Interdisciplinary Complex Systems: Theoretical Physics Methods in Systems Biology.

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0.2 Participants

0.2.1 ICRANet participants

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0.3 External Collaborations

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0.4 Brief description

This group has started recently the study of problems of nonlinear dynamics of complex systems focusing on biological problems using a theoretical physics approach. The term "biophysics" is today changing in its meaning and appears not to be sufficient to contain areas like "theoretical biology", "living matter physics" of "complex biological systems". On the other hand, the term "Theoretical Physics applied to biological systems" appears to be wide enough to describe very different areas. It is well established both numerically and experimentally that nonlinear systems involving diffusion, chemotaxis, and/or convection mechanisms can generate complicated time-dependent patterns. Specific examples include the Belousov-Zhabotinskii reaction, the oxidation of carbon monoxide on platinum surfaces, slime mold, the cardiac muscle, nerve fibres and more in general excitable media. Because this phenomenon is global in nature, obtaining a quantitative mathematical characterization that to some extent records or preserves the geometric structures of the complex patterns is difficult.

Following Landau's course in theoretical physics, we have worked in Theoretical Biophysics focusing our studies on pathological physiology of cardiac and neural tissues. Finite element simulations of electro-thermo-visco-elastic models describing heart and neural tissue dynamics in 1D and 2D have been performed ([1],[2]), searching for a possible way to understand the topological defects which drive the spiral associated with typical arrythmias (Figure 1), typical of reaction diffusion equations, whose prototype, with two variables for the sake of simplicity, is shown below

$$V_t = D_1 \nabla^2 V + f(U, V)$$
$$U_t = D_2 \nabla^2 U + g(U, V) \,, \qquad\qquad (0.1)$$

where the V variable refers to an activator and the U variable to the inhibitor respectively. The f and g terms are typically highly nonlinear in U and V. We have analyzed [3] in particular the coupling of the reaction-diffusion equations governing the electric dynamics of the tissue with finite elasticity (see Figures 2, 3 and 4). The problem, due to the free boundary conditions, must be formulated in weak form (integral form) on deformable domains, and requires a massive use of differential geometry and numerical techniques like finite elements methods. The experience obtained in this field will be adapted in future studies for problems of self-gravitating systems and cosmology. Moreover computational cardiology and neurology for cancer research in 3D using NMR imported real heart geometries have been studied ([4]-[6]) (Figures 5,6 and 7). More in detail the RMN import of a real brain geometry in Comsol Multiphysics (a powerful finite element PDEs solver) via an interpolating function has been performed. The physical property associated with the greyscale is the diffusivity tensor, assumed to be isotropic but inhomogeneous. Applications to antitumoral drug

delivery and cancer growth processes have been presented. In 2009 specifically the group has published an article on heat transfer in excitable biological tissues of neural type extending the previous studies focused on the FitzHugh-Nagumo model. More in detail, an extension of the Hodgkin-Huxley mathematical model for the propagation of nerve signal taking into account dynamical heat transfer in biological tissue has been derived in accordance with existing experimental data[7]. The model equations, summarized are:

$$
\begin{aligned}
C_m \frac{\partial V}{\partial t} &= \vec{\nabla} \cdot (\hat{G}\vec{\nabla}V) + \eta(T)[g_{Na}m^3 h(V_{Na} - V) + g_K n^4(V_K - V) + g_\ell(V_\ell - V)]\,, \\
\frac{\partial m}{\partial t} &= \phi(T)[\alpha_m(V)(1 - m) - \beta_m(V)m]\,, \\
\frac{\partial h}{\partial t} &= \phi(T)[\alpha_h(V)(1 - h) - \beta_h(V)h]\,, \\
\frac{\partial n}{\partial t} &= \phi(T)[\alpha_n(V)(1 - n) - \beta_n(V)n]\,.
\end{aligned}
\tag{0.2}
$$

where $\alpha_j(V), \beta_j(V)$ (with $j = m, n, h$) are specific functions (the rate constants) of the form

$$
\begin{aligned}
\alpha_n(V) &= \frac{0.01(10 + V)}{[e^{(10+V)/10} - 1]}\,, \quad \beta_n(V) = 0.125 e^{V/80}\,, \\
\alpha_m(V) &= \frac{0.1(25 + V)}{[e^{(25+V)/10} - 1]}\,, \quad \beta_m(V) = 4e^{V/18}\,, \\
\alpha_h(V) &= 0.07 e^{V/20}\,, \qquad \beta_h(V) = \frac{1}{e^{(30+V)/10} + 1}\,,
\end{aligned}
\tag{0.3}
$$

$$
\underbrace{\rho\, c_p\, \partial_t T}_{\text{energy storage rate}} = \underbrace{\nabla_i(k_{il}\nabla_\ell T)}_{\text{conduction}} + \underbrace{\sigma_{ik}\nabla_i V \nabla_k V}_{\text{heat source}} + \underbrace{w_*(T_* - T)}_{\text{perfusion}-\text{sink}}\,,
\tag{0.4}
$$

(the meaning of the remaining quantities can be found in the publication relative to this study). The medium, heated by the Joule's effect associated with action potential propagation, manifests characteristic thermal patterns (see figures0.8 and 0.9) in association with spiral and scroll waves. The introduction of heat transfer—necessary on physical grounds—has provided a novel way to directly observe the movement, regular or chaotic, of the tip of 3D scroll waves in numerical simulations and possibly in experiments. The model will open new perspective also in the context of cardiac dynamics: at the moment in fact the authors are approaching the problem in the same context. The group has also developed a more fundamental study on general theory of reaction-diffusion [8]. It is commonly accepted in fact that reaction-diffusion equations cannot be obtained by a Lagrangian formulation. Guided by the well known connection between quantum and diffusion equations, we implemented a Lagrangian approach valid for totally general nonlinear reacting-diffusing systems allowing

the definition of global conserved observables derived using Noethers theorem. Specifically, for the case of two diffusing species, denoting with an odd suffix the physical real field and with an even one the auxiliary ones, we define the following Lagrangian density

$$
\begin{aligned}
\mathcal{L} = \ & - \ D_1(\nabla\psi_2) \cdot (\nabla\psi_1) - D_2(\nabla\psi_4) \cdot (\nabla\psi_3) + \\
& - \ \frac{1}{2}\left(\psi_2\frac{\partial\psi_1}{\partial t} - \psi_1\frac{\partial\psi_2}{\partial t}\right) + S(\psi_1,\psi_3)(\psi_2 - C_1) + \\
& - \ \frac{1}{2}\left(\psi_4\frac{\partial\psi_3}{\partial t} - \psi_3\frac{\partial\psi_4}{\partial t}\right) + H(\psi_1,\psi_3)(\psi_4 - C_2).
\end{aligned} \tag{0.5}
$$

This quantity, once inserted into Euler-Lagrange equations gives:

$$
\begin{aligned}
\frac{\partial\psi_2}{\partial t} &= -D_1\nabla^2\psi_2 + \frac{\partial S}{\partial\psi_1}(C_1 - \psi_2) + \frac{\partial H}{\partial\psi_1}(C_2 - \psi_4) \\
\frac{\partial\psi_4}{\partial t} &= -D_2\nabla^2\psi_4 + \frac{\partial S}{\partial\psi_3}(C_1 - \psi_2) + \frac{\partial H}{\partial\psi_3}(C_2 - \psi_4) \\
\frac{\partial\psi_1}{\partial t} &= D_1\nabla^2\psi_1 + S(\psi_1,\psi_3) \\
\frac{\partial\psi_3}{\partial t} &= D_2\nabla^2\psi_3 + H(\psi_1,\psi_3),
\end{aligned} \tag{0.6}
$$

Noether's theorem then can be adopted to obtain conserved quantities. The group has published in the past also a chapter devoted on mathematical modelling of cardiac tissue dynamics on a monograph on Mechano-sensitivity in biological cells [9]. In 2010 the group has investigated the spiral wave solutions of the diffusion equation through mathematical physics methods [10]. Moreover a study in cardiac dynamics [11] has been published discussing the electrical arrhythmias suppression in portions of cardiac tissue. In the heart in fact an action potential vortex pinned by an obstacle can be removed through defibrillation protocols fine-tuned theoretically by using electrophysiological nonlinear mathematical models. Finally similar mathematical methods have been implemented to analyse the nonlinear electrophysiological dynamics of intestinal tissue in the case of strong thermal gradients as experienced during surgery [12]. In this case it has been predicted that in these situations unstable behaviors similar to cardiac electrical turbulence can occur. This formulation has been linked to the clinical problem of postoperative paralytic ileus. In 2011 the group has analyzed problems of fluid dynamics in biology [13]. Specifically space-time patterns of Wall Shear Stress (WSS) resulting from the numerical simulation of pulsating hemodynamic flows in semi-coronal domains have been analyzed, both in the case of regular semi-coronal domains and semi-coronal domains with bumpy insertions (see Fig. 10), with the aim of simulating aneurysm-like geometries. These studies have been obtained by numerically integrating via Finite Elements Techniques the equations for a viscous Newtonian incompressible fluid. New

cardiovascular risk indicators, named Three-Band Diagrams (TBD) have been introduced extending the ones already existing in the literature. These indicators allow a quick visual assessment of the risk level to individual fluctuations of the physiological risk thresholds. Due to its generality, such a new mathematical tool is expected to be useful for several problems of Physics, Chemistry, Engineering and Biomedicine. In 2012 the group activities have been focused on cancer dynamics and biomechanics modelling. The authors have adopted partial differential equations to model cancer spread [14], a dynamical process occurring in time but also in space which, for solid tumors at least, can be modelled quantitatively by reaction and diffusion equations with a bistable behavior. Tumor cell colonization happens in a portion of tissue and propagates, but in some cases the process is stopped. The authors have then extended this formulation by using the highly nonlinear porous medium equation

$$\frac{\partial C}{\partial T} = \sigma^{-m} \nabla \cdot (C^m \nabla C) + F(C) \tag{0.7}$$

with the aforementioned nonlinear reaction bistable dynamics

$$F(C) = aC(1 - C)(C - \alpha). \tag{0.8}$$

Here C stands for cancer cell concentration, while m, a, α, σ are model parameters to be fine tuned to qualitatively fit experiments. Other studies have been devoted to nonlinear solid mechanics problems. In Ref. [15] the authors have specifically produced a mathematical model to numerically quantify the stress induced on the scar of a human nasal columella by a constant load, through a finite elasticity continuum model. The fine tuning of model parameters has been performed in order to match with clinical scenarios, with the aim of helping the surgeon in choosing the best type of shape of incision which would minimize mechanical stresses. Finally in Ref.[16] the authors have been extended previous results of Ref.[11], in which the nonlinear cardiac dynamics phenomenon of vortex pinning by obstacles was investigated in absence of elasticity. In this 2012 article, the authors have included the electro-elastic feedback typical of real heart tissue finding the modification of the unpinning regimes caused by tissue domain deformations. In particular Fig.11 has been selected by Phys Rev E. for the March 2012 Kaleidoscope Images Selection (See **http://pre.aps.org/kaleidoscope/pre/85/3/031908**). In 2013 the research activities of the group have focused on several new topics of Complex systems in biology. In Ref. [17] the authors have implemented a stochastic model for the electrophysiology of a cluster of murine beta cells. Schematically, each cell is governed by the following set of differential equations plus a stochastic process:

$$C_m \frac{dV_j}{dt} = -I_K(V_j, n_j) - I_{Ca}(V_j) - \bar{g}_{K-Ca} x_j (V_j - V_K) - g_c \sum_{k \in \Omega_j} (V_j - V_k)$$

$$
\begin{aligned}
\frac{dn_j}{dt} &= \lambda \left[\frac{n_\infty(V_j) - n_j}{\tau_n(V_j)} \right] \\
\frac{dCa_j}{dt} &= f \left[\alpha I_{Ca}(V_j) - k_c Ca_j \right] \\
\langle x_j \rangle &= \frac{Ca_j}{K_d + Ca_j}
\end{aligned}
\tag{0.9}
$$

where Ω_j is the Von Neumann neighborhood of the j-th cell, V_j the corresponding cell action potential, n_j the gating variable, Ca_j the free intracellular calcium concentration and x_j is is a random variable indicating the fraction of open K-Ca stochastic channels of the jth cell (see further details in the reference in exam). Finally k_c governs the control parameter of the model. i.e. the glucose bath concentration. The typical stochastic voltage pattern for a single cell is shown in Fig. (12). We have the simulated a progressive cellular loss in the cluster due to type-I diabetes together with a change in the glucose concentration, discussing the robustness of the cluster architecture upon such an autoimmune attack. We have then worked (Ref.[18]) on the thermal effects affecting spatiotemporal behavior of cardiac tissue. This study has been carried out both theoretically and experimentally. By introducing a thermoelectric coupling in a minimal model of cardiac tissue in fact, we have been able to reproduce experimentally measured dynamics obtained simultaneously from epicardial and endocardial canine ventricles kept at different temperatures. The nature of alternans in cardiac dynamics has been investigated instead in ref.[19] on the basis of experimental data, showing that such a nonlinear phenomenon is essentially three-dimensional and manifests noticeably differences depending on the heart's portion under exam. In Ref. [20] the risk conferred by HLA-DRB1, INS-VNTR and PTPN22 single genes on the onset of type one diabetes and the joint risk conferred by all these three susceptibility loci was quantified using the theoretical tool of the Bayesian Network (BN) approach in both population-based case-control and family clustering data sets. Finally in the reference [21] (still in press) we have investigated, through the nonlinear theory of elasticity, the dynamics of a cardiac myocyte. Several numerical tests have been implemented in order to illustrate the ability of the model in predicting key experimentally established characteristics.

0.5 Publications (2005-2013)

1. Bini D., Cherubini C., Filippi S., "Heat Transfer in FitzHugh-Nagumo models," Physical Review E, Vol. 74 041905 (2006).

   Abstract: An extended FitzHugh-Nagumo model coupled with dynamic al heat transfer in tissue, as described by a bioheat equation, is derived and confronted with experiments. The main outcome of this analysis is that traveling pulses and spiral waves of electric activity produce temperature variations on the order of
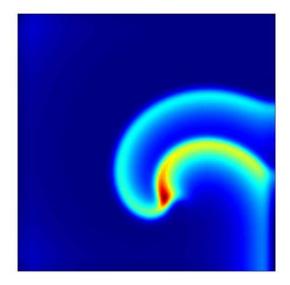
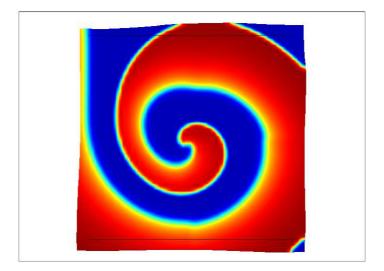Figure 0.1: Spiral wave in the temperature domain at a given time.

Figure 0.2: 2D Evolution of a spiral wave in voltage domain coupled to finite elastic deformations at a given time.
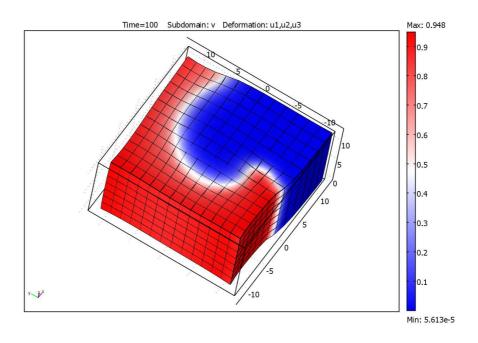
Figure 0.3: 3D spiral wave coupled to strong mechanical deformations.

tens of C . In particular, the model predicts that a spiral wave's tip, heating the surrounding medium as a consequence of the Joule effect, leads to characteristic hot spots. This process could possibly be used to have a direct visualization of the tip's position by using thermal detectors

2. Bini D., Cherubini C., Filippi S., "Viscoelastic FitzHugh-Nagumo models," Physical Review E, Vol. 72 041929 (2005).

Abstract: An extended Fitzhugh-Nagumo model including linear viscoelastici ty is derived in general and studied in detail in the one-dimensional case. The equations of the theory are numerically integrated in two situations: i) a free insulated fiber activated by an initial Gaussian distribution of action potential, and ii) a clamped fiber stimulated by two counter phased currents, located at both ends of the space domain. The former case accounts for a description of the physiological experiments on biological samples in which a fiber contracts because of the spread of action potential, and then relaxes. The latter case, instead, is introduced to extend recent models discussing a strongly electrically stimulated fiber so that nodal structures associated on quasistanding waves are produced. Results are qualitatively in agreement with physiological behavior of cardiac fibers. Modifications induced on the action potential of a standard Fitzhugh-Nagumo model appear to be very small even when strong external electric stimulations are activated. On the other hand, elastic backreaction is
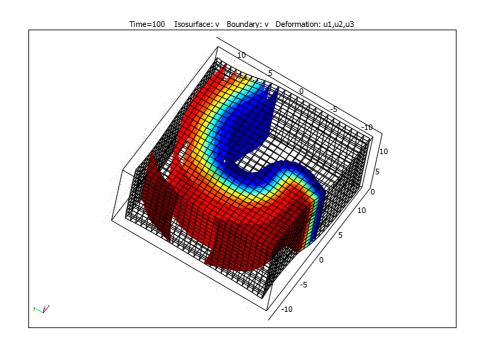
Figure 0.4: 3D spiral waves iso-voltage lines embedded in a mechanically deformed domain.
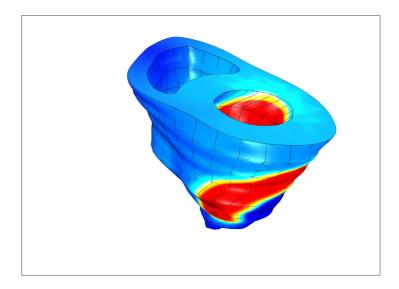

Figure 0.5: Voltage distribution at a given time on a real 3D NMR imported heart geometry.
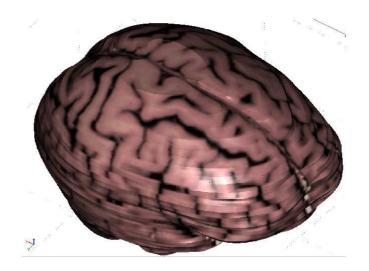
Figure 0.6: 3D NMR imported brain geometry associated with a diffusion tensor.
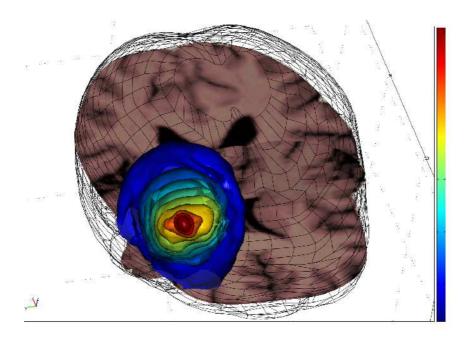

Figure 0.7: Mathematical model of tumor growth on the reconstructed brain geometry.
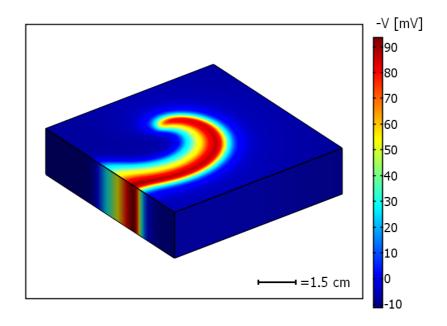
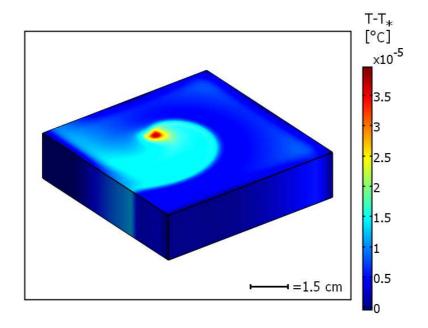Figure 0.8: 3D scroll wave of action potential

Figure 0.9: 3D thermal pattern associated with the electric scroll wave of the previous figure.
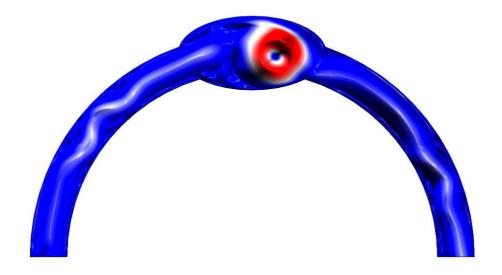
Figure 0.10: Snapshot at a given time of the velocity amplitude in the domain adopted to simulate a viscous hemodynamical flow.

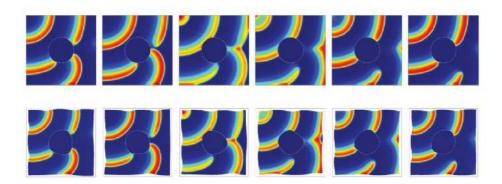Figure 0.11: Defibrillation protocol for a pinned vortex shown at different times. On the first row electro-elastic feedback is inactivated, while on the lower one this effect is switched on. Coloring here denotes different values of action potential.
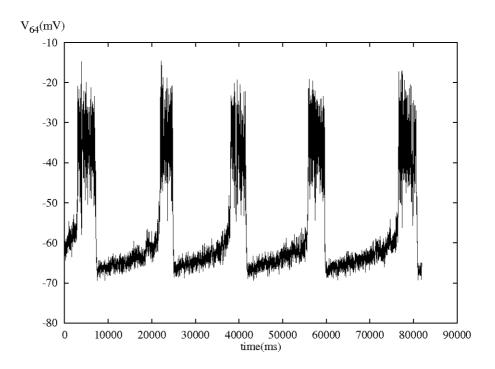
Figure 0.12: Typical action potential stochastic pattern for a beta cell embedded in a connected cluster sufficiently stimulated by glucose presence.

evident in the model

3. Cherubini C., Filippi S., Nardinocchi P., Teresi L., "An electromechanical model of cardiac tissue: Constitutive issues and electrophysiological effects," Progress in Biophysics and Molecular Biology vol. 97, 562−573 (2008)
   Abstract: We present an electromechanical model of myocardium tissue coupling a modified FitzHughNagumo type system, describing the electrical activity of the excitable media, with finite elasticity, endowed with the capability of describing muscle contractions. The high degree of deformability of the medium makes it mandatory to set the diffusion process in a moving domain, thereby producing a direct influence of the deformation on the electrical activity. Various mechanoelectric effects concerning the propagation of cylindrical waves, the rotating spiral waves, and the spiral breakups are discussed

4. S.Filippi, C.Cherubini, Electrical Signals in a Heart, Comsol Multiphysics Model Library, Sept. p.106-116.(2005)

5. S.Filippi, C.Cherubini, Models of Biological System, Procceedings of COMSOL Conference, Milan (2006).
   Abstract: This article discusses the RMN import of a brain geometry in Comsol Multiphysics via an interpolating function. The physical property associated with the grayscale is the diffusivity tensor, assumed here to be isotropic but inhomogeneous. Applications to antitumoral drug delivery and cancer growth processes are discussed.

6. C.Cherubini, S.Filippi, A.Gizzi, Diffusion processes in Human Brain using Comsol Multiphysics, Procceedings of COMSOL Conference, Milan (2006).
   Abstract:This article presents different applications of Comsol Multiphysics in the context of mathematical modeling of biological systems. Simulations of excitable media like cardiac and neural tissues are discussed.

7. Bini D., Cherubini C., Filippi S., "On vortices heating biological excitable media," Chaos, Solitons and Fractals vol. 42 (2009) 20572066

   Abstract: An extension of the HodgkinHuxley mathematical model for the propagation of nerve signal which takes into account dynamical heat transfer in biological tissue is derived and fine tuned with existing experimental data. The medium is heated by Joules effect associated with action potential propagation, leading to characteristic thermal patterns in association with spiral and scroll waves. The introduction of heat transfernecessary on physical groundsprovides a novel way to directly observe the movement, regular or chaotic, of the tip of spiral waves in numerical simulations and possibly in experiments regarding different biological excitable media.

8. Cherubini C. and Filippi S., "Lagrangian field theory of reaction-diffusion," Physical Review E, Vol. 80 046117 (2009).

   Abstract: It is commonly accepted that reaction-diffusion equations cannot be obtained by a Lagrangian field theory. Guided by the well known connection between quantum and diffusion equations, we implement here a Lagrangian approach valid for totally general nonlinear reacting-diffusing systems which allows the definition of global conserved observables derived using Nthers theorem

9. Cherubini C., Filippi S., Nardinocchi P., Teresi L., "Electromechanical modelling of cardiac tissue", in "Mechanosensitivity of the Heart Series: Mechanosensitivity in Cells and Tissues , Vol. 3", Kamkin, A.; Kiseleva, I. (Eds.) (2009), Springer.

10. D. Bini, C. Cherubini, S. Filippi, A.Gizzi and P. E. Ricci, "On Spiral Waves Arising in Natural Systems", Commun. Comput. Phys. Vol. 8, No. 3, pp. 610-622 (2010)

    Abstract: Spiral waves appear in many different natural contexts: excitable biological tissues, fungi and amoebae colonies, chemical reactions, growing crystals, fluids and gas eddies as well as in galaxies. While the existing theories explain the presence of spirals in terms of nonlinear parabolic equations, it is explored here the fact that self-sustained spiral wave regime is already present in the linear heat operator, in terms of integer Bessel functions of complex argument. Such solutions, even if commonly not discussed in the literature because diverging at spatial infinity, play a central role in the understanding of the universality of spiral process. In particular,we have studied how in nonlinear reaction-diffusion models the linear part of the equations determines the wave front appearance while nonlinearities are mandatory to cancel out the blowup of solutions. The spiral wave pattern still requires however at least two cross-reacting species to be physically realized. Biological implications of such a results are discussed.

11. A. Pumir, S. Sinha, S. Sridhar, M. Argentina, M. Horning, S. Filippi, C. Cherubini, S. Luther, and V. Krinsky, "Wave-train-induced termination of weakly anchored vortices in excitable media", Phys Rev E vol. 81, 010901 (2010).

    Abstract: A free vortex in excitable media can be displaced and removed by a wave train. However, simple physical arguments suggest that vortices anchored to large inexcitable obstacles cannot be removed similarly. We show that unpinning of vortices attached to obstacles smaller than the core radius of the free vortex is possible through pacing. The wave-train frequency necessary for unpinning increases with the obstacle size and we present a geometric explanation of this dependence. Our model-independent results suggest that decreasing

excitability of the medium can facilitate pacing-induced removal of vortices in cardiac tissue.

12. A Gizzi, C Cherubini, S Migliori, R Alloni, R Portuesi and S Filippi, "On the electrical intestine turbulence induced by temperature changes", Phys. Biol. vol.7 016011 (2010)

Abstract: Paralytic ileus is a temporary syndrome with impairment of peristalsis and no passage of food through the intestine. Although improvements in supportive measures have been achieved, no therapy useful to specifically reduce or eliminate the motility disorder underlying postoperative ileus has been developed yet. In this paper, we draw a plausible, physiologically fine-tuned scenario, which explains a possible cause of paralytic ileus. To this aim we extend the existing 1D intestinal electrophysiological AlievRichardsWikswo ionic model based on a double-layered structure in two and three dimensions. Thermal coupling is introduced here to study the influence of temperature gradients on intestine tissue which is an important external factor during surgery. Numerical simulations present electrical spiral waves similar to those experimentally observed already in the heart, brain and many other excitable tissues. This fact seems to suggest that such peculiar patterns, here electrically and thermally induced, may play an important role in clinically experienced disorders of the intestine, then requiring future experimental analyses in the search for possible implications for medical and physiological practice and bioengineering.

13. A. Gizzi, M. Bernaschi, D. Bini, C. Cherubini, S. Filippi, S. Melchionna, and S. Succi, "Three-band decomposition analysis of wall shear stress in pulsatile flows", Phys Rev. E vol. 83, 031902 (2011)

Abstract: Space-time patterns of wall shear stress (WSS) resulting from the numerical simulation of pulsating hemodynamic flows in semicoronal domains are analyzed, in the case of both regular semicoronal domains and semicoronal domains with bumpy insertions, mimicking aneurysm-like geometries. A new family of cardiovascular risk indicators, which we name three-band diagrams (TBDs), are introduced, as a sensible generalization of the two standard indicators, i.e., the time-averaged WSS and the oscillatory shear index. TBDs provide a handy access to additional information contained in the dynamic structure of the WSS signal as a function of the physiological risk threshold, thereby allowing a quick visual assessment of the risk sensitivity to individual fluctuations of the physiological risk thresholds. Due to its generality, TBD analysis is expected to prove useful for a wide host of applications in science, engineering, and medicine, where risk assessment plays a central role.

14. C. Cherubini, A. Gizzi, M. Bertolaso, V. Tambone and S. Filippi, "A Bistable FieldModel of Cancer Dynamics" Commun. Comput. Phys., Vol. 11, 1-18 (2012)

Abstract:Cancer spread is a dynamical process occurring not only in time but also in space which, for solid tumors at least, can be modeled quantitatively by reaction and diffusion equations with a bistable behavior: tumor cell colonization happens in a portion of tissue and propagates, but in some cases the process is stopped. Such a cancer proliferation/extintion dynamics is obtained in many mathematical models as a limit of complicated interacting biological fields. In this article we present a very basic model of cancer proliferation adopting the bistable equation for a single tumor cell dynamics. The reaction-diffusion theory is numerically and analytically studied and then extended in order to take into account dispersal effects in cancer progression in analogy with ecological models based on the porous medium equation. Possible implications of this approach for explanation and prediction of tumor development on the lines of existing studies on brain cancer progression are discussed. The potential role of continuum models in connecting the two predominant interpretative theories about cancer, once formalized in appropriate mathematical terms, is discussed.

15. A. Gizzia, C. Cherubini, N. Pomella, P. Persichetti, M. Vasta, S. Filippi, "Computational modeling and stress analysis of columellar biomechanics", Journal of the Mechanical Behavior of Biomedical Materials Vol. 15, 4658 (2012)

Abstract: The open approach for rhinoplasty offers excellent exposure of the various components of the nose in situ. The biggest advantage of the external approach is the complete anatomic exposure, which allows the surgeon to inspect the osteo-cartilagineous framework, while the biggest disadvantage is represented by the transcolumellar scar. The goal of this study is to numerically quantify the stress induced on the scar of a human columella by a constant load, through a fine tuned finite elasticity continuum model. Specifically we want to determine the best shape of incision which would minimize this stress. The columellar portion of the nose, together with the various constituting tissues, has been modeled in a first approximation as a hyperelastic body and seven types of scars have been studied. The determination of the best incision must be a compromise among different factors: shape and size primarily, but also position with respect to the internal structures and external loads. From this point of view, the best class of scar appears to be, both at simulated and real levels, the V-shaped one, inducing a maximum logarithmic von Mises stress in tissue of 4.67 Pa, and an absolute minimum stress distribution on the scar of 4.17 Pa. Numerical simulations appear to be in agreement with the evidence-based results coming from surgical practice, thus confirming the necessity to minimize local stresses on the tissue. A parameters sensitivity analysis further highlighted our optimal choice. The proposed mathematical model can be applied both to theoretically designed and numerically verified new non-conventional scar geometries.

Abstract:Spiral waves in excitable biological media are associated with pathological situations. In the heart an action potential vortex pinned by an obstacle has to be removed through defibrillation protocols fine-tuned theoretically by using electrophysiological nonlinear mathematical models. Cardiac tissue, however, is an electroelastic medium whose electrical properties are strongly affected by large deformations. In this paper we specifically investigate the electroelastic pinning-unpinning mechanism in order to include cardiac contraction in the preexisting theoretically modeled defibrillation scenarios. Based on a two-dimensionalminimal electromechanical model, we show numerically the existence of an unpinning band characterized by the size of the obstacle, the pacing site, and the frequency. Similar numerical simulations, performed in the absence of elastic coupling, show small differences in comparison with the electroelastic studies, suggesting for this specific scenario of pinning-unpinning dynamics a nonprominent role of elasticity.

Abstract: Background: The integrity of the interactions and the 3D architecture among beta cell populations in pancreatic islets is critical for proper biosynthesis, storage and release of insulin. The aim of this study was to evaluate the effect on electrophysiological signalling of beta cells that is produced by progressive lymphocytic islet cell infiltration (insulitis), by modelling the disruption of pancreatic islet anatomy as a consequence of insulitis and altered glucose concentrations. Methods: On the basis of histopathological images of murine islets from nonobese diabetic mice, we simulated the electrophysiological dynamics of a 3D cluster of mouse beta cells via a stochastic model. Progressive damage was modelled at different glucose concentrations, representing the different glycaemic states in the autoimmune progression towards type 1 diabetes. Results: At 31% of dead beta cells (normoglycaemia) and 69% (hyperglycaemia), the system appeared to be biologically robust to maintain regular $Ca2+$ ion oscillations guaranteeing an effective insulin release. Simulations at 84%, 94% and 98% grades (severe hyperglycemia) showed that intracellular calcium oscillations were absent. In such conditions, insulin pulsatility is not expected to occur. Conclusions: Our results suggest that the islet tissue is biophysically robust enough to compensate for high rates of beta cell loss. These predictions can be experimentally tested in vitro by quantifying space and time electrophysiological dynamics of animal islets kept at different glucose gradients. The

model indicates the necessity of maintaining glycaemia within the physiological range as soon as possible after diabetes onset to avoid a dramatic interruption of Ca2+ pulsatility and the consequent drop of insulin release.

18. F.H. Fenton, A. Gizzi, C. Cherubini, N. Pomella and S. Filippi."Role of temperature on nonlinear cardiac dynamics", Phys. Rev. E,, vol. 87, p. 042717-1-042717-11 (2013)

Abstract: Thermal effects affecting spatiotemporal behavior of cardiac tissue are discussed by relating temperature variations to proarrhythmic dynamics in the heart. By introducing a thermoelectric coupling in a minimal model of cardiac tissue, we are able to reproduce experimentally measured dynamics obtained simultaneously from epicardial and endocardial canine right ventricles at different temperatures. A quantitative description of emergent proarrhythmic properties of restitution, conduction velocity, and alternans regimes as a function of temperature is presented. Complex discordant alternans patterns that enhance tissue dispersion consisting of one wave front and three wave backs are described in both simulations and experiments. Possible implications for model generalization are finally discussed.

19. A. Gizzi, E. M. Cherry, R.F. Gilmour Jr., S. Luther, S. Filippi and F.H. Fenton, "Effects of pacing site and stimulation history on alternans dynamics and the development of complex spatiotemporal patterns in cardiac tissue", Front. Physiol., 4 (2013), p.1-20

Alternans of action potential duration has been associated with T wave alternans and the development of arrhythmias because it produces large gradients of repolarization. However, little is known about alternans dynamics in large mammalian hearts. Using optical mapping to record electrical activations simultaneously from the epicardium and endocardium of 9 canine right ventricles, we demonstrate novel arrhythmogenic complex spatiotemporal dynamics. (i) Alternans predominantly develops first on the endocardium. (ii) The postulated simple progression from normal rhythm to concordant to discordant alternans is not always observed; concordant alternans can develop from discordant alternans as the pacing period is decreased. (iii) In contrast to smaller tissue preparations, multiple stationary nodal lines may exist and need not be perpendicular to the pacing site or to each other. (iv) Alternans has fully three-dimensional dynamics and the epicardium and endocardium can show significantly different dynamics: multiple nodal surfaces can be transmural or intramural and can form concave/convex surfaces resulting in islands of discordant alternans. (v)The complex spatiotemporal patterns observed during alternans are very sensitive to both the site of stimulation and the stimulation history. Alternans in canine ventricles not only exhibit larger amplitudes and persist for longer cycle length regimes compared to those found in smaller

mammalian hearts, but also show novel dynamics not previously described that enhance dispersion and show high sensitivity to initial conditions. This indicates some underlying predisposition to chaos and can help to guide the design of new drugs and devices controlling and preventing arrhythmic events.

20. R. Portuesi, P. Pozzilli, B. Boehm, R. Buzzetti, S. Filippi "Assessment of Type 1 Diabetes Risk Conferred by HLA-DRB1, INS-VNTR and PTPN22 Genes Using the Bayesian Network Approach ", Plos One, 8 (2013) p.1-7,

Background: Determining genetic risk is a fundamental prerequisite for the implementation of primary prevention trials for type 1 diabetes (T1D). The aim of this study was to assess the risk conferred by HLA-DRB1, INS-VNTR and PTPN22 single genes on the onset of T1D and the joint risk conferred by all these three susceptibility loci using the Bayesian Network (BN) approach in both population-based case-control and family clustering data sets.
Methodology/Principal Findings: A case-control French cohort, consisting of 868 T1D patients and 73 French control subjects, a French family data set consisting of 1694 T1D patients and 2340 controls were analysed. We studied both samples separately applying the BN probabilistic approach, that is a graphical model that encodes probabilistic relationships among variables of interest. As expected HLA-DRB1 is the most relevant susceptibility gene. We proved that INS and PTPN22 genes marginally influence T1D risk in all risk HLA-DRB1 genotype categories. The absolute risk conferred by carrying simultaneously high, moderate or low risk HLA-DRB1 genotypes together with at risk INS and PTPN22 genotypes, was 11.5%, 1.7% and 0.1% in the case-control sample and 19.8%, 6.6% and 2.2% in the family cohort, respectively.
Conclusions/Significance: This work represents, to the best of our knowledge, the first study based on both case-control and family data sets, showing the joint effect of HLA, INS and PTPN22 in a T1D Caucasian population with a wide range of age at T1D onset, adding new insights to previous findings regarding data sets consisting of patients and controls ,15 years at onset.

21. R. Ruiz-Baier, A. Gizzi, S. Rossi, C. Cherubini, A. Laadhari, S. Filippi and A. Quarteroni, "Mathematical modeling of active contraction in isolated cardiomyocytes", Mathematical Medicine and Biology (2013), in press.

We investigate the interaction of intracellular calcium spatiotemporal variations with the self-sustained contractions in cardiac myocytes. A consistent mathematical model is presented considering an hyperelastic description of the passive mechanical properties of the cell, combined with an active-strain framework to explain the active shortening of myocytes and its coupling with cytosolic and sarcoplasmic calcium dynamics. A finite element method based on a Taylor-Hood discretization is employed to approximate the nonlinear elasticity equations, whereas the calcium concentration and mechanical activation vari-

ables are discretized by piecewise linear finite elements. Several numerical tests illustrate the ability of the model in predicting key experimentally established characteristics including: (i) calcium propagation patterns and contractility, (ii) the influence of boundary conditions and cell shape on the onset of structural and active anisotropy, and (iii) the high localized stress distributions at the focal adhesions. Besides, they also highlight the potential of the method in elucidating some important subcellular mechanisms affecting e.g. cardiac repolarization.

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