The role of abnormal inhibitory transmission at the gap junctions of cardiac cells in fibrillation

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Abstract

The noisy aspect of data recorded by electrodes, on the inner surface of human atria during episodes of atrial fibrillation, exhibit intriguing features for excitable media. Instead of phase chaos as typically expected, it shares many common traits of non-equilibrium fluctuations in disordered systems or strong turbulence. To assess those peculiar observations we investigate a *synaptic plasticity* that affects conduction properties. Electrical synapses comprise many different kinds of connexins, which may be affected by diverse factors, so we use a generic approach. Slight detuning of their linear response leads to an instability of the modulating agents, here an excess charge. Acting on slow time scales of repolarisation, it is understood as *collective modes* propagating through and retroacting on each synapse: The medium is *desynchronised*. It is not a syncytium. Transient states are here associated with a phenomenon called *electrical remodelling*, which has not received any accepted description thus far. Moreover, from the properties of the model it is possible to start exploring phase space. Transitions between different regimes could help decipher stages in the evolution of the disease from acute to chronic, one main goal of cardiovascular research.

Excitability

Theoretically, a myocardium is an excitable tissue acting under normal circumstances as a functional syncytium of myocardial cells. Models of excitability for the heart are reaction-diffusion systems describing the propagation of electric pulses called action potentials similarly to models for axons. Reaction results from ionic exchange cycles between the cytoplasm of excitable cells and their extra-cellular medium, when initiated by a stimulus above some threshold. Pulses are robust topological structures.

Chaos

Considering the stable fixed point as a phase resetting state, even under periodic forcing, no return map can be drawn, therefore no chaos. Chaos may arise in temporal sequences. As propagation becomes further involved in the arrhythmia, spatio-temporal chaos amounts to the breakup of spirals from direct fore front and back front collisions within the pulse train. This is the paradigm for cardiac fibrillation.

Complexity of facts

Numerous facts are not described at all within the paradigm. Here is a short list: At the tissue level, recorded signals have wildly fluctuating amplitudes, with specific properties. Recorded patterns of activation form various defects and domains in relation to the substrate. Each pulse forms a « complex » that looks scattered and fragmented. At the cellular level, early after depolarisations are observed. Common wisdom for EADs tells that inward currents must overwhelm outward currents, specifically Ca over K. This is like a Hopf bifurcation dynamically. It suggests that chaotic pulses are possible. Finally, at the organic level, Ca overload being cytotoxic, cells respond by trying to lower Ca concentrations, which response in turn is arrhythmogenic. This vicious circle is called remodelling. It starts immediately after a first episode and evolves slowly through the years.

Human data

The distributions of amplitudes all collapse on a scaling function G. We map exponents on 5 patients showing non-universal properties. Singular exponents are observed with consistent Hausdorff dimension of sets D(h). Negative contribution is high, suggesting an underlying multiplicative process.

$$P(A,A_c) = A^{-\tau} G\left(\frac{A}{A_c}\right) \qquad \tau = \max_{h<0} \frac{(D(h)-1)}{h}$$

Computational model

Excess charge in cells like of Ca may perturb the dynamics of synapses. We consider a physiologically plausible linear response of synapses to the electro-chemical potential. This response is unknown as of today. The new dynamics may interact with excitability. It has the specific form of a Rayleigh instability here. Cycles become retarded or advanced. Hopf bifurcation and chaos are allowed creating EADs. Regarding propagation, pulses are pinned and released on a chaotic background. Cycle modulations create defects via facilitation through the third dimension. Defects proliferate creating a glassy phase, which back-scatter fronts in 1D and roughens them in 2D. Further effective inhibitor diffusion splits them. All the above properties for pseudo-recordings are retrieved. Electrical remodelling is the time by which the background has pervaded the tissue.

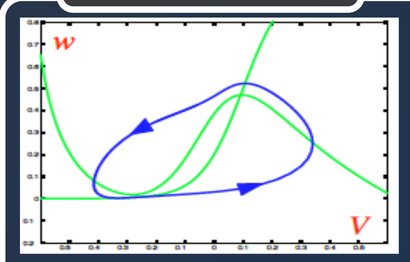
Discussion

There are features of SOCs in large regions of phase space. Pulses have a phase and propagate on a random medium. For instance one paradigm would be:

$$\nu\,\partial_t\theta + \sin(\theta+\tilde{\varphi}) = \Omega + \partial_{xx}\theta$$

Randomness reactualises non-linearly, which tells that the noise is quenched and reseted. For instance in 1 + 1D, spatio-temporal maps look very much like optimal directed paths along diagonals. In 1 + 2D, we are guessing that pulses do propagate in the (q)KPZ universality class, just as the remodelling front does. We will need refined numerical computations to confirm this. This is consistent with a multiplicative process. Physiologically, one interesting bonus is the interpretation of non-reentrant Tachycardia as dislocation patterns slowly evolving.

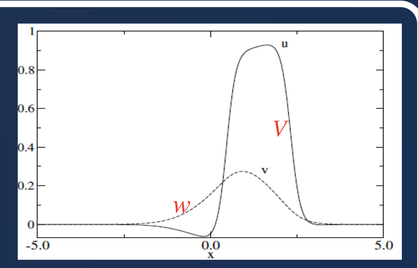
Packed in brief I

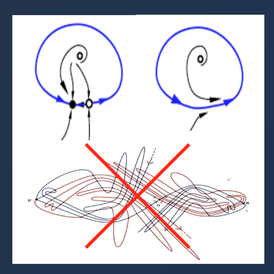


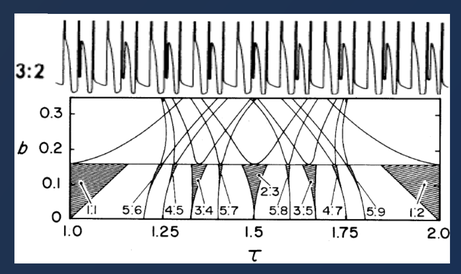
Only acceptable transition is excitable to automatic:

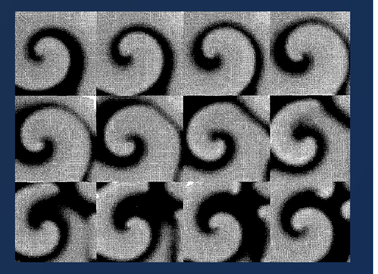
$$\nu\,\partial_t\theta + \sin\theta = \Omega + \partial_{xx}\theta$$

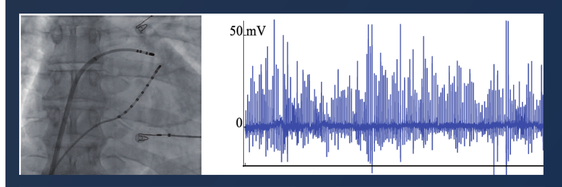
No easy cycle modulation.
No chaotic tangle.

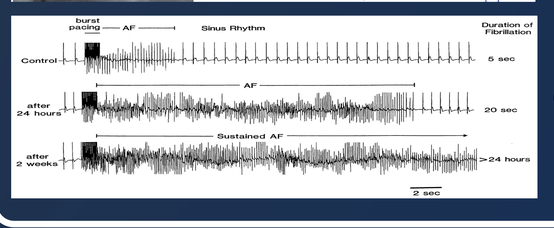


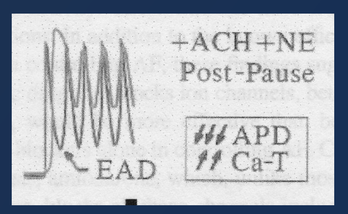




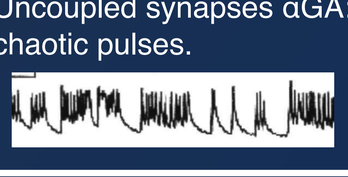


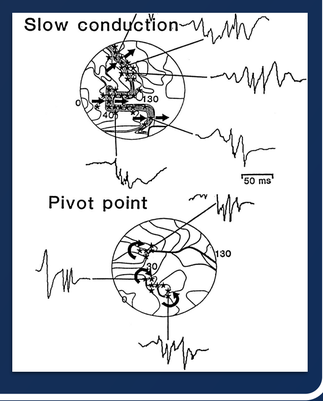






Uncoupled synapses αGA: chaotic pulses.





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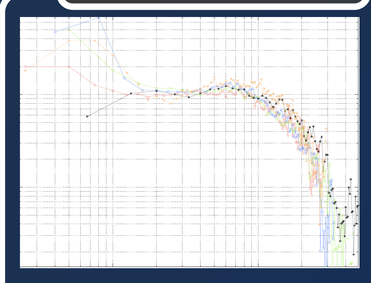
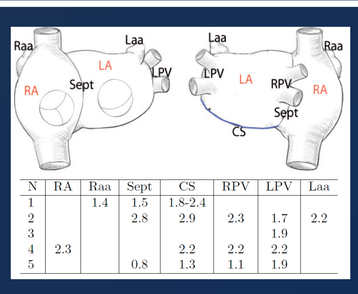
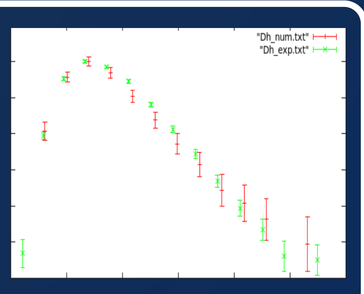
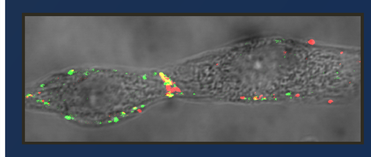


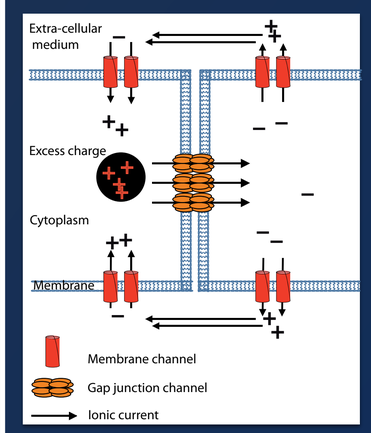


N	RA	Raa	Sept	CS	RPV	LPV	Laa
1		1.4	1.5	1.8-2.4			
2			2.8	2.9	2.3	1.7	2.2
3						1.9	
4	2.3			2.2	2.2	2.2	
5			0.8	1.3	1.1	1.9	

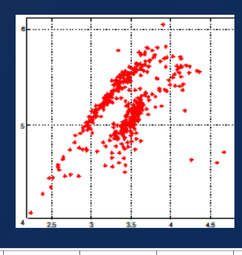


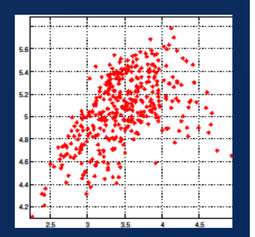


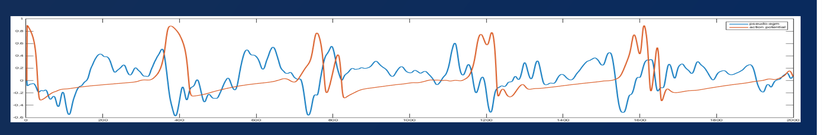
$$\begin{cases} \partial_t U_m &= \mu U_m - \beta U_m^3 - J_m + D\Delta(U_m) - \nabla(g\rho) \\ \partial_t J_m &= \gamma U_m - \sigma J_m \\ \partial_t g &= \alpha\rho - \nu g \\ \partial_t \rho &= -g\nabla(U_m) - \nu\rho \end{cases}$$

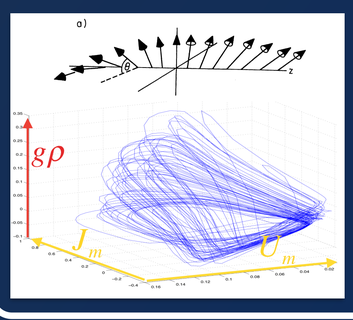


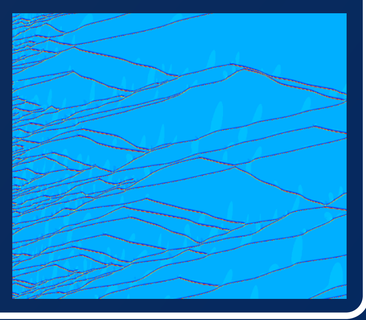
$$R_a = \frac{\alpha J_0}{D\nu^2}$$











Conclusions

We have addressed specific properties observed in human data with a model of electrical synapse dynamic plasticity. The model reproduces the data well, which suggests that fibrillation is a phenomenon in the *directed paths universality class* or *KPZ*. Measuring signals and extracting proper exponents might help to decipher between diseased and healthy substrates as well as structurally from functionally remodelled hearts.