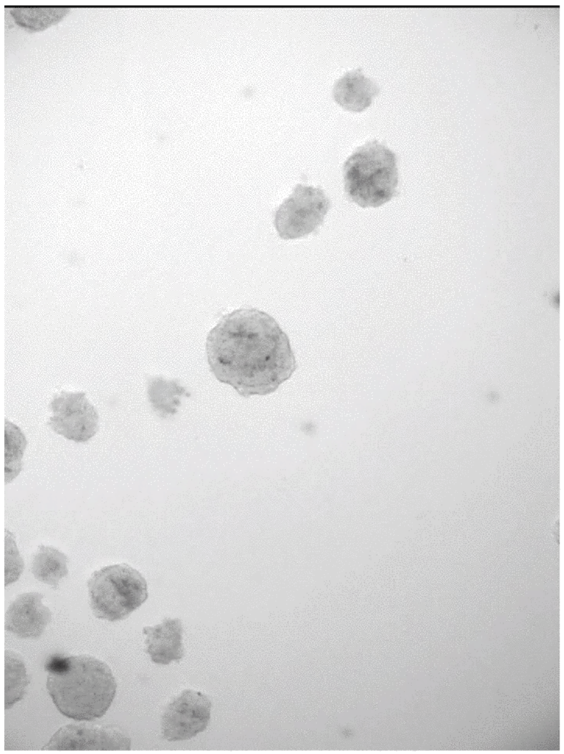

If cardiac arrhythmias exhibit universal bifurcations what are the roles for detailed ionic models?

Leon Glass

Isadore Rosenfeld Chair in Cardiology, McGill University

Universal bifurcations: qualitative changes in dynamics in generic mathematical models under parameter changes

Universal bifurcations of dynamics in nonlinear systems provide the theoretical basis for classification of arrhythmias by cardiologists ("dynamical disease").

BIG PROBLEMS

- Understand the mechanisms underlying the onset of serious arrhythmias
- Figure out who is likely to have a serious arrhythmia (risk stratification)
- Figure out how to prevent serious arrhythmias from starting
- Figure out how to stop serious arrhythmias if they start

6 Problems

- AV nodal conduction
- Alternans
- Resetting, phase locking and chaos during periodic stimulation of cardiac oscillators
- Nonsustained ventricular tachycardia (and other reentrant rhythms)
- Classification of dynamics of premature ventricular complexes
- Dynamics of early afterdepolarizations

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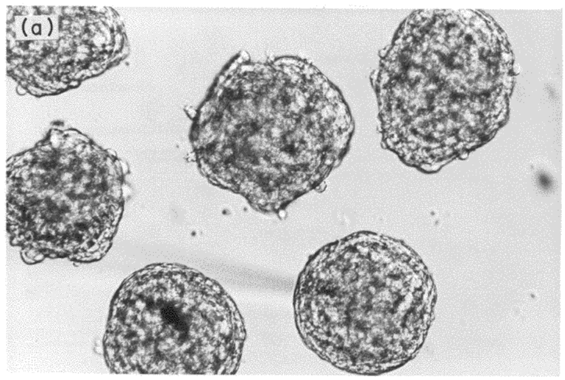
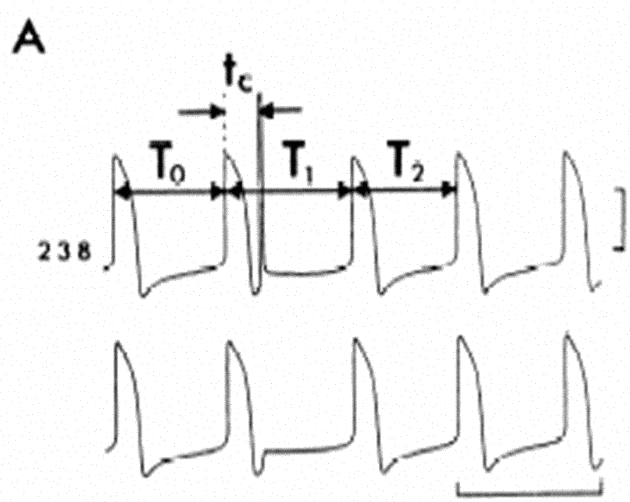
Model System – Embryonic chick heart tissue culture (Guevara, Shrier, Glass, 1980s)

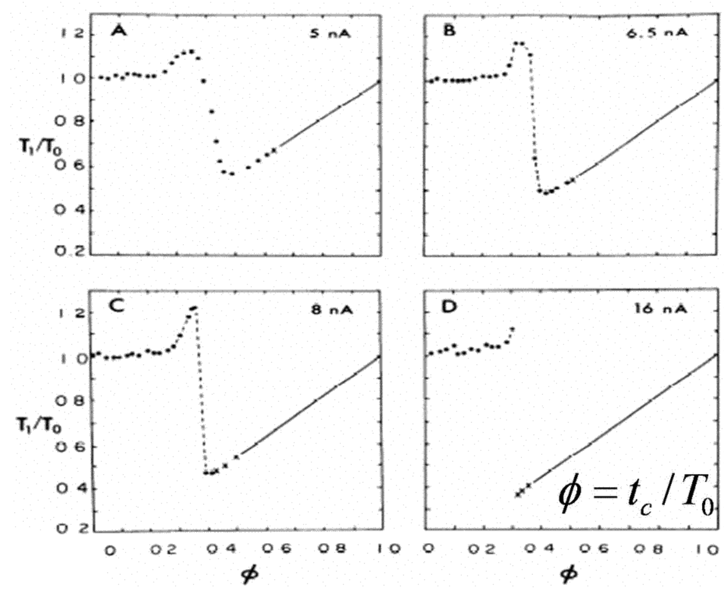


Thanks to Alvin Shrier my colleague and collaborator for over 20 years.

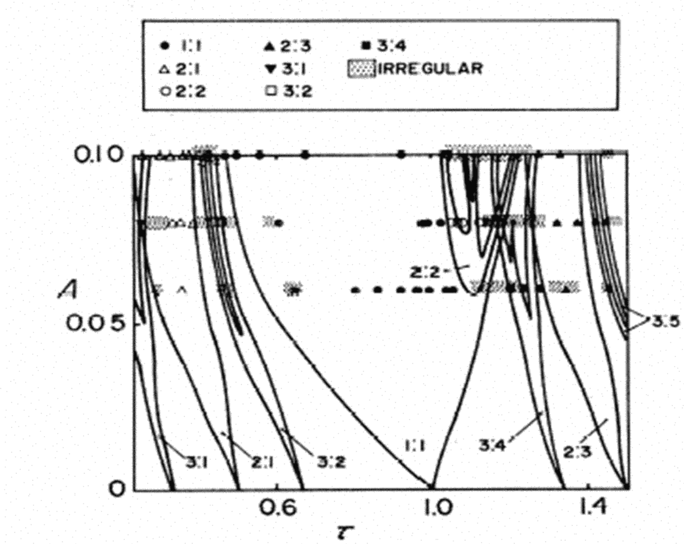
A Resetting Experiment (in chicken heart)

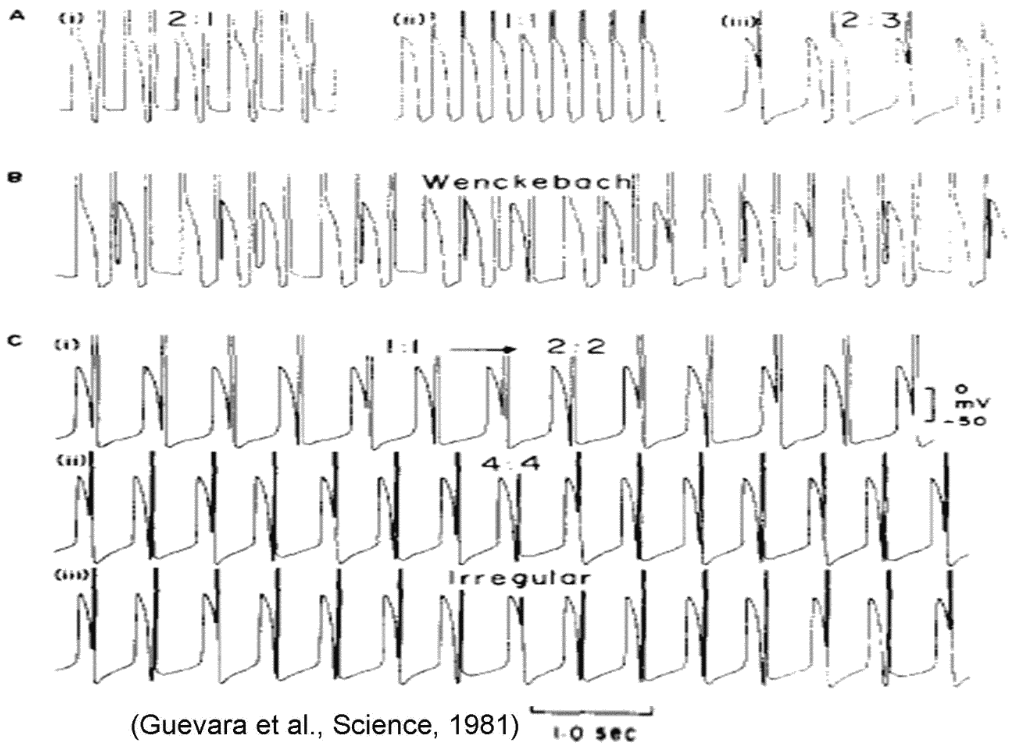


Perturbed Cycle Length Curves



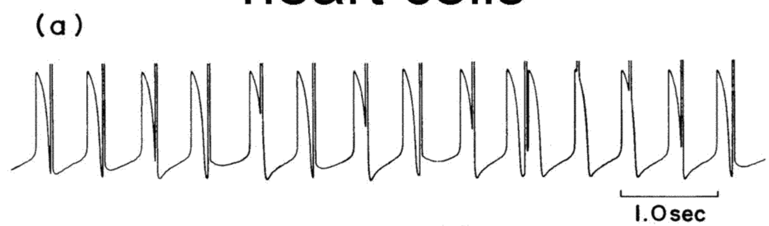
Theoretical computations of locking zones based on 1-dimensional circle maps

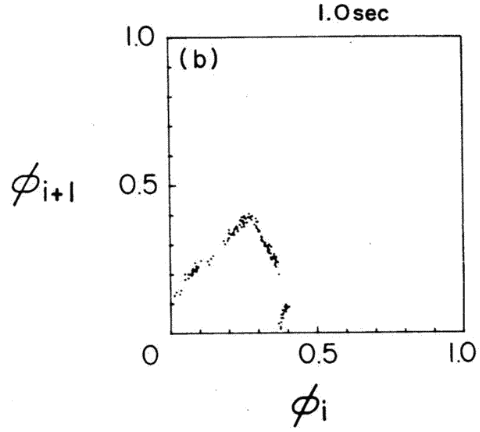




(Guevara et al., Science, 1981)

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)

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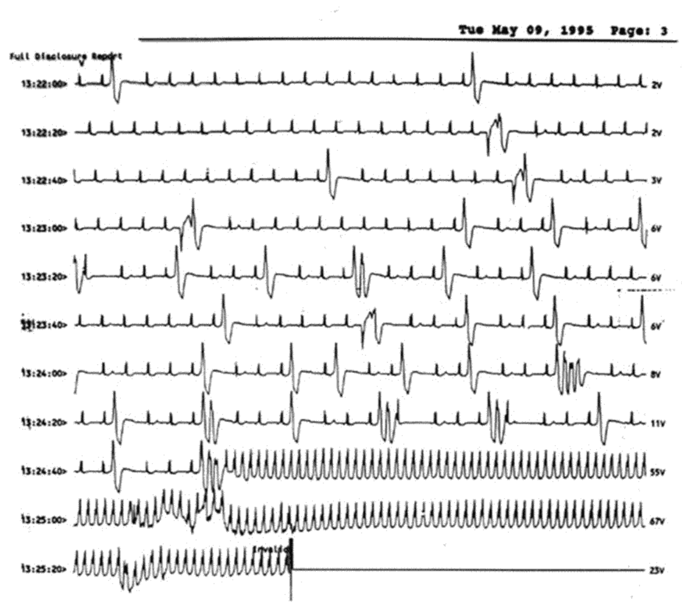
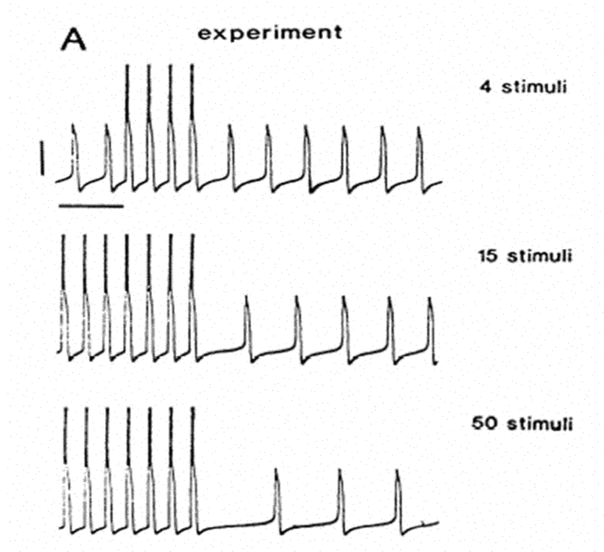
Cardiac arrhythmias suddenly start and stop

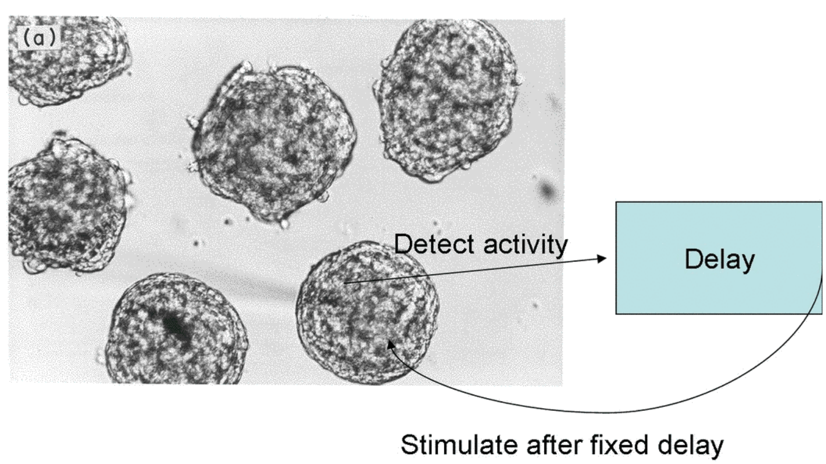


Rapid Stimulation Leads to a Slower Rhythm (Overdrive Suppression)

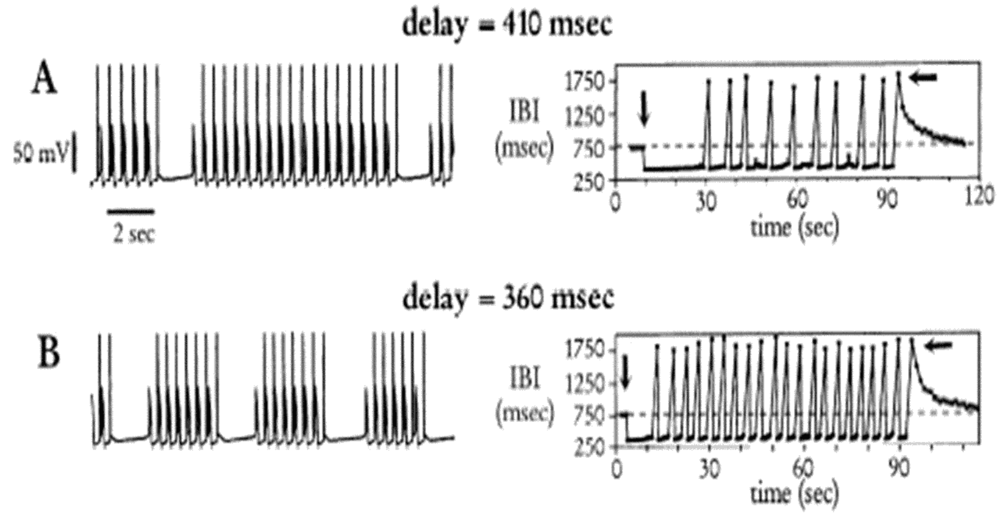


(Kunysz, Glass, Shrier 1995)

Fixed Delay Stimulation



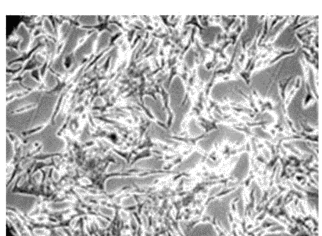
Fixed Delay Stimulation of Cardiac Aggregates Leads to Bursting

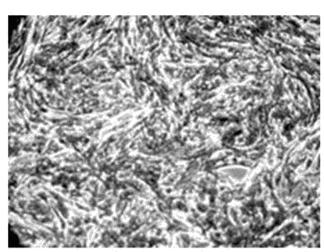


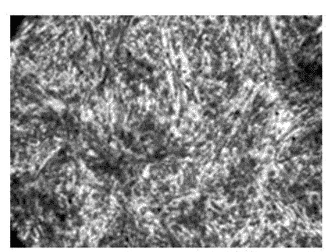
(Kunysz, Shrier, Glass 1997)

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.

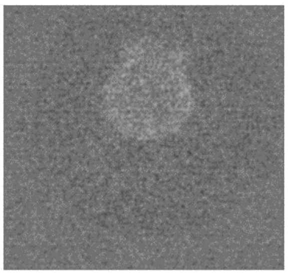

$0.5x10^3 /cm^2$


$1.0x10^3 /cm^2$

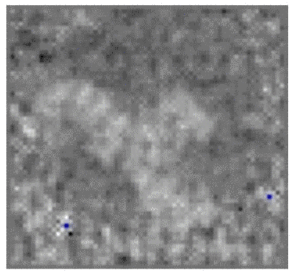

$2.0x10^3 /cm^2$

Pacemakers and Reentry in Tissue Culture

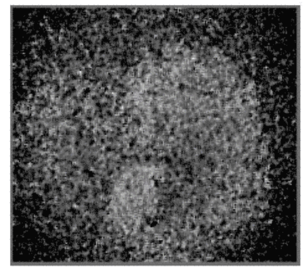
Calcium Target
(Calcium Green)



Calcium Spiral
(Calcium Green)

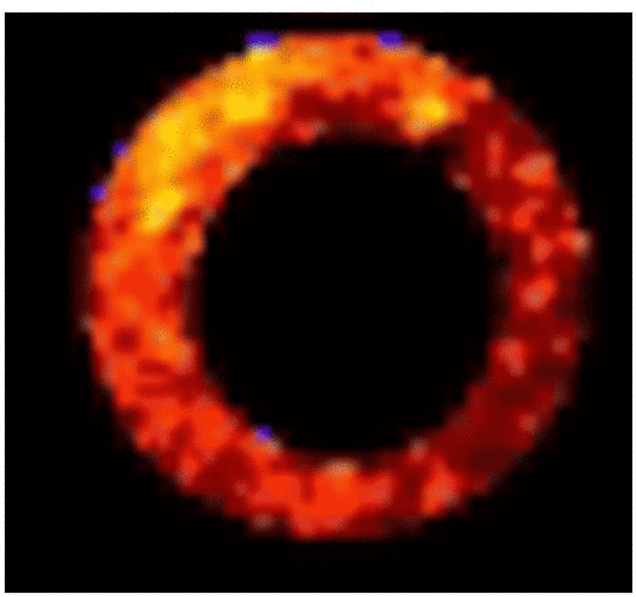


Voltage Spiral
(di-4-ANEPPS)



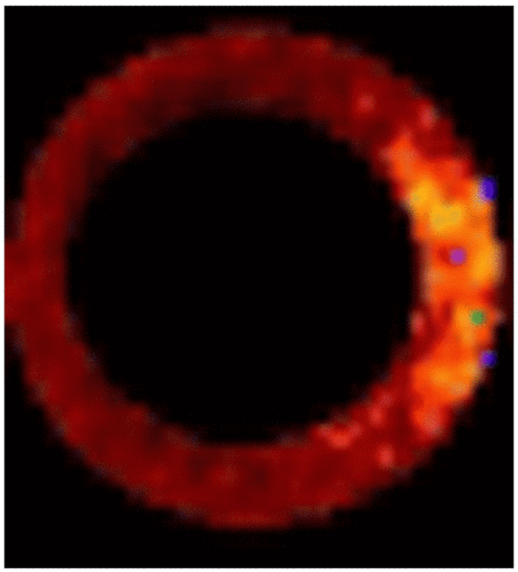
Spiral waves have been hypothesized as a mechanism for VT and VF (Wiener and Rosenblueth, Krinsky, Winfree, Allessie, Jalife, and many others)

Dynamics in a Ring of Cardiac Cells

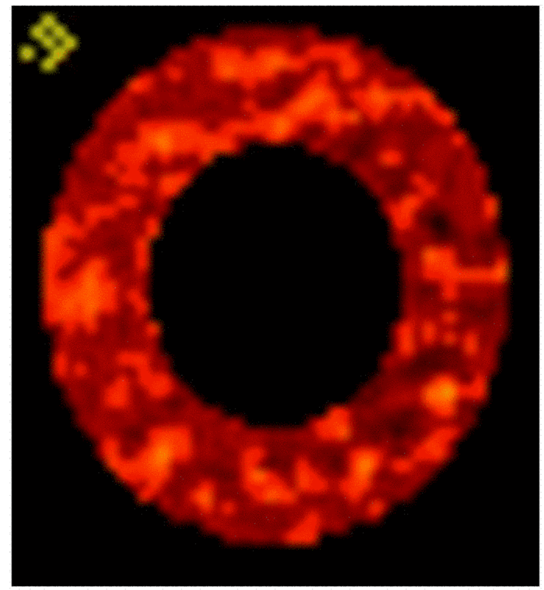


Nagai, Gonzalez, Shrier, Glass, PRL (2000)

Reentry



Cardiac Ballet



FitzHugh-Nagumo Model of Propagation

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

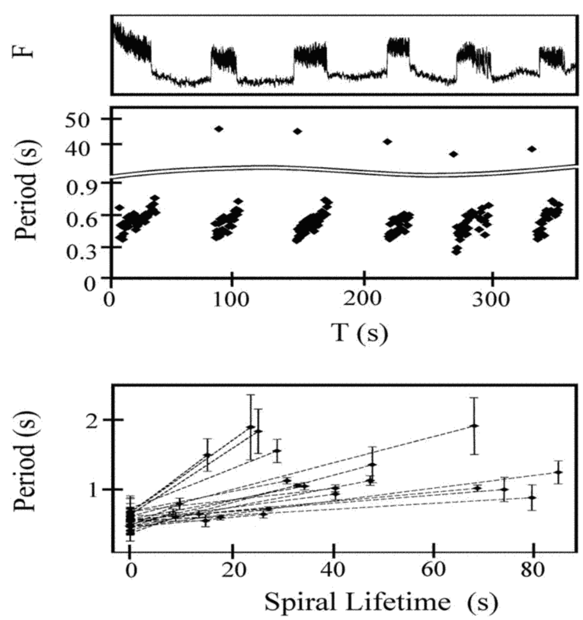
$$\frac{\partial w}{\partial t} = (.005v - .01w + .0005)R(\zeta, v),$$

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

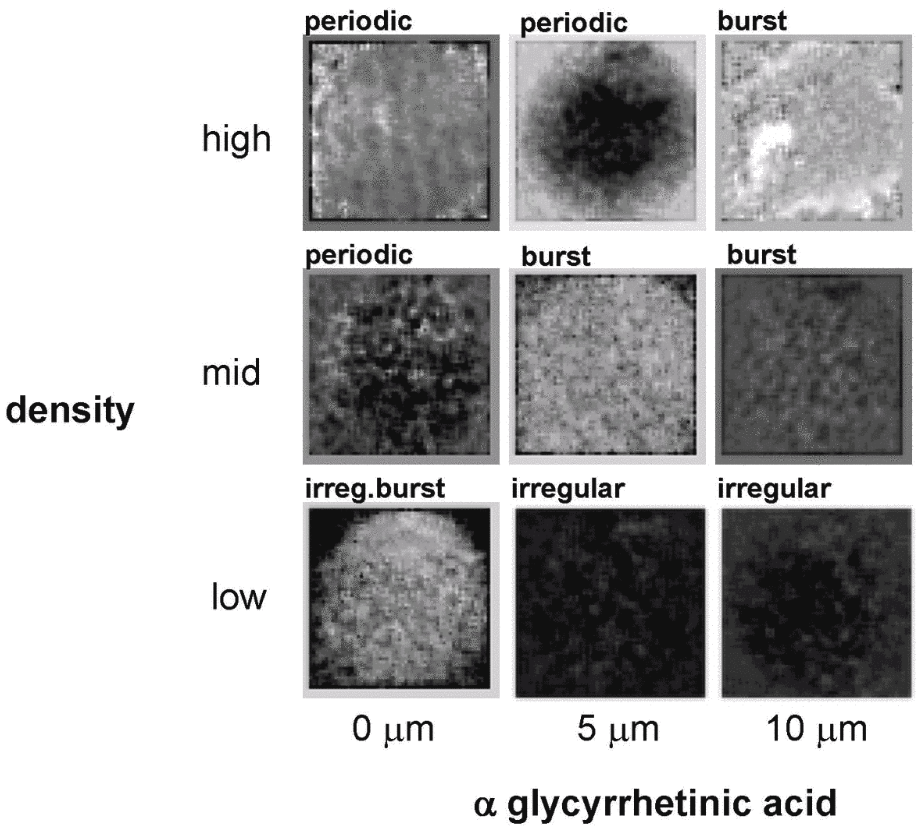
$$\zeta(z) = \frac{.015}{z+1.},$$

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

Bursting Rhythms in Tissue Culture



Bub, Glass, Publicover, Shrier, PNAS (1998)



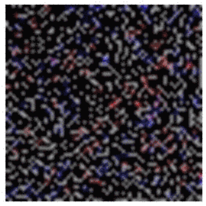
Basic properties of cardiac cells

- Heterogeneity
- Spontaneous oscillation (of some cells)
- Excitability
- Fatigue

Simulating bursting dynamics as a function of connectivity

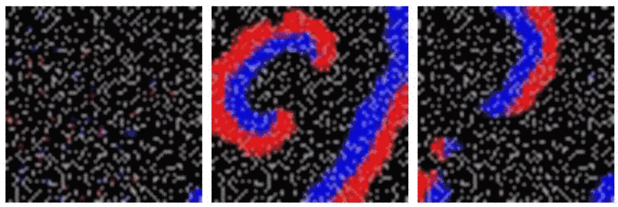
1)Add spontaneous activity by giving excitable cells a probability of firing.
2) Add fatigue by giving each cell a fatigue variable η where
a) if the cell just became excited, $\eta_{i,j}(t+1) = \eta_{i,j}(t) + F$,
b) Otherwise, $\eta_{i,j}(t+1) = \chi\eta_{i,j}(t)$, where $0<\chi<1$ (exponential decay)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

R=3, θ=0.35



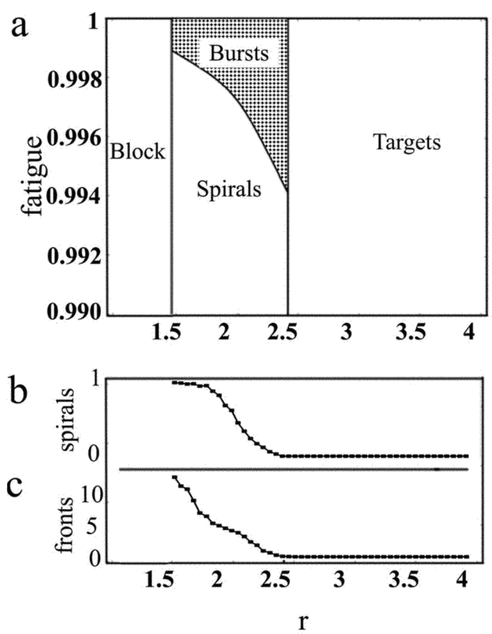
Target patterns ('periodic')

R=1.8, θ=0.35



bursting

Universal organization: Fatigue vs Coupling



(Bub, Shrier,Glass, PRL, 2005)

Propagation velocity for different sink densities and diffusion coefficients in FHN

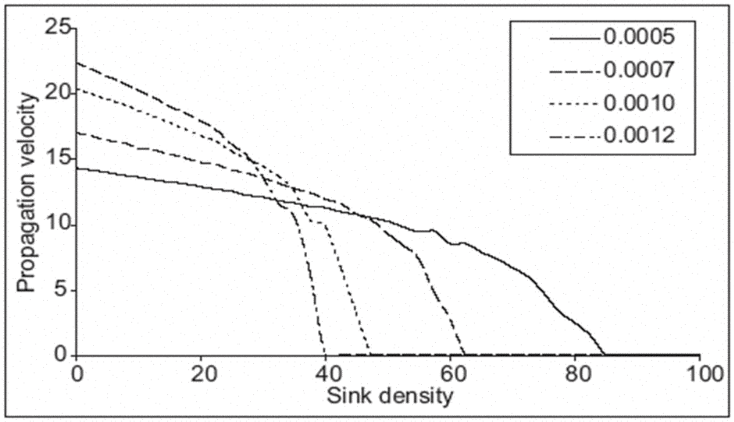


Figure 3. The mean v_p of the simulations run at a given ρ for $D = 0.0005\ \mathrm{cm^2\ s^{-1}}$, $0.0007\ \mathrm{cm^2\ s^{-1}}$, $0.0010\ \mathrm{cm^2\ s^{-1}}$, and $0.0012\ \mathrm{cm^2\ s^{-1}}$. At low numbers of current sinks there is an approximately linear decrease in v_p for increasing ρ. The linear regime is followed by an abrupt transition to wave block. The transition occurs at lower values of ρ as D is increased, suggesting decreased plane wave stability at increased D.

Dimensionless number for plane wave breakup

R=refractory period

D=diffusion coefficient

ρ Density of defects

τ Rise time of action potential

$$\sigma = R\sqrt{\frac{\rho D}{\tau}}$$

Steinberg, Glass, Shrier, Bub (2006)

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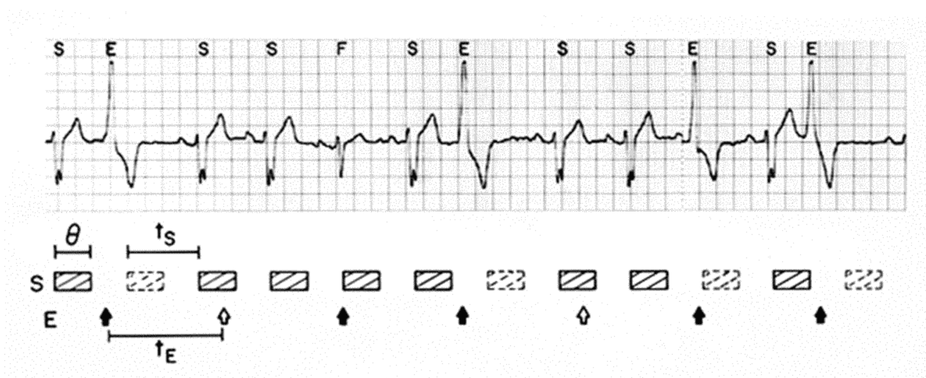
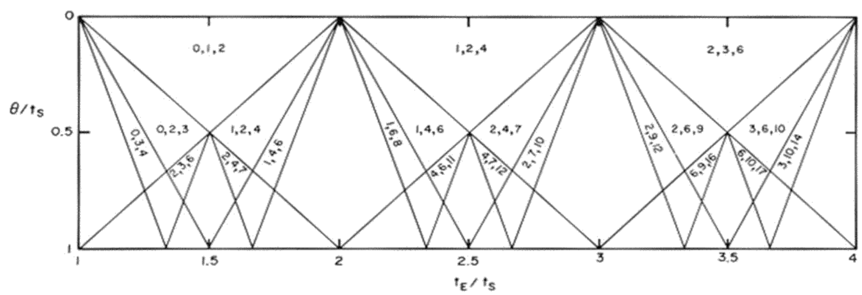
Pure Parasystole



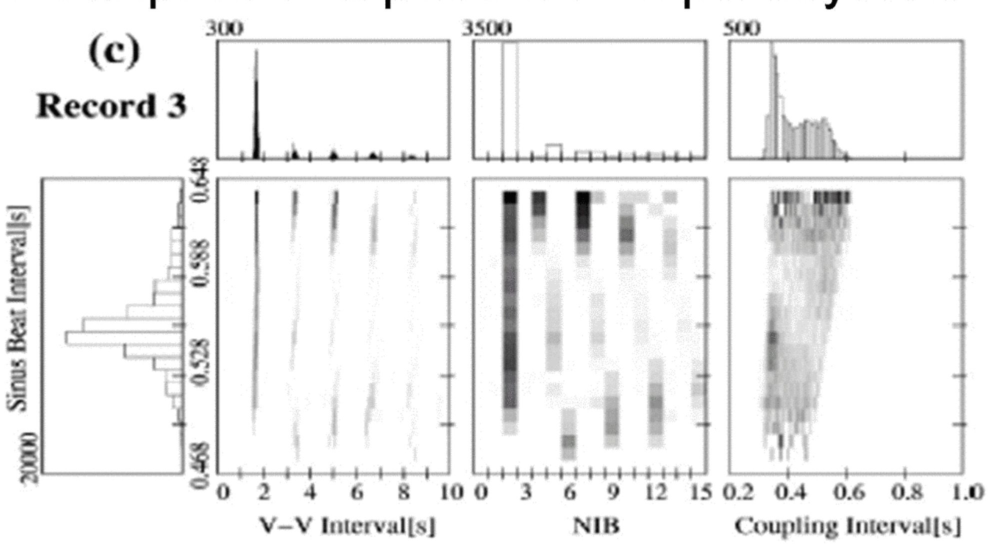
Rules of Pure Parasystole

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)

Heartprint of a patient with parasystole



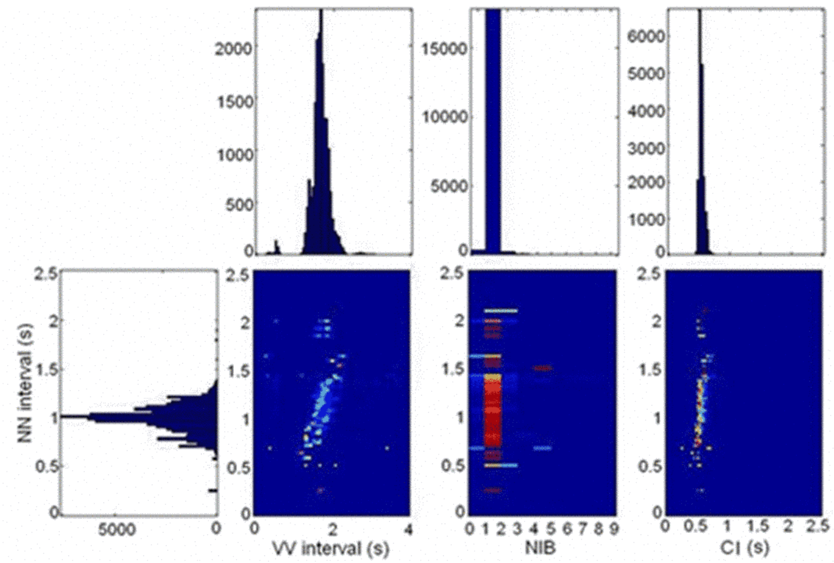
PHYSICAL REVIEW E 66, 031901 (2002)

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]

PhysioBank's Sudden Cardiac Death Database

Heartprint from a patient who had sudden cardiac death
- Record 47 -



Striking ECG characteristics from dynamical analysis in 6/15 SCD patients

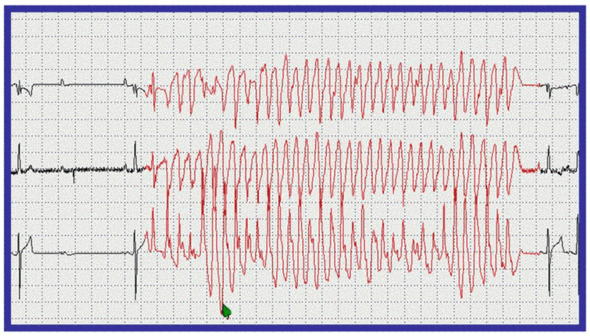
Analysis using the PhysioNet Sudden Cardiac Death Holter Database

(i) Frequent ventricular bigeminy (>5% of total ventricular arrhythmias)
(ii) Long QTc > 0.5 s
(iii) Fixed CI
(iv) Onset of torsade de pointes after a long-short RR sequence

Consistent with a mechanism of early afterdepolarizations leading to SCD

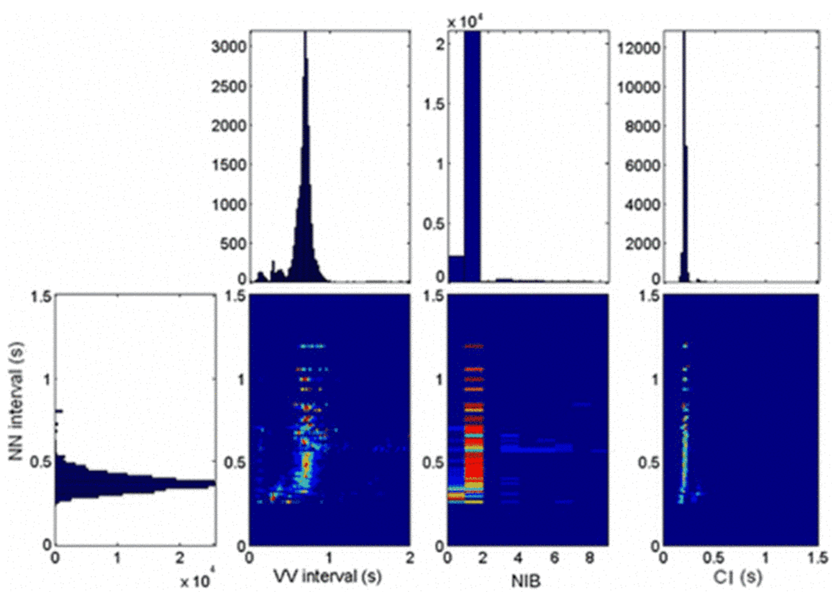
Lerma et al., J. Electrocardiol. In Press

German Shepherd Dog Inherited Ventricular Arrhythmia



Sydney Moise, DVM and Robert Gilmour, PhD,
Cornell University College of Veterinary Medicine

- Record from Dog # 4 who suffered sudden cardiac death -



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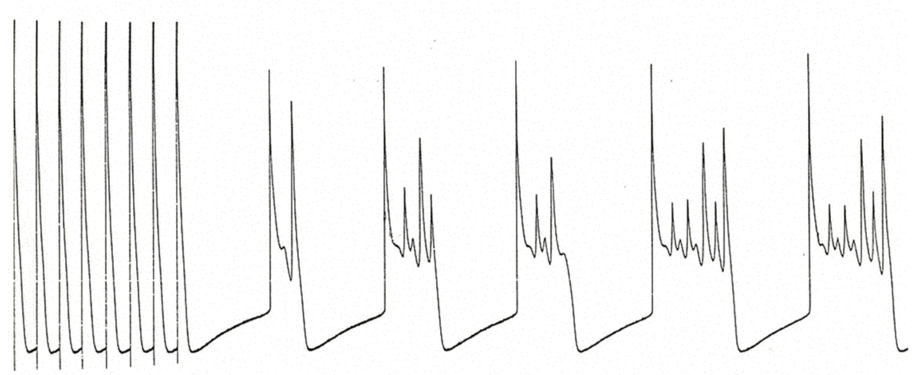
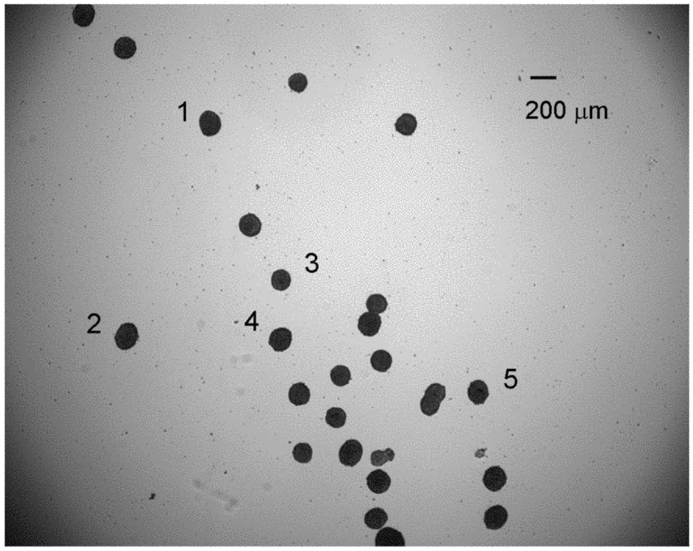
Early Afterdepolarizations

Present in Purkinje fibres in 4 week-old German Shepherd



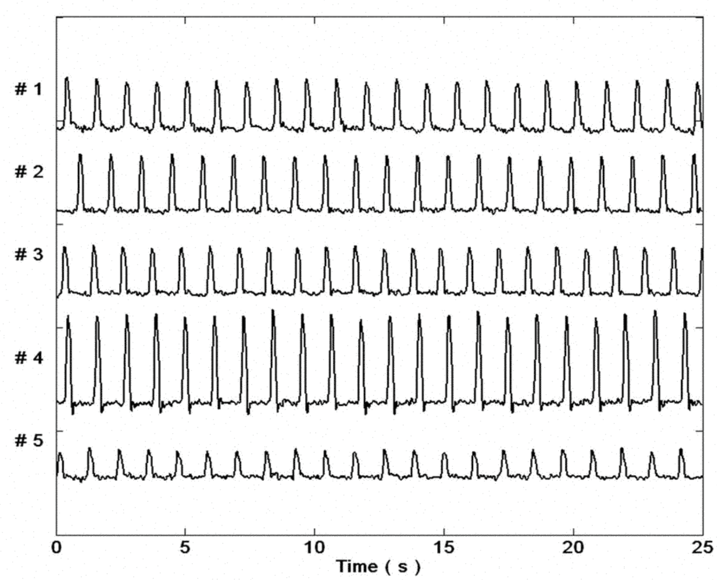
(Gilmour et al., JACC, 1996)

Aggregates of 7-day-old embryonic chick ventricular myocytes



Min-Young Kim

Recording of motion artifacts from chick heart cell aggregates



Effect of 1 mM E-4031 (IKr blocker)

6 Problems

- AV nodal conduction – Devil's staircase
- Alternans – Period doubling bifurcation
- Periodic stimulation – Arnold tongues plus
- Plane wave breakup; bursting reentrant rhythms – Universal for excitable systems with heterogeneities and fatigue
- Parasystole – "Gaps and steps" problem in number theory
- Bifurcations in systems with early afterdepolarizations – still to be done

If cardiac arrhythmias exhibit universal bifurcations what are the roles for detailed ionic models?

- **To model experiments (e.g. voltage clamp, addition of drugs, optical mapping of spirals)**
- **To predict new phenomena**
- **To better understand the limits of universal bifurcations in simple models (all of the early models based on 1D maps for AV heart block, alternans, and entrainment break down since they do not include time dependent changes in physiological properties during stimulation)**