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To cite this version:
Guillaume Attuel, Hussein Yahia. Cardiac arrhythmias and Griffiths phase: desynchronization of excitable cells. IUPAP; ENS Lyon; CNRS; Université de Lyon. STATPHYS 26, Jul 2016, Lyon, France. STATPHYS26 - Palais des Congres - Lyon 18-22 July 2016, 2017. hal-01568714

HAL Id: hal-01568714
https://inria.hal.science/hal-01568714
Submitted on 25 Jul 2017

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Cardiac arrhythmias and Griffiths phase: desynchronization of excitable cells

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Keywords: Cardiac Arrhythmias, Intermittency, Memory, Collective phenomena, Gap junction polarization, Domain growth

Challenges of C arrhythmias raised by the data

- Most frequent cause of embolic stroke (AF), with evolution to chronic disease. Major cause of natural death (VF), about 3% only are saved.
- Prevalence: strike twice and patient resuscitates.
- Most models refer to chaotic dynamics, but this does not describe spontaneous reversions to lesser C arrhythmias.

Figure 1: Cardiac arrhythmia forces reverberation by applying electric shocks. A kind of hysteresis.

Some features suggest intrinsic disorder:

- The data show intermittency of beat-to-beat intervals and peaks amplitude.
- Slow evolution of vulnerability (the susceptibility), so called remodeling. Conduction velocity is not known to be very much affected. Intermittency may instead reveal nucleation and contamination processes à la Pomeau. However, the medium is excitable and excitability is a robust cycle to any home- or heteroclinic nucleation.

Figure 2: (Left) Biomechanics of atria showing catheters. (Right) Turbulent like temporal series of a complex atrial

The basic idea is that cycles become coupled to a new doF, inducing an effective heat-to-heat interaction, i.e., memory, which induces intermittency.

The probability distribution of amplitude increments shows scaling $\rho(A) \sim A^\nu$, with seemingly non-universal Fisher exponents in the range $0.5 \leq \nu < 1$. Moreover, long range correlations are found systematically.

Figure 3: Excitable cycles are immune to tangles. They can become excitable but not easily chaste.

The plausible physiology

- Memory can be a responsive sensitivity to left-overs after each pulse passage.
- Intermittency suggests some sort of nucleation process. For instance with a bistable cell cycle.
- The model introduces resonant interactions between cell cycles and inter-cell modulations. Temporal chaotic dynamics follow for two or three coupled cells, spatio-temporal intermittency for any greater number of cells.
- The coupling is induced by abnormal gating polar asymmetries and sensitivities of cardiac connexins.

An unstable modulation of the gap junction channel conductances is described. The argument is essentially as follows: above an instability, inter-cell cycles may locally saturate the connections, which temporarily become inhibitory.

$$\frac{dI_{m}}{dt} = m_{\alpha} - m_{\alpha} \beta_{\alpha} - I_{m} + \Delta I_{\alpha m} \sin(\theta_{\alpha})$$

where $\Delta I_{\alpha m}$ is the membrane potential and membrane current of cells. (\(\alpha, \beta\)) are the common gap junction conductance and density of abnormally opened channels. This model simply stipulates the conservation of free and bound charges. Parameters account for intrinsic properties. $D$ is the resting conductivity, while $\beta$ encodes fluctuations of the directional conductance. There exists a Rayleigh number $R_{\alpha} \equiv \frac{\beta_{\alpha}}{\alpha_{\alpha}}$, where $\beta_{\alpha}$ is a forcing boundary current.

Figure 4: (Left) Schematic drawing of gap junctional ionic exchanges, where the excess (black) is due to bound charges. (Right) Schematic cycle of gap junction conductance induced by the instability.

For a few coupled cells only, chaotic dynamics are found. With spatial dimension, the system quickly bifurcates toward turbulent dynamics.

Figure 5: (Left) Two consecutive instances in one patient of the signal trace, with an envelope estimation by Hilbert transform. (Right) Beat-to-beat long range correlations.

Domain growth and signal analysis

- Gap junction channels have altered couplings with "turbulent" dynamics.
- Back-scattering is normally protected by chirality and refractory period. Occurrences are like abnormal excitations (with continued pulses) or micro-reeentries (with discontinued pulses). Random annihilation and re-emission give a hierarchical structure of propagation in 1xD. Pulses in 2D somehow split.

$$\text{Write } \mathbf{U} = \mathbf{U}_{0} \pm \mathbf{A} \text{towards necessary symmetry breaking terms are } \frac{1}{2} (\mathbf{U}^2 + \mathbf{U}^2 - \mathbf{U} \mathbf{U})^2 \frac{\partial}{\partial t} \text{total internal dynamics from excitabile (Pitugh-Ha-Nagumo) to oscillatory (CGL). Anything in between with equilibrium locally modified } \delta \mathbf{U} \rightarrow \delta \mathbf{U} + \mathbf{U} \text{. The phase model describes change density waves.}

\text{The phenomenon should be that of depinning directed fronts on a disordered medium. Since disorder is turbulent (heavy-tail PDFs, } \mathbf{K}_{F} \text{, } \mathbf{K}_{F}) \text{, the rare-events dominated KPZ fixed point may well describe the dynamics multi-scaling.}

Figure 6: Table of the measured Fisher exponents for 5 patients. It appears that regional gradients may indicate a source of activity.

Figure 7: Schematic temporal map of the membrane potential showing many back-scattering events, some abnormal autonomy, and an overall hierarchial branching propagation.

Figure 8: Spatio-temporal map of the membrane potential showing many back-scattering events, some abnormal autonomy, and an overall hierarchial branching propagation.

The electrotonic coupling of fibroblasts to connexins

- Since pulses are chiral, back-scattering may be related to a chiral-anomaly (\(\theta\) term).
- With the gap junction functions, the relevant symmetries jumps from compact (\(\mathbb{U}\)) to (\(\mathbb{O}\)). It is possible to define a critical coupling $\sim T^{-1}$, like $T \rightarrow 0^{+}$.
- Would this define a sudden death critical point?

References


Acknowledgment

Work partially supported by FP7/2007-2013 and CANEXION 2014-086082-00003295

Figure 9: Instance of three traces of the gap junction flux deterioration near, at mid distance, and far from the border source. Fisher exponents decrease gradually with the distance from the source.

Figure 10: Spatio-temporal map of the membrane potential showing many back-scattering events, some abnormal autonomy, and an overall hierarchial branching propagation.

Figure 11: An Ising-Bloch transition associated with a back-scattering event. (Right) Phase portraits at three different points.

Figure 12: Singularity spectrum of one experimental and one numerical time series, with equal Fisher exponents. The spectrum shows the Hausdorff Dimension $\mathcal{D}(\mathbb{U})$ of the set of points with Holder singularity $\delta_{+}^{\mathcal{D}}(\mathbb{U}) = \frac{\mathcal{D}(\mathbb{U})}{\delta_{+}}$, for a scale of

Figure 13: Singularity spectrum of one experimental and one numerical time series, with equal Fisher exponents. The spectrum shows the Hausdorff Dimension $\mathcal{D}(\mathbb{U})$ of the set of points with Holder singularity $\delta_{+}^{\mathcal{D}}(\mathbb{U}) = \frac{\mathcal{D}(\mathbb{U})}{\delta_{+}}$, for a scale of

Discussion

- In summary, the data show multi-fractal scaling and rare events.
- P. Hanov et al. revealed the multi-fractal scaling of heat-to-beat intervals, with only mono-fractal scaling for heart failure. This underpins the collective response in the sinus node to competing hormonal stimuli. Here, a collective behavior of cardiac excitable cells emerges because of high beating rates and memory effects. Physiologically, what our model crucially builds on is that slight alterations of the electrical synapse kinetics, make the network of cells undergo a transition to spatio-temporal desynchronization. The hypothesis is straightforwardly extending steady-state properties of connexins: voltage-gated hemi-channels are also sensitive to local electrically mediated potential gradients (third line of eq.[8]).

- The abnormal physiology may be related to polarized connexins.

- The electronic coupling of fibrinogen to connexin (Cx43 and Cx45). This has the correct time scale of $100 \mu s$. Ryanodine sensitive (RyR2) calcium channels of the sarcoplasmic reticulum, in excitation-contraction coupling: However the time scale is reported to be shorter.

- The coupling of abnormal conduction properties throughout the tissue is a candidate description of electrical remodeling. Down regulation (e.g. from the accumulation of Calcium) with slower time scales would lead to long term remodeling. As the coupling velocity increases, vulnerability decreases.

- Randomly driven excitatory and inhibitory couplings: is there a glassy phase transition, which mimics parasympathetic toachic ones?

- Critical region is very large, Griffiths in a broad sense. Infinite range correlations, power law tail PDFs, $\mathbf{K}_{F}$ power spectrum, broad singularity spectrum. This is common to many models of disordered networks exhibiting avalanches, here of defects.

- Since pulses are chiral, back-scattering may be related to a chiral anomaly (\(\theta\) term).

- With the gap junction functions, the relevant symmetries jumps from compact (\(\mathbb{U}\)) to (\(\mathbb{O}\)). It is possible to define a critical coupling $\sim T^{-1}$, like $T \rightarrow 0^{+}$.

- Would this define a sudden death critical point?