



The Abdus Salam  
International Centre for Theoretical Physics



*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**

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**Dynamics and Control of Cardiac Arrhythmias**

**Leon Glass**  
McGill University, Quebec - Canada

# Dynamics and Control of Cardiac Arrhythmias

Leon Glass

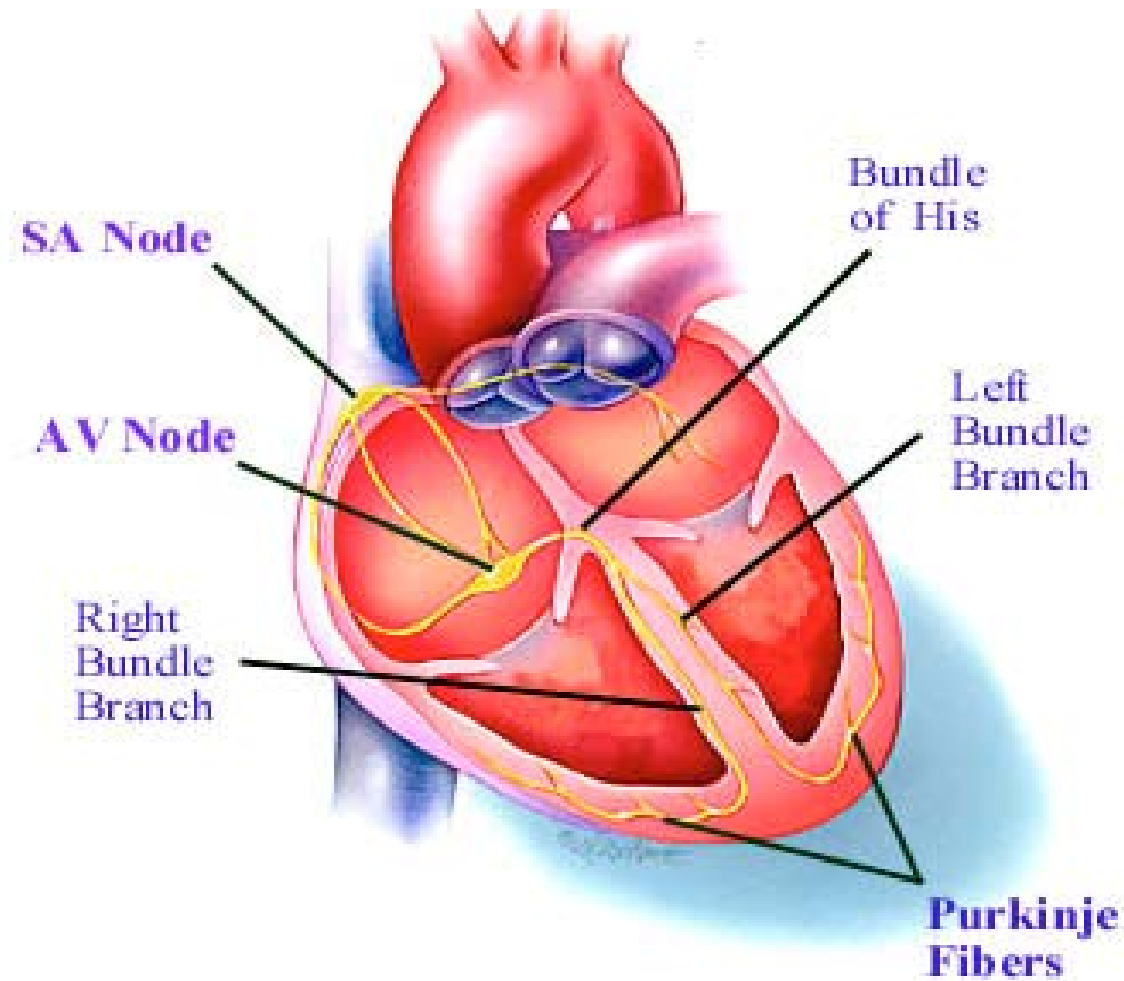
Isadore Rosenfeld Chair in  
Cardiology, McGill University,  
Montreal, Quebec

# Outline

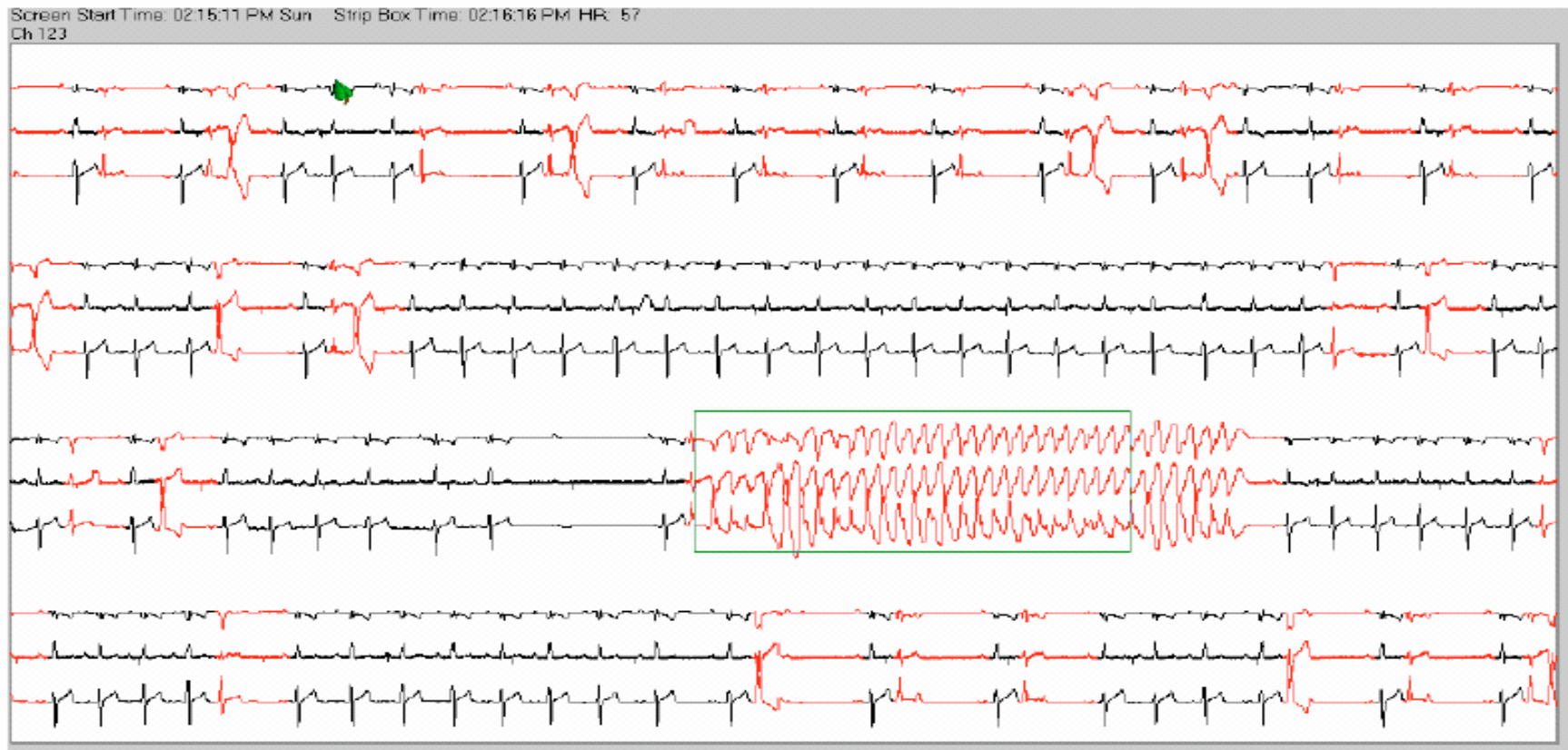
- Dynamics: Paroxysmal rhythms
- Dynamics: Resetting oscillations
- Dynamics: Excitation in a ring
- Dynamics: Universal organization dynamics in excitable media
- Control: Better diagnosis of arrhythmia
- Control: Stimulation to control arrhythmia

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

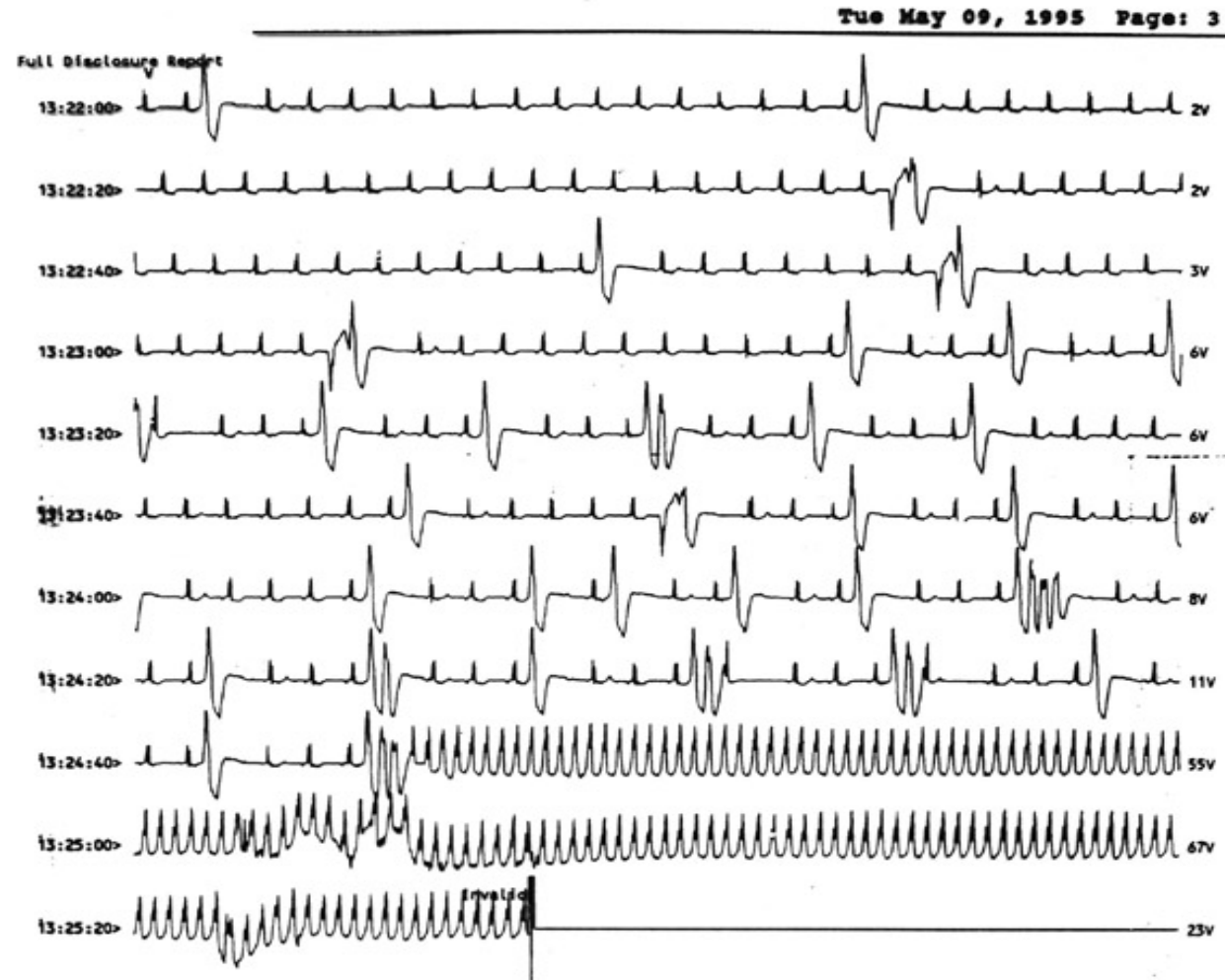


# Complex ectopic beats precede polymorphic VT in a German Shepherd dog (provided by Dr. S. Moise, Cornell)



**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



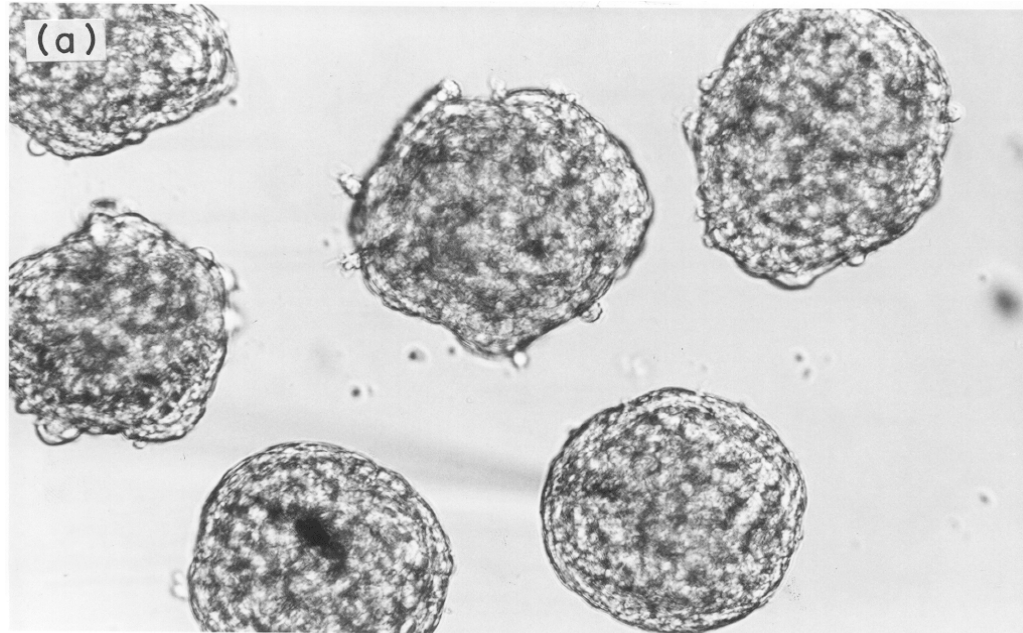
WE DO NOT KNOW EXACTLY  
WHAT IS HAPPENING IN THE  
HEART DURING THESE  
ARRHYTHMIAS



# Physiological properties of **real** heart cells

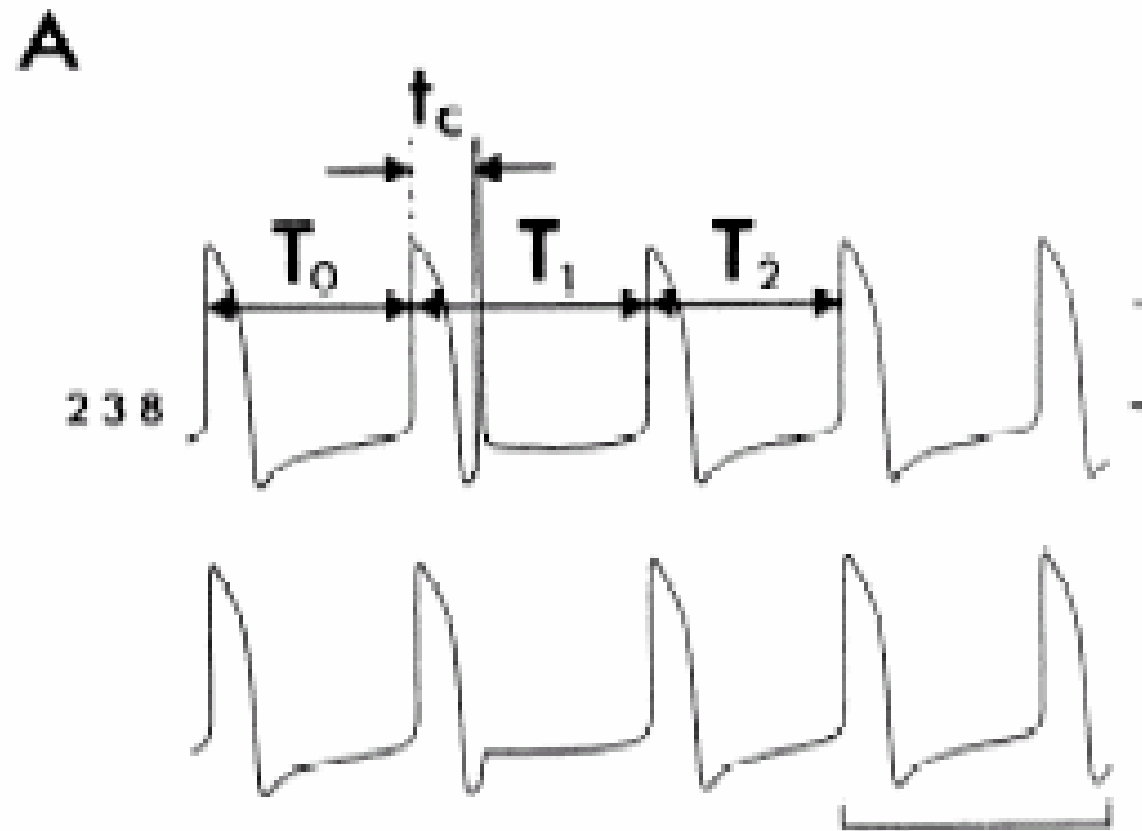
- Excitable
- Refractory time (depends on the history)
- Oscillatory (can be reset and entrained)
- Fatigue (less excitable following rapid stimulation – overdrive suppression)
- Heterogeneous

# Model System – Embryonic chick heart tissue culture

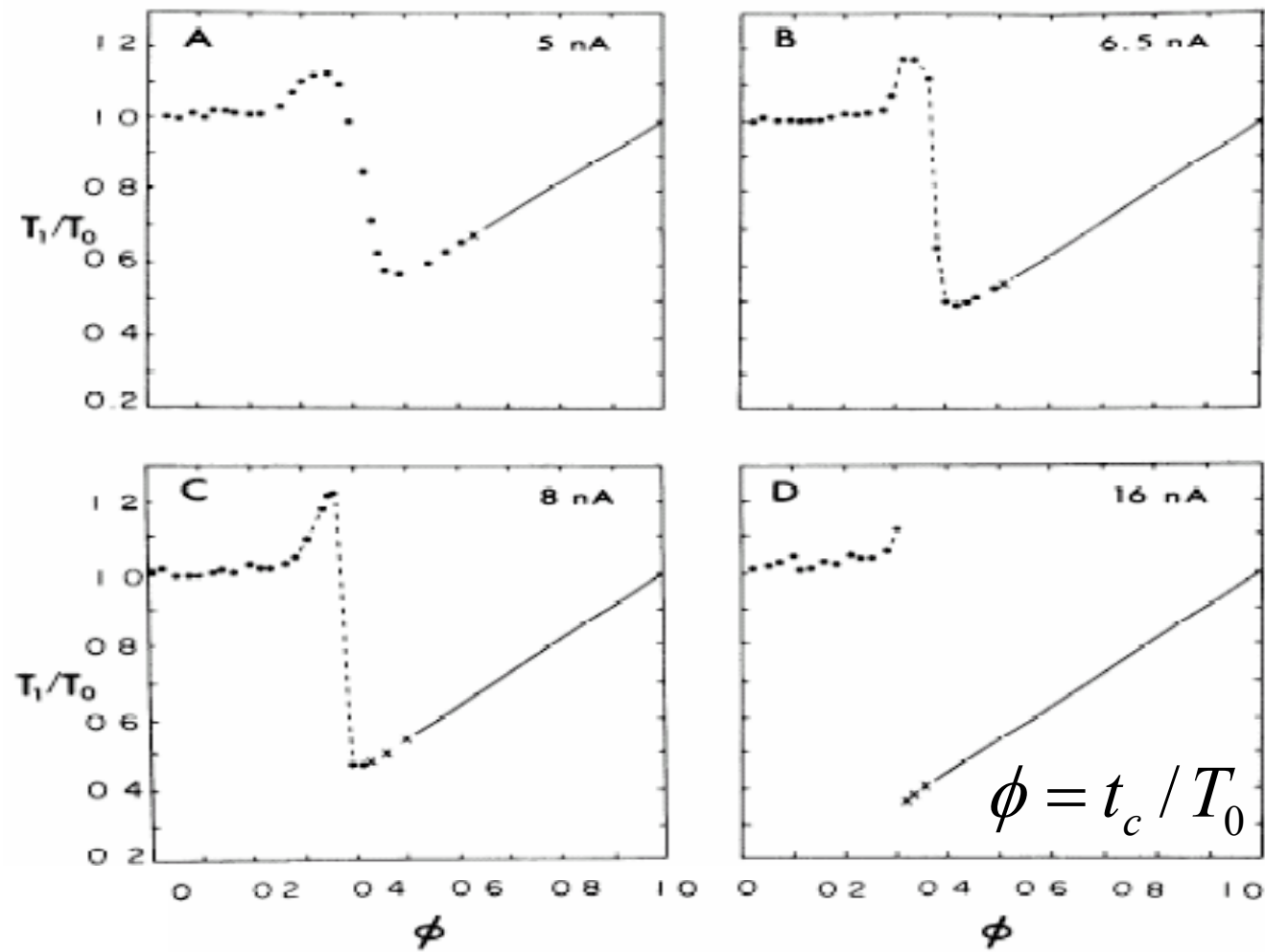


Thanks to Alvin Shrier my colleague and collaborator for over 20 years.

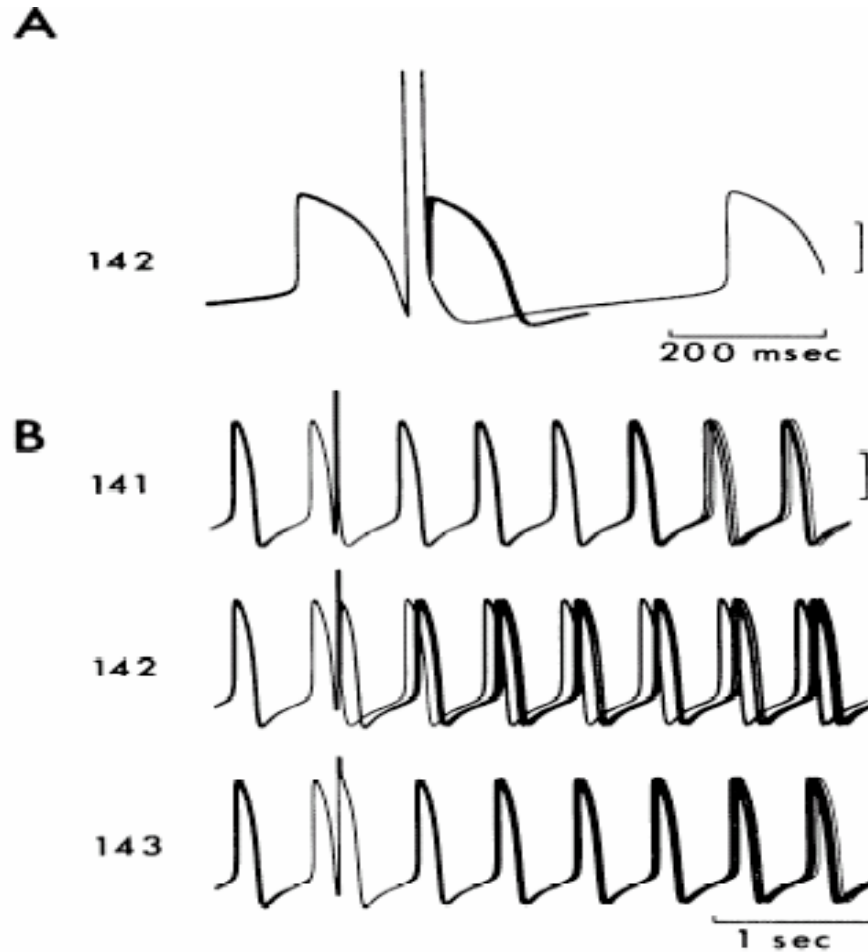
# A Resetting Experiment



# Perturbed Cycle Length Curves

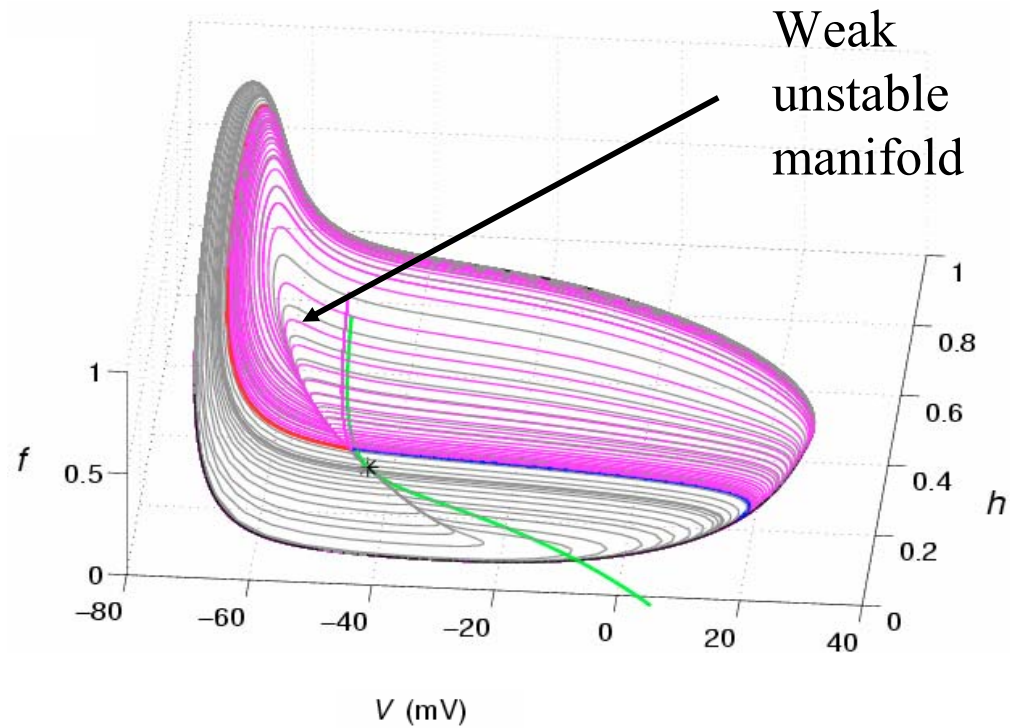


# Puzzle: How can there be discontinuous resetting?

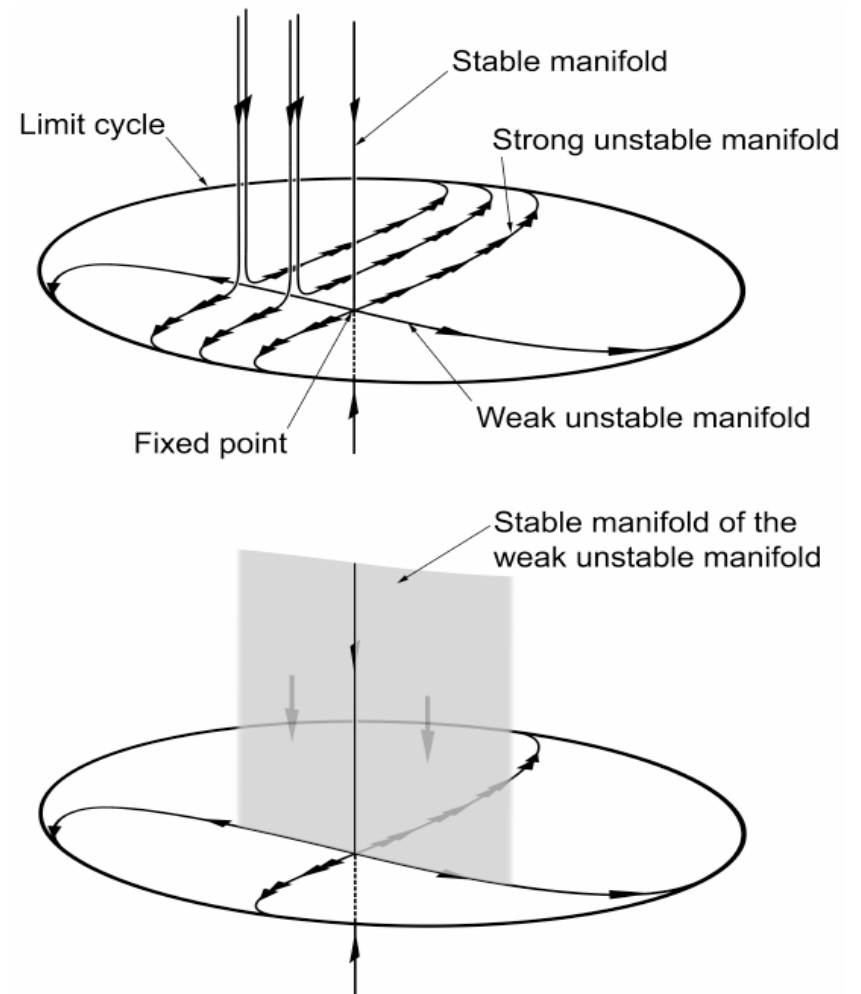


Guevara, Shrier, Glass (1986)

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

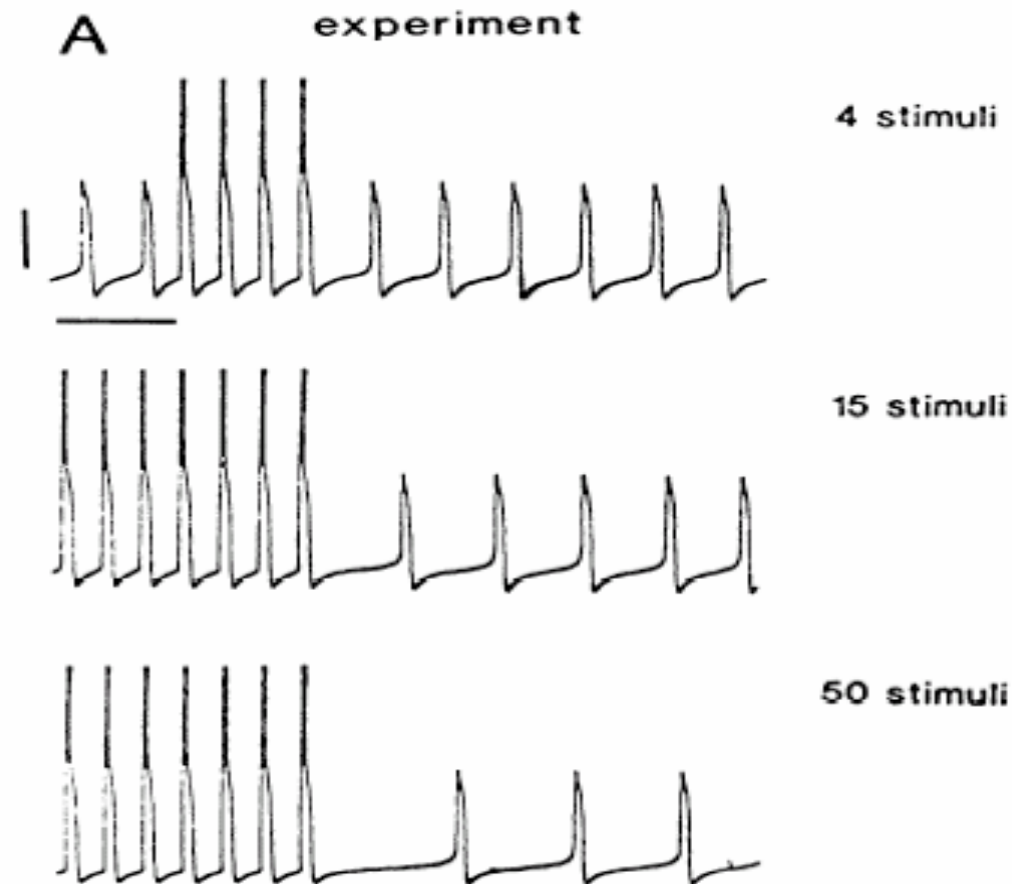


the stochastic opening of a single channel can lead to either an immediate action potential or a delayed action potential.



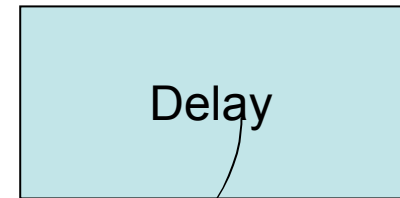
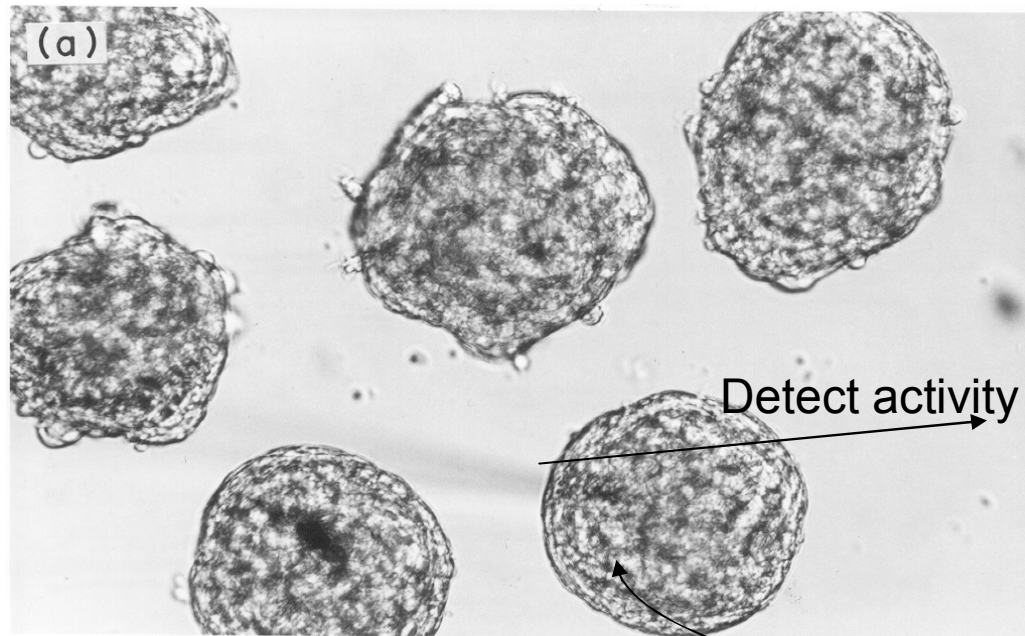
Krogh-Madsen, Glass, Doedel, Guevara (2004)

# Rapid Stimulation Leads to a Slower Rhythm (Overdrive Suppression)



(Kunysz, Glass, Shrier 1995)

# Fixed Delay Stimulation

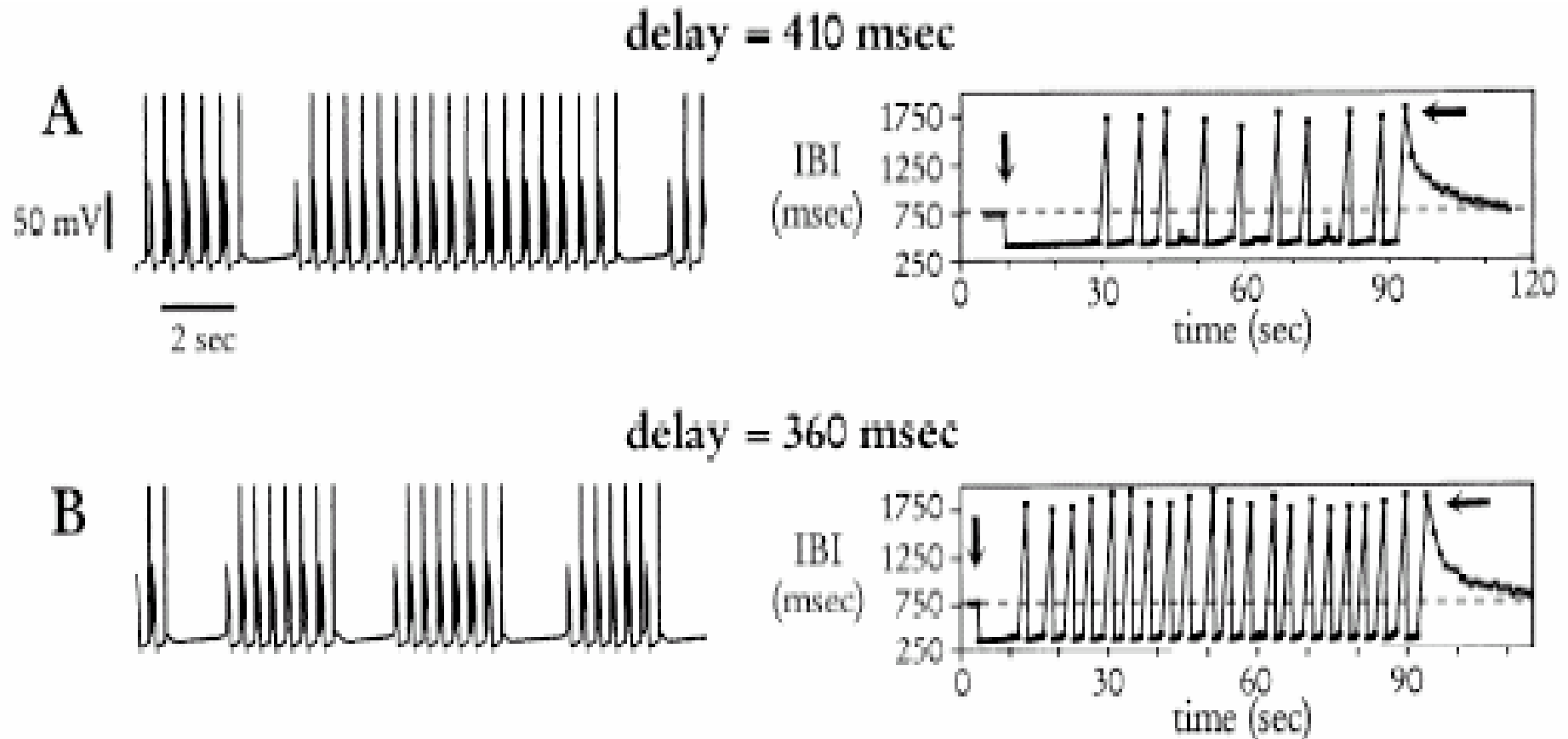


Stimulate after fixed delay

An arrow originates from the bottom of the "Delay" box and points back to the cell in the micrograph, indicating the timing of the stimulation.

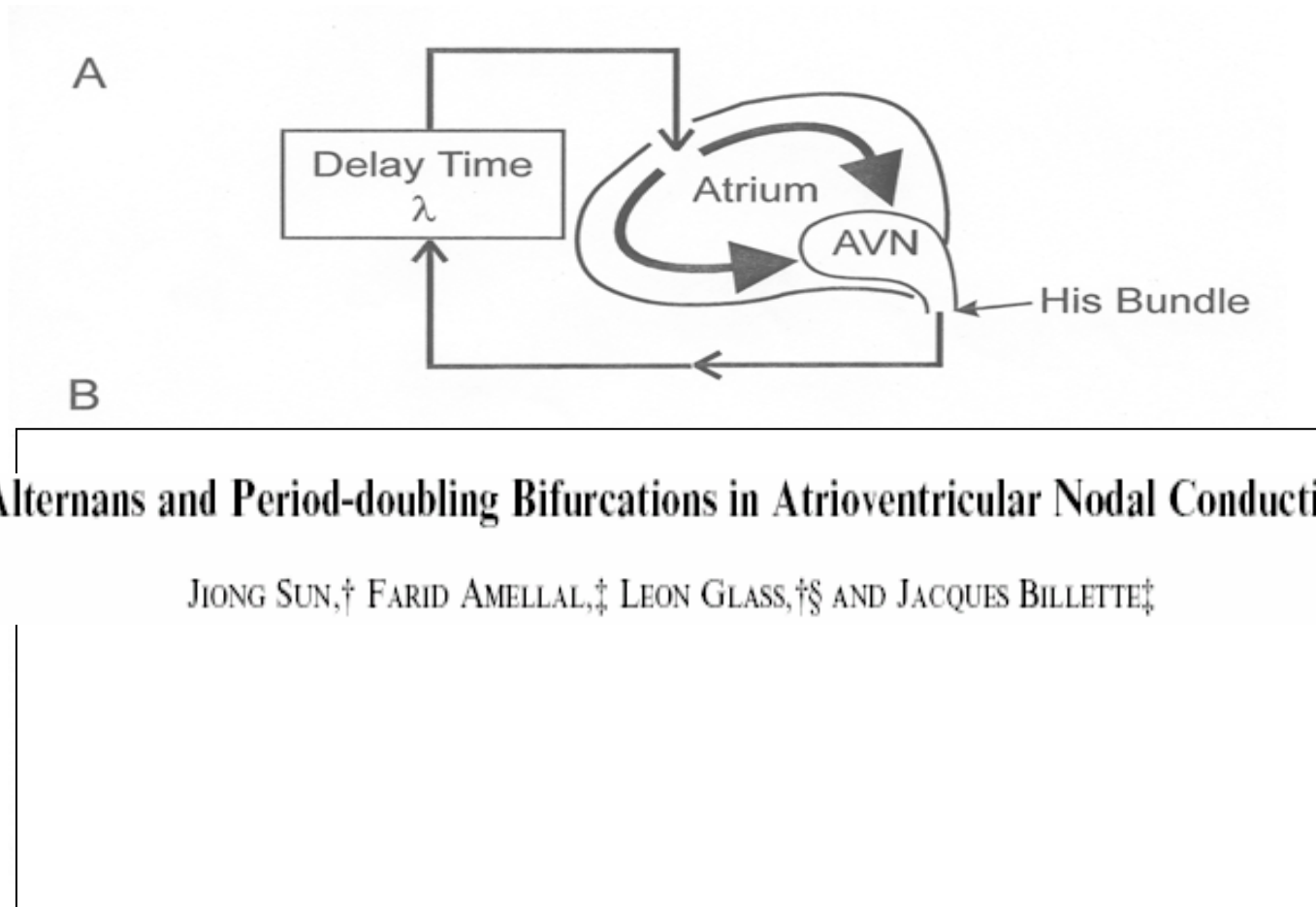


# Fixed Delay Stimulation of Cardiac Aggregates Leads to Bursting

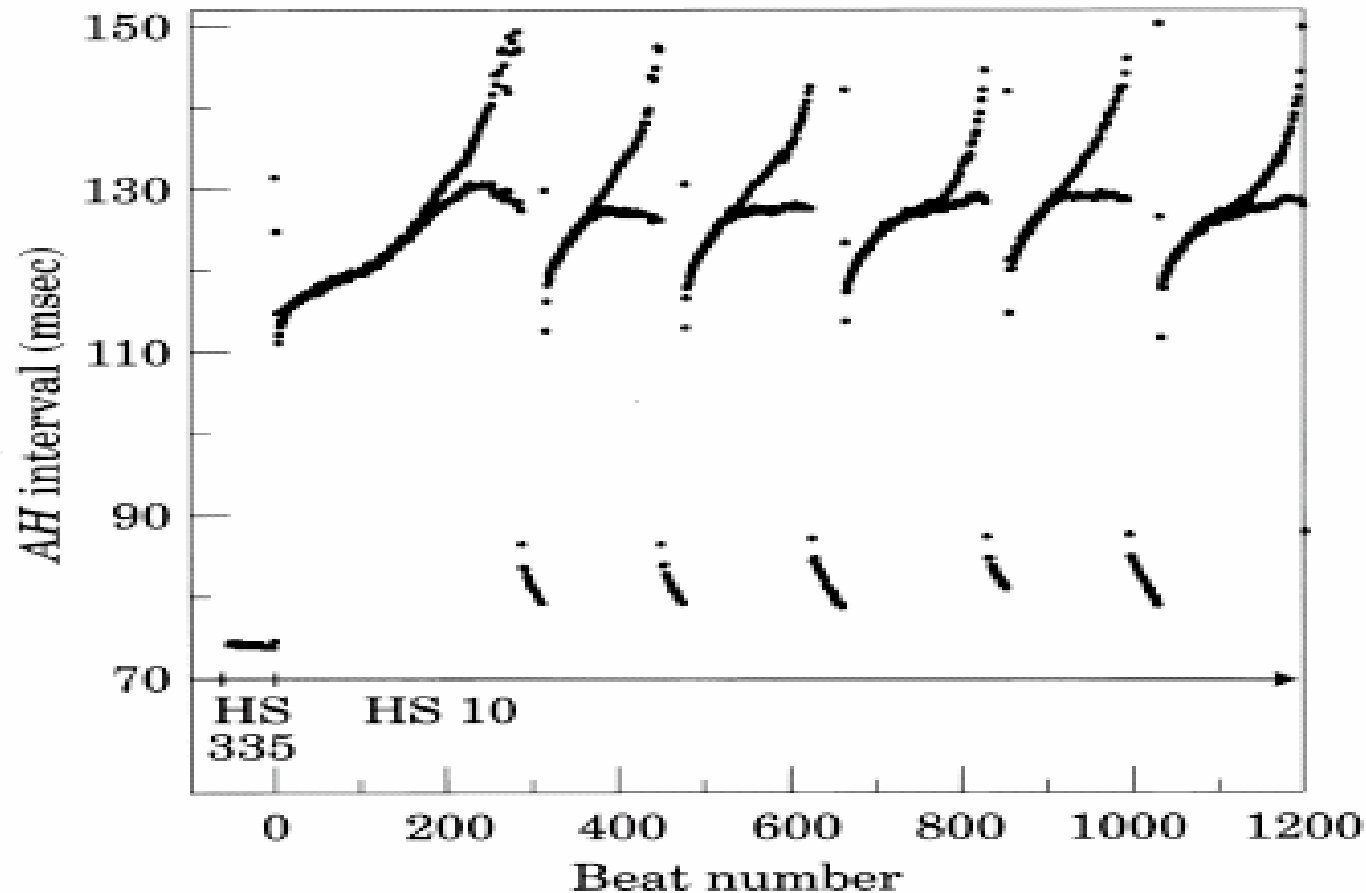


...  
(Kunysz, Shrier, Glass 1997)

# Cardiac Alternans in a Rabbit Heart in Vitro (1995)

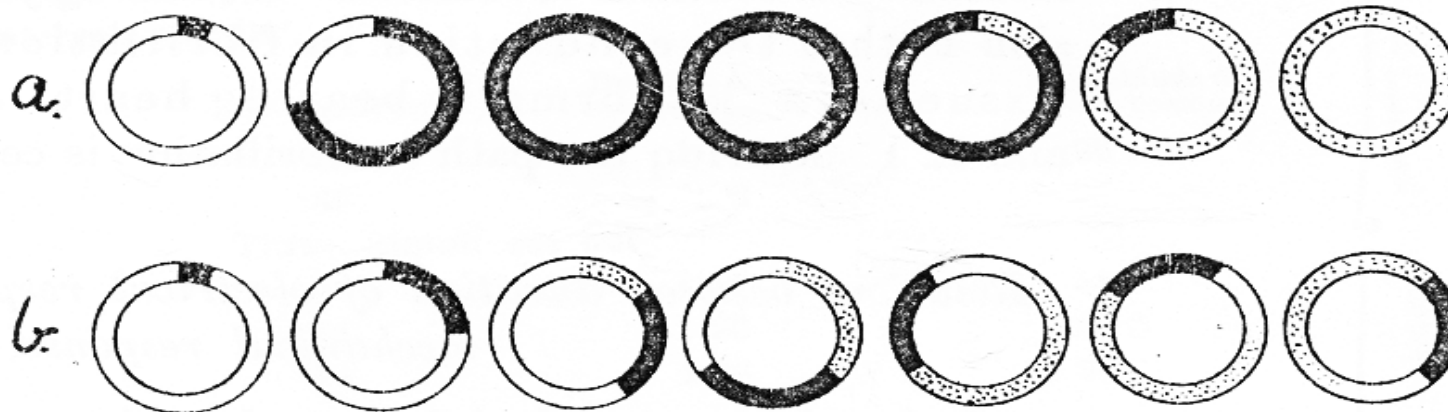
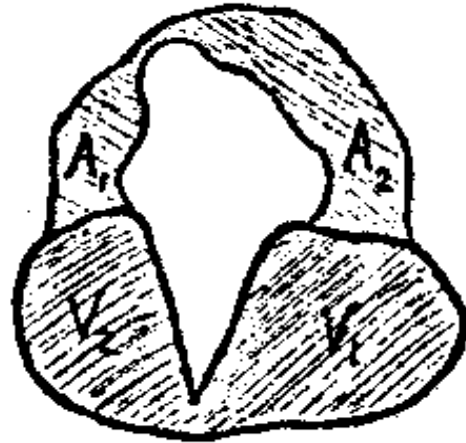


# Bursting rhythms in reentrant rabbit preparation (1995)



(Model of tachycardia in WPW patients)

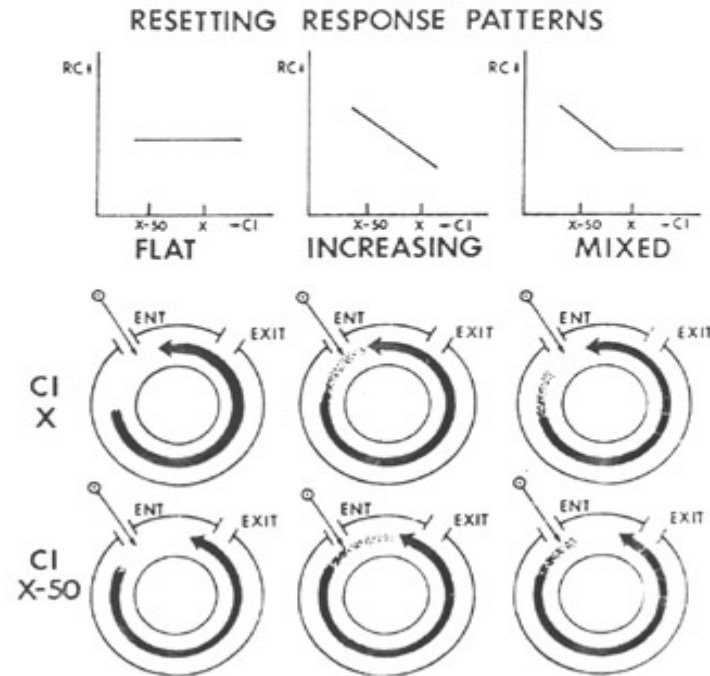
# Anatomical Reentry



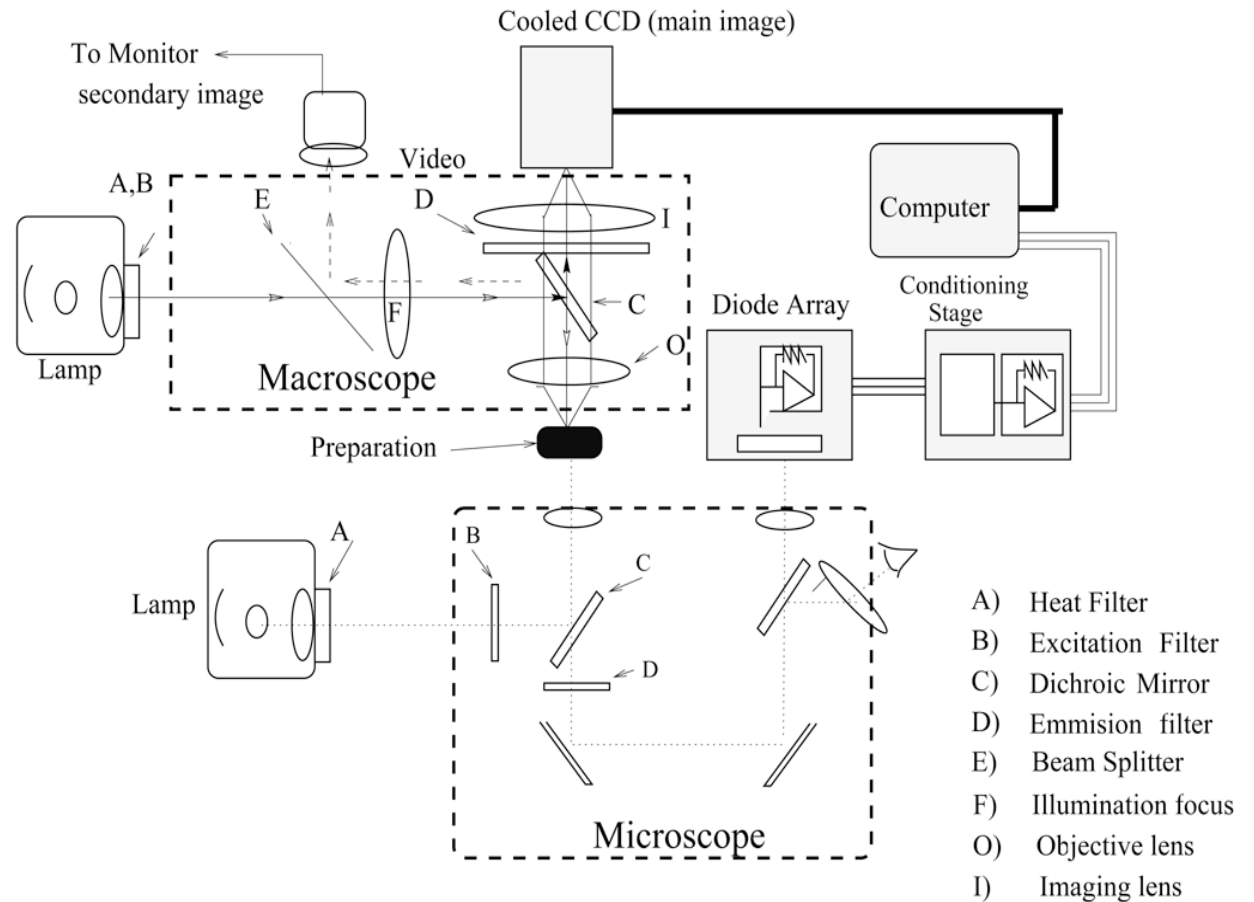
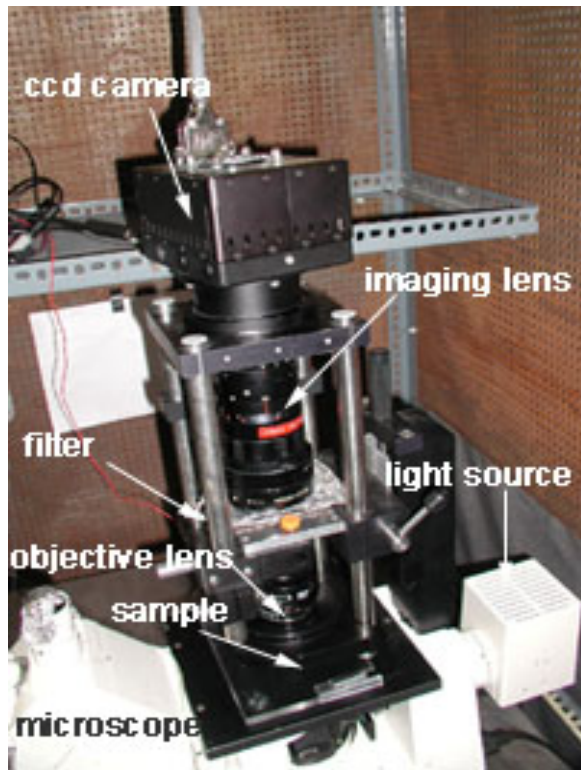
G. R. Mines (1913)

# 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



# Macroscopic for studying dynamics in tissue culture (Gil Bub, Alvin Shrier, Yoshihiko Nagai, Katsumi Tateno)



## Cell Culture

Incubate 30 White Leghorn eggs for 7 days.

Isolate ventricles.

Dissociate with DNase and trypsin.

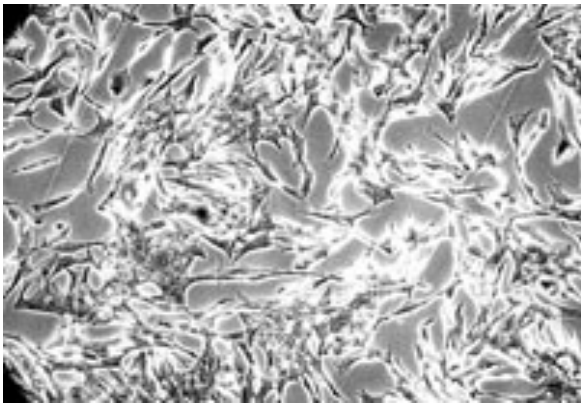
Add inactivating medium and filter.

Centrifuge and resuspend in maintenance media.

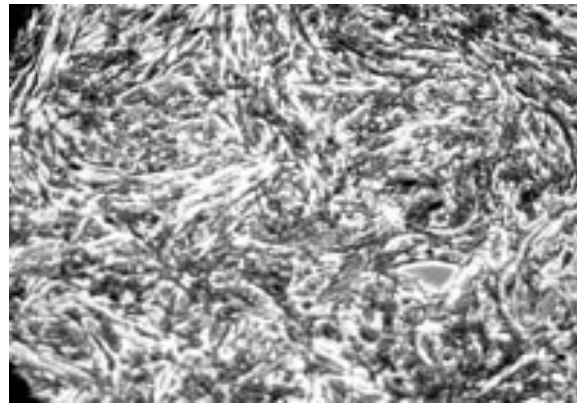
Plate at various densities.

Incubate for 1-2 days.

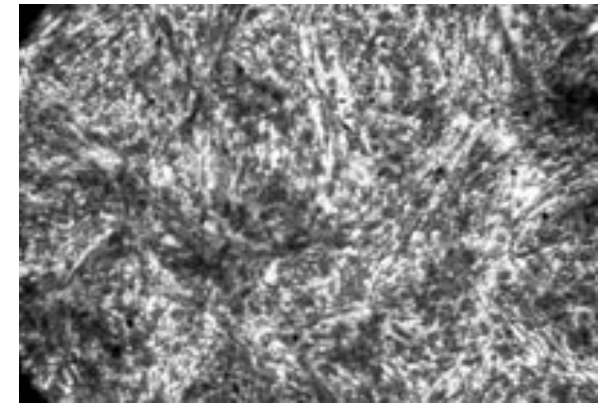
Load with dye, perform experiment.



$0.5 \times 10^3 / \text{cm}^2$

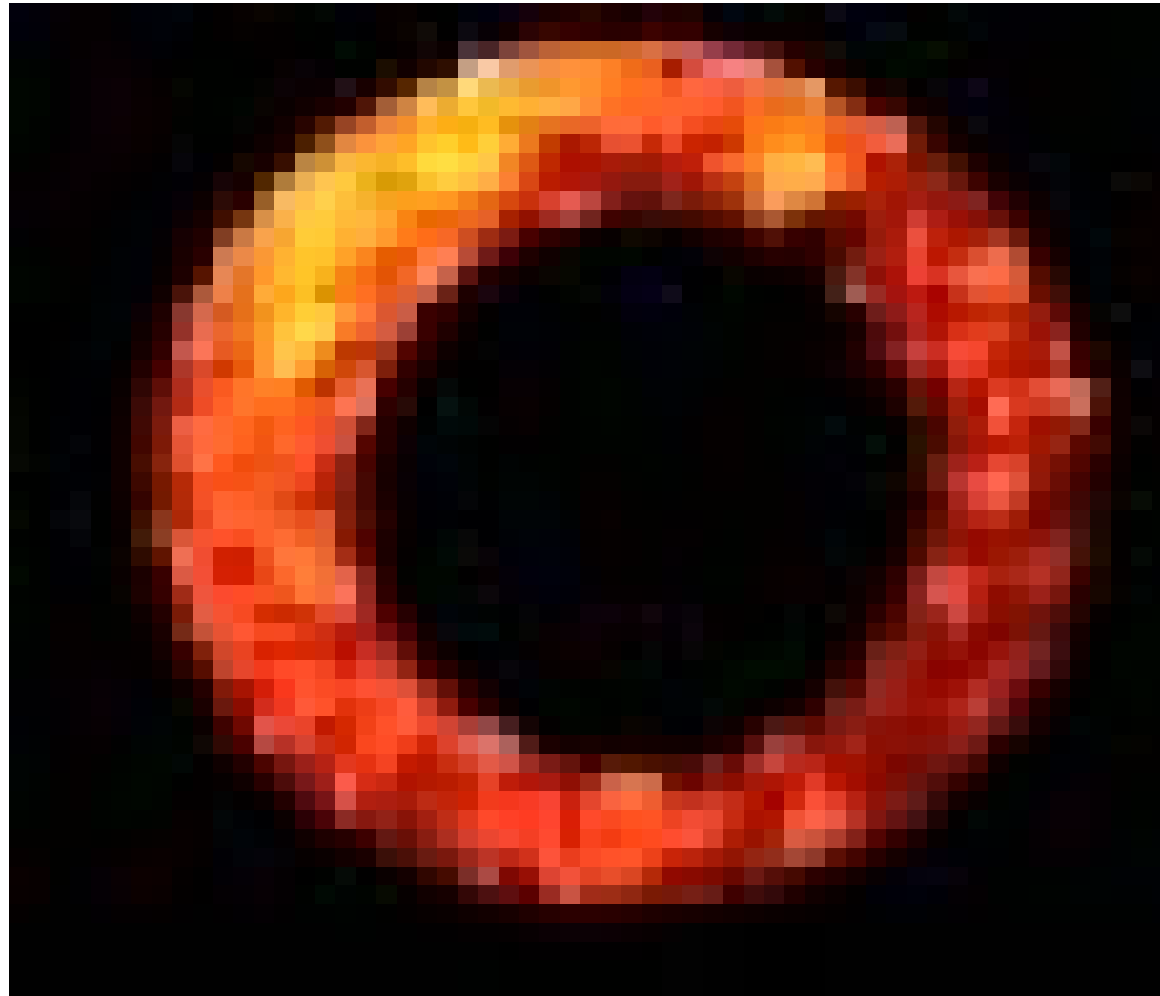


$1.0 \times 10^3 / \text{cm}^2$



$2.0 \times 10^3 / \text{cm}^2$

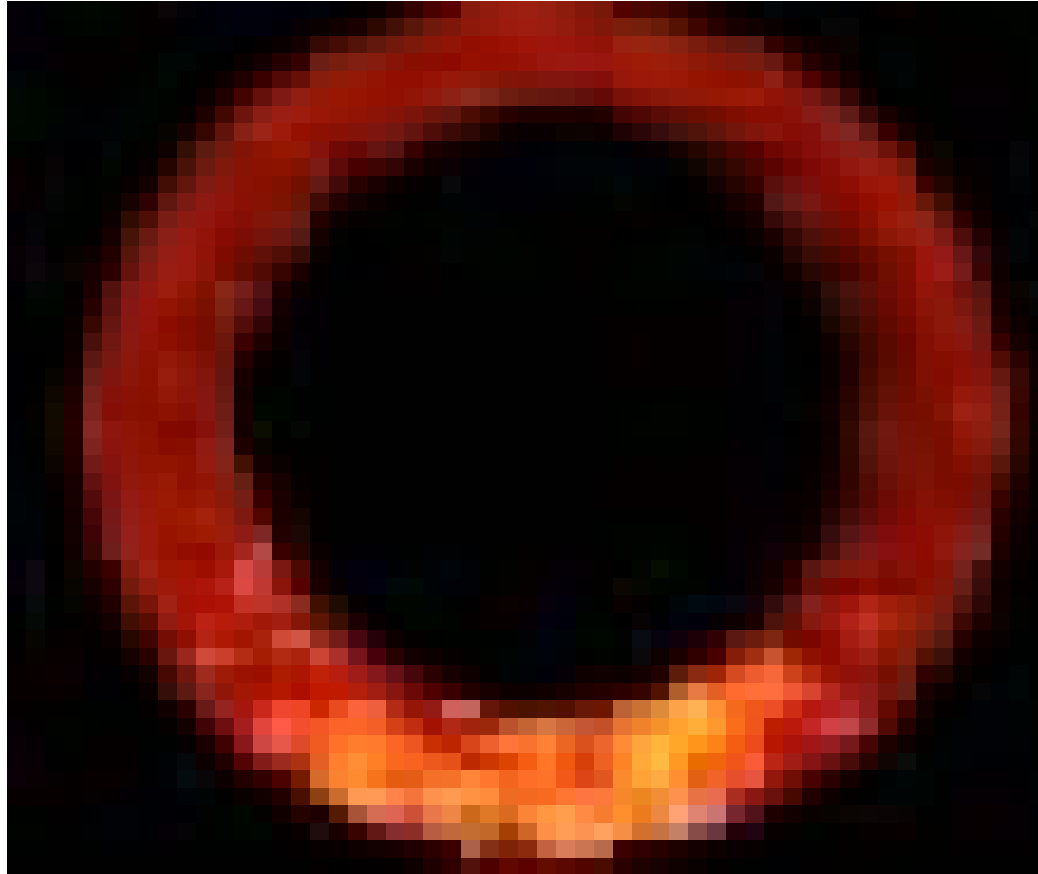
# Dynamics in a Ring of Cardiac Cells



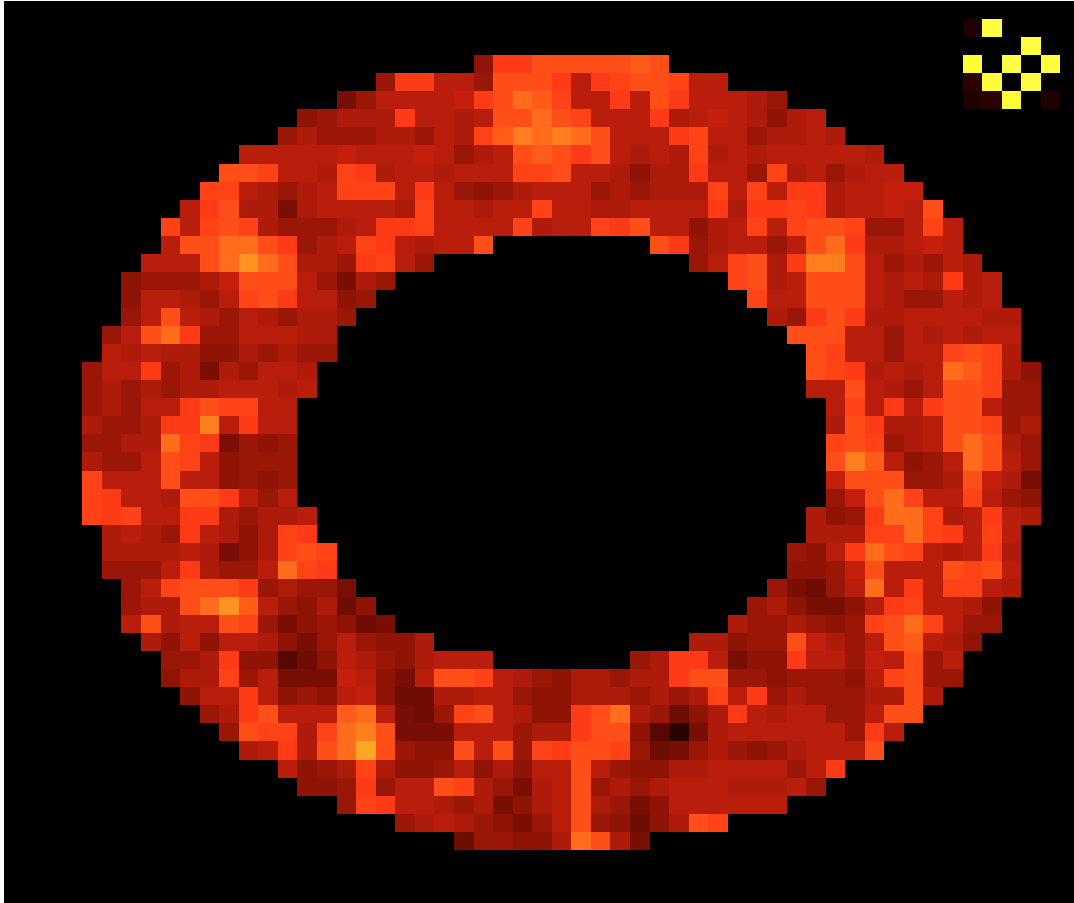
**Pacemaker**

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





**Reentry**



Cardiac Ballet

# FitzHugh-Nagumo Model of Propagation

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

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

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

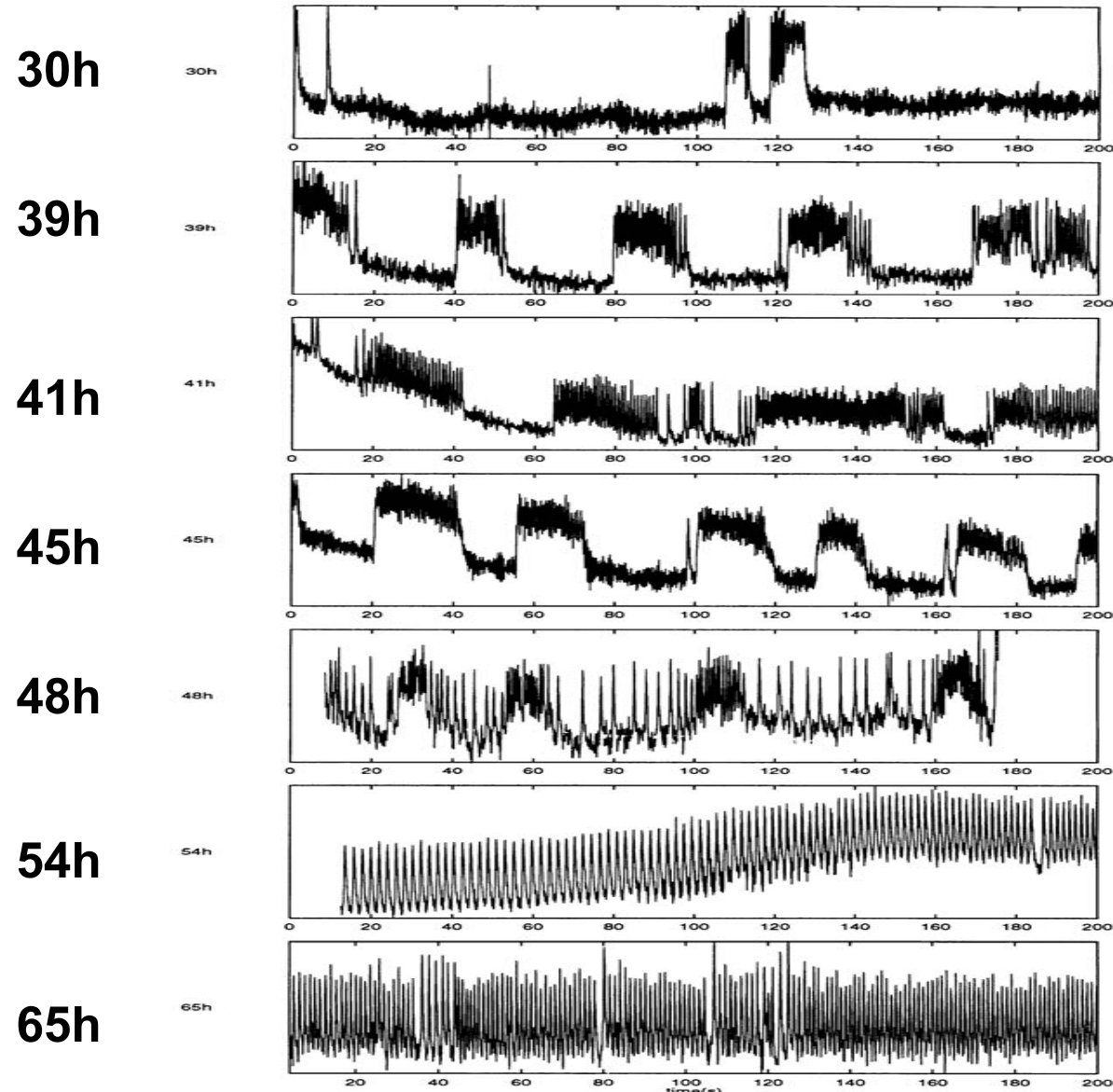
$$\zeta(z) = \frac{.015}{z + 1},$$

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

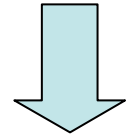


# Dynamic Changes with Time in Culture

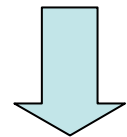
**Time in Culture:**



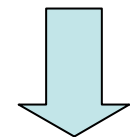
irregular activity



bursting spirals

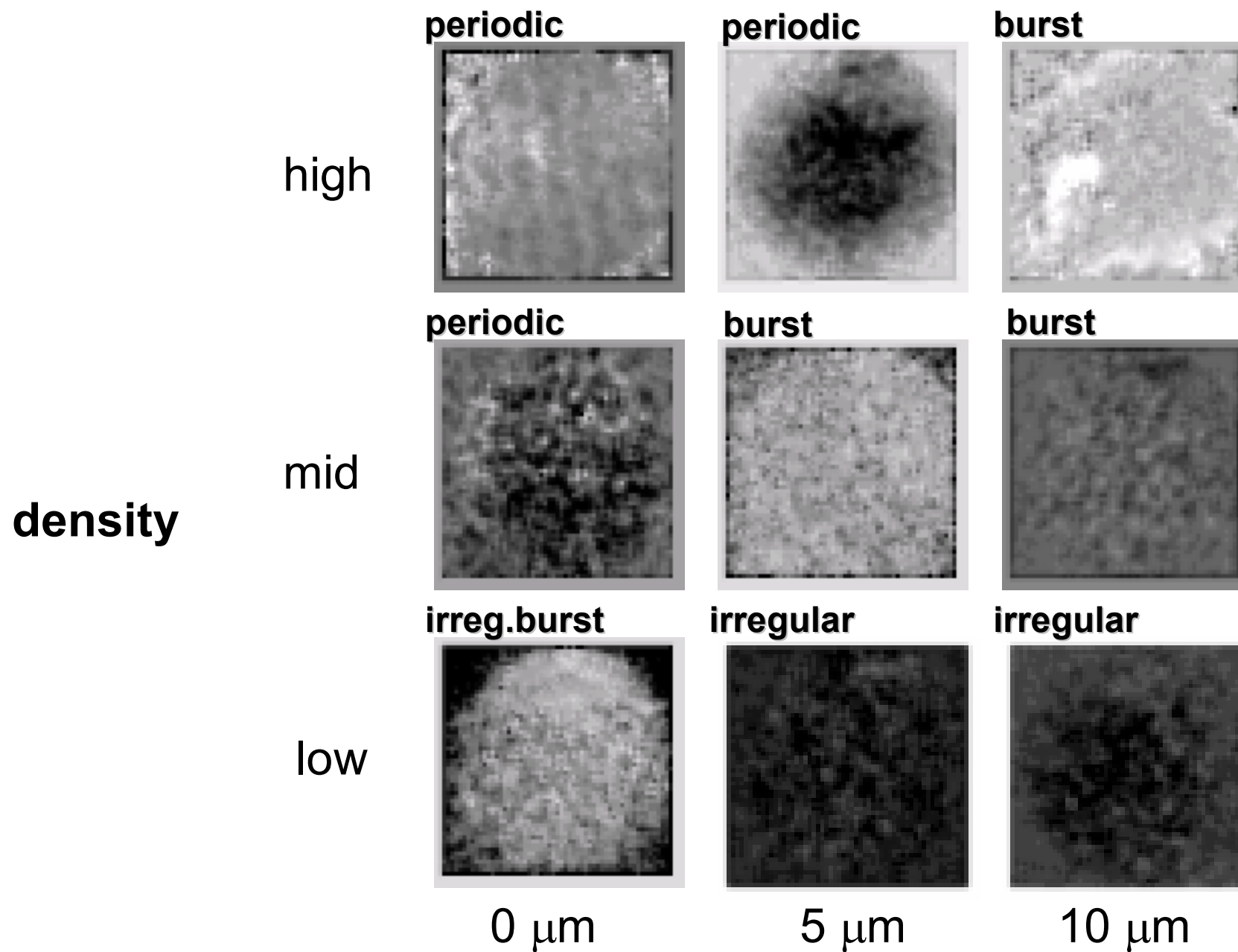


stable spirals



targets

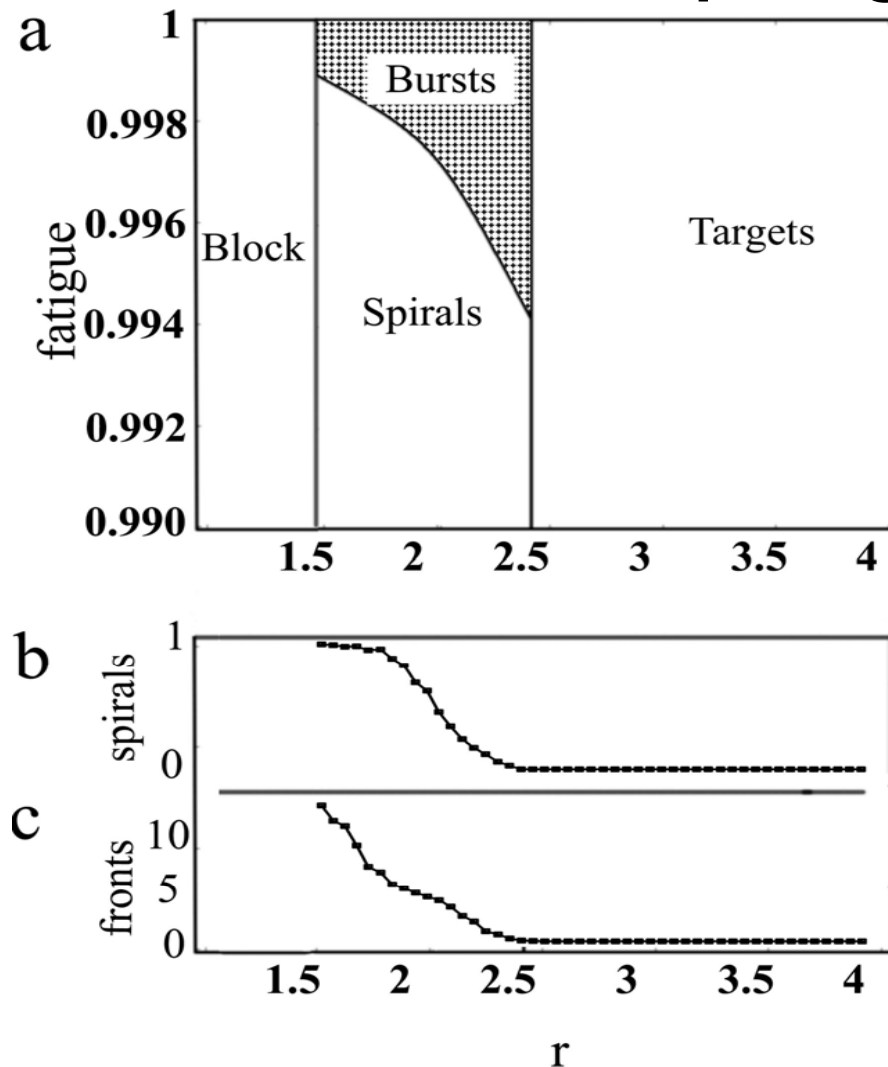
([Bub, Tatenko, Glass, Shrier JCE 2003](#))



(Bub, Glass, Shrier, PRL 2005)

$\alpha$  **glycyrrhetic 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.

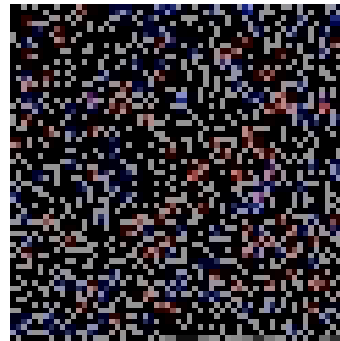
2) Add fatigue by giving each cell a fatigue variable  $\eta$  where

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)

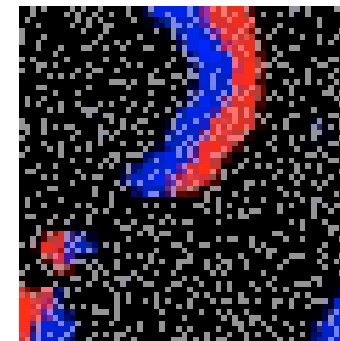
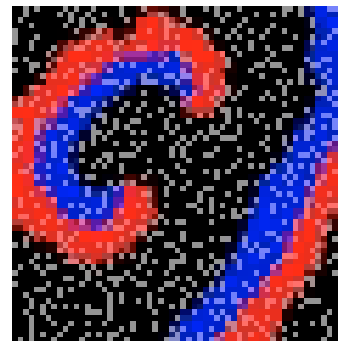
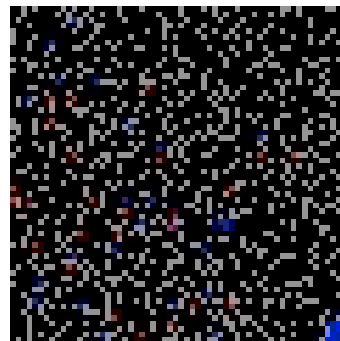
Now a cell is activated if  $\eta_{i,j} + \theta < \text{active/inactive}$

$R=3, \theta=0.35$



Target patterns ('periodic')

$R=1.8, \theta=0.35$



bursting

# One mechanism for paroxysmal rhythms

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

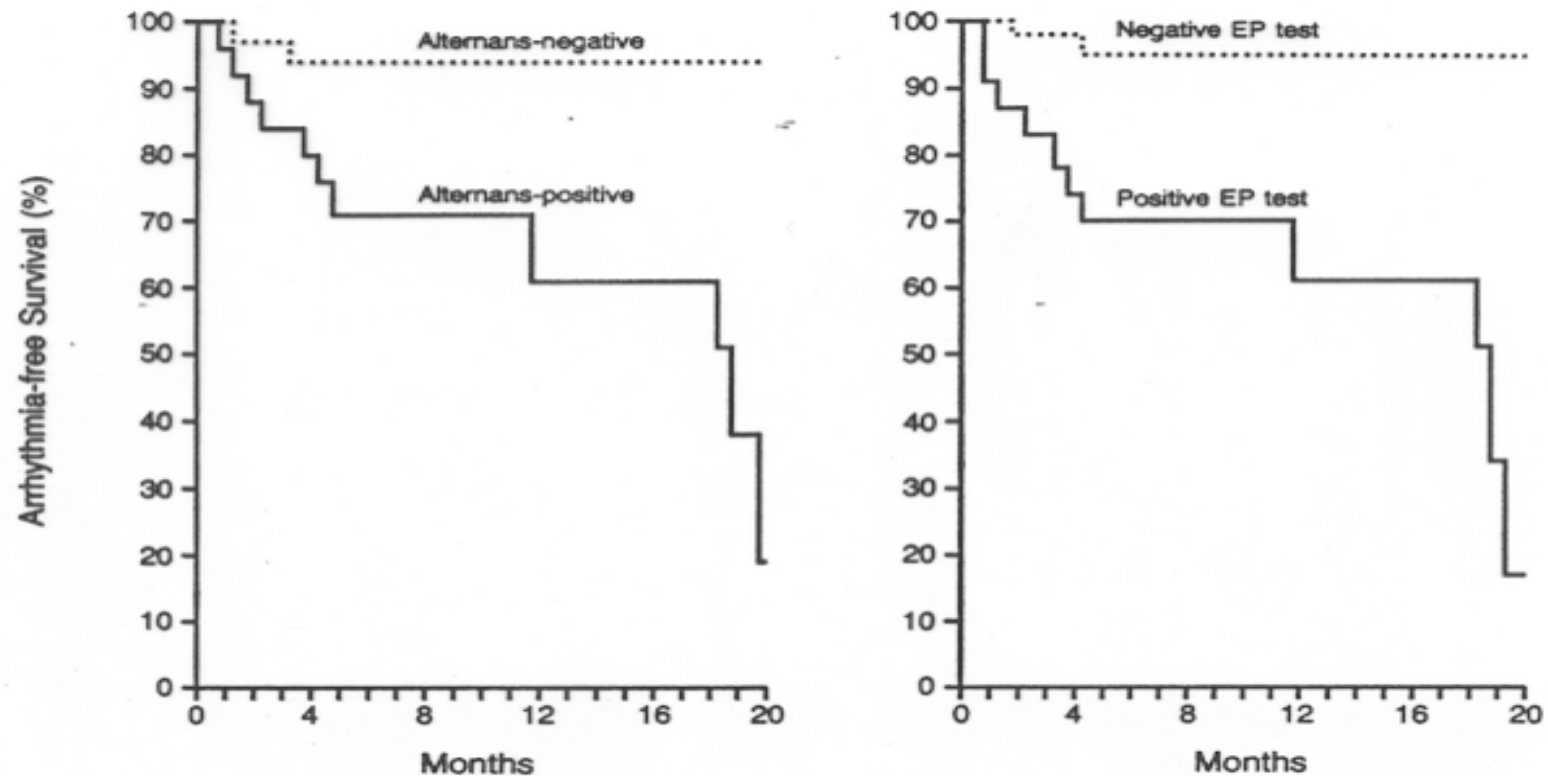


Control: Use quantitative methods to better identify arrhythmia and assess the risk for sudden cardiac death

- Warning: Methods are still controversial

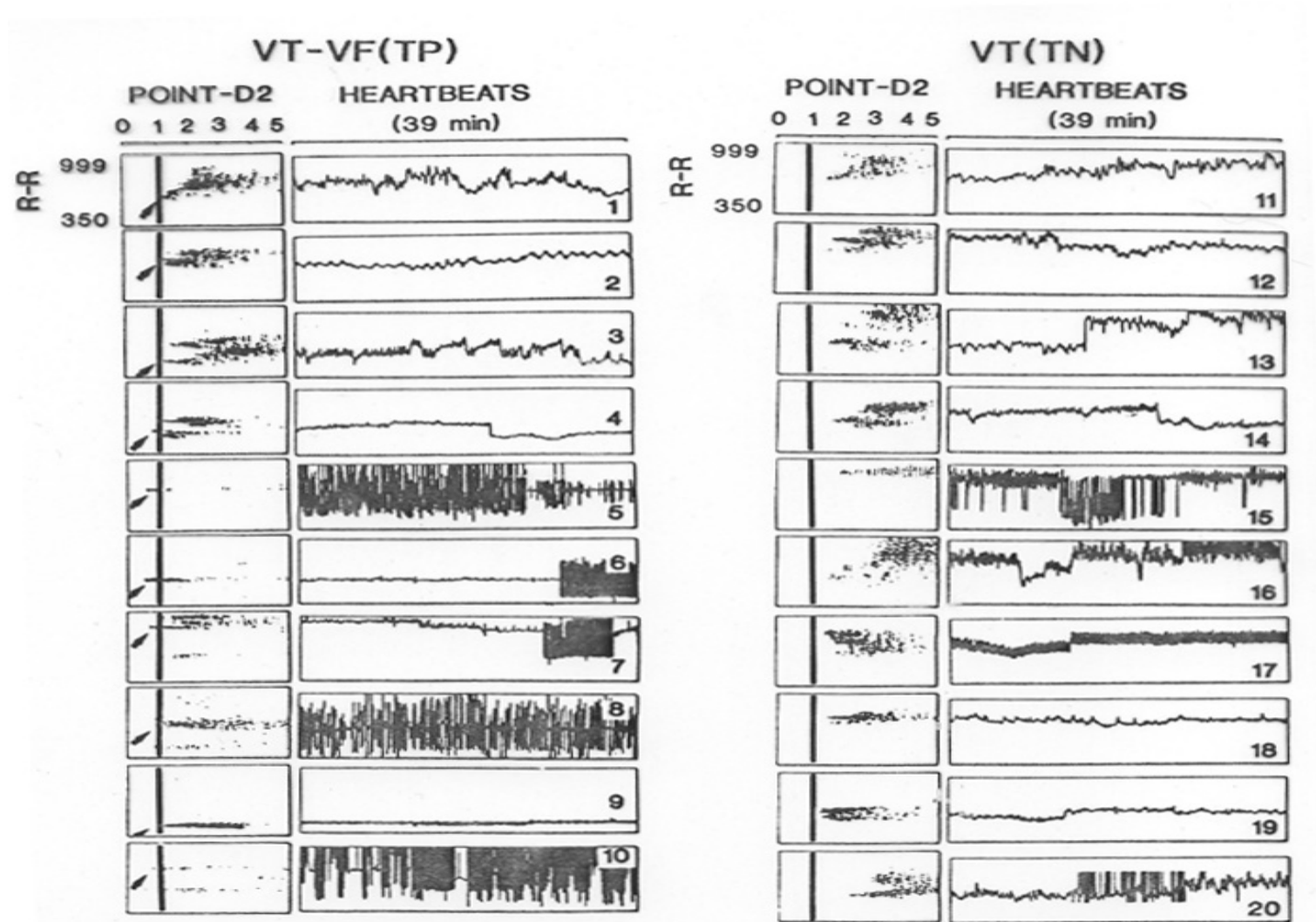


# T-wave Alternans Predicts Arrhythmia



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?

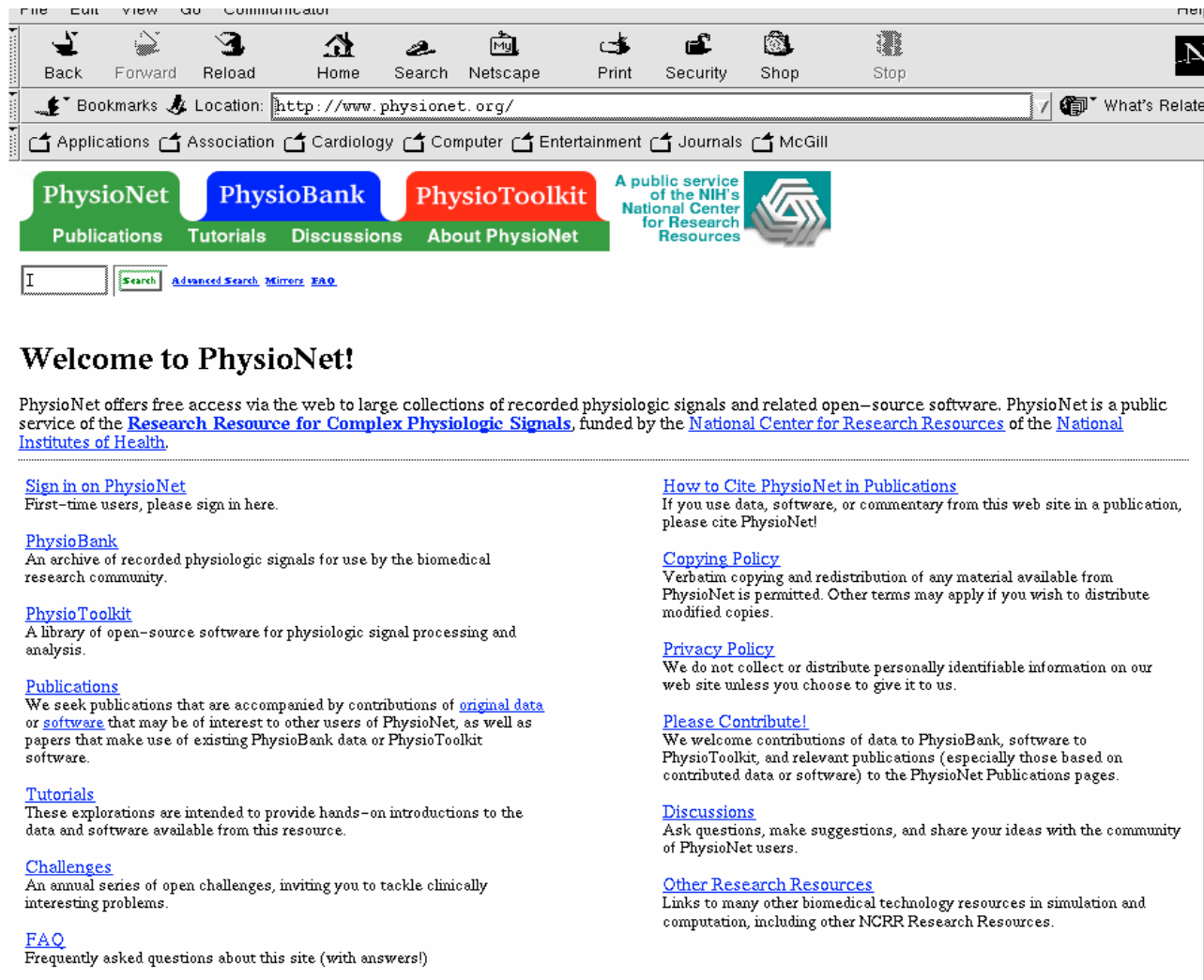
# Point D2 Dimension



Skinner, Pratt, Vybiral (1993)

# National Resource for Complex Physiologic Signals

## A. Goldberger, Director



The screenshot shows a Netscape browser window displaying the PhysioNet website. The browser's address bar shows the URL <http://www.physionet.org/>. The website header features three main navigation buttons: "PhysioNet" (green), "PhysioBank" (blue), and "PhysioToolkit" (red). Below these are sub-navigation links: "Publications", "Tutorials", "Discussions", and "About PhysioNet". A search bar is located below the navigation buttons, with a "Search" button and links to "Advanced Search", "Mirrors", and "FAQ". The main content area is titled "Welcome to PhysioNet!" and contains several sections of text and links. The left column includes links for "Sign in on PhysioNet", "PhysioBank", "PhysioToolkit", "Publications", "Tutorials", "Challenges", and "FAQ". The right column includes links for "How to Cite PhysioNet in Publications", "Copying Policy", "Privacy Policy", "Please Contribute!", "Discussions", and "Other Research Resources".

**Welcome to PhysioNet!**

PhysioNet offers free access via the web to large collections of recorded physiologic signals and related open-source software. PhysioNet is a public service of the [Research Resource for Complex Physiologic Signals](#), funded by the [National Center for Research Resources](#) of the [National Institutes of Health](#).

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These explorations are intended to provide hands-on introductions to the data and software available from this resource.

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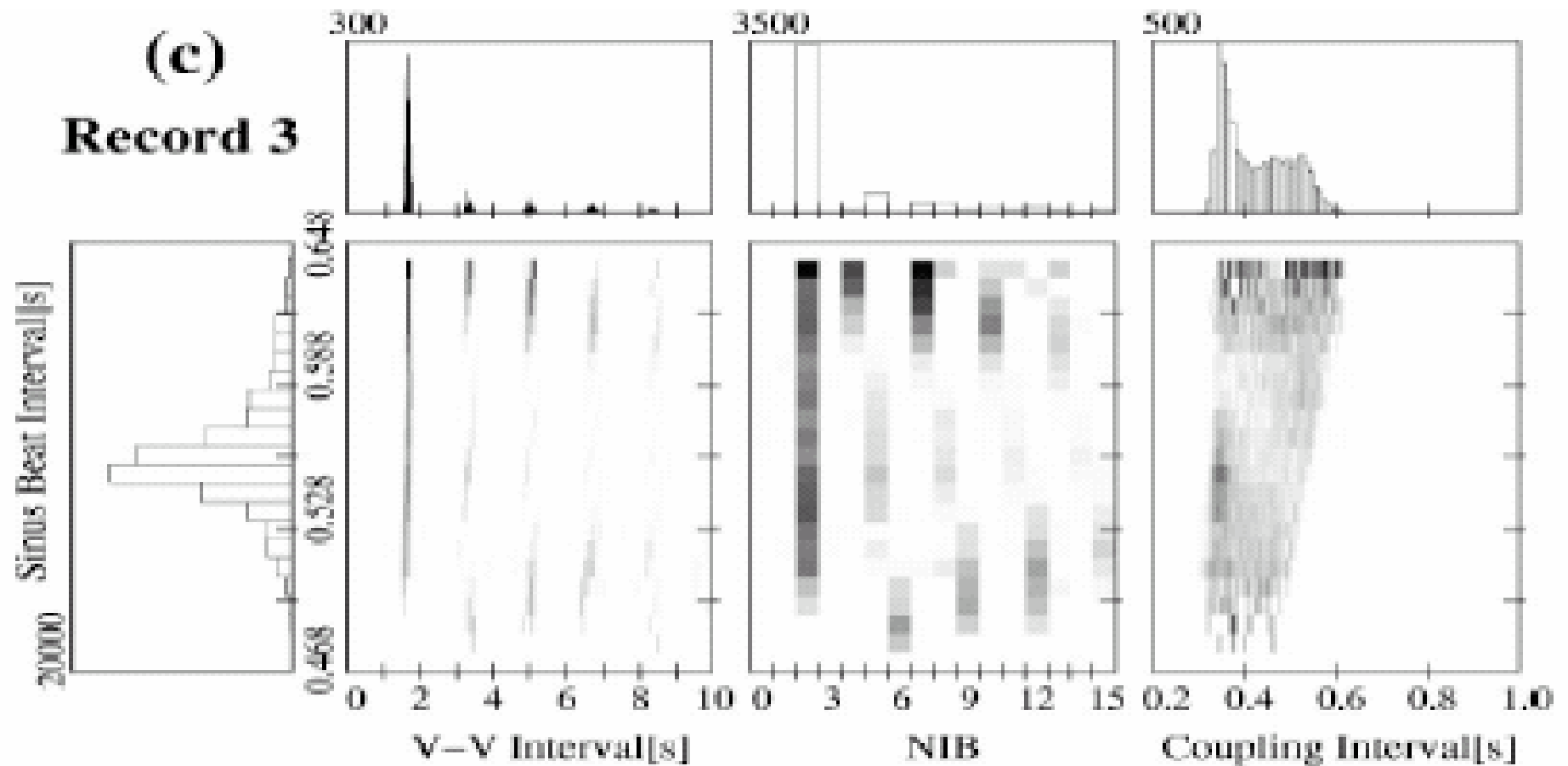
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Ask questions, make suggestions, and share your ideas with the community of PhysioNet users.

[Other Research Resources](#)  
Links to many other biomedical technology resources in simulation and computation, including other NCRR Research Resources.

<http://www.physionet.org>

# Heartprint of a Patient

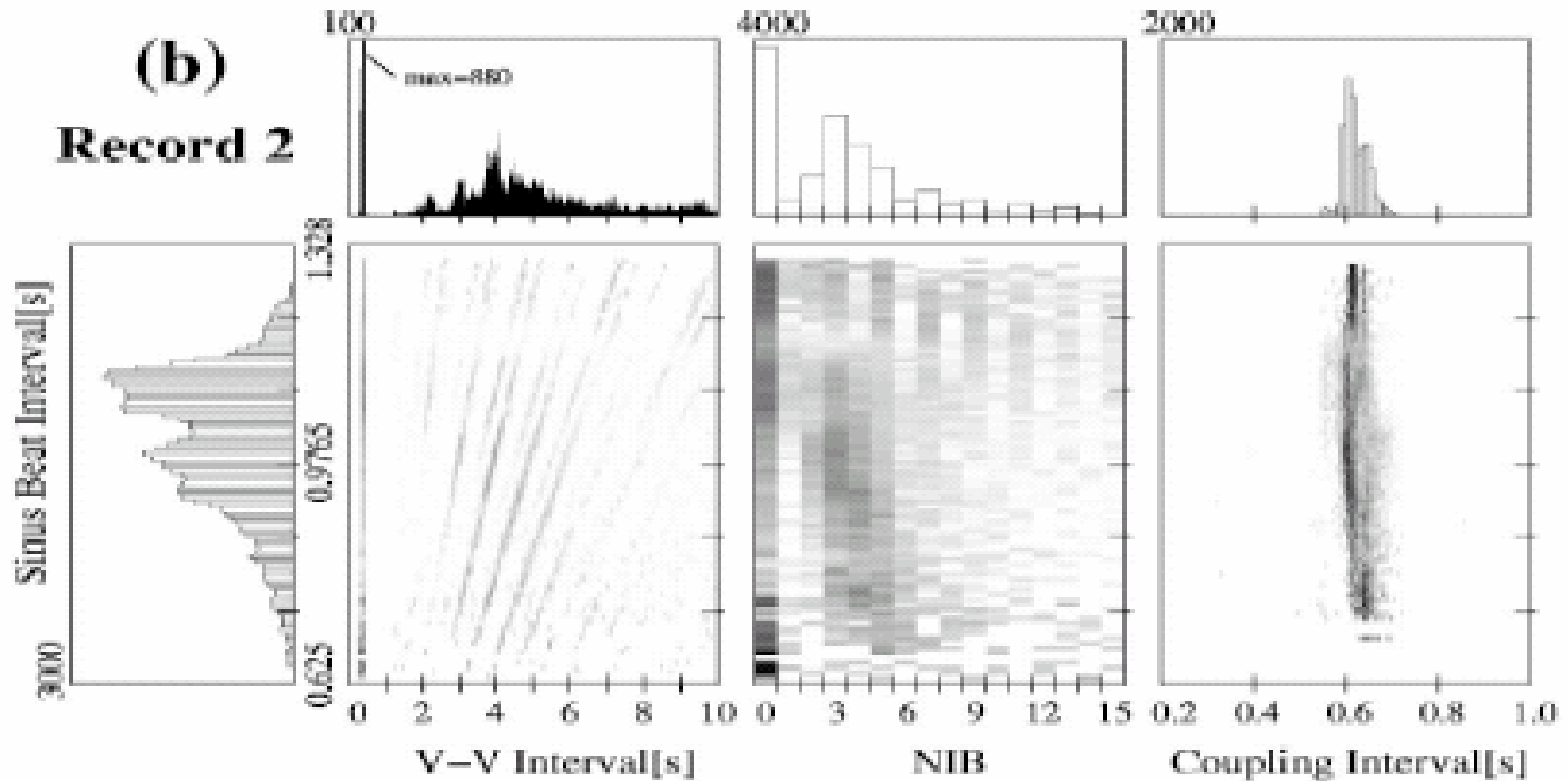


PHYSICAL REVIEW E 66, 031901 (2002)

## Complex patterns of abnormal heartbeats

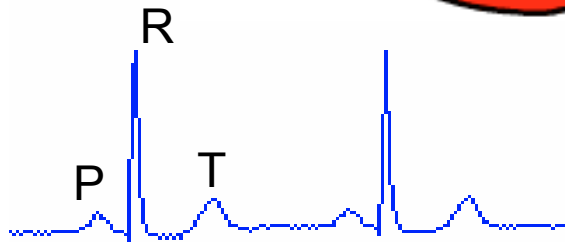
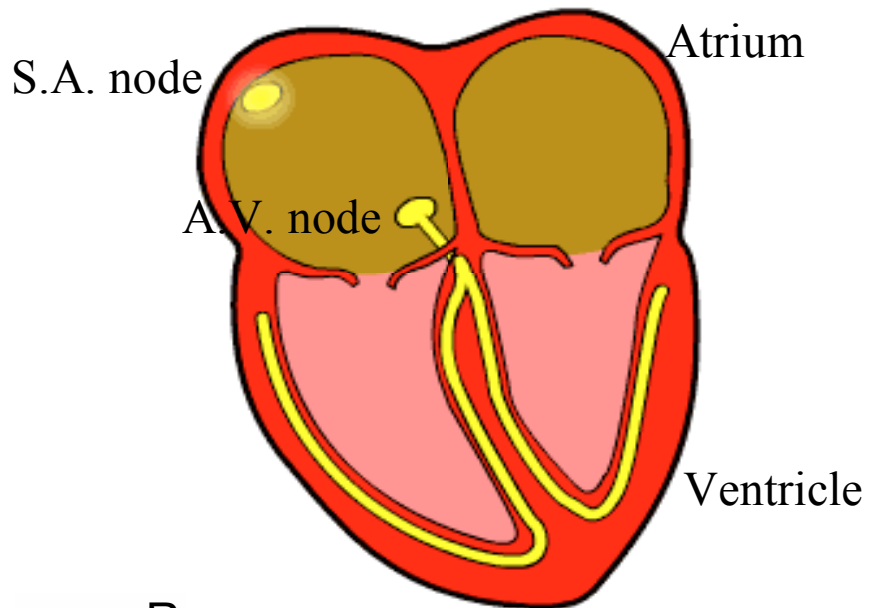
Verena Schulte-Frohlinde,<sup>1,2,\*</sup> Yosef Ashkenazy,<sup>1,3</sup> Ary L. Goldberger,<sup>2</sup> Plamen Ch. Ivanov,<sup>1</sup> Madalena Costa,<sup>2</sup>  
Adrian Morley-Davies,<sup>4</sup> H. Eugene Stanley,<sup>1</sup> and Leon Glass<sup>5</sup>

# Heartprint of Another Patient

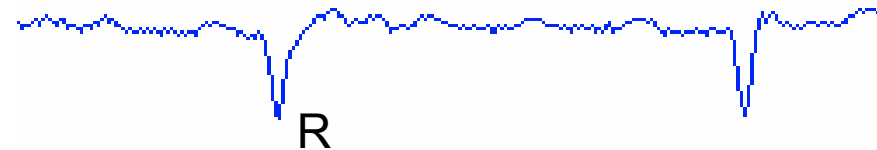


# Can you detect atrial fibrillation based on the RR intervals?

Normal



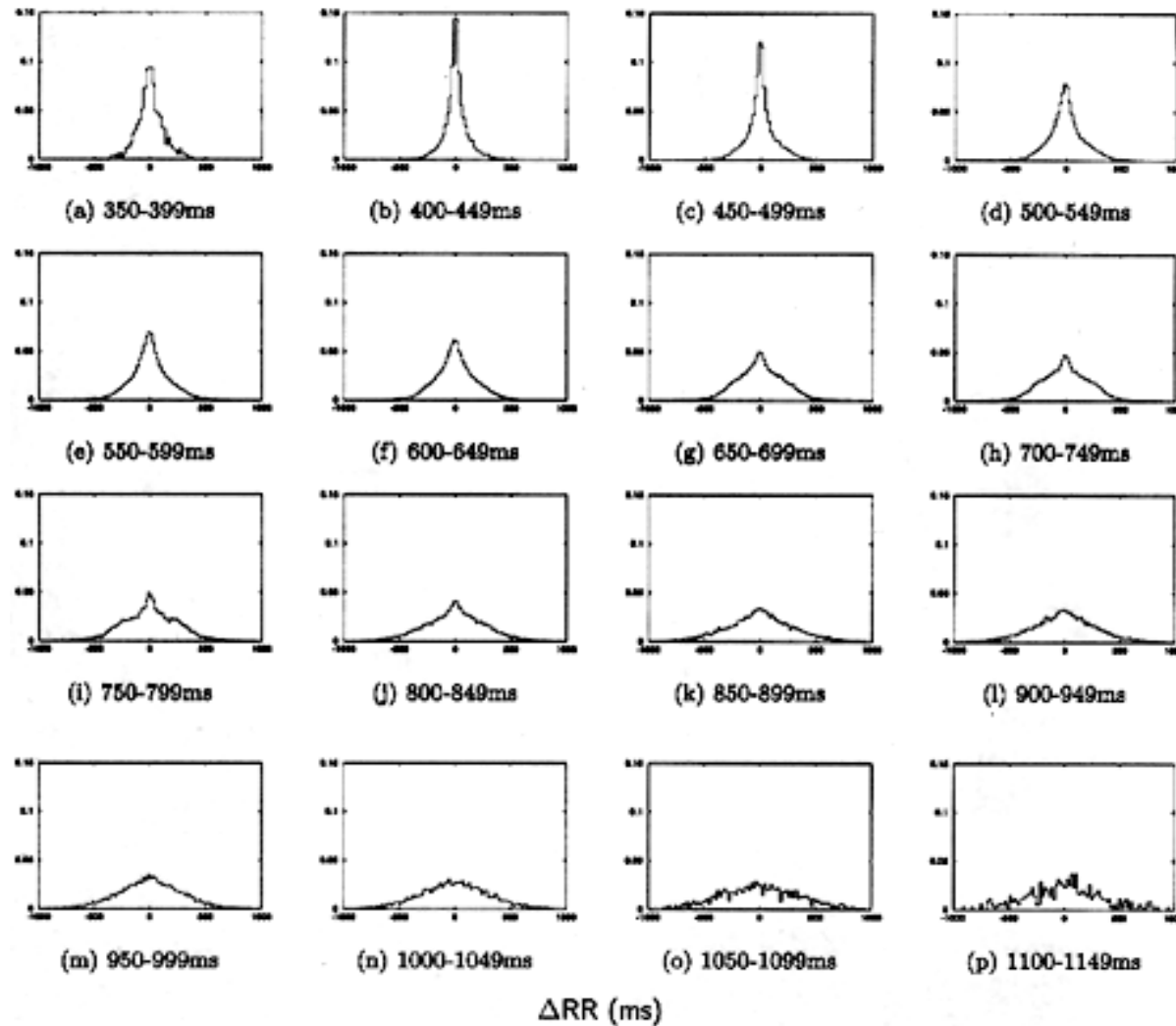
Atrial fibrillation



<http://www.aboutatrialfibrillation.com>

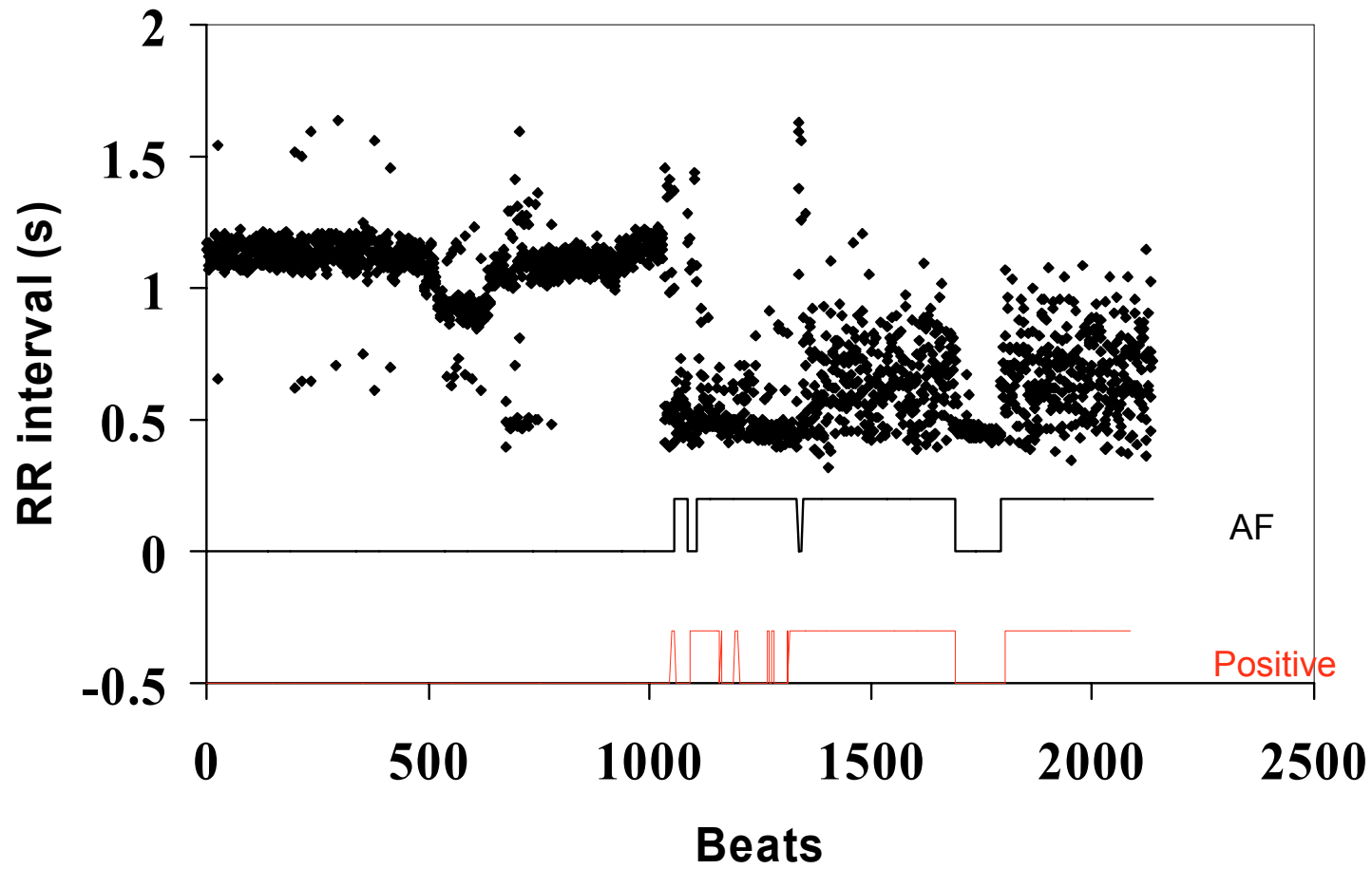


# Use Histograms of $\Delta RR$ Intervals to detect AF

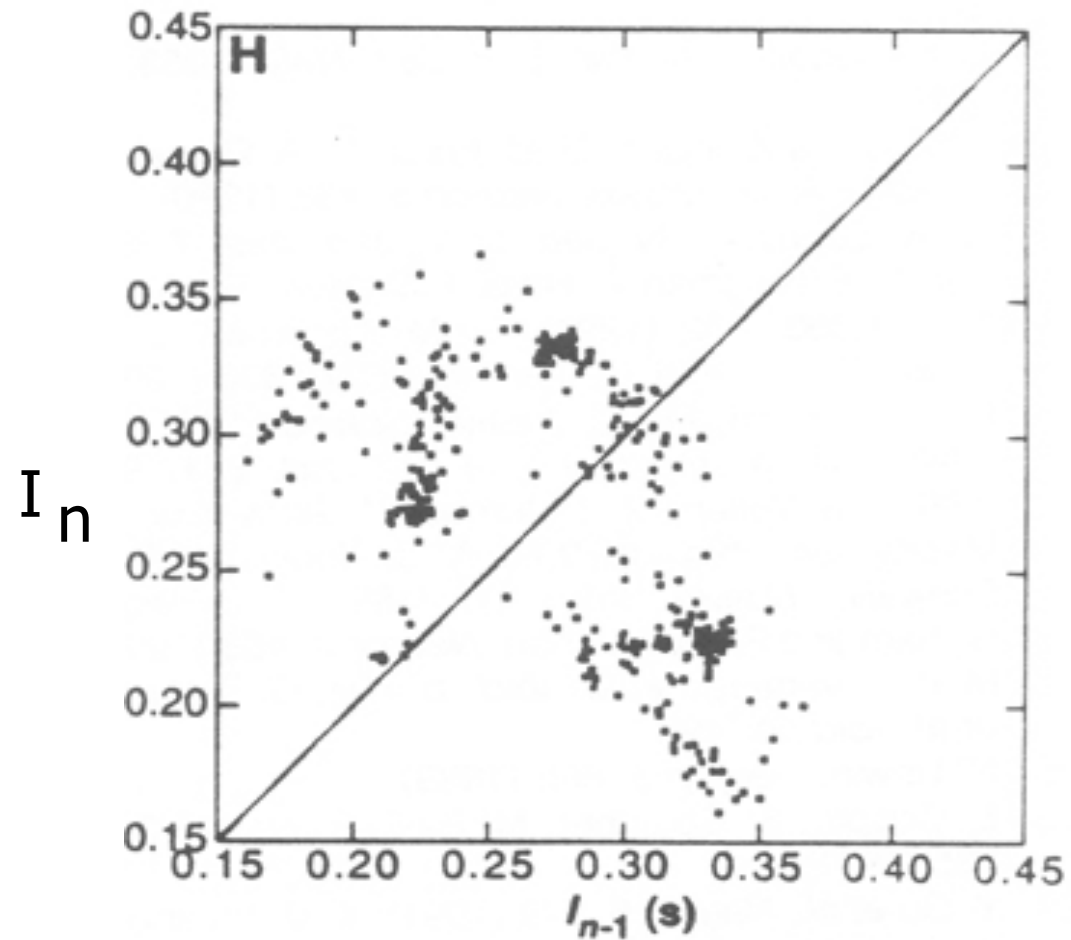


Tateno and Glass (2001)

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

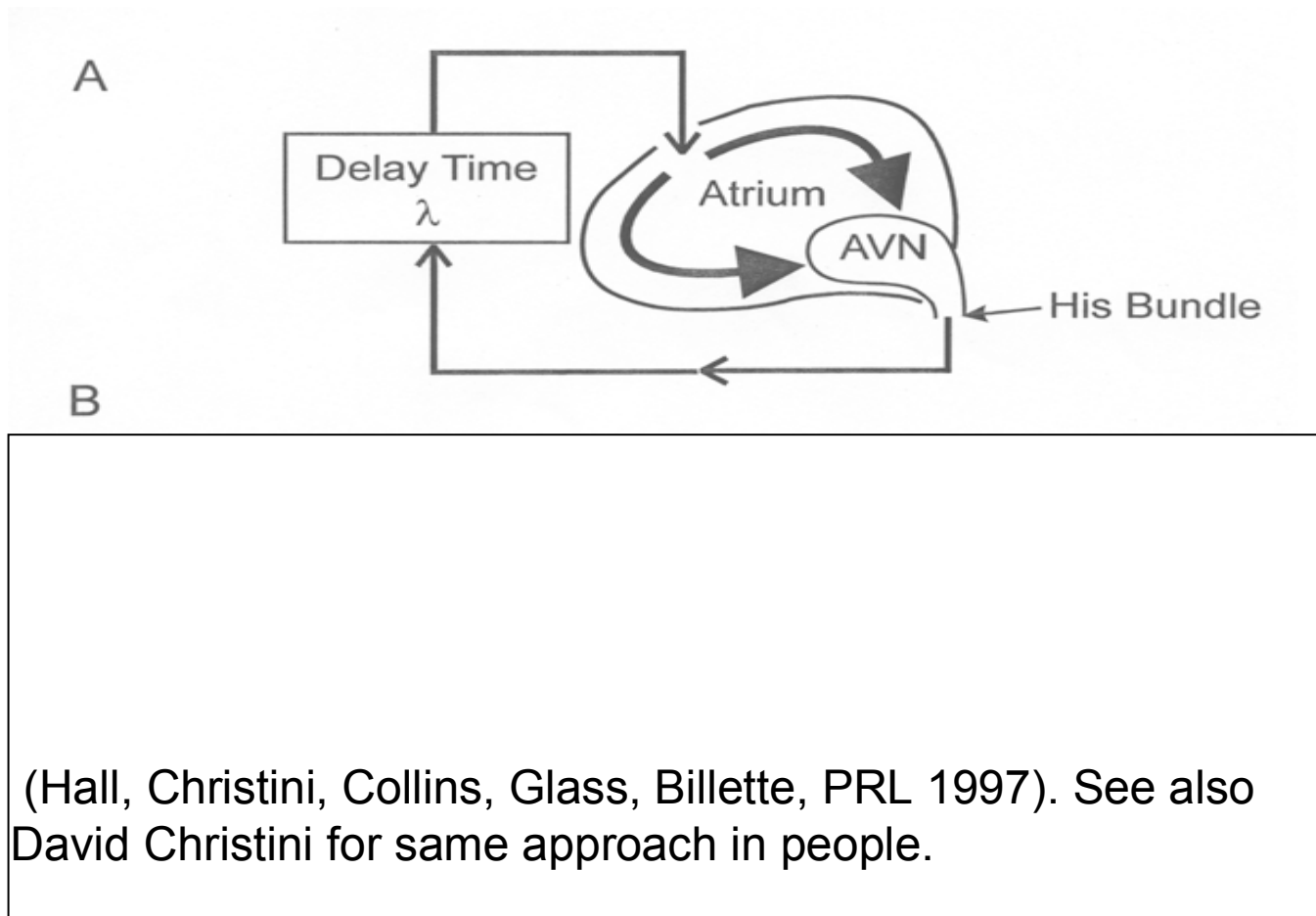


# Control of Cardiac Chaos

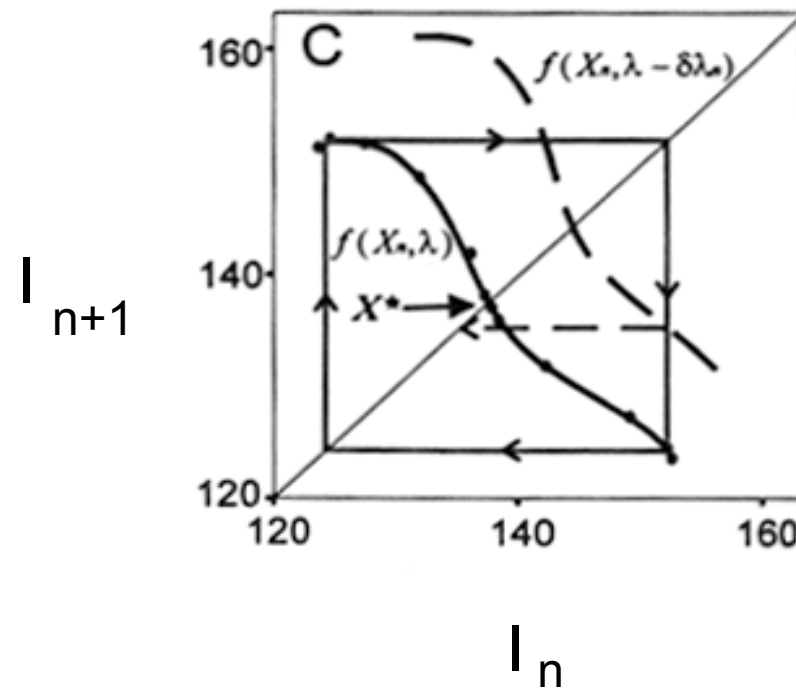


Garfinkel, Spano, Ditto, Weiss, Science (1992)

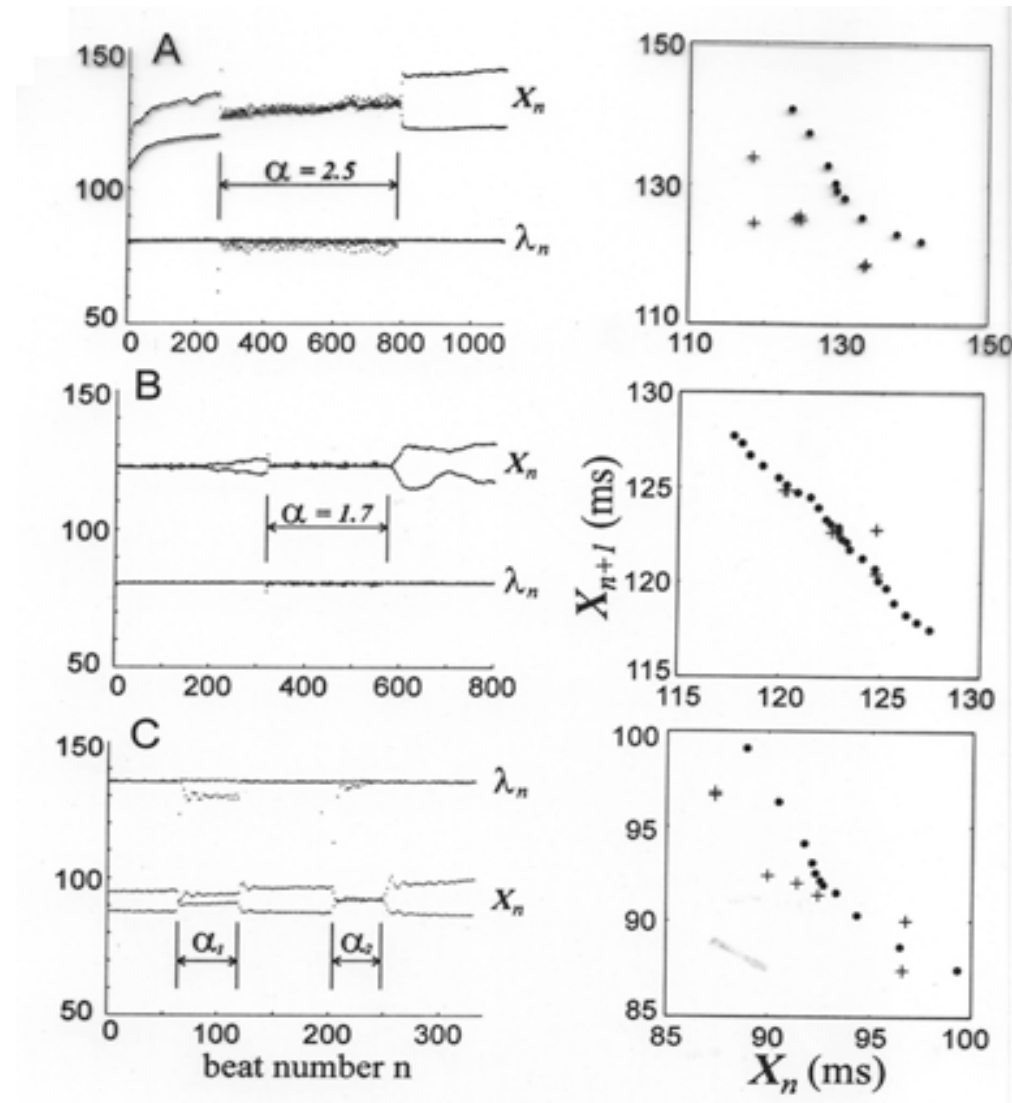
# Control Cardiac Alternans in a Rabbit Heart in Vitro (1997)



# Target Unstable Fixed Point



# 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.