HRV 2006

Heart Rate Dynamics and Complex Arrhythmogenesis

Leon Glass

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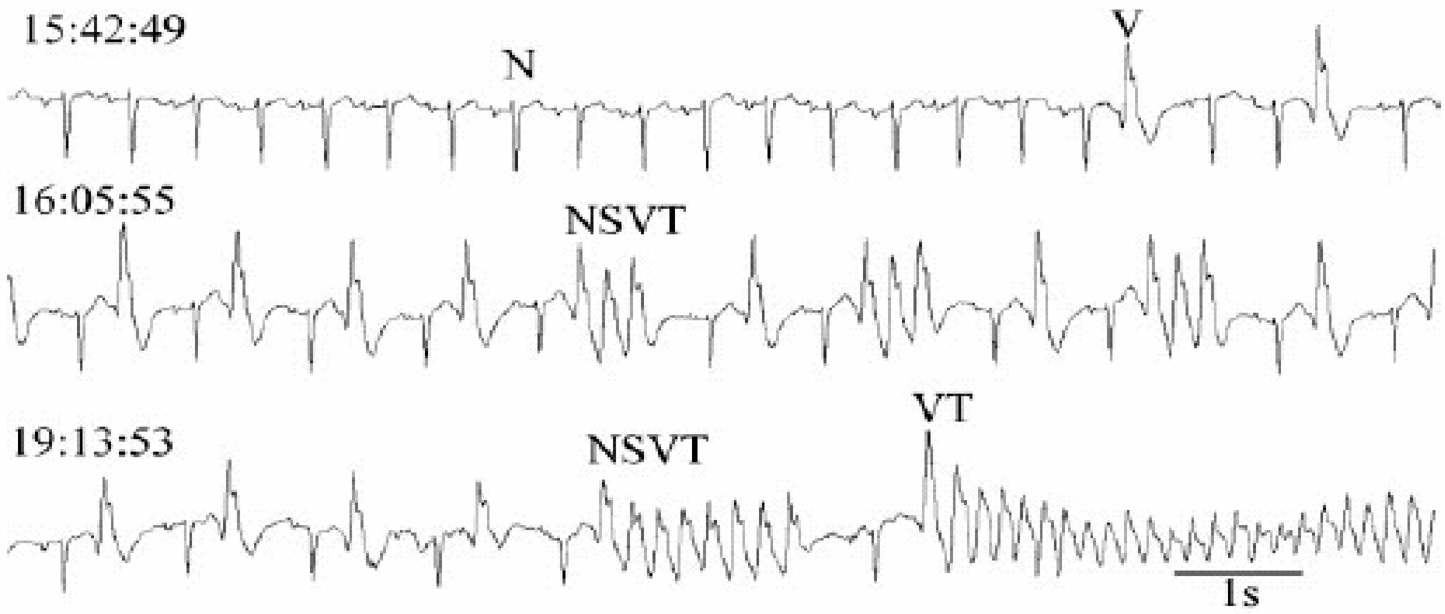
Links Between Mathematics and Cardiology

- Cardiology – A branch of medicine in which qualitative properties of complex rhythms are used to help classify and diagnose disease
- Nonlinear dynamics – A branch of mathematics that deals with qualitative properties of rhythms and changes in rhythms
- Link – Identify and model the mechanisms of arrhythmias (this must involve nonlinear math)

Main Ideas From Nonlinear Dynamics

- A simple model can give many different types of dynamics as a parameter is changed ("universal" bifurcations)
- These behaviors include alternating rhythms, periodic rhythms, and aperiodic (chaotic or quasiperiodic) rhythms
- In cardiology parameter changes may be associated with changes in sinus or pacing rates, structural changes, drugs, etc.

Sudden death. Why did this 82 yr old woman die at 19:13:53 and not at 16:05:55 ?



www.physionet.org

Strategy 101 to investigate Sudden Cardiac Death (SCD)

- Observation: Premature Ventricular Contractions (PVCs) occur with increasing frequency before SCD
- Hypothesis: Decrease of PVCs will lead to decreased SCD
- Experiment: Give 730 people a drug that reduces the number of PVCs and give 725 people a placebo. Count the number of people that die as a function of time.

Cardiac Arrhythmia Suppression Trial. NEJM 321:406 (1989)

- During an average of 10 months of follow-up, the patients treated with active drug had a higher rate of death from arrhythmia than the patients assigned to placebo. Encainide and flecainide accounted for the excess of deaths from arrhythmia and nonfatal cardiac arrests (33 of 730 patients taking encainide or flecainide [4.5 percent]; 9 of 725 taking placebo [1.2 percent]; relative risk, 3.6; 95 percent confidence interval, 1.7 to 8.5).

Cardiac Arrhythmia Suppression Trial (CAST). NEJM 321:406 (1989)

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- That is: the hypothesis was disproved.

Significance of CAST Trial

- Difficulties with using “surrogate” end points for prevention of sudden cardiac death
- Sodium channel blocker may be proarrhythmic
- Utility of placebo controlled double blind randomized clinical trial

Main Flaws of CAST and Similar Clinical Trials

- They do not elucidate the mechanisms of arrhythmias
- A significant improvement in one arm of the trial would lead to that treatment for all individuals meeting selection criteria, ignoring individual physiologic differences (i.e. there is a strong economic incentive for broadly defined classes)

Crisis in the Management of Arrhythmias Associated with Sudden Cardiac Death

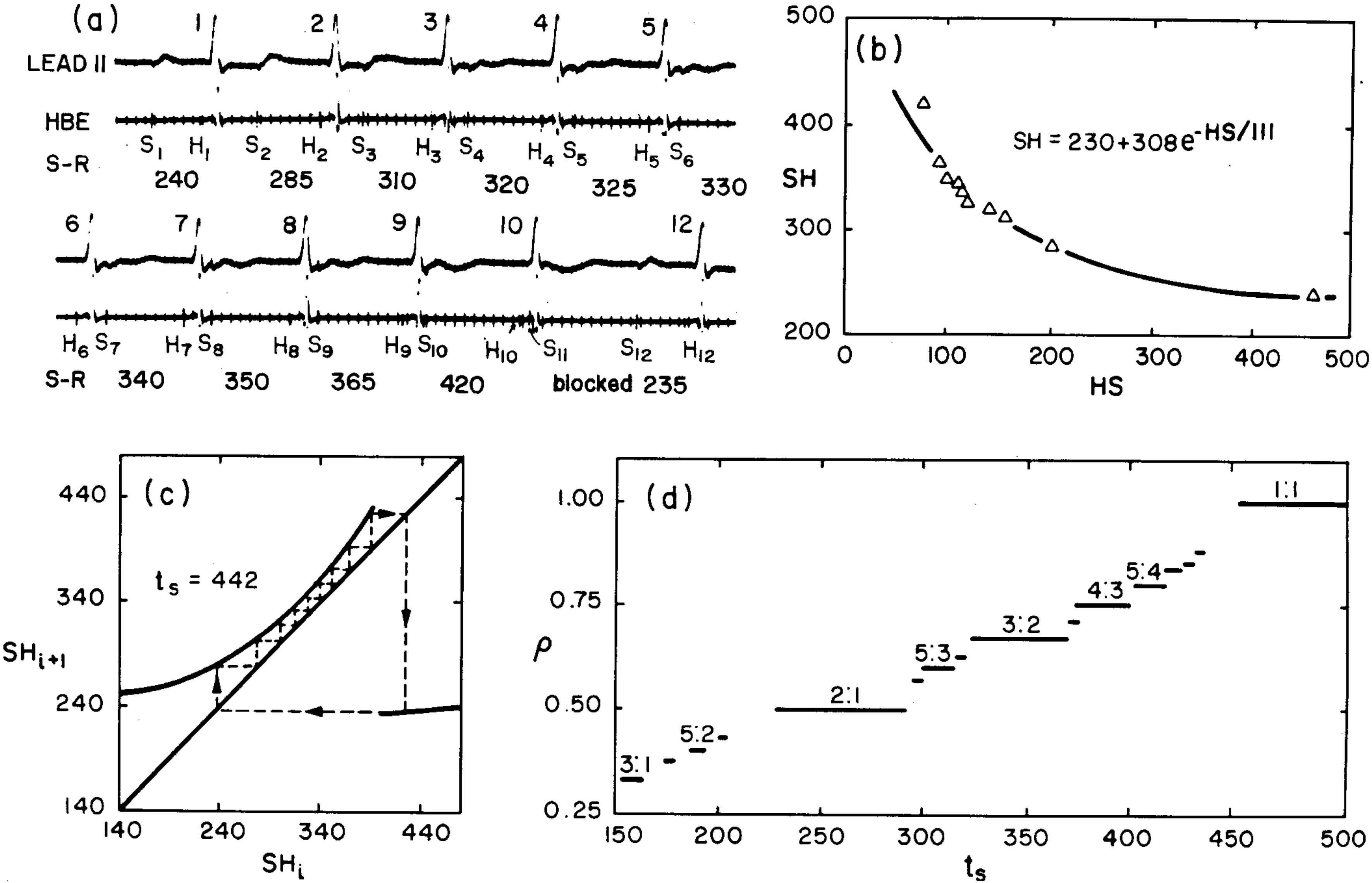
- There is a good therapy for patients at risk for sudden cardiac death (implantable cardiac defibrillators)
- This therapy is expensive and there can be associated morbidity
- Most people who die of sudden cardiac death do not fall into known risk classes
- Many people who fall into known risk classes and receive defibrillators never have the defibrillator activate

(Josephson and Wellens, Circulation, 2004)

Strategy 102. Use nonlinear dynamical models to analyze mechanisms of arrhythmia by confronting theory and experiment (one problem at a time).

- AV heart block
- Parasystole
- Alternans
- Dynamics in heart cell aggregates: resetting and entrainment
- Reentrant rhythms. Universal patterns of spatio-temporal dynamics

AV Heart Block



Glass, Guevara, Shrier (1987)

Über die unvollständige Störung der Erregungsüberleitung zwischen Vorhof und Kammer des menschlichen Herzens.

Von

W. Mobitz.

(Aus der I. medizinischen Klinik zu München [Direktor: Prof. *von Romberg*].)

Mit 26 Textabbildungen.

(Eingegangen am 29. Dezember 1923.)

5:3

Wenck

1903

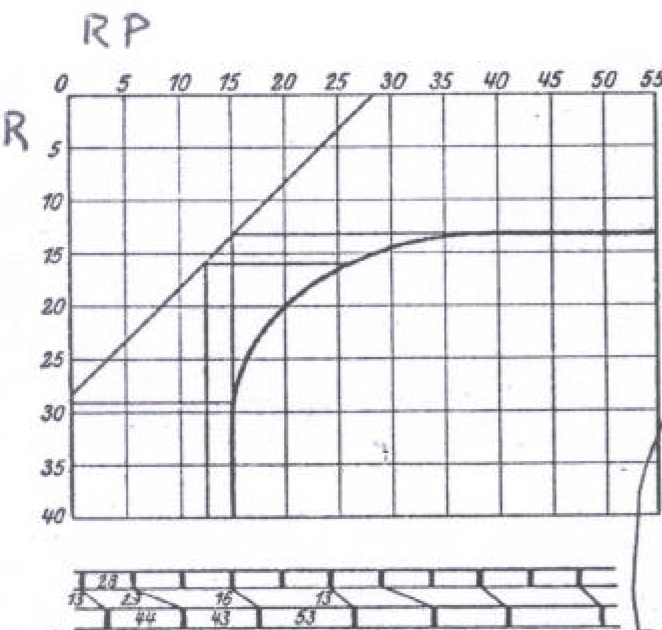


Abb. 14. Zwischenstadium zwischen Bigeminus und Halbrhythmus.

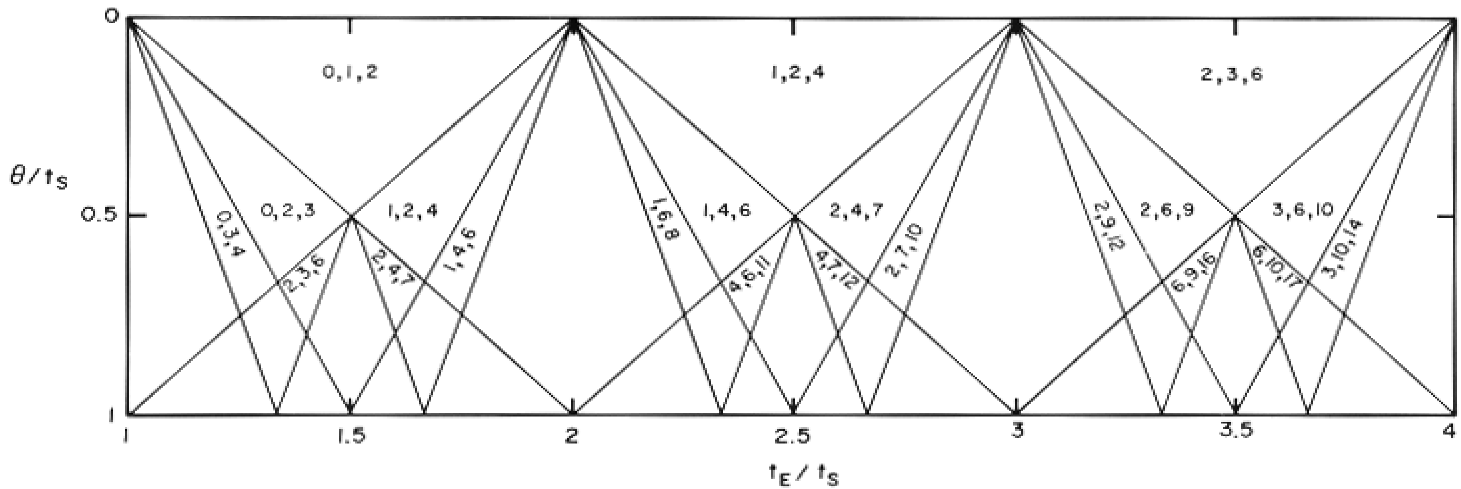
Klinik häufigsten Formen von partiellem Block dar (Fig. 11, 12, 13). Während die Vorhofperiode von 30 einen fortdauernden 3:2-Rhythmus ergab — einen auf Überleitungsstörung beruhenden Bigeminus —, findet ein Alternieren von 3:2 mit 2:1-Rhythmus bei einer Vorhofperiode von 28 statt. Ein derartiger Rhythmus ist von *Wenckebach* als Überleitungsstörung 1903 beschrieben worden (Abb. 14).

Die Vorhofperiode von 26

Pure Parasystole

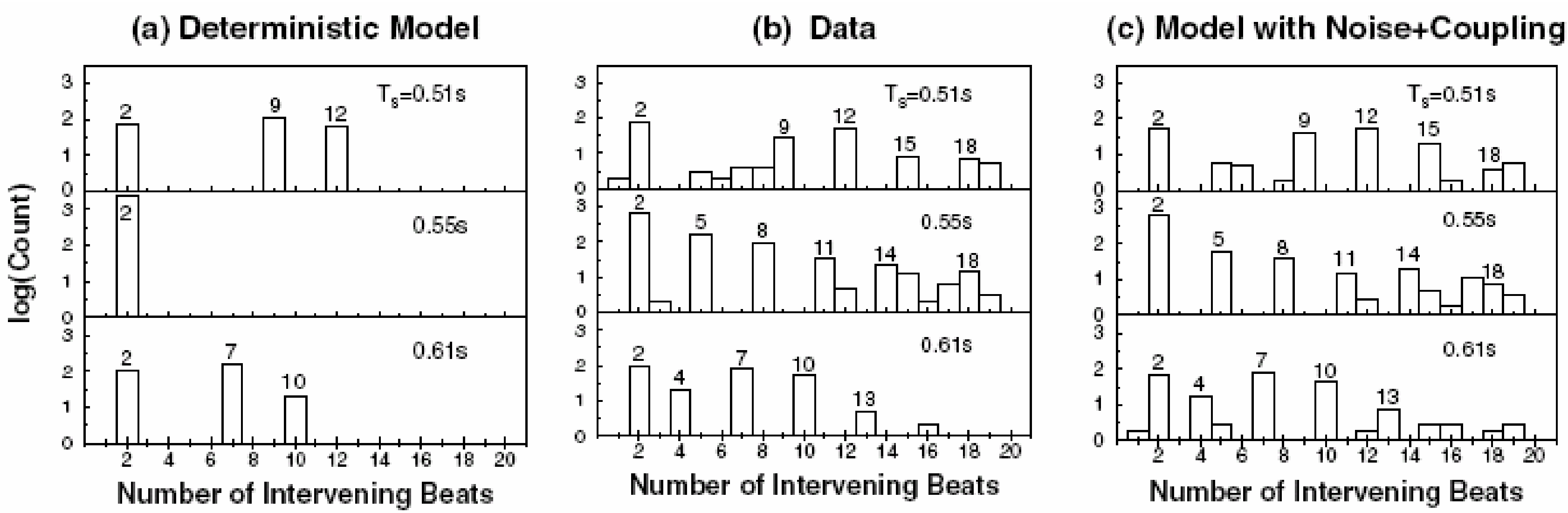
Rules of Pure Parasystole

Count the number of sinus beats between ectopic beats. In this sequence: (1) there are 3 integers; (2) one is odd; (3) the sum of the two smaller is one less than the largest.



Glass, Goldberger, Belair (1986)

Stochastic Model of Parasystole

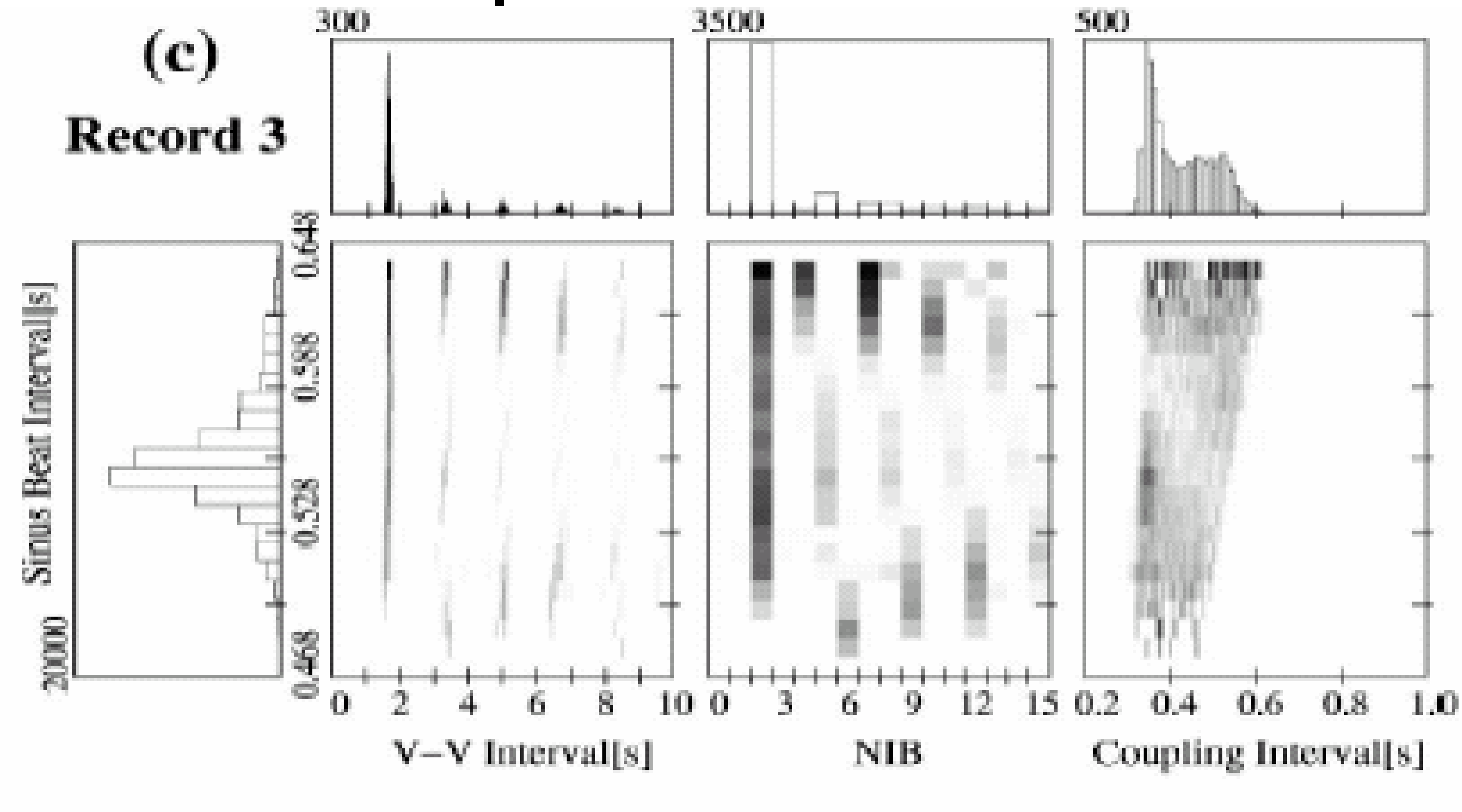


VOLUME 87, NUMBER 6 PHYSICAL REVIEW LETTERS 6 AUGUST 2001

Noise Effects on the Complex Patterns of Abnormal Heartbeats

Verena Schulte-Frohlinde,[1] Yosef Ashkenazy,[1] Plamen Ch. Ivanov,[1,2]
Leon Glass,[3] Ary L. Goldberger,[2] and H. Eugene Stanley[1]

Heartprint of a Patient

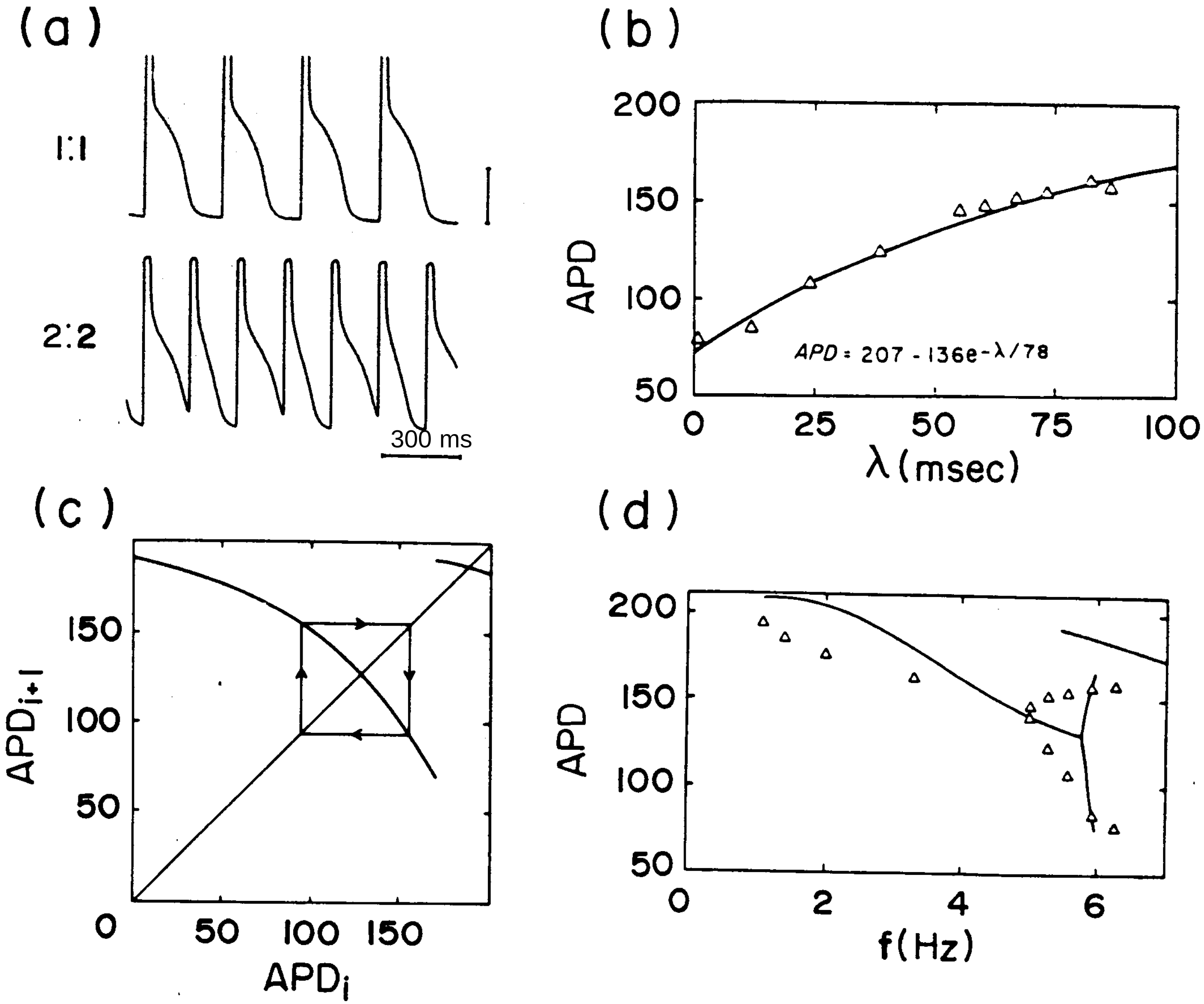


PHYSICAL REVIEW E **66**, 031901 (2002)

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]

Alternans in chick hearts



Guevara, Ward, Shrier, Glass (1984)

Period multupling-evidence for nonlinear behaviour of the canine heart

Amy L. Ritzenberg*, Dan R. Adam† & Richard Jonathan Cohen*†

* MIT Department of Physics and † Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

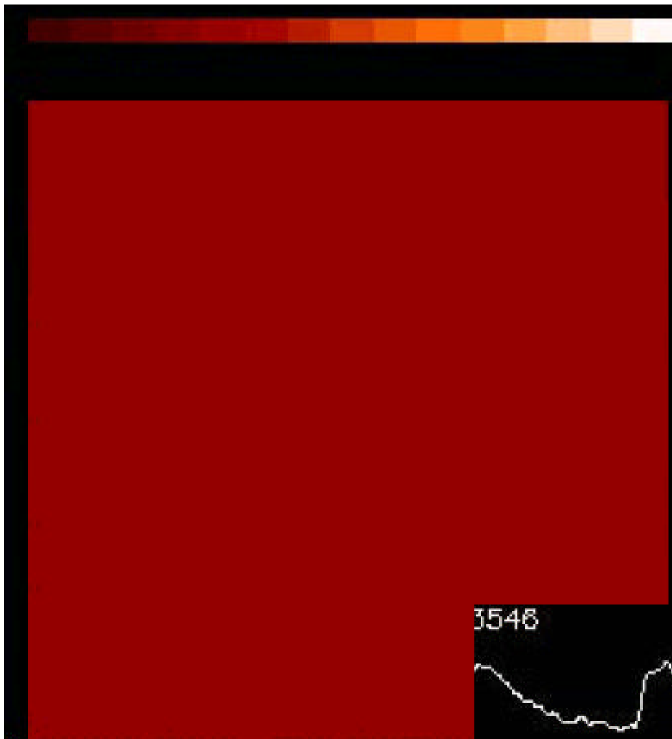
Although there has recently been considerable interest in applying the theory of nonlinear dynamics to the analysis of complex systems[1,2], as yet applications of the theory to biological systems *in vivo* have been very limited. We report here evidence of nonlinear behaviour in the electrocardiogram and arterial blood pressure traces of the noradrenaline-treated dog. Noradrenaline produces variations in these traces that repeat themselves with regular periods of integral numbers of heart-beats (period multupling), an effect that resembles the 'period-doubling' and other 'bifurcative' behaviour[3–5] observed when the driving frequency of a nonlinear oscillator is increased above a critical value[6–9]. The simplest type of periodic variation that we report is the so-called 'electrical alternans', which has long been known as one response of cardiac electrical activity to certain stresses and disease states[10–13].

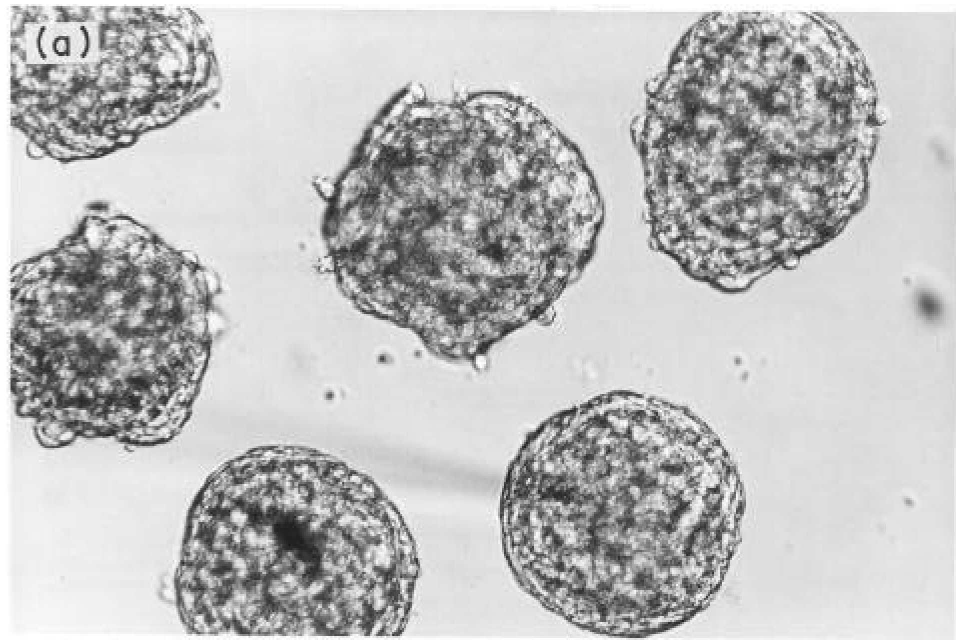
(Nature 1984)

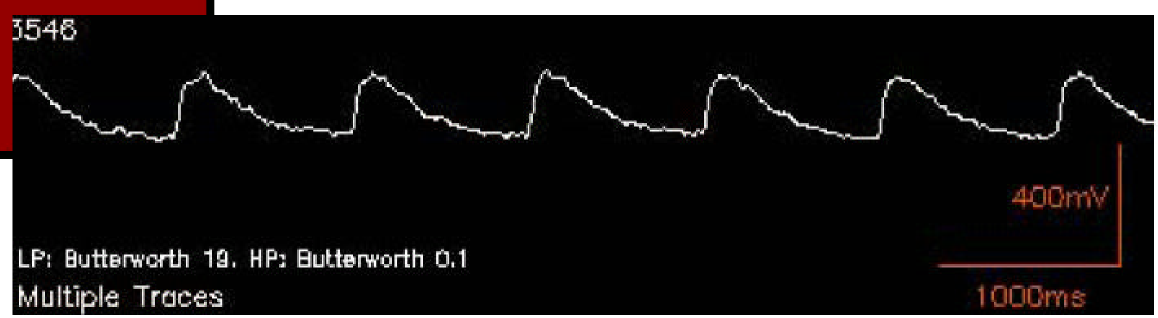
Rationale to Study Model Systems

- Most real arrhythmias (like the first one I showed are very hard to understand)
- Model systems present fascinating theoretical problems and are amenable to careful experiments
- BUT – may not be relevant to clinical cardiology

Model System – Embryonic chick heart tissue culture (Guevara, Shrier, Glass 1980s)

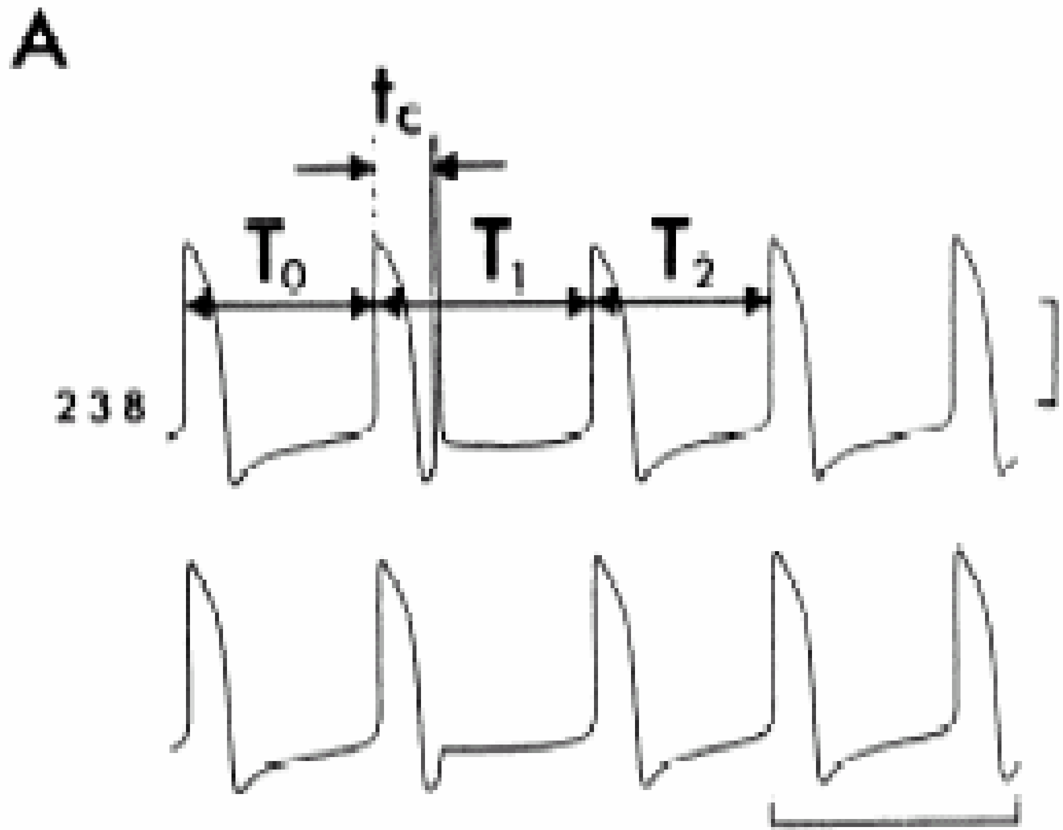




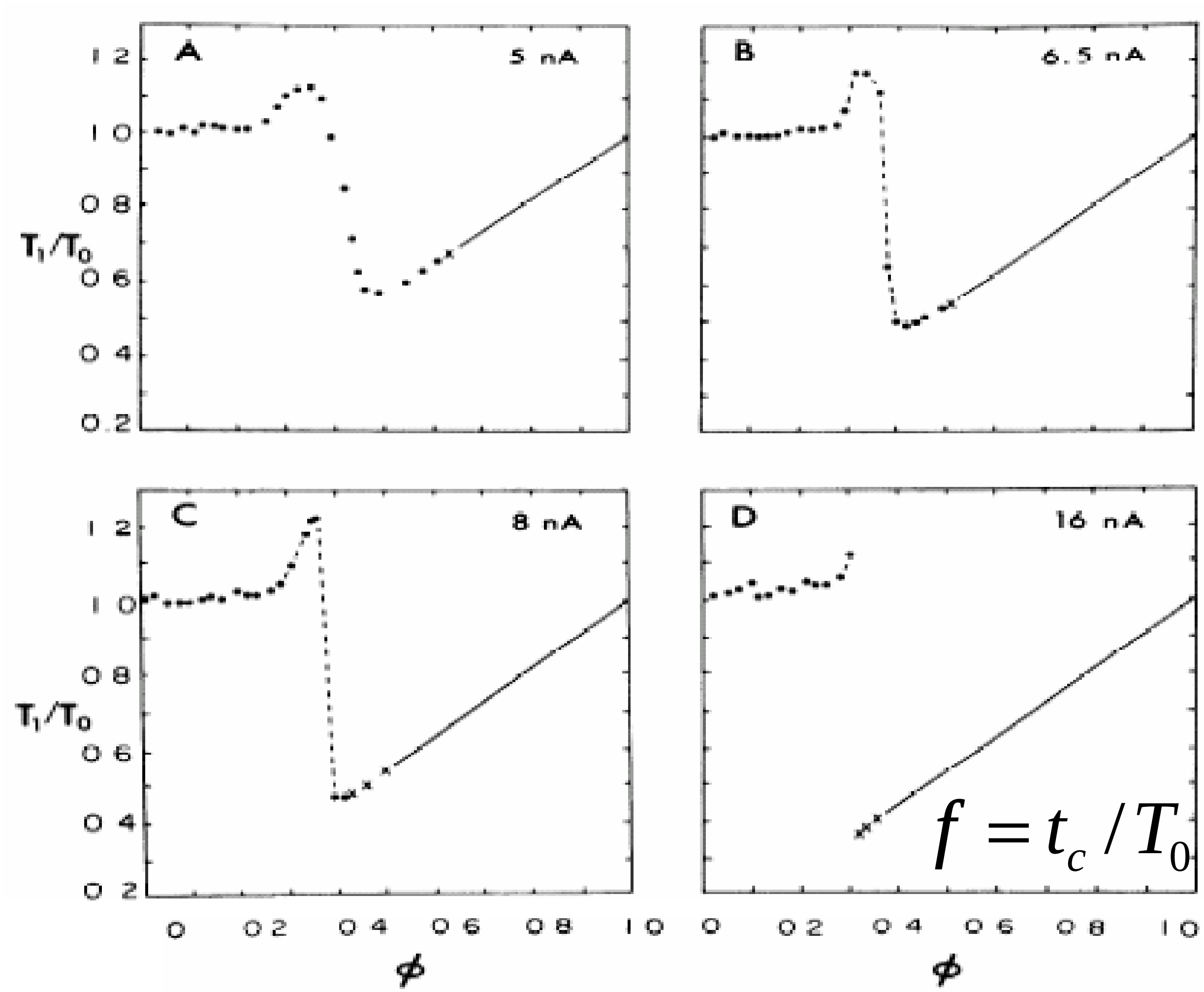


A. Hodge, M.-Y Kim

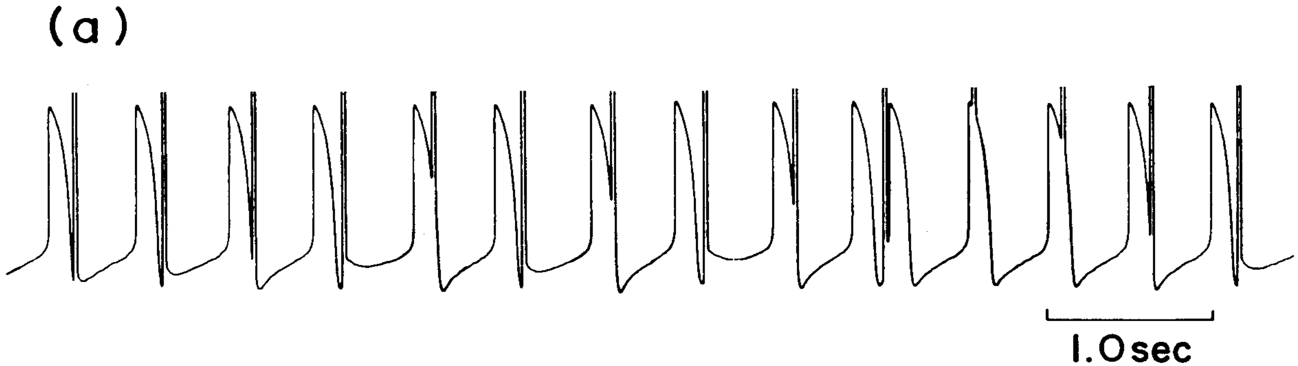
A Resetting Experiment (in chicken heart)



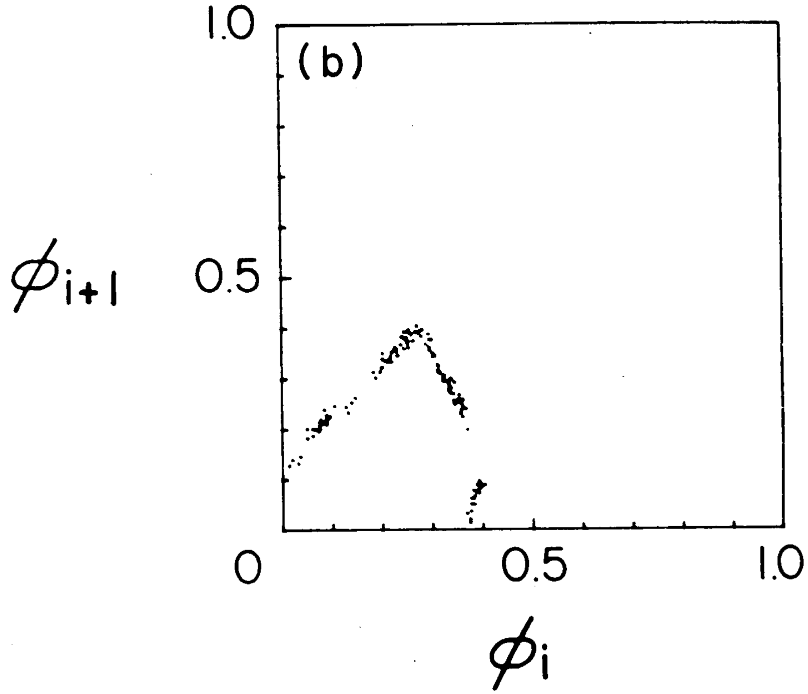
Perturbed Cycle Length Curves



Chaos in periodically stimulated heart cells

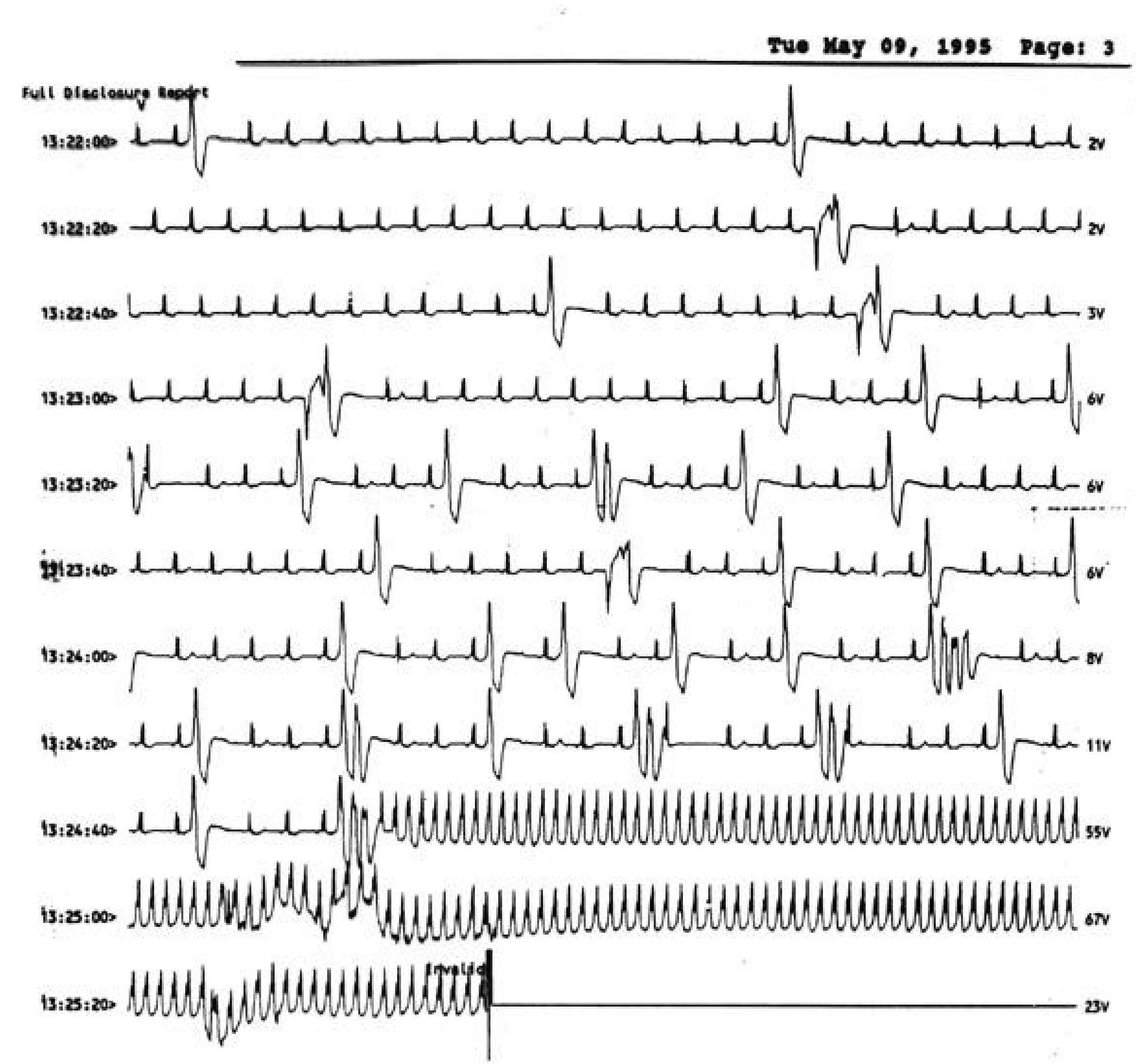


Predict chaos based on
1D circle maps determined
from resetting experiments.
Resetting depends on phase
of stimulus.



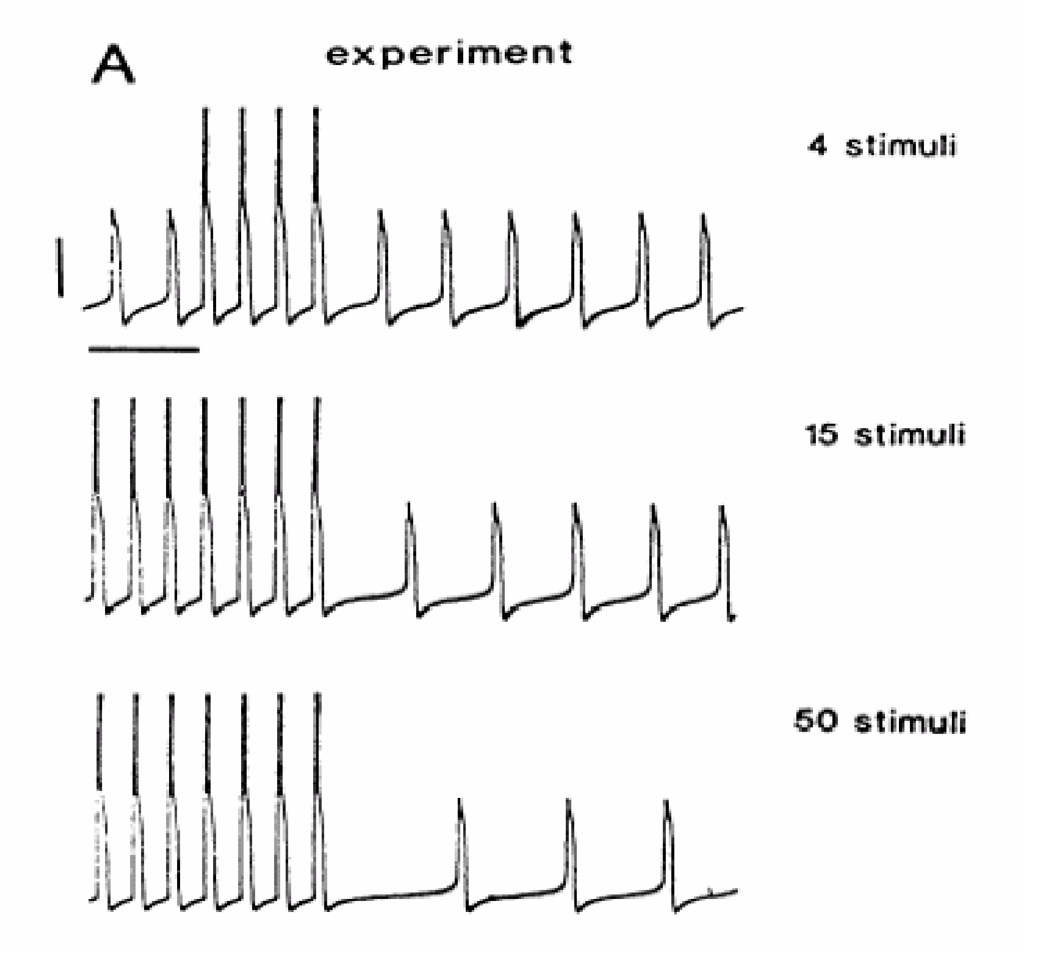
(Guevara, Glass, Shrier 1981)

Cardiac arrhythmias suddenly start and stop



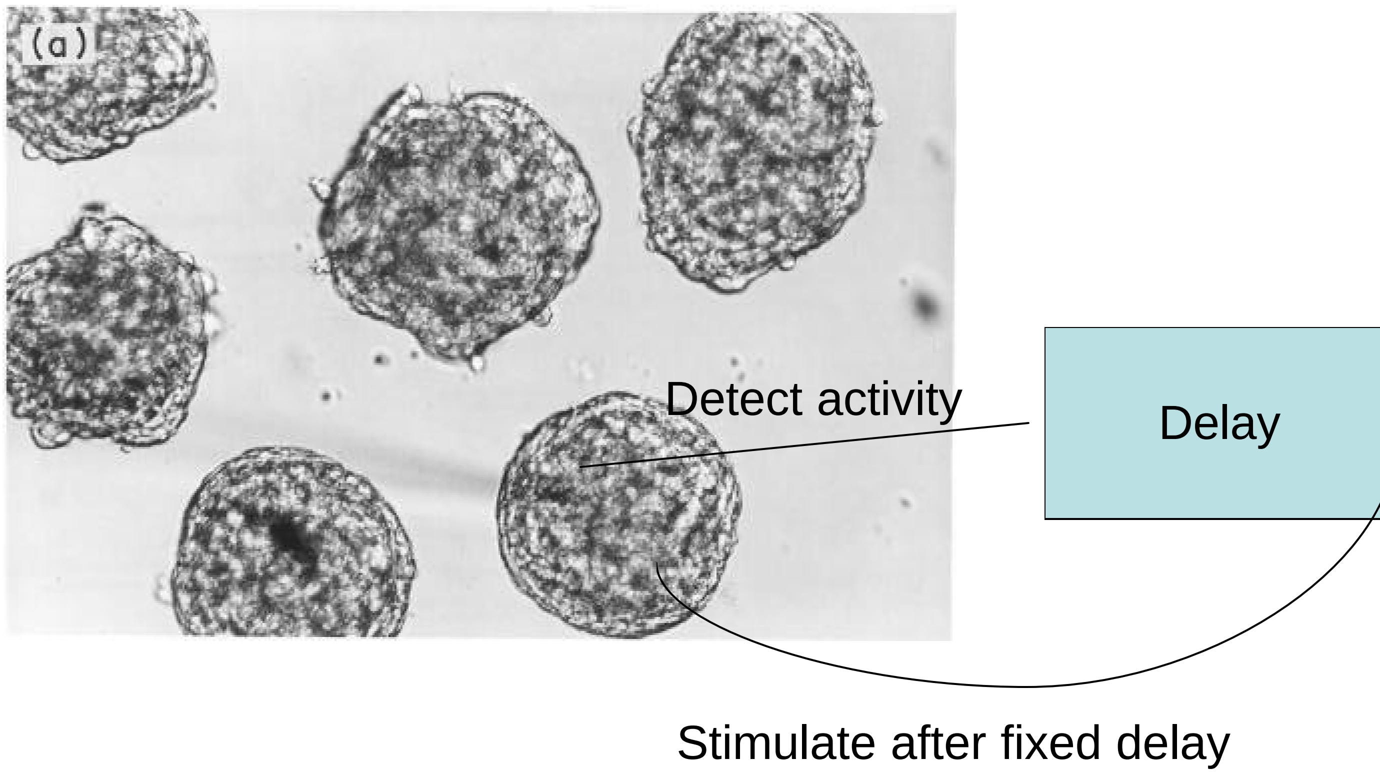
Problem: how can arrhythmias spontaneously start and stop?

Rapid Stimulation Leads to a Slower Rhythm (Overdrive Suppression)

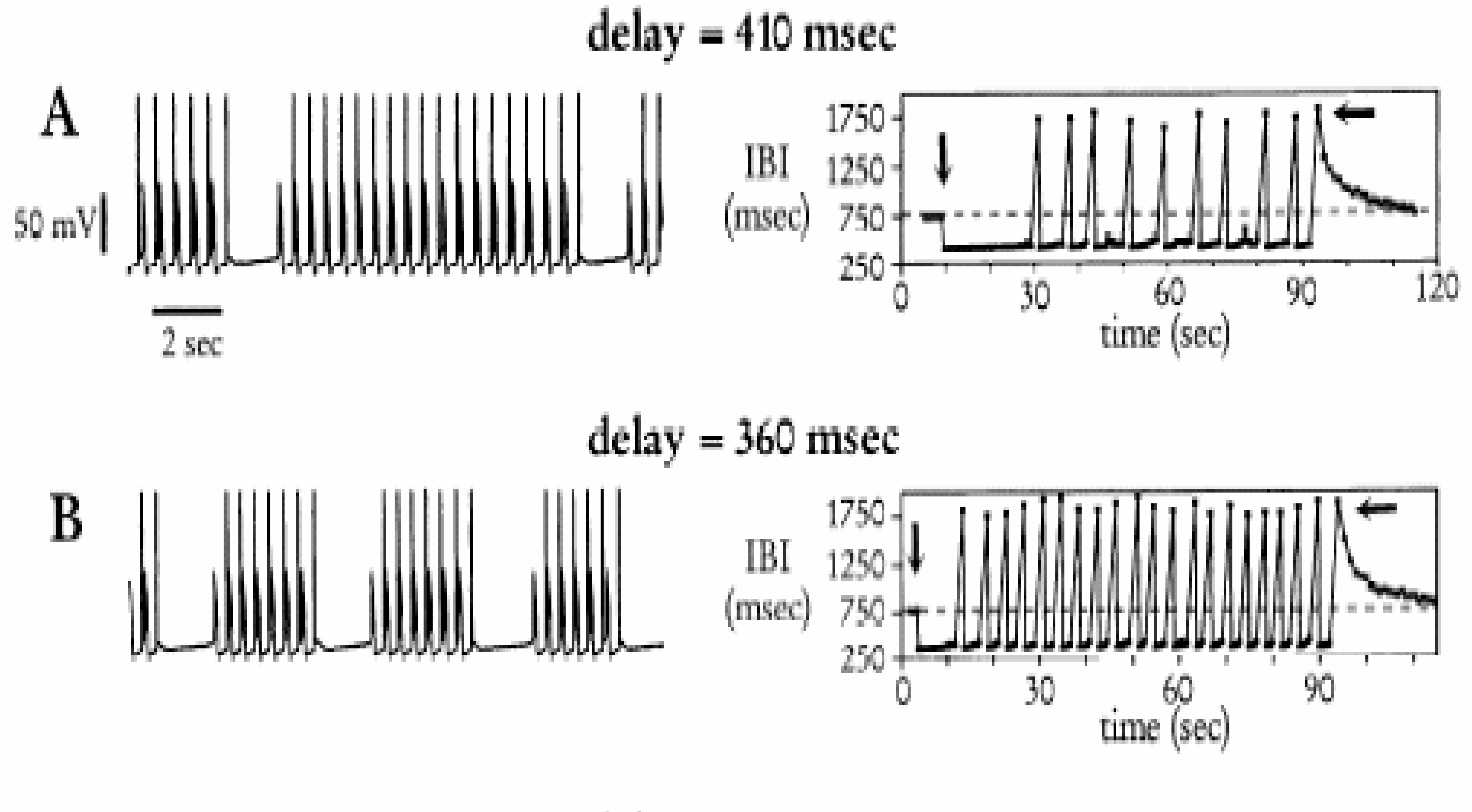


(Kunysz, Glass, Shrier 1995)

Fixed Delay Stimulation

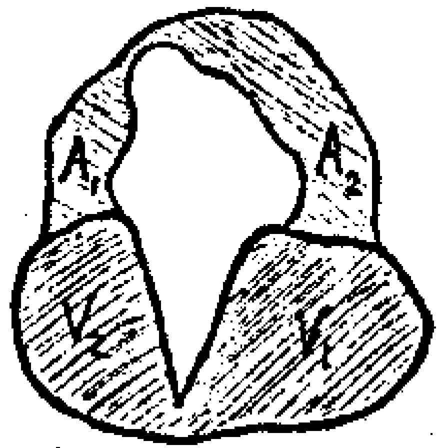


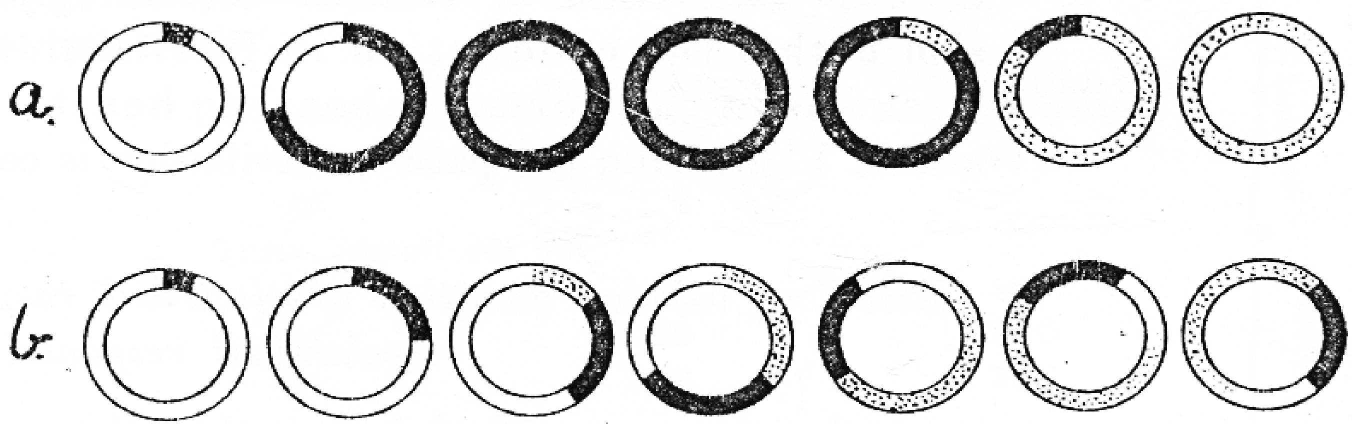
Fixed Delay Stimulation of Cardiac Aggregates Leads to Bursting



(Kunysz, Shrier, Glass 1997)

Anatomical Reentry



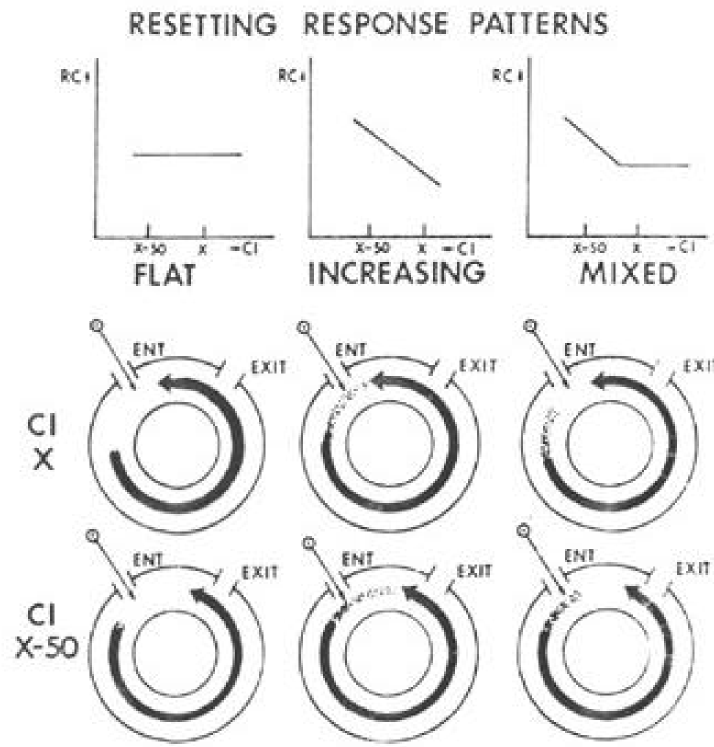


G. R. Mines (1913)

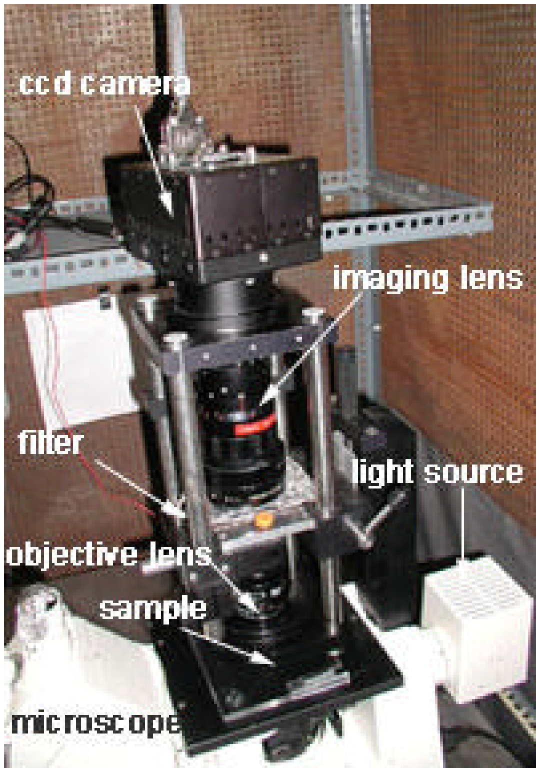
Reentrant arrhythmias: period of oscillation is set by a reentrant circuit NOT a pacemaker

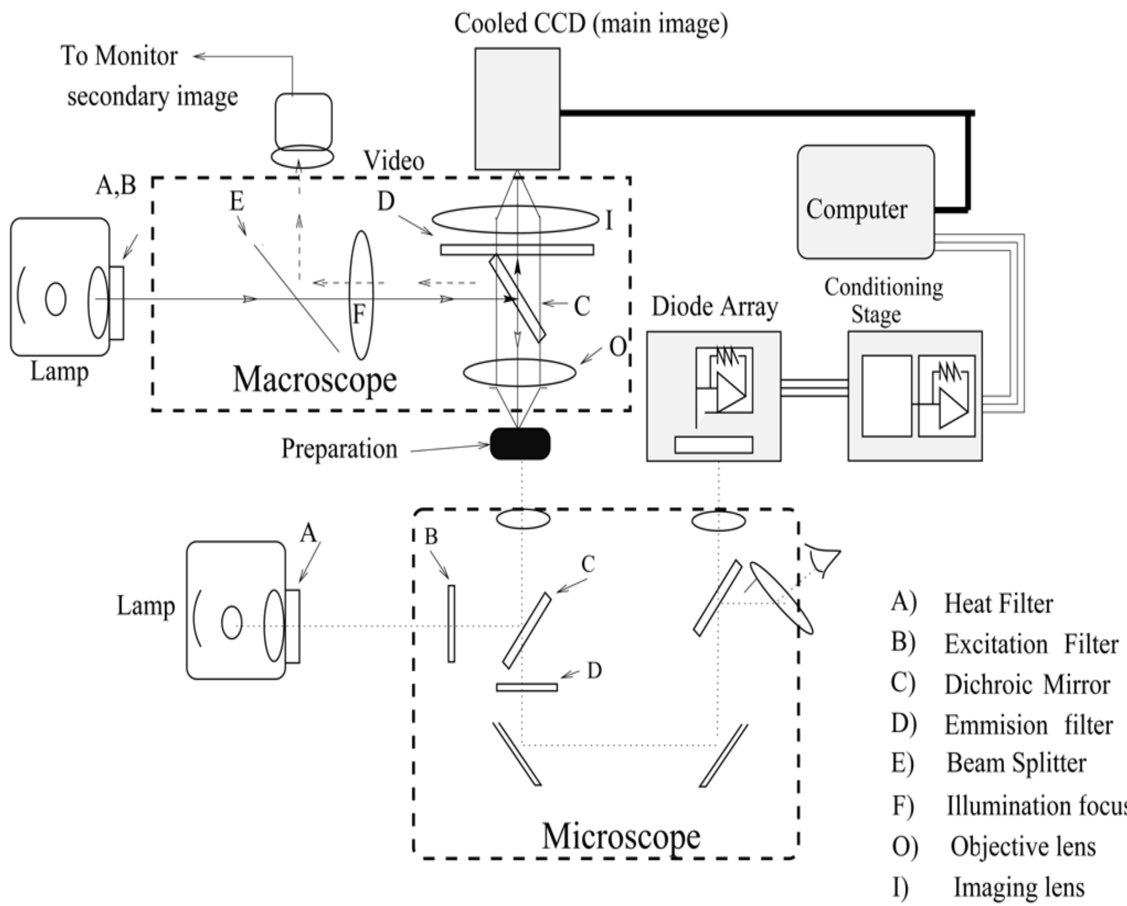
Resetting and Entrainment of Ventricular Tachycardia Associated with Infarction: ***Clinical and Experimental Studies***

M. E. JOSEPHSON, D. CALLANS, J. M. ALMENDRAL, B. G. HOOK, R. B. KLEIMAN



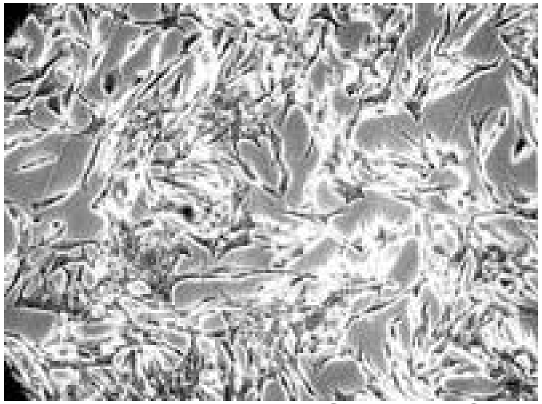
Macroscope for studying dynamics in tissue culture
(Gil Bub, Alvin Shrier, Yoshihiko Nagai, Katsumi Tateno)



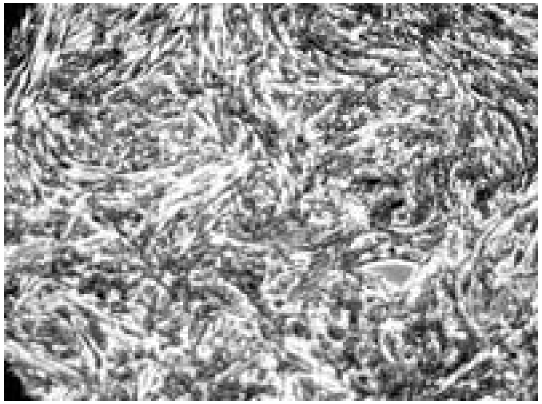


Cell Culture

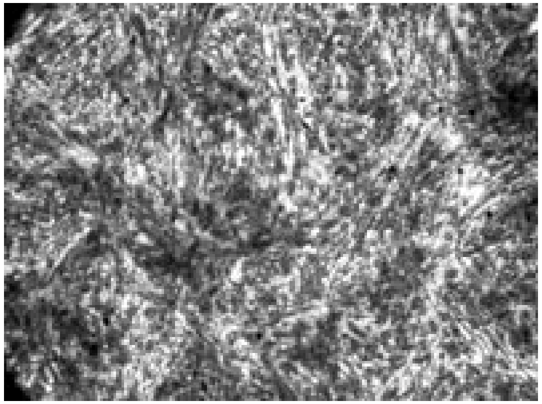
Incubate 30 White Leghorn eggs for 7 days.
Isolate ventricles.
Dissociate with DNAse and trypsin.
Add inactivating medium and filter.
Centrifuge and resuspend in maintenance media.
Plate at various densities.
Incubate for 1-2 days.
Load with dye, perform experiment.



0.5×10^3 /cm^2

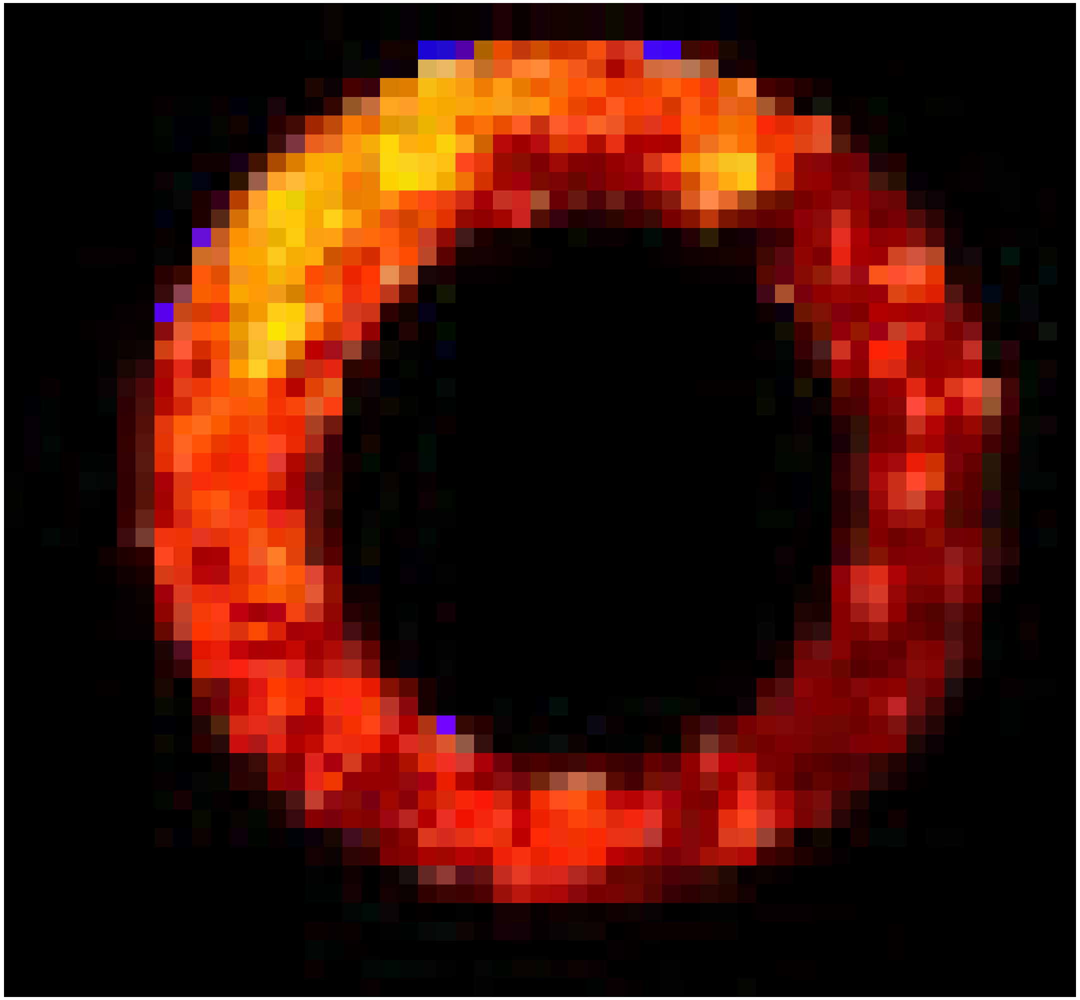


1.0×10^3 /cm^2



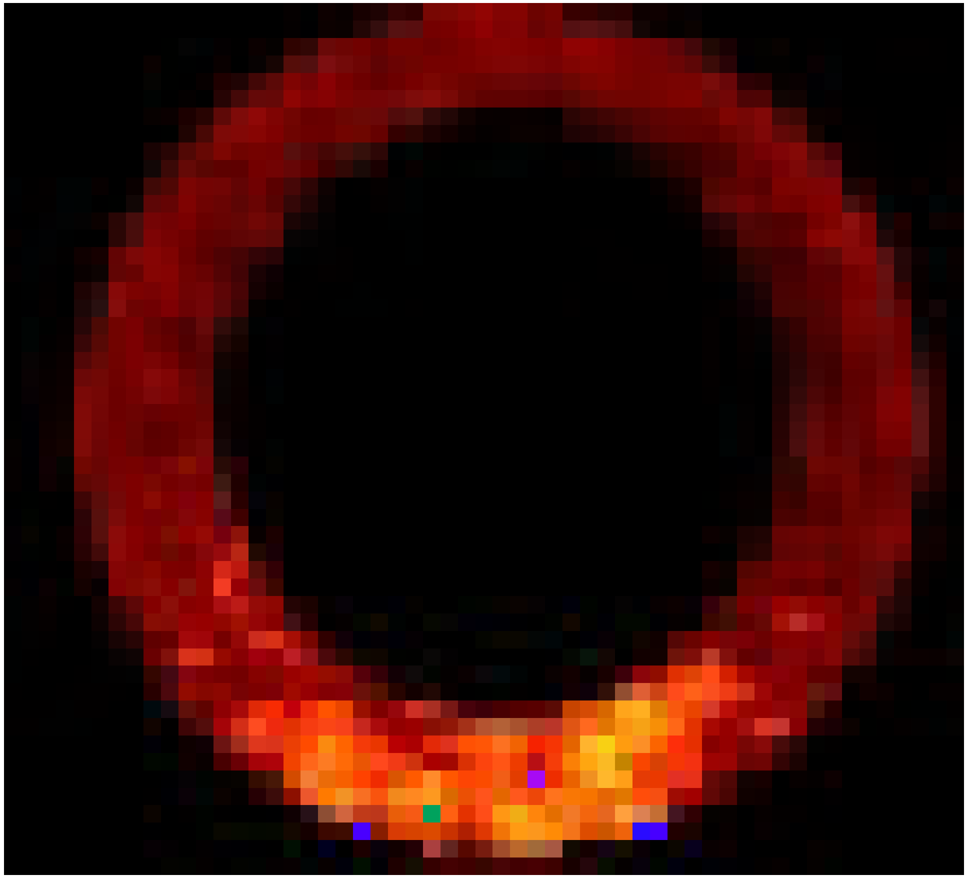
2.0×10^3 /cm^2

Dynamics in a Ring of Cardiac Cells

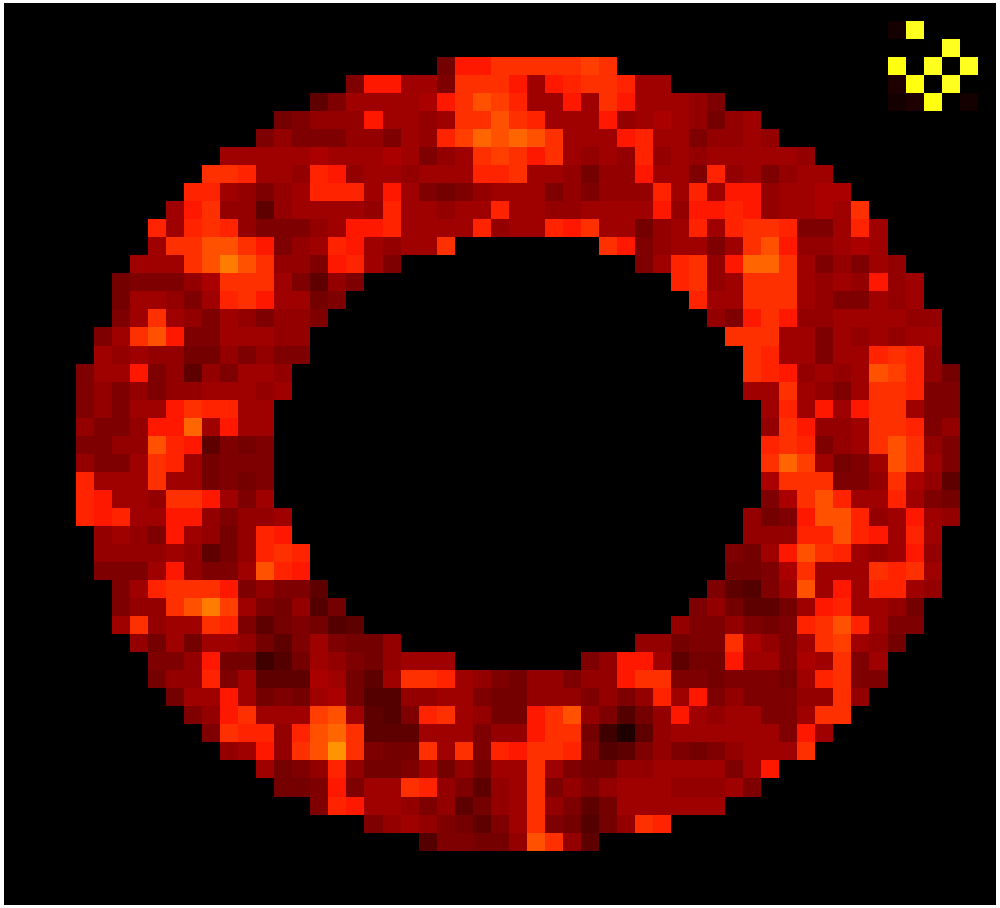


Pacemaker

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



Reentry



Cardiac Ballet

Physiological properties of real heart cells

- Excitable
- Oscillatory (can be reset and entrained)
- Fatigue (less excitable following rapid stimulation – overdrive suppression)
- Heterogeneous

FitzHugh-Nagumo Model of Propagation

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

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

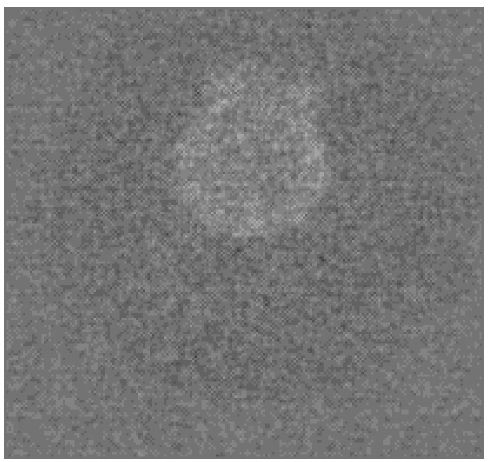
$$\frac{dz}{dt} = -\gamma_\alpha z + (\Delta z)\delta(t - t_{AP}),$$

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

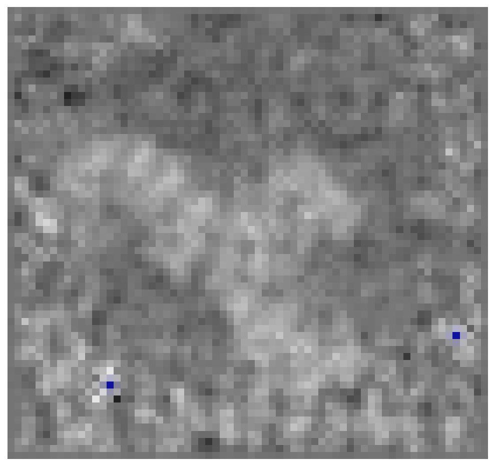
$$R(\zeta, v) = \begin{cases} \frac{(1-\zeta)}{1+10e^{-10(v-.1)}} + \zeta, & \textbf{Pacemaker cells} \\ 1 & \textbf{Otherwise} \end{cases}$$

Pacemakers and Reentry in Tissue Culture

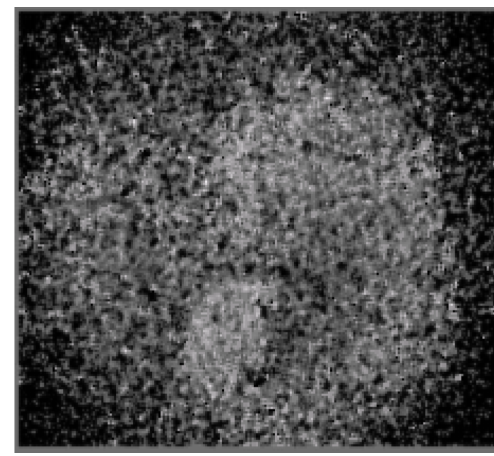
Calcium Target
(Calcium Green)



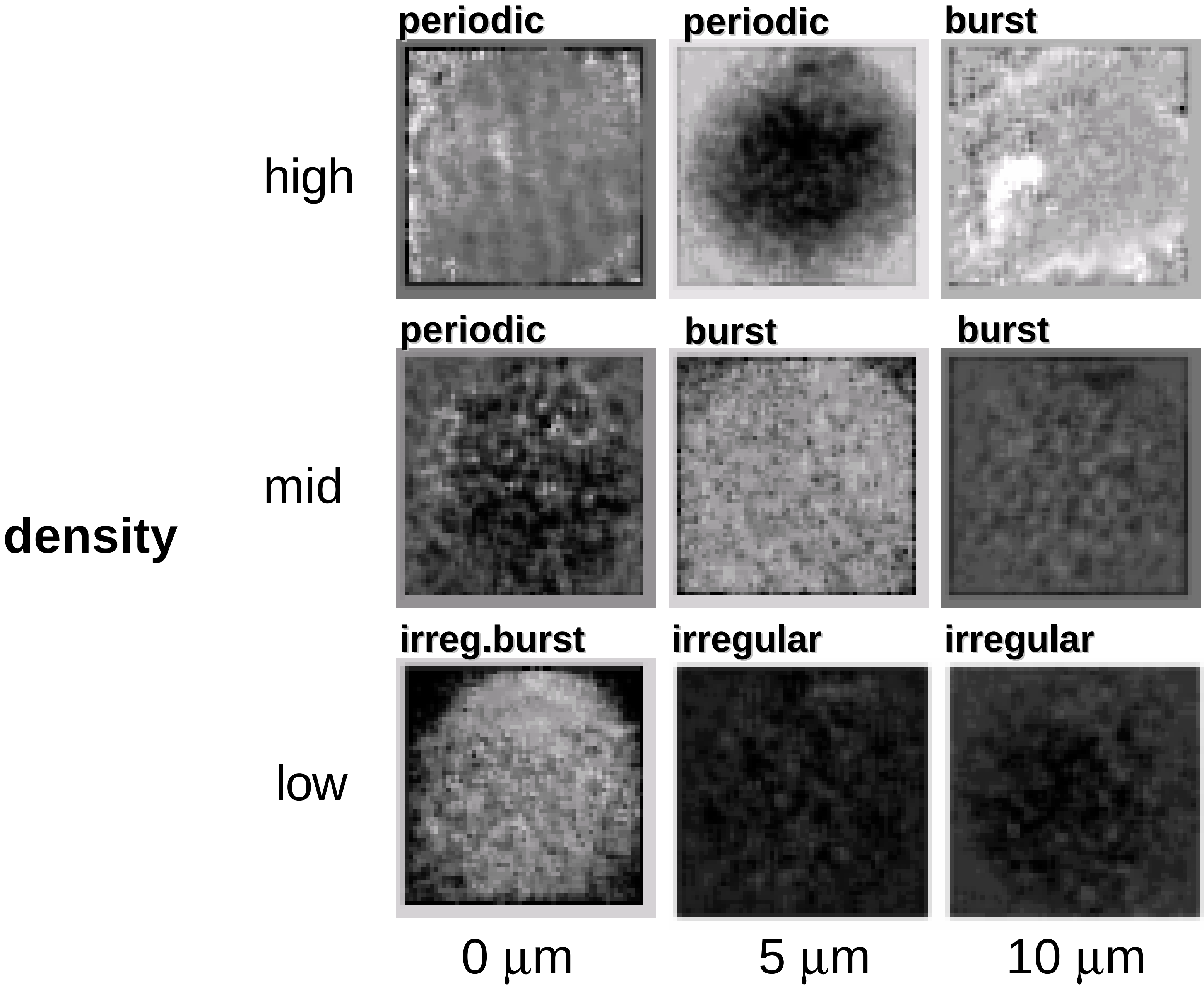
Calcium Spiral
(Calcium Green)



Voltage Spiral
(di-4-ANEPPS)



Spiral waves have been hypothesized as a mechanism for VT and VF (Wiener and Rosenblueth, Krinsky, Winfree, Allessie, Jalife, and many others)



(Bub, Glass, Shrier, PRL 2005)

a glycyrrhetinic acid

Simulating bursting dynamics as a function of connectivity

1)Add spontaneous activity by giving excitable cells a probability of firing.

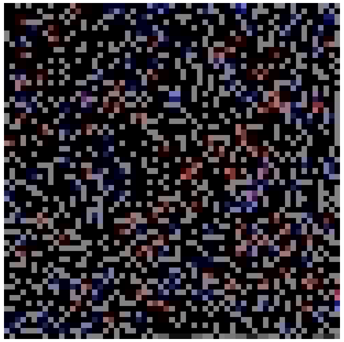
2) Add fatigue by giving each cell a fatigue variable η where

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)

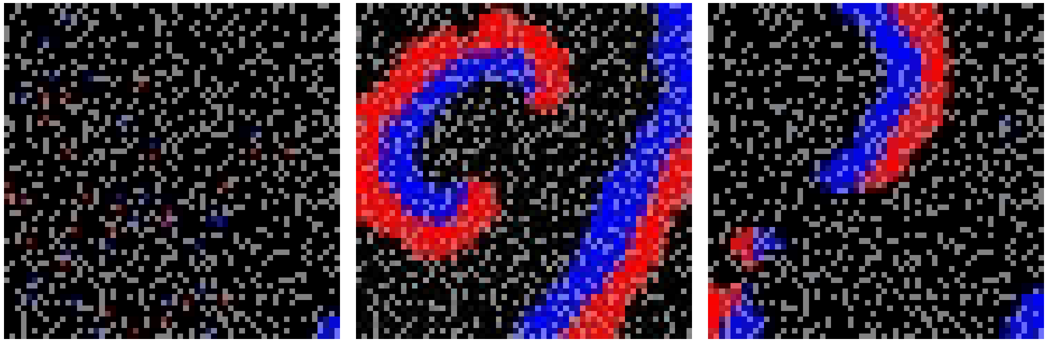
Now a cell is activated if $\eta_{i,j} + \theta <$ active/inactive

R=3, θ=0.35



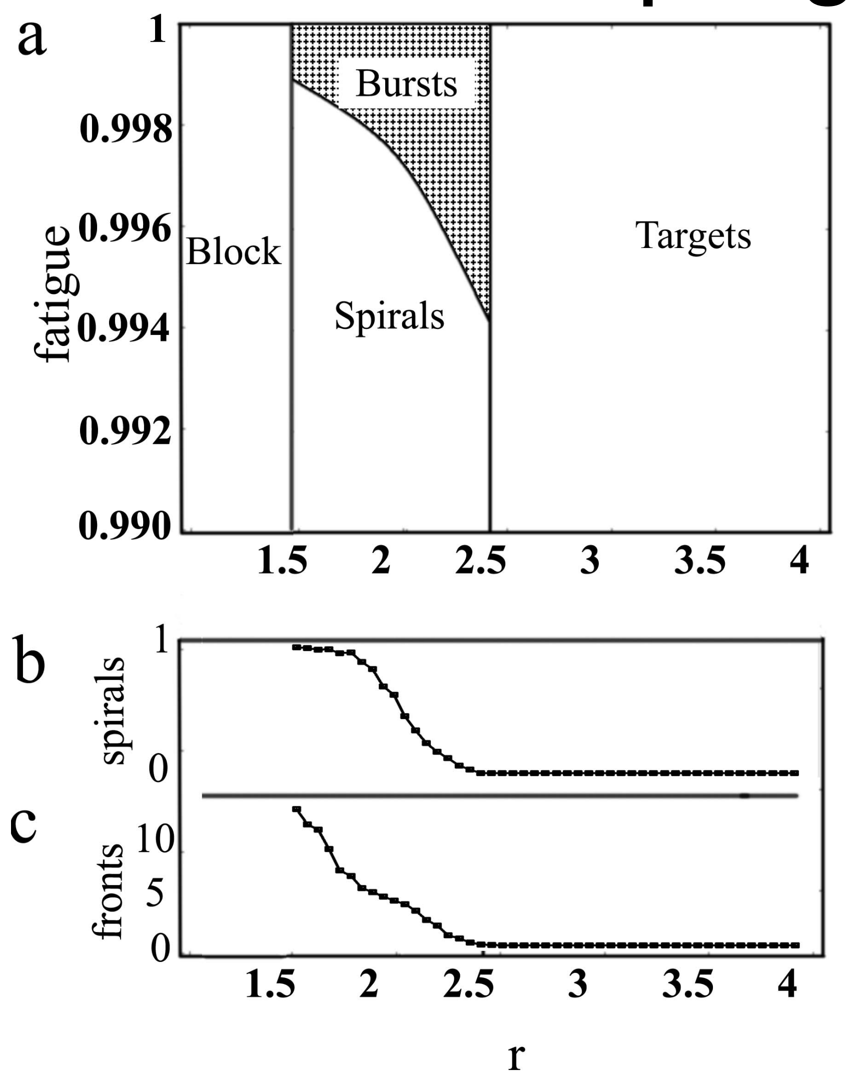
Target patterns ('periodic')

R=1.8, θ=0.35



bursting

Universal organization: Fatigue vs Coupling



(Bub, Glass, Shrier, PRL 2005)

One mechanism for paroxysmal rhythms

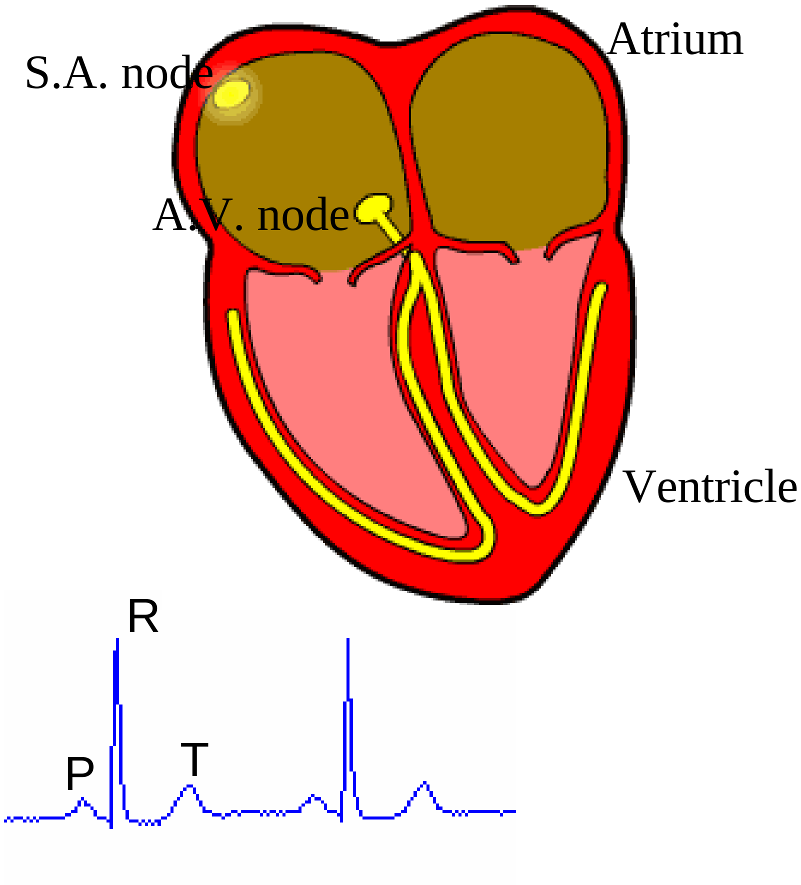
- Initiation by reentry in heterogeneous excitable systems
- Termination as a result of “fatigue” – loss of excitability

Practical Applications

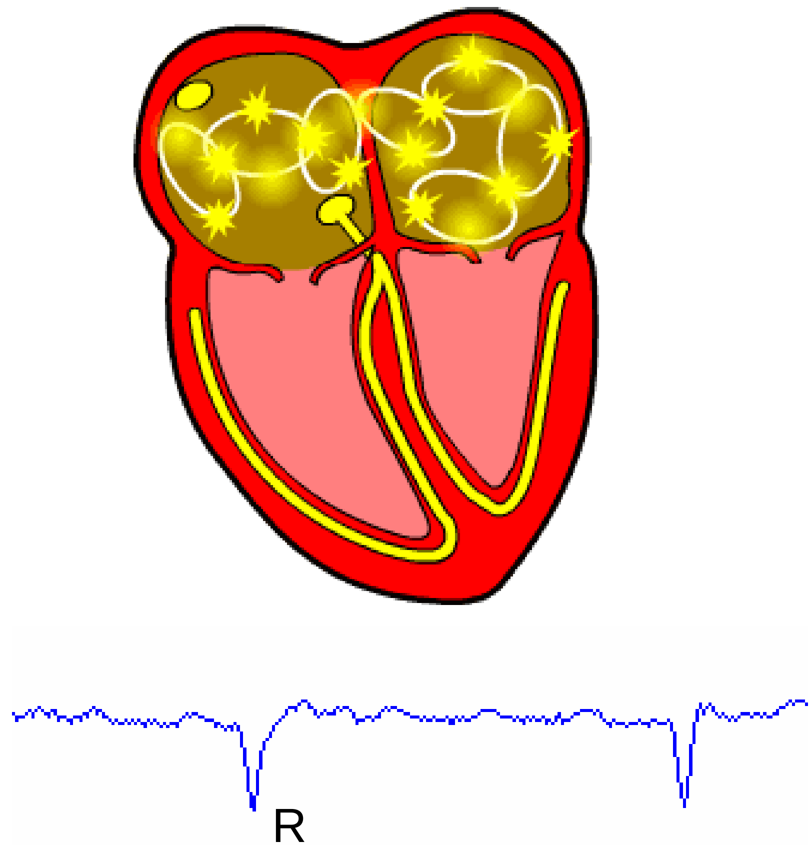
- Analyze complex rhythms for diagnosis and prognosis
- Develop novel methods for control based on dynamics of physiological system

Can you detect atrial fibrillation based on the RR intervals?

Normal

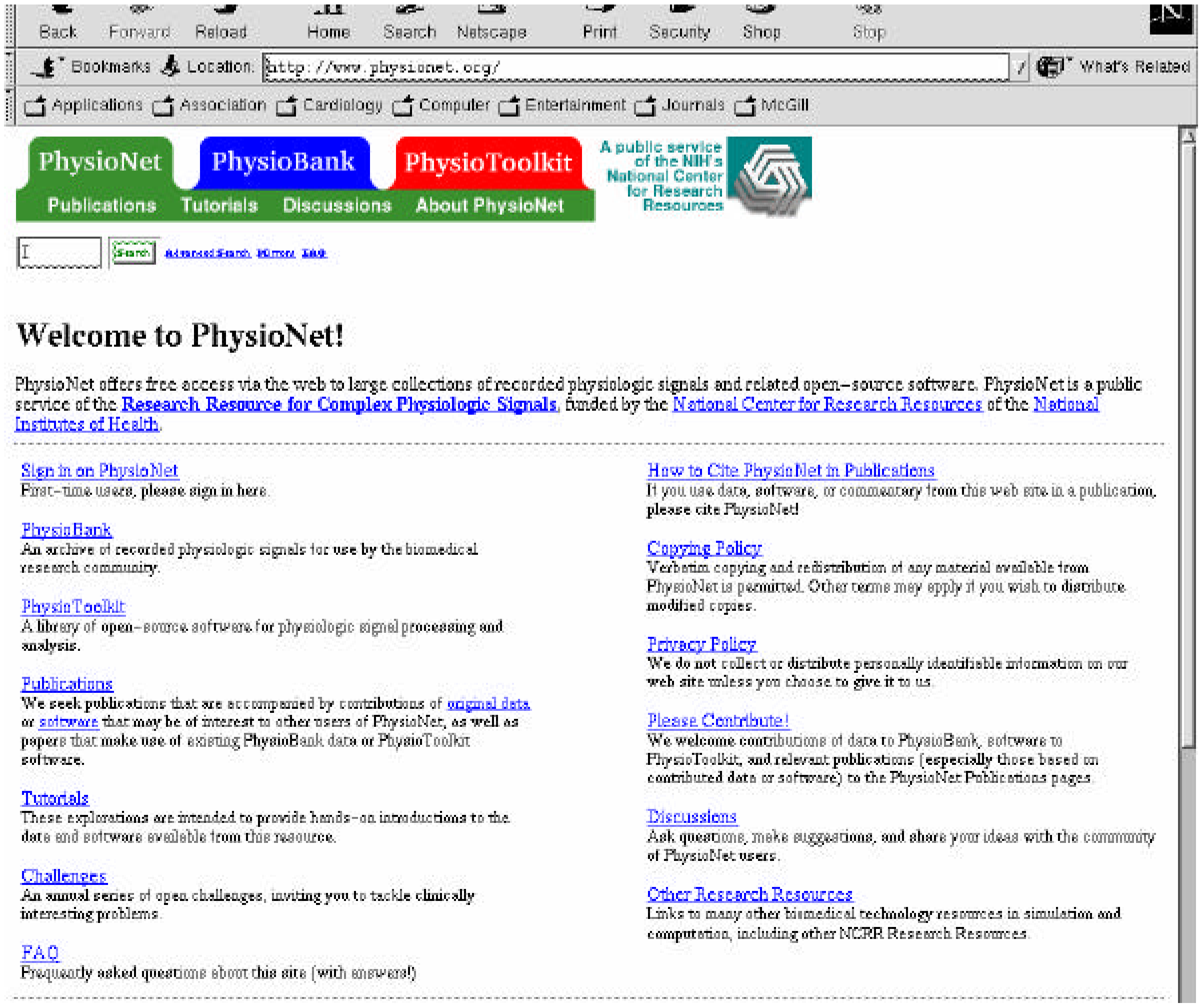


Atrial fibrillation



http://www.aboutatrialfibrillation.com

National Resource for Complex Physiologic Signals
A. Goldberger, Director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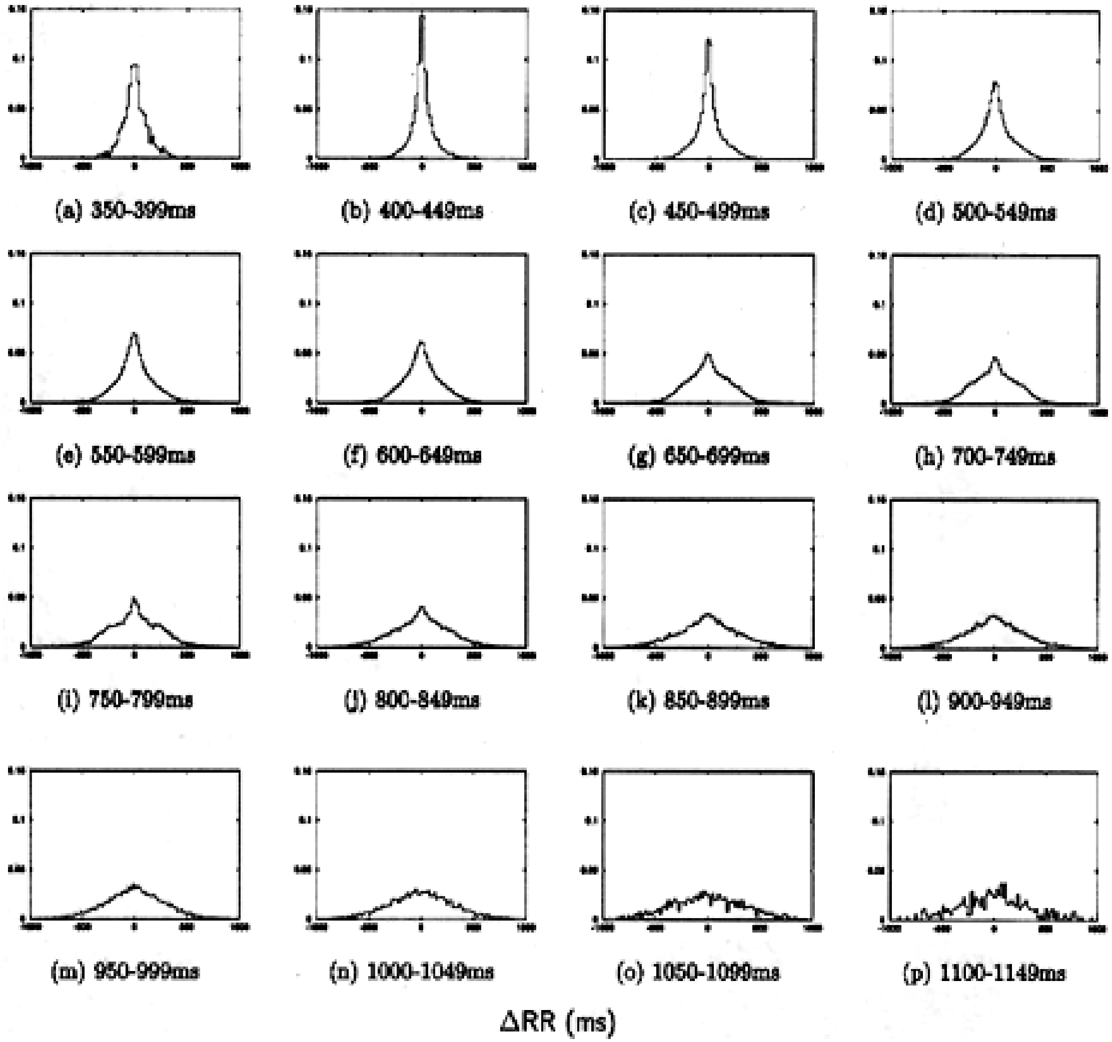
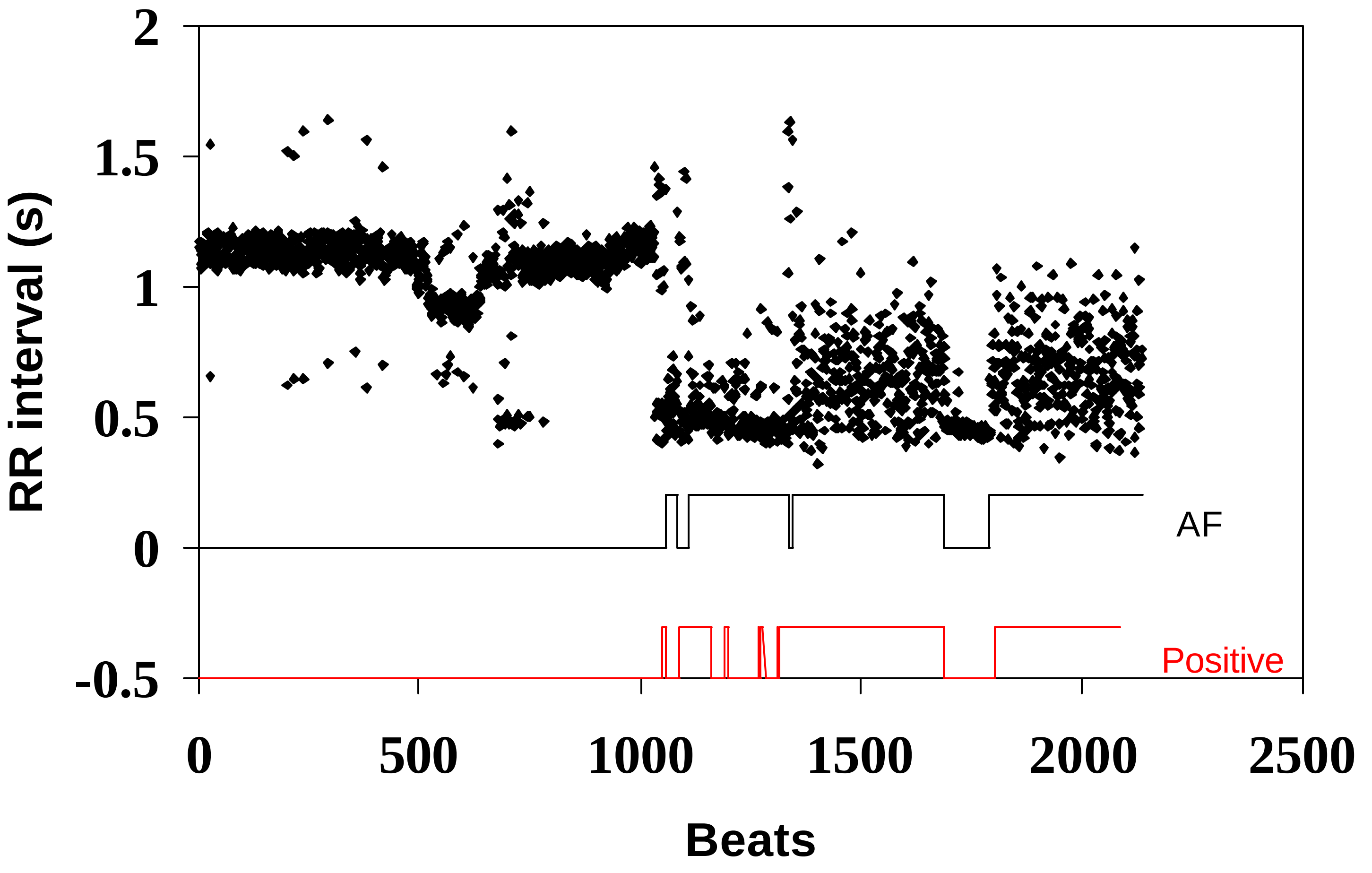
Use Histograms of ?RR Intervals to detect AF

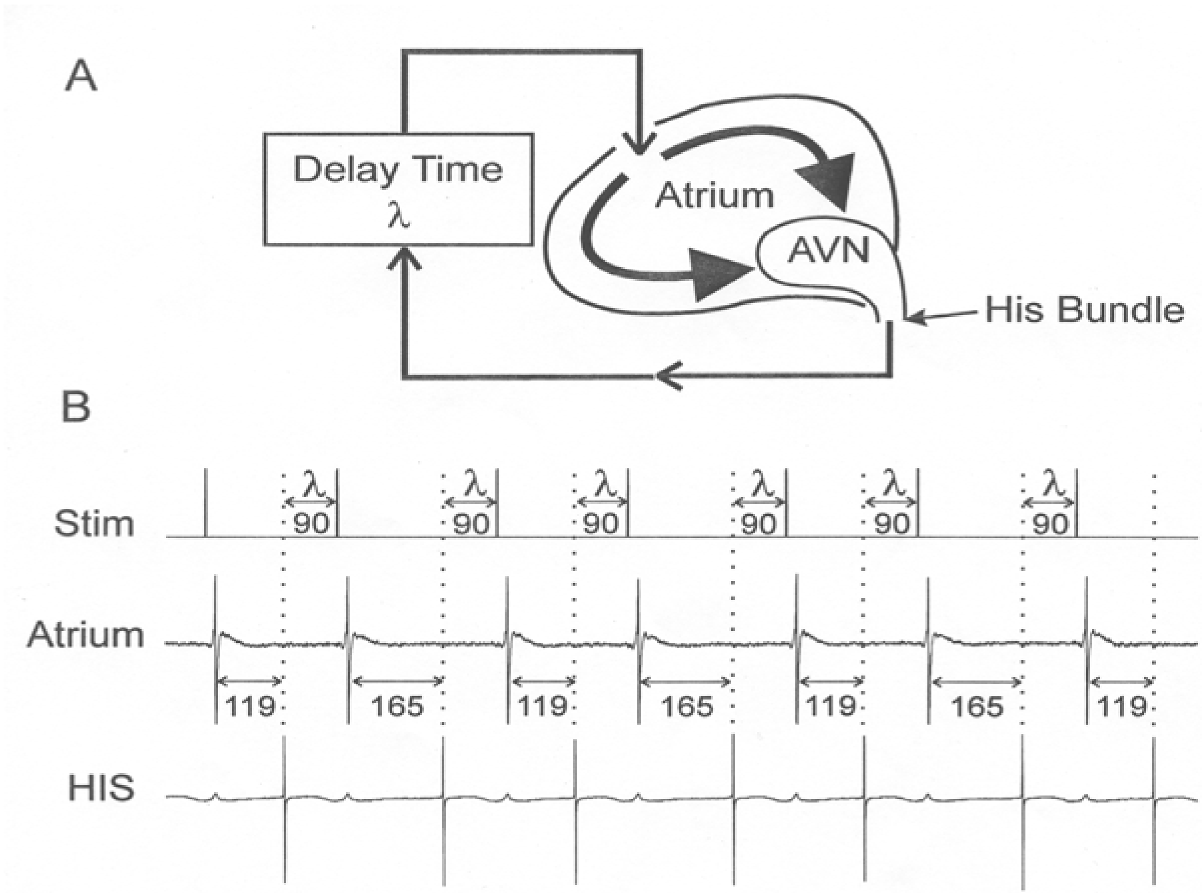


Tateno and Glass (2001)

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

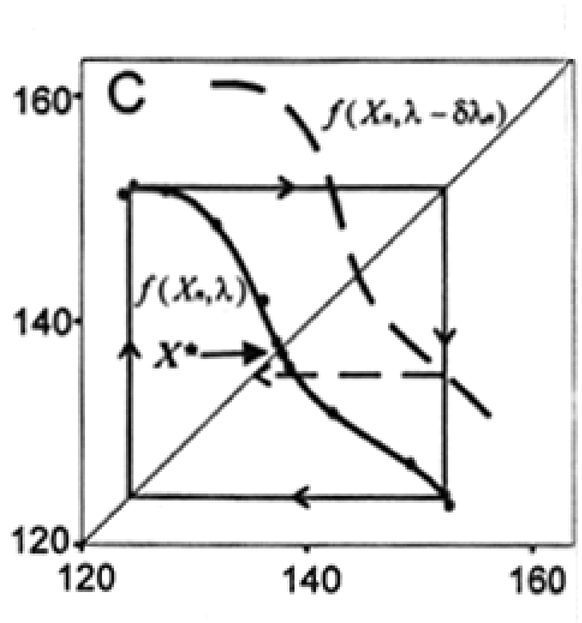


Controlling Cardiac Alternans



Hall, Christini, Tremblay, Collins, Glass, Billette, PRL (1997)

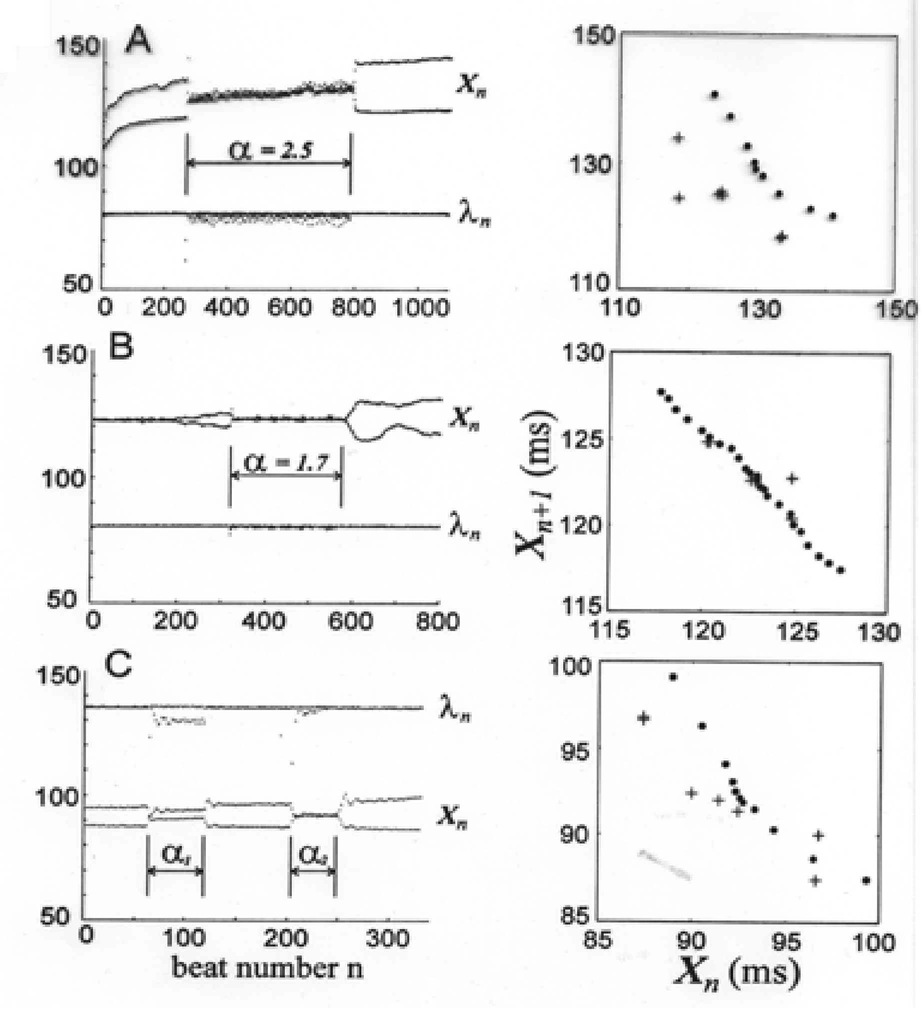
Target Unstable Fixed Point



I_{n+1}

I_n

Stimulate to Control Alternans



Same strategy works in people, Christini et al. (2001).

Conclusions

- Real cardiac arrhythmias show complex dynamics. It should be possible to understand the mechanisms of many of these arrhythmias based on quantitative analysis of electrocardiographic data over long times
- Theoretical understanding should lead to better methods for risk stratification and therapy