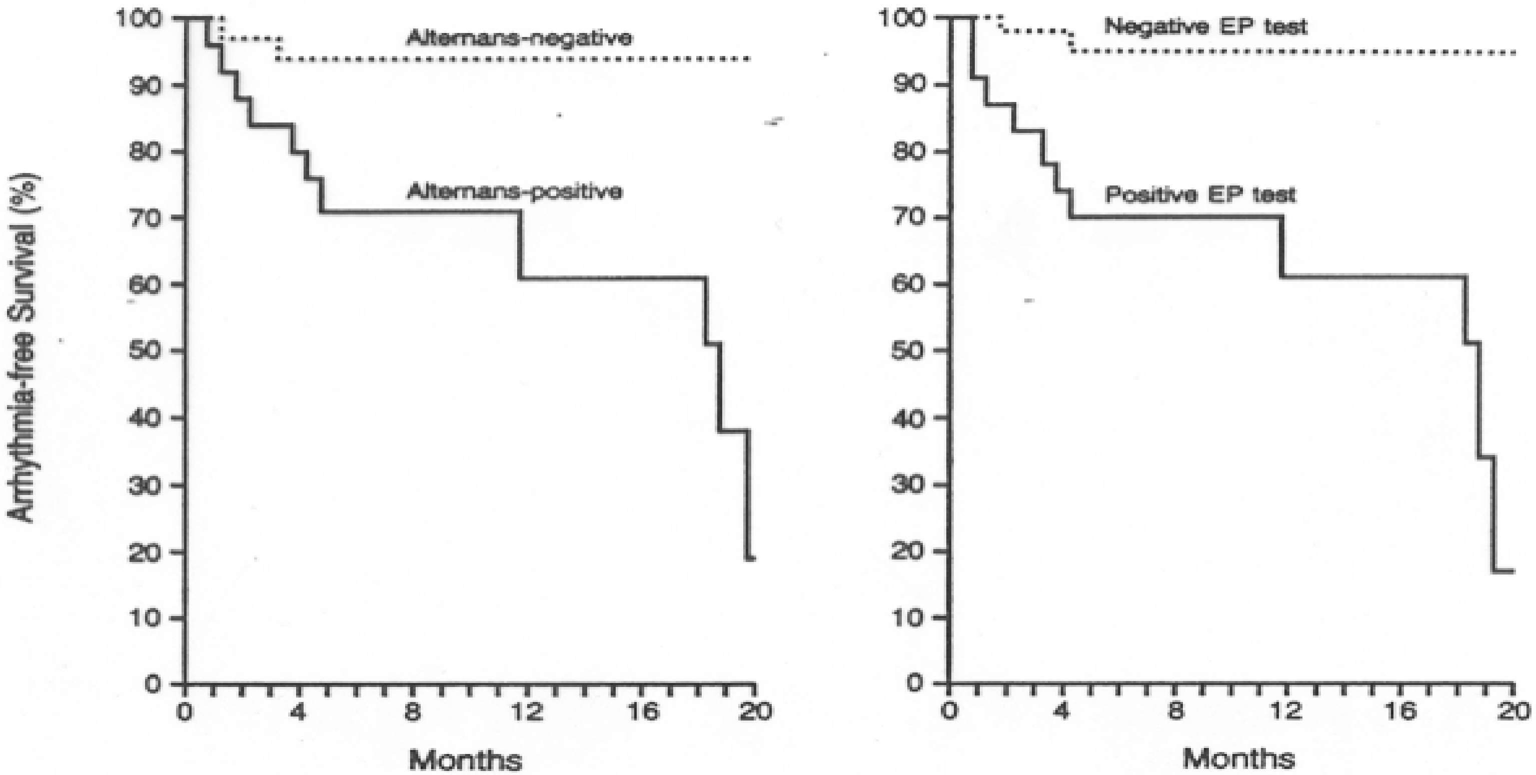
- Warning: Methods are still controversial

T-wave alternans



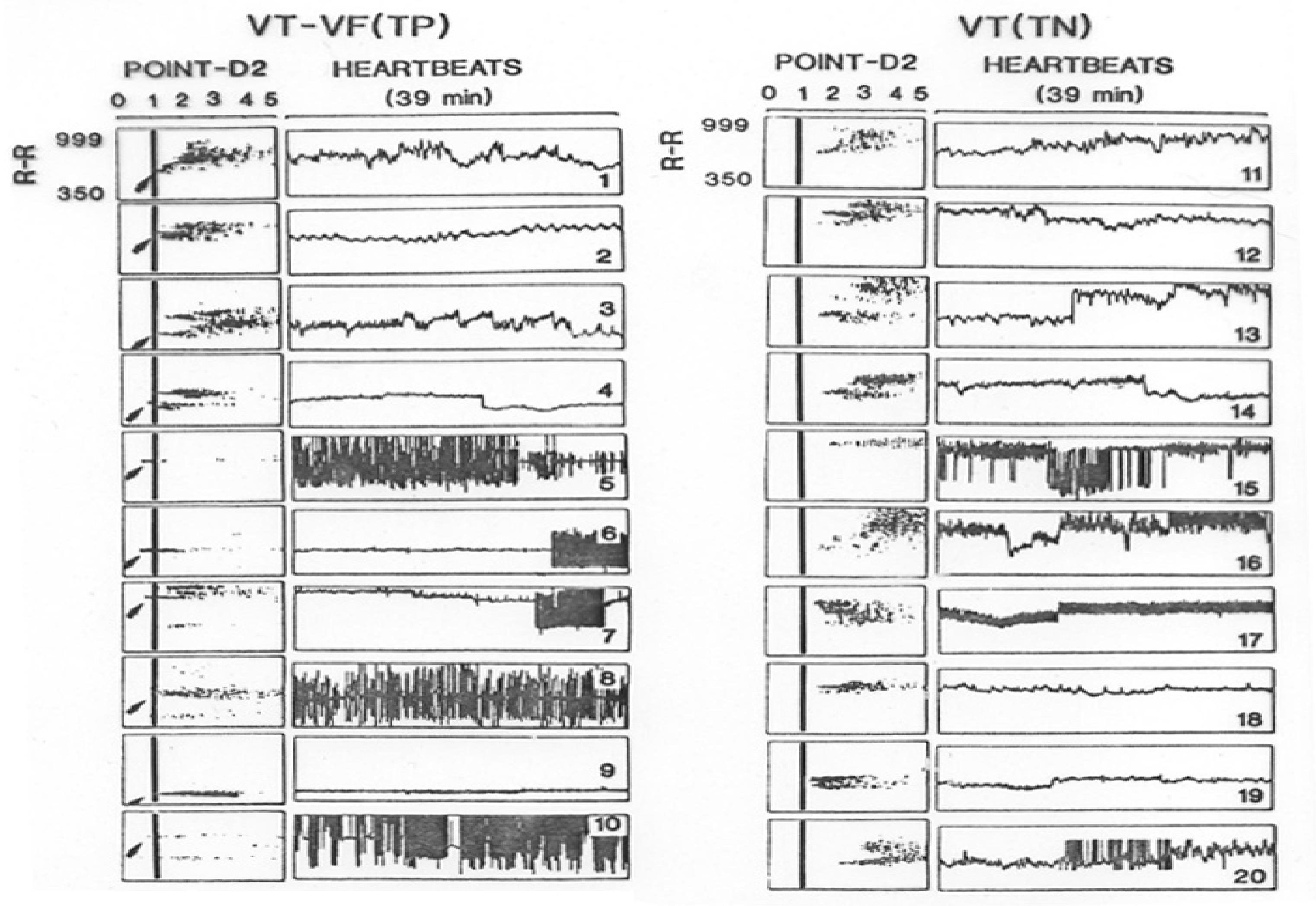
Rosenbaum et al., NEJM (1994)

T-wave Alternans Predicts Arrhythmia



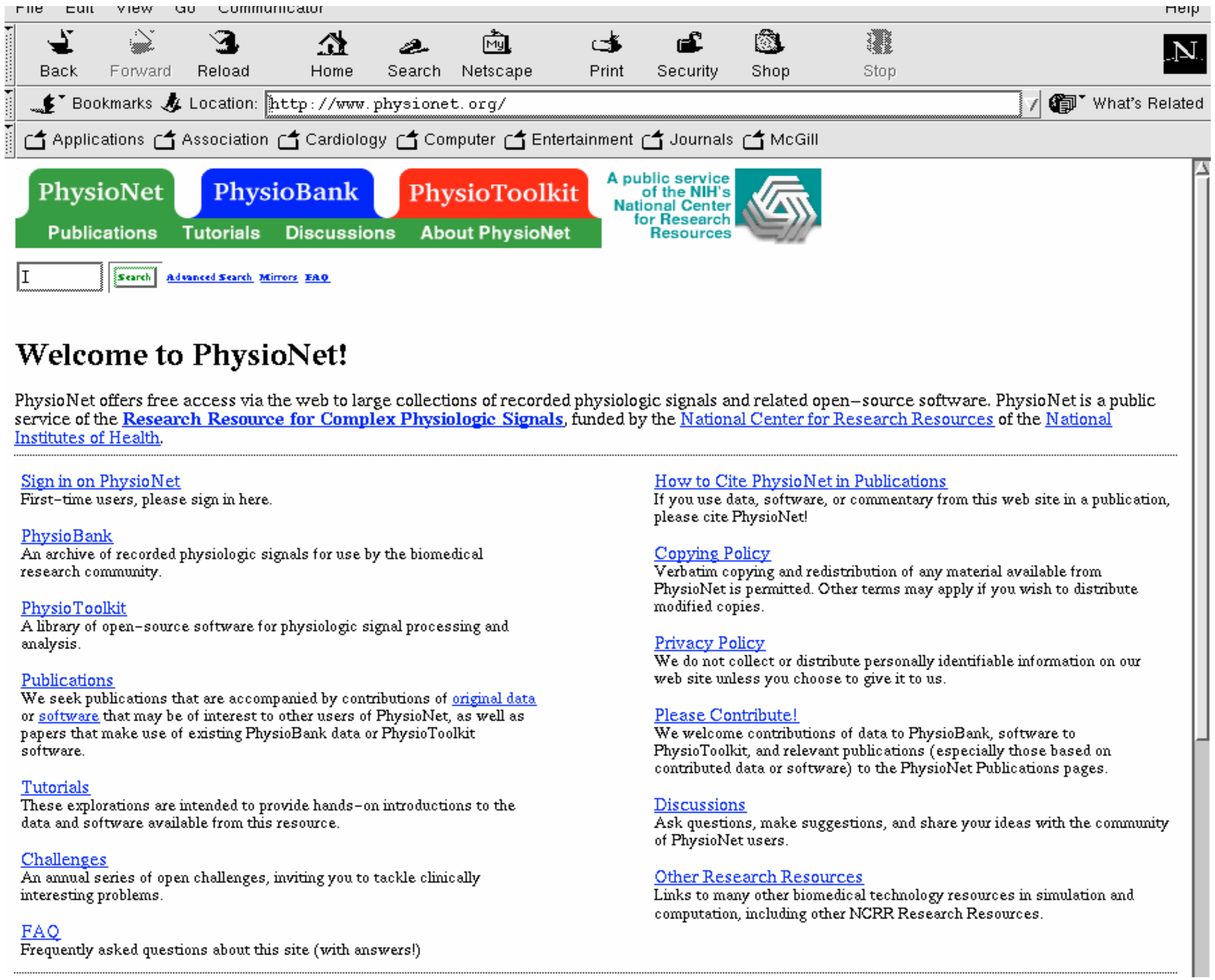
Questions for discussion: What mechanisms might link T-wave alternans to increased risk for VT? Would the same mechanisms lead to inducibility of VT using premature stimuli in the EP lab?

Point D2 Dimension



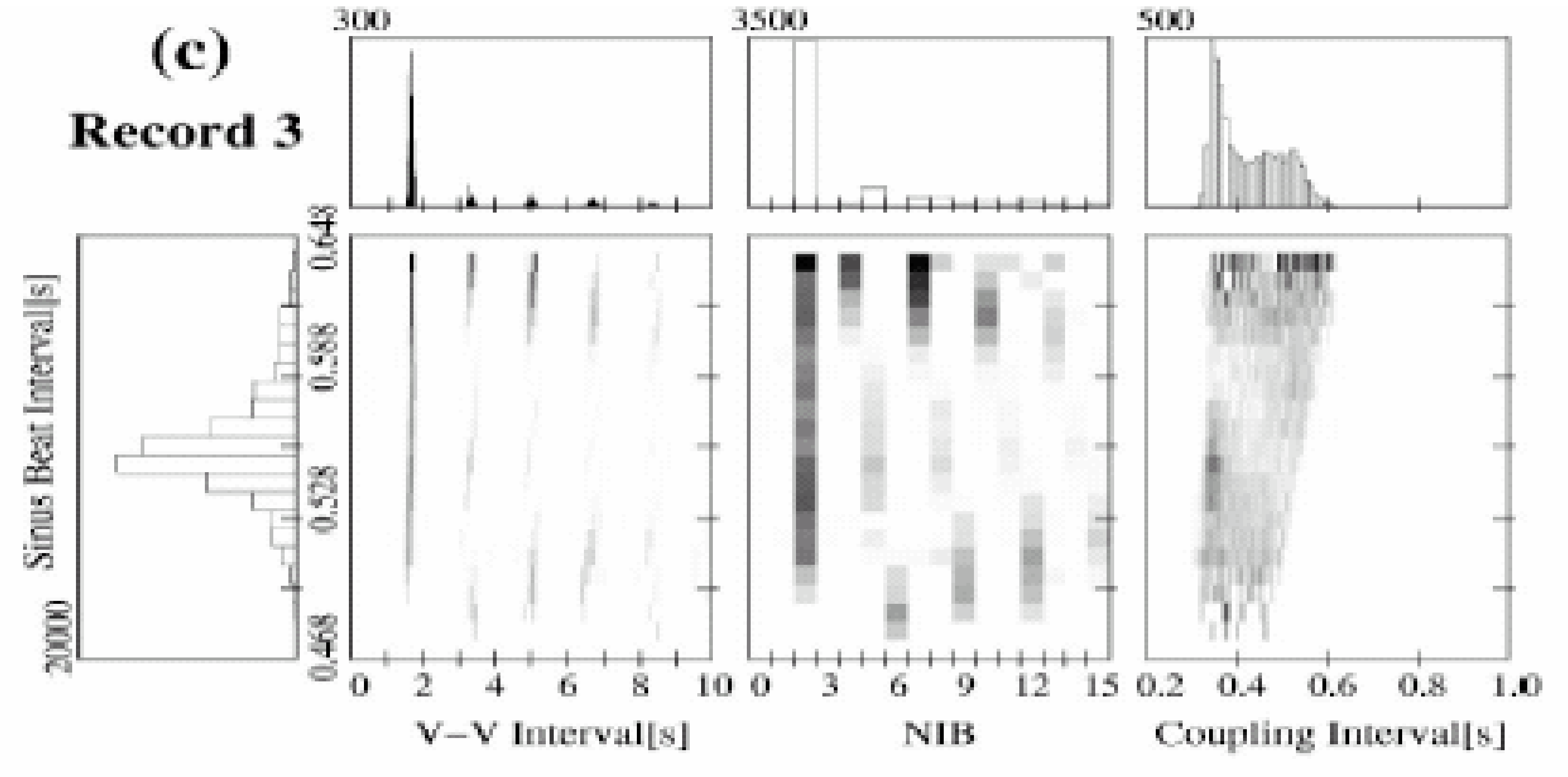
Skinner, Pratt, Vybiral (1993)

National Resource for Complex Physiologic Signals
A. Goldberger, Director



http://www.physionet.org

Heartprint of a Patient

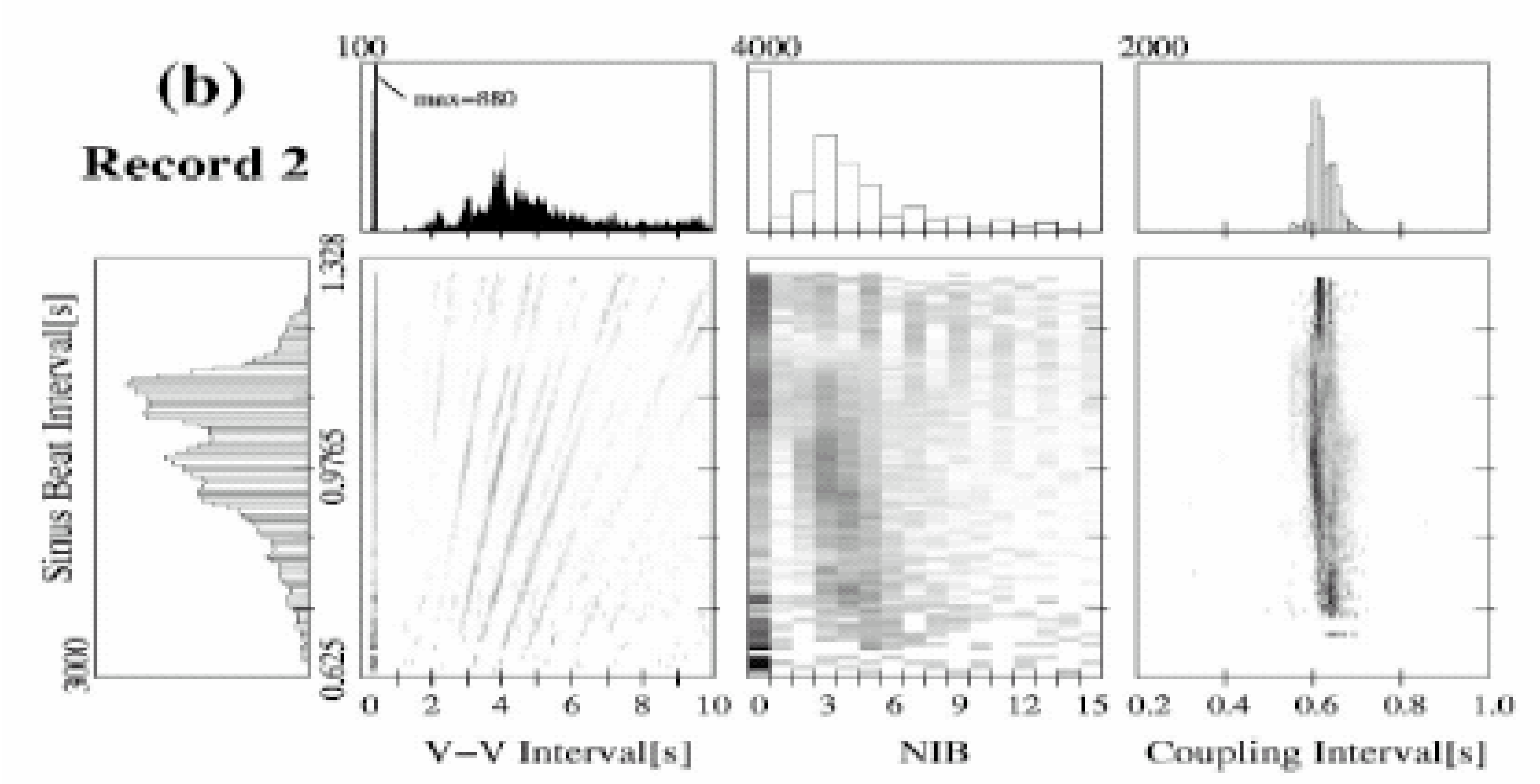


PHYSICAL REVIEW E **66**, 031901 (2002)

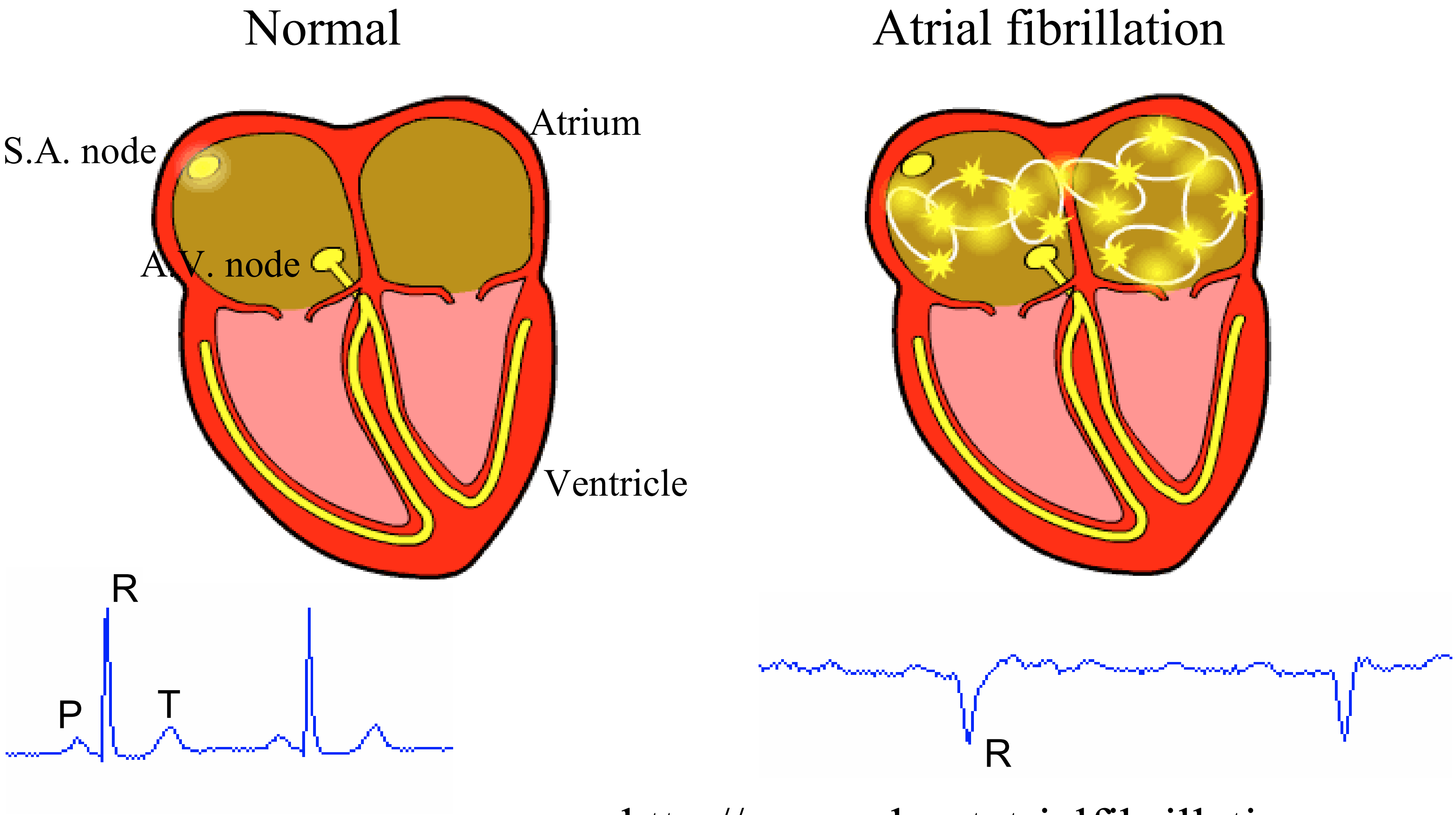
Complex patterns of abnormal heartbeats

Verena Schulte-Frohlinde,[1,2,*] Yosef Ashkenazy,[1,3] Ary L. Goldberger,[2] Plamen Ch. Ivanov,[1] Madalena Costa,[2]
Adrian Morley-Davies,[4] H. Eugene Stanley,[1] and Leon Glass[5]

Heartprint of Another Patient

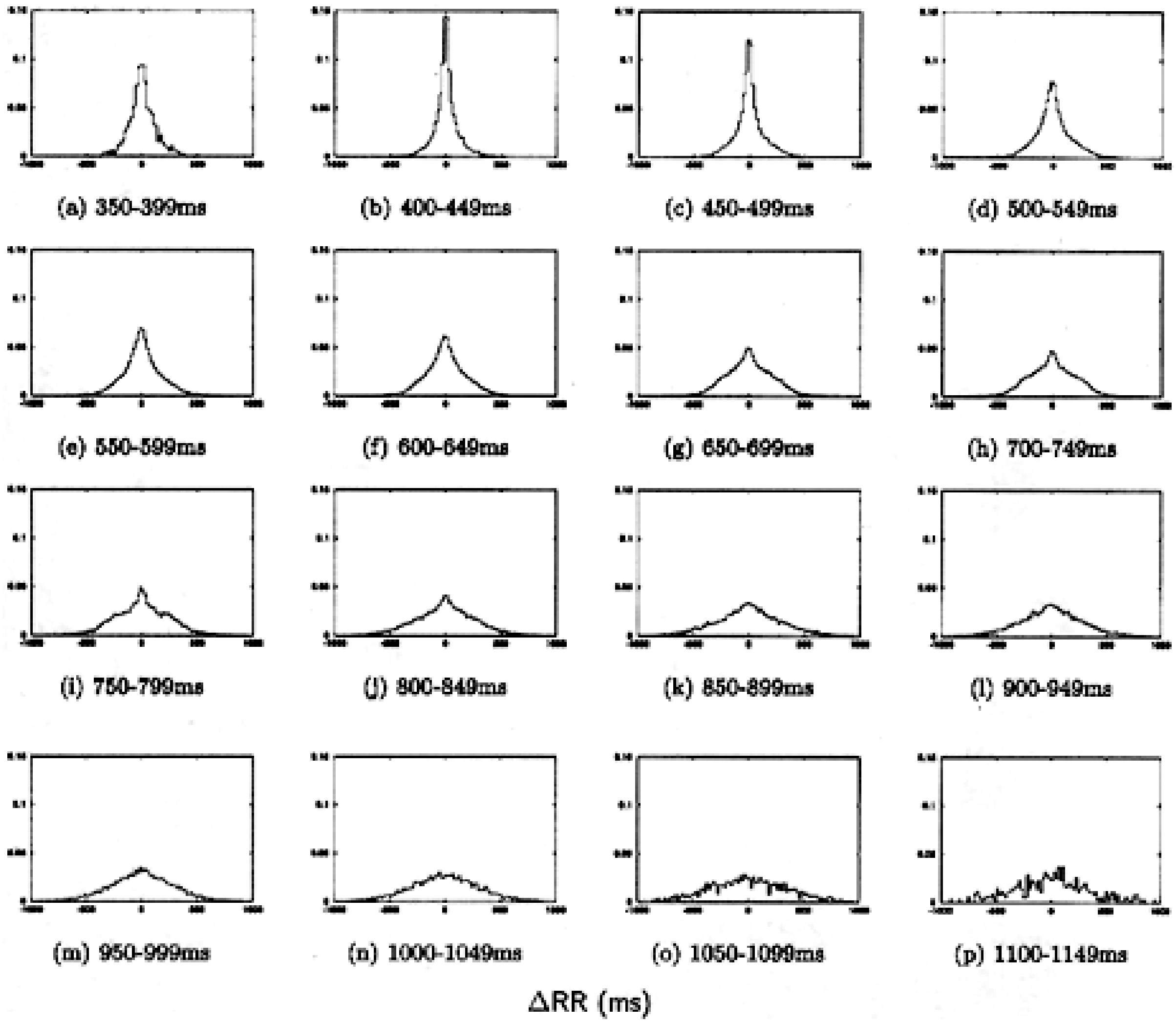


Can you detect atrial fibrillation based on the RR intervals?



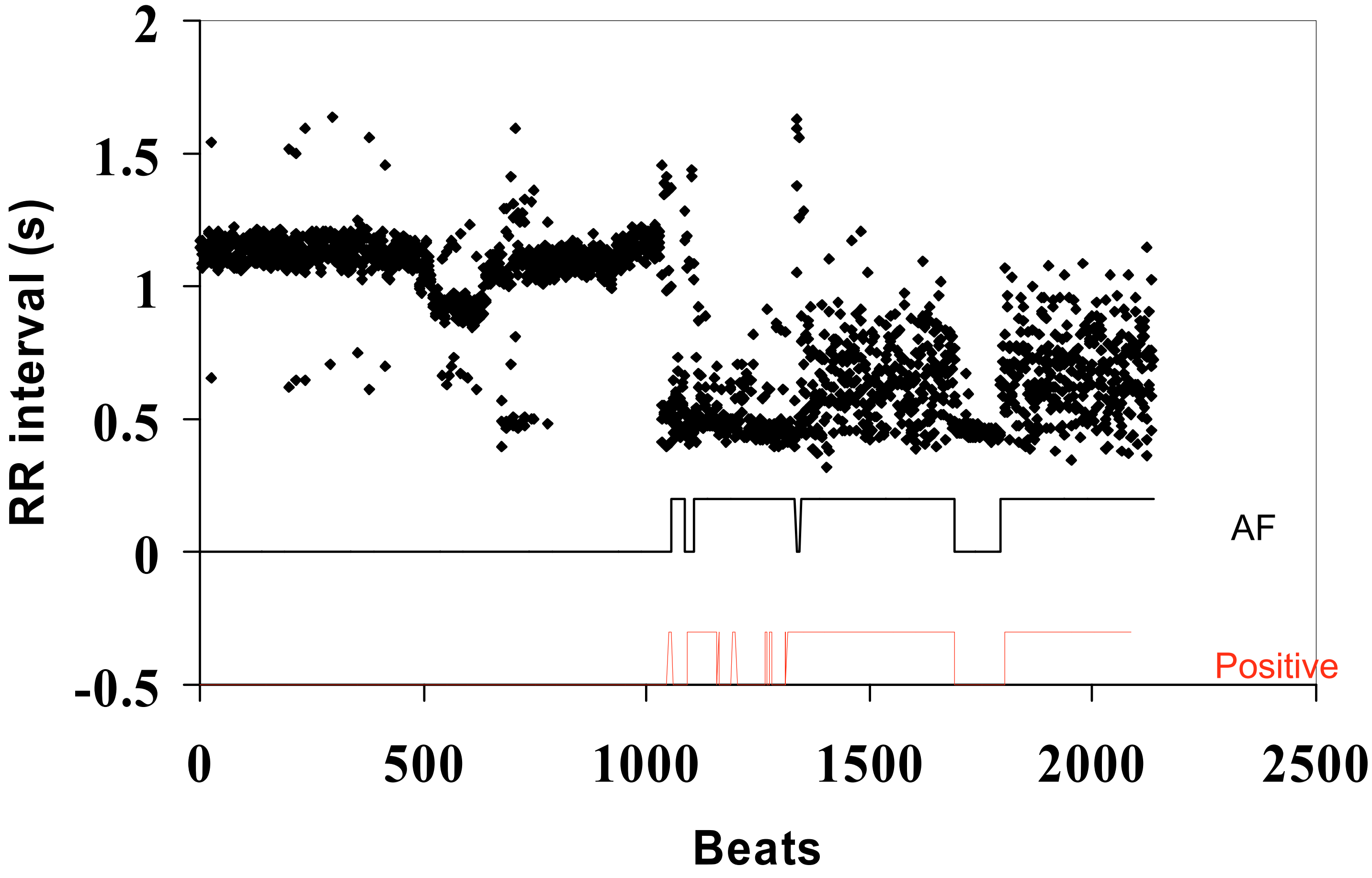
http://www.aboutatrialfibrillation.com

Use Histograms of ΔRR Intervals to detect AF

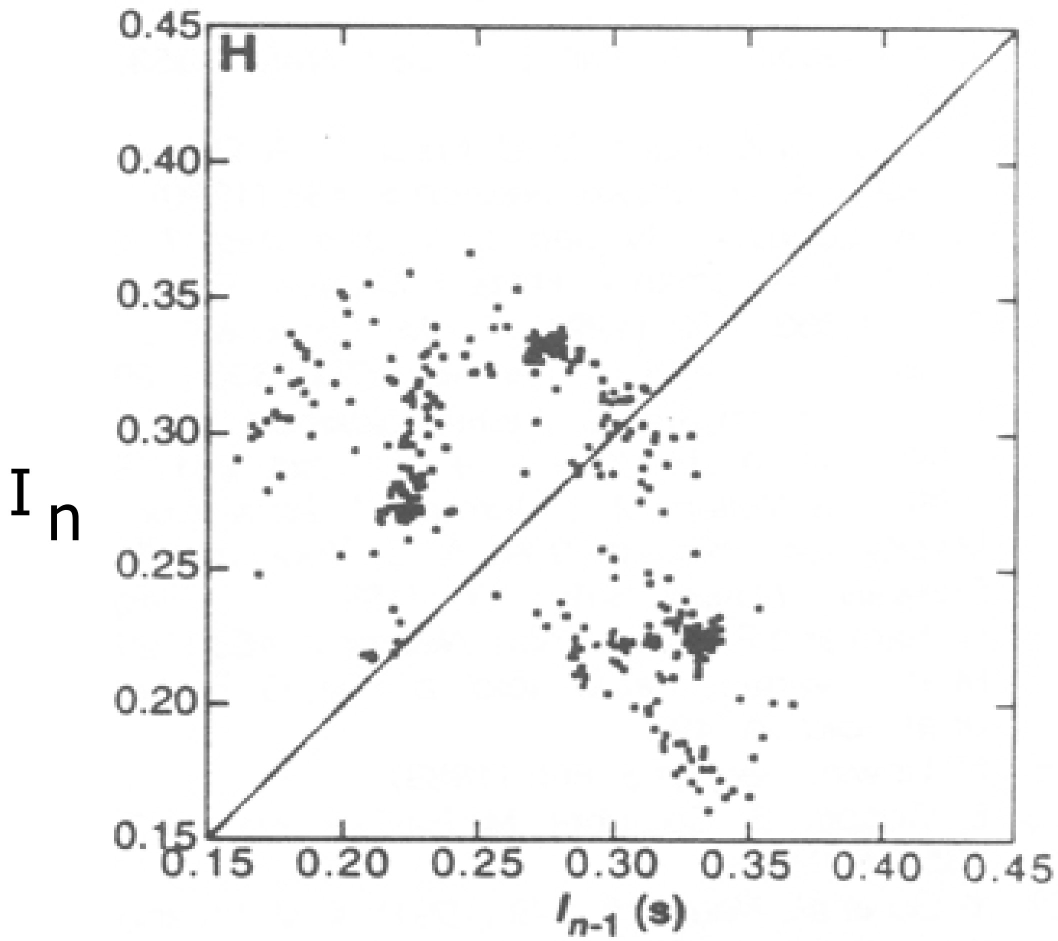


Tateno and Glass (2001)

Data Analysis: MIT-BIH arrhythmia database (From PhysioNet)



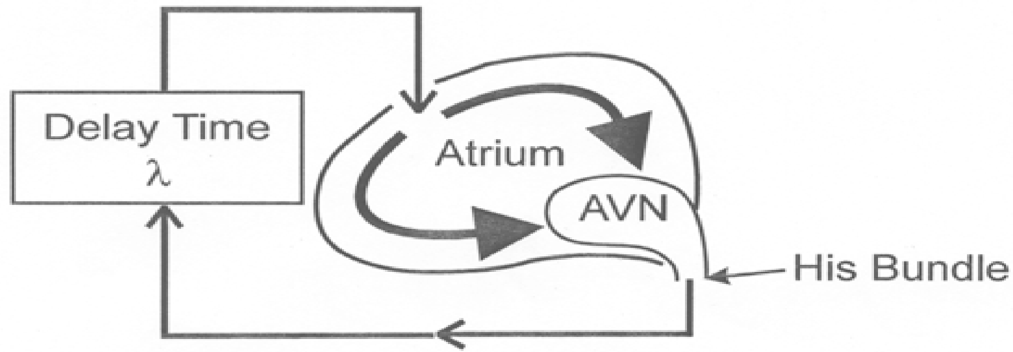
Control of Cardiac Chaos



Garfinkel, Spano, Ditto, Weiss, Science (1992)

Control Cardiac Alternans in a Rabbit Heart in Vitro (1997)

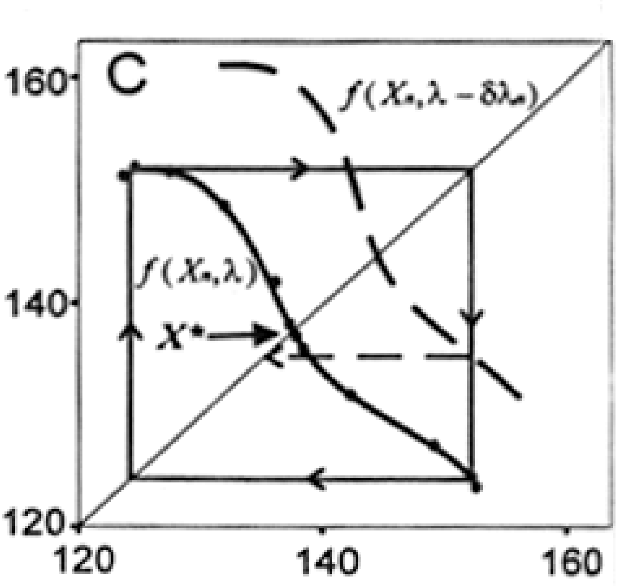
A



B

(Hall, Christini, Collins, Glass, Billette, PRL 1997). See also David Christini for same approach in people.

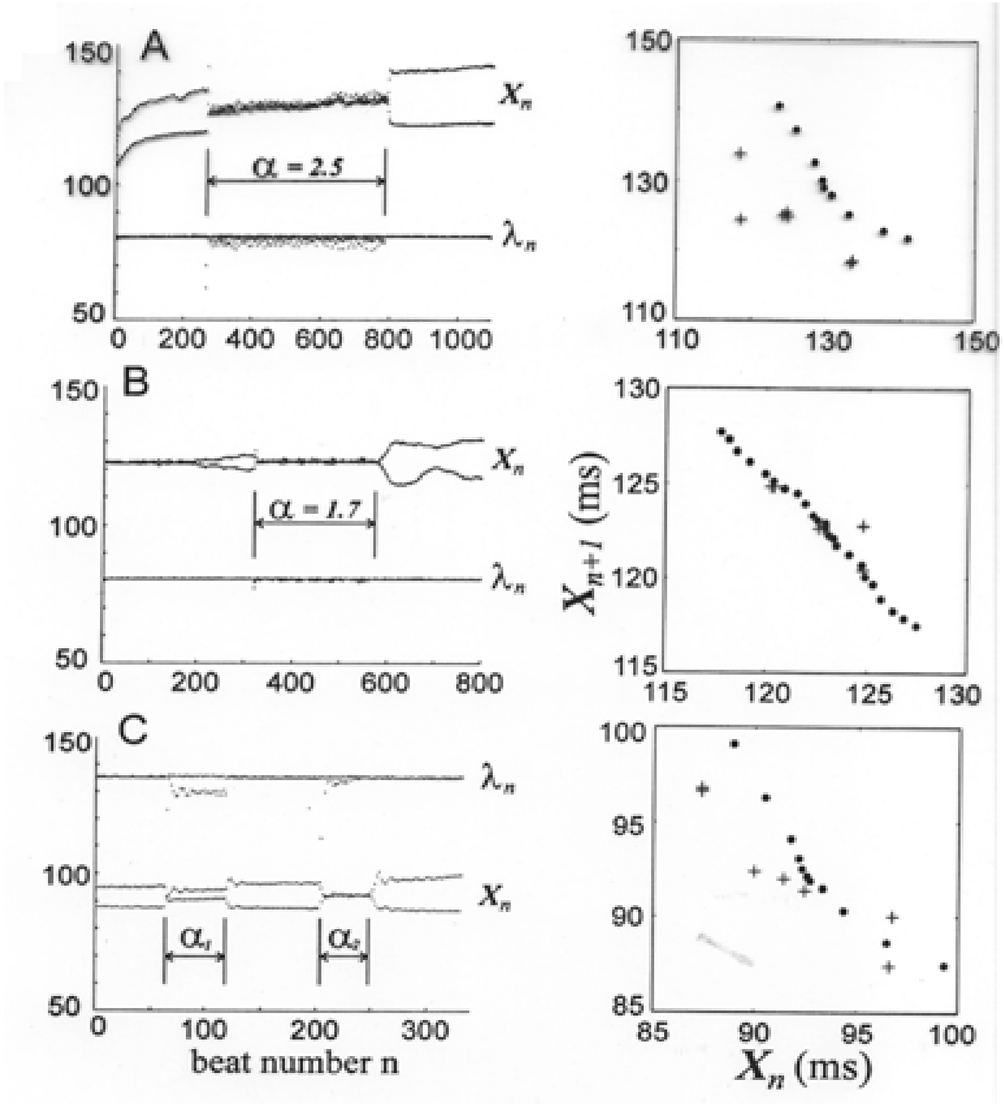
Target Unstable Fixed Point



I_{n+1}

I_n

Stimulate to Control Alternans



Conclusions

- Model cardiac systems can display complex rhythms. The types of the dynamics and the organization as a function of parameters governing the system are understood in some simple cases. These examples provide a challenge for “realistic” models of cardiac tissue.
- In intact animals, we need to study complex arrhythmia in detail in individuals since there is more than one mechanism.
- It will be possible to classify the mechanisms of complex arrhythmia, and perhaps it will be possible to better stratify risk.