

**Interdisciplinary Complex Systems:
Theoretical Physics Methods in
Systems Biology.**

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0.1 Topics

- Reaction-diffusion equations
- Turbulence in vortex dynamics
- Heat Transfer in excitable tissues
- Mechano-electric Feedback
- Computational Cardiology
- Stochastic systems in Biophysics
- Mathematical Models of Tumor Growth
- Fluid Dynamics in biological systems
- Complex Networks

0.2 Participants

0.2.1 ICRANet

- Christian Cherubini (Nonlinear Physics and Mathematical Modeling Lab and ICRA, Campus Bio-Medico University of Rome, Italy)
- Simonetta Filippi, project leader (Nonlinear Physics and Mathematical Modeling Lab and ICRA, Campus Bio-Medico University of Rome, Italy)

0.3 Collaborations

- Flavio Fenton (School of Physics, Georgia Institute of Technology, USA)
- Anna Pandolfi (Politecnico di Milano, Italy)
- Alessio Gizzi (Associate Professor, Campus Bio-Medico University of Rome, Italy)
- Letizia Chiodo (Associate Professor, Campus Bio-Medico University of Rome, Italy)
- Alessandro Loppini (Researcher, Campus Bio-Medico University of Rome, Italy)
- Martina Nicoletti, (Postdoc, Campus Bio-Medico University of Rome, Italy)

0.4 Brief description

This group is involved in 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" or "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 arrhythmias (Figure 1), typical of reaction diffusion equations, whose prototype, with two variables for the sake of simplicity, is shown below

$$\begin{aligned} V_t &= D_1 \nabla^2 V + f(U, V) \\ U_t &= D_2 \nabla^2 U + g(U, V), \end{aligned} \tag{0.1}$$

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:

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

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

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

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

(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 figures 0.8 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 Noether's 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

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

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

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

Noether's theorem then can be adopted to obtain conserved quantities. The group has published in the past also a chapter devoted on mathematical mod-

elling 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

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

with the aforementioned nonlinear reaction bistable dynamics

$$F(C) = aC(1 - C)(C - \alpha). \quad (0.8)$$

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:

$$\begin{aligned} C_m \frac{dV_j}{dt} &= -I_K(V_j, n_j) - I_{Ca}(V_j) - \bar{g}_{K-Ca} x_j (V_j - V_K) - g_c \sum_{k \in \Omega_j} (V_j - V_k) \\ \frac{dn_j}{dt} &= \lambda \left[\frac{n_\infty(V_j) - n_j}{\tau_n(V_j)} \right] \\ \frac{dCa_j}{dt} &= f [\alpha I_{Ca}(V_j) - k_c Ca_j] \end{aligned}$$

$$\langle x_j \rangle = \frac{Ca_j}{K_d + Ca_j} \quad (0.9)$$

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 a random variable indicating the fraction of open K-Ca stochastic channels of the j th 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 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 noticeable 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.

In 2014 the research activities mainly focused on cardiac mechanics In Ref. [21] a mathematical model for the myocyte, which represents the minimal building block for the cardiac muscle has been produced. In this situation, a nonlinear coupling between the nonlinear electrodynamics and the finite elasticity which governs the electromechanical feedback has been built. The model has been studied then by using advanced numerical schemes for coupled nonlinear PDEs. In Ref. [22] instead the role of temperature in nonlinear cardiac dynamics has been investigated by using ad hoc computational tools (WEB GL). The occurrence of turbulence in the nonlinear dynamics described by coupled reaction-diffusion PDEs has been specifically analyzed upon thermal bath changes. In Ref. [23] instead numerical simulations of

ECG in cardiac models have been performed. On the other hand, in Ref. [24], the nonlinear stochastic dynamics of clusters of beta-cells in pancreas as discussed in the previous reference [17] has been analyzed by increasing the cluster dimension, so the number of degrees of freedom of the system. By using methods typical of quantum mechanics (coherent states), a parallelism with phase transition phenomena of field theory has been evidenced. Finally in [25] an analysis of the network tools from the point of view of philosophy of science has been given, while in Ref. [26] both an experimental evidence and mathematical modelling of thermal effects on human colonic smooth muscle contractility have been discussed.

In 2015 the research activities focused again on several topics. In ref. [27] the activity of pancreatic beta-cells has been described by biological networks of coupled nonlinear oscillators that, via electrochemical synchronization, release insulin in response to augmented glucose levels. In this work the emergent behavior of regular and percolated beta-cells clusters has been investigated through a stochastic mathematical model where functional networks arise. It has been shown that the emergence and robustness of the synchronized dynamics depend both on intrinsic and extrinsic parameters. Moreover, the cellular noise level, glucose concentration, network spatial architecture, and cell-to-cell coupling strength are shown to be the key factors for the generation of a rhythmic and robust activity so their role in the functional network topology associated with beta-cells clusters has been analyzed and discussed. In Ref.[28] instead the research activity by Emilio Del Giudice on the possibility to move towards a unified view of some long-range dynamics in nature, ranging from quantum field theory in physics up to biology has been linked to the synchronized electrical behavior of pancreatic beta cells via stochasticity. This phenomenology conceptually links to ideas of coherent dynamics in quantum physics. In Ref. [29] the gradient of the fluid stresses exerted on curved boundaries, conventionally computed in terms of directional derivatives of a tensor, has been analyzed by using the notion of intrinsic derivative which represents the geometrically appropriate tool for measuring tensor variations projected on curved surfaces. Relevant differences in the two approaches have been found by using the classical Stokes analytical solution for the slow motion of a fluid over a fixed sphere and a numerically generated three dimensional dynamical scenario. Finally implications for theoretical fluid dynamics and for applied sciences (especially in hemodynamics) have been discussed. In Ref. [30] a general theoretical framework for the formulation of the nonlinear electromechanics of poly-

meric and biological active media has been introduced. The approach developed is based on the additive decomposition of the Helmholtz free energy in elastic and inelastic parts and on the multiplicative decomposition of the deformation gradient in passive and active parts. In view of possible numerical applications, the general approach has been applied to a particular material model accounting for the behavior of fiber reinforced tissues. Finite elements techniques are adopted to study a uniaxial electromechanical problem dynamically activated by an electrophysiological stimulus. Finally, possible implications for nonlinear solid mechanics and computational electrophysiology have been presented. In Ref [31] a computational modelling of hemodynamic alterations relevant in the onset and development of vascular pathologies has been presented using two novel hemodynamics synthetic indicators, based on a three-band decomposition (TBD) of the shear stress signal. Extensive fluid-structure computer simulations of patient-specific scenarios confirm the enhanced risk-prediction capabilities of these indicators. In Ref. [32] the interaction of intracellular calcium spatio-temporal variations with the self-sustained contractions in cardiac myocytes has been studied. A 3D continuum mathematical model has been presented based on a hyperelastic description of the passive mechanical properties of the cell, combined with an active-strain framework to describe the active shortening of myocytes and its coupling with cytosolic and sarcoplasmic calcium dynamics with some numerical tests illustrating the ability of our model in reproducing key experimentally established features. In Ref. [33] a study similar to the one discussed in Ref. [27] and [28] was performed but on models based on human pancreas data, while in Ref.[34] a numerical study on the spatio-temporal dynamics of the transmembrane potential in paced isotropic and anisotropic cardiac tissues was performed.

In 2016 the research activities have focused in fluid-structure problems in hemodynamics in arbitrary Lagrangian-Eulerian formulations, a mathematically involved theory which describes systems of partial differential equations with free boundary conditions. Specifically in Ref. [35] the nonlinear equations 'set which describes the fluid and the elastic wall within which the fluid flows have been numerically integrated and the previously introduced (Ref. [13]) risk indicator TDB has been applied to this more involved case in order to perform a risk assessment. In Ref.[36] on the other hand, a numerical analysis of the same mathematical problem, but here focused to the case of different biomedical prostheses applied to real patients' geometries has been carried out in order to perform a quantitative comparison of the

mechanical behavior of the different scenarios, having in mind as ultimate target the best outcomes for patients' health. Other articles regarding elastic wave propagation in realistic head models aiming to model bone conduction phenomena, electromechanical feedback in cardiac tissue, temperature effects and advanced analyses of turbulence occurrence in cardiac dynamics are expected to be submitted for publication before the end of the present year.

In **2017** the research activities of the group regarded specific aspects of theoretical biophysics. In Ref. [37], inspired by the classical volume by Landau and Lifshits on the "Electrodynamics of Continuous Media", the authors have introduced the concept of stress-driven anisotropic diffusion and its role in active deformable media, taking into account large deformations for which the use of the nonlinear continuum mechanics theory, strongly based on differential geometry, is mandatory. The role of nonlinear diffusion in union with heat transfer processes in biological media of cardiac type has been investigated in Ref. [38] instead. In Ref. [39] the concept of multiband decomposition analysis (a renaming of the TBD previously discussed more appropriate for this context) has been applied to the study of cardiac alternans upon temperature variations, representing a delicate topic in the realm of nonlinear cardiac dynamics. Finally in Ref. [40], a theoretical computational study of a multi-axial actuated microfluidic chip device for biological uses has been performed.

In **2018** several theoretical biophysics problems have been investigated. In Ref. [41] a 3-dimensional viscoelastic finite element model of the human head based on computed tomography and magnetic resonance biomedical images has been presented with a numerical investigation of sound wave transmission and attenuation within the human head-neck system comprising skull and brain tissues. In Ref. [42] instead a novel hybrid discrete-continuum mathematical model, coupling the stochastic electrical dynamics of β -cell clusters to nonlinear reaction-diffusion of glucose has been introduced. In particular it is described how functional features are strongly linked to synchronization patterns, in which coordinated sub-clusters of cells naturally emerge from the underlying dynamics. Ref. [43] has been devoted to a numerical investigation of the role of mechanical stress in modifying the conductivity properties of cardiac tissue assessing the impact of these effects in the solutions generated by computational models for cardiac electromechanics. Finally in Ref. [44] a Systems Biology study, specifically focused to cancer, has been presented by using a basic toy model for solid tumor spread

for framing together two apparently different conceptual leading paradigms of Oncogenesis.

In **2019** the research activities focused on nonlinear cardiac dynamics studies again and on critical behaviors in complex networks. In particular in Ref. [45], through optical mapping experimental studies and mathematical simulations, a characteristic spatial length of cardiac dynamics in animal ventricles has been introduced using a spatiotemporal correlation analysis for different stimulation frequencies as well as in fibrillation scenarios. It has been found that the characteristic length decreases and reaches the value of one cm during fibrillation. Moreover a nonlinear constitutive phenomenological law has been obtained correctly fitting experimental data and relating the conduction velocity restitution curve and the system's characteristic length. In Ref. [46] instead, collapse phenomena in complex networks have been studied by adopting a minimal two-state dynamics on a complex network. As a main result it has been shown that before the critical transition point is reached by the system, an important loss of low-degree nodes develops, being masked however by the minimal failure of higher-degree nodes. On these grounds, it has been argued then that a significant reduction in less connected nodes can be a good indicator of a -close to occur- global failure of the network itself.

In **2020** the research activities studied aspects of cardiac dynamics with particular attention to the mechanoelectric feedback and to temperature effects. Moreover a study on the organization and signaling of cellular aggregates has been published. In detail in Ref. [47] a novel mathematical model for the active contraction of cardiac muscle has been introduced taking into account different thermo-electric and nonlinear conductivity properties. A passive hyperelastic response of the tissue has been adopted by using an orthotropic exponential model, while the ionic activity governing the active contraction has been included via an orthotropic active strain. Several numerical simulations have been performed then in order to understand the role of these additional physical ingredients into the possible development of arrhythmia. In Ref. [48] instead spatio-temporal correlation properties in heart at varying pacing frequencies have been discussed in search of a possible novel indicator of alternans development and arrhythmias onset. In Ref. [49] finally we studied calcium dynamics in cellular populations. Plenty of studies have described the relevance of calcium signaling in regulating differentiation, apoptosis, mitosis and functions. We specifically focused on the space-time structure of such a complex regulation, taking into account synchronization across long distances and emergent space-time dynamics. Us-

ing a mathematical model based on hepatic non-excitable cells, we analyzed emerging calcium dynamics of cells clusters both of physiological and pathological nature. Exploring the severity of dysfunction and size of pathological aggregates we demonstrated how local heterogeneity in cellular properties can profoundly affect the system. The major finding of the study is that coordinated calcium dynamics produces sub-populations of cells with their own coordinated organization which interfere with healthy cells' coordinated rhythms. Such a reorganization of calcium activity has been finally speculated in the study to be possibly related to cancer initiation.

In **2021** the attention was focused on nonlinear cardiac dynamics studies. Specifically, in Ref. [50] an extension of the analysis presented in Ref. [45] by including the effects of temperature was presented. Again, the point here was the study of alternans of cardiac action potential duration which represent critical precursors for the development of possible lifethreatening arrhythmias. Adopting high-resolution optical mapping recordings of canine ventricular wedges' electrical activity performed at different temperatures and pacing frequencies, an extracted characteristic length as a potential predictive index of cardiac alternans onset and evolution was obtained. In particular it has been shown that that a reduction of temperature causes a drop of the characteristic length pointing out the impact of thermal instabilities on nonlinear cardiac dynamics. Theoretically, an investigation of the use of such an index to identify and predict different alternans regimes was presented, finally obtaining a constitutive phenomenological law which links conduction velocity, characteristic length, and temperature.

In **2022** the studies on theoretical electrophysiology have continued. Particular attention has been devoted to clarify the role of specific stimulation protocols of the His bundle in real hearts. Moreover the effect of temperature in cardiac ablation procedures has been studied. Finally, the meaning of the so-called 'black holes' in latency diagrams has been investigated and an article on these matters is expected to be submitted for publication during the present year.

In **2023** studies on theoretical electrophysiology of pancreatic cells have been performed with a publication. In this case the synchronization of metabolic and electrical activities in beta-cells clusters has been studied via numerical simulations. Another analysis with a publication has been devoted to the study of hidden regulation mechanisms in unfolded protein response via structural controllability. Finally the work on the meaning of the so-called 'black holes' in latency diagrams discussed in the previous year is still under

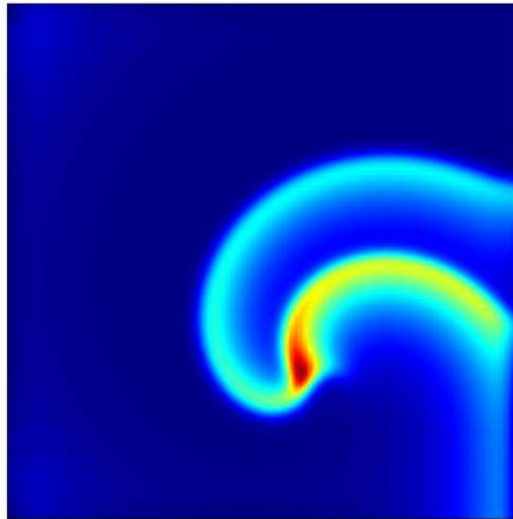


Figure 0.1: Spiral wave in the temperature domain at a given time.

study.

0.5 Publications (2005-2023)

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 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).

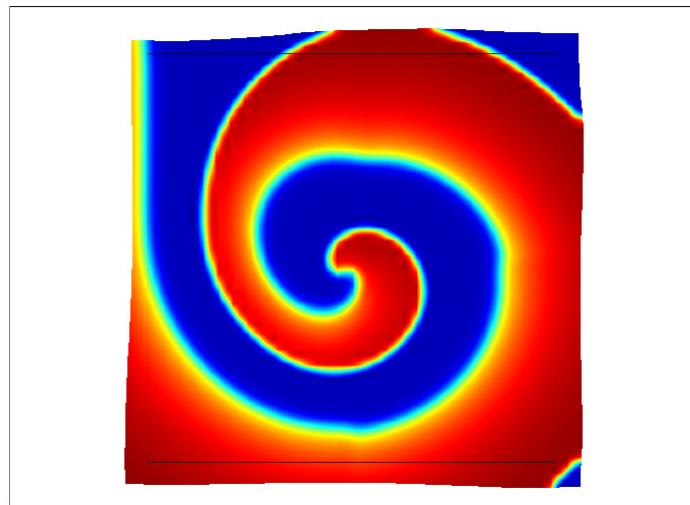


Figure 0.2: 2D Evolution of a spiral wave in voltage domain coupled to finite elastic deformations at a given time.

Abstract: An extended Fitzhugh-Nagumo model including linear viscoelasticity 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 evident in the model

3. Cherubini C., Filippi S., Nardinocchi P., Teresi L., "An electromechanical model of cardiac tissue: Constitutive issues and electrophysiological

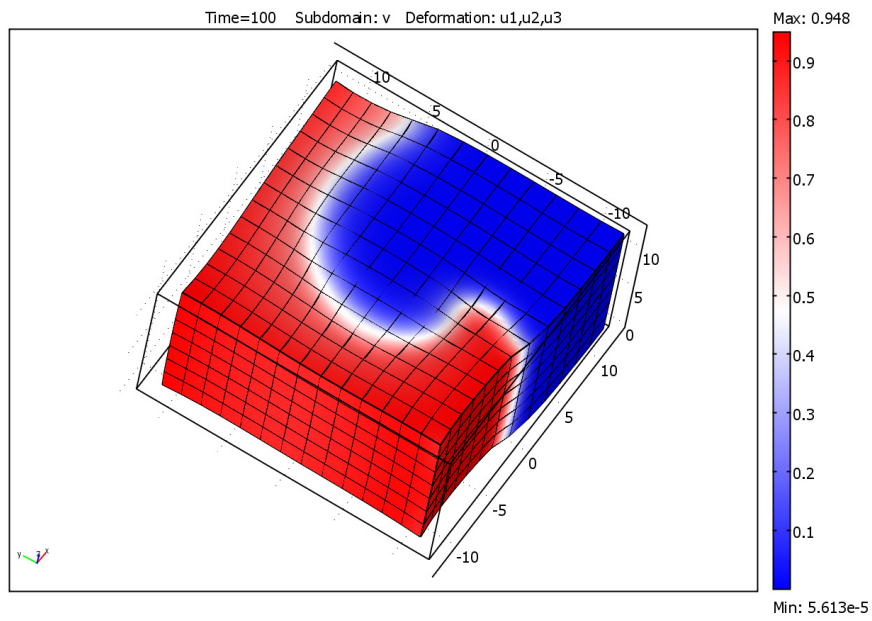


Figure 0.3: 3D spiral wave coupled to strong mechanical deformations.

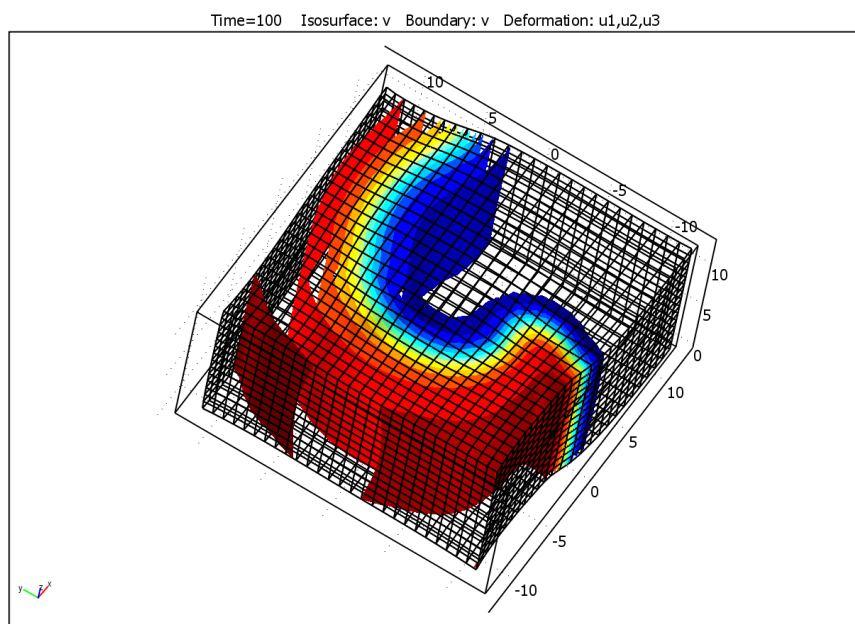


Figure 0.4: 3D spiral waves iso-voltage lines embedded in a mechanically deformed domain.

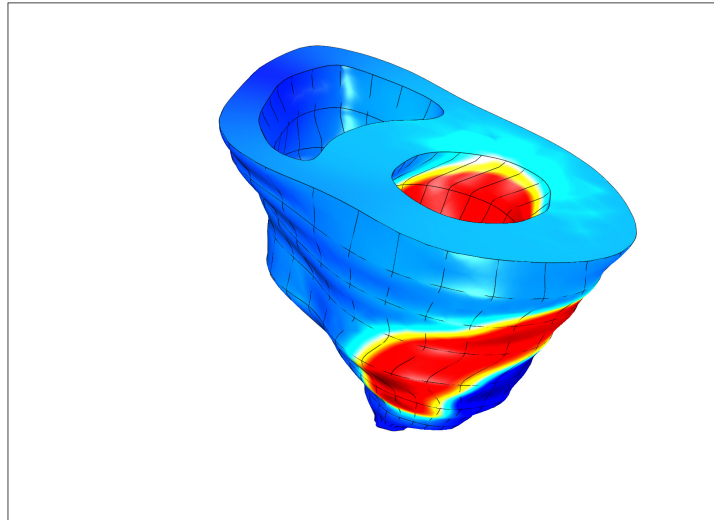


Figure 0.5: Voltage distribution at a given time on a real 3D NMR imported heart geometry.

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*, *Proceedings 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

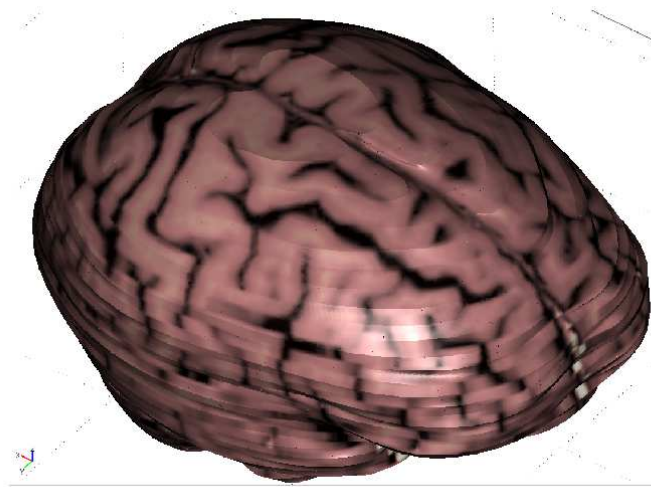


Figure 0.6: 3D NMR imported brain geometry associated with a diffusion tensor.

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, Proceedings 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

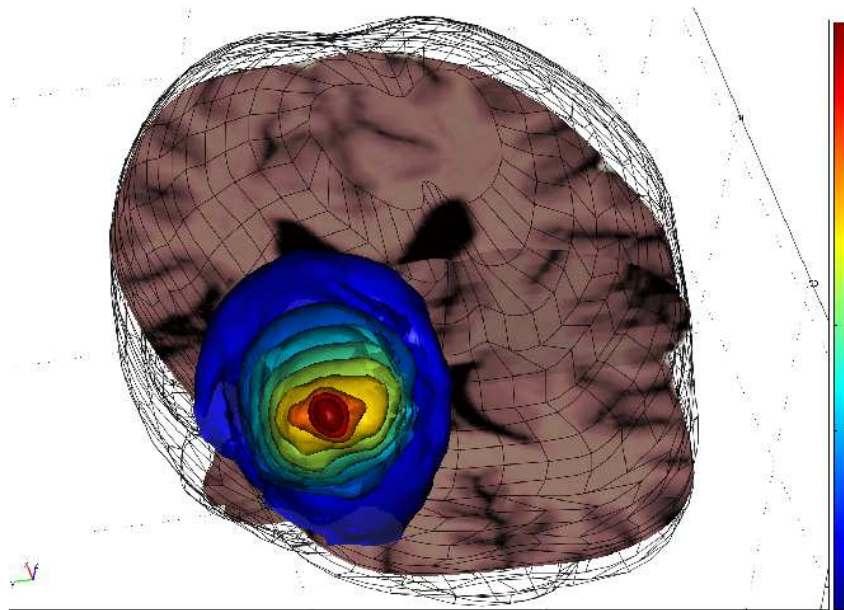


Figure 0.7: Mathematical model of tumor growth on the reconstructed brain geometry.

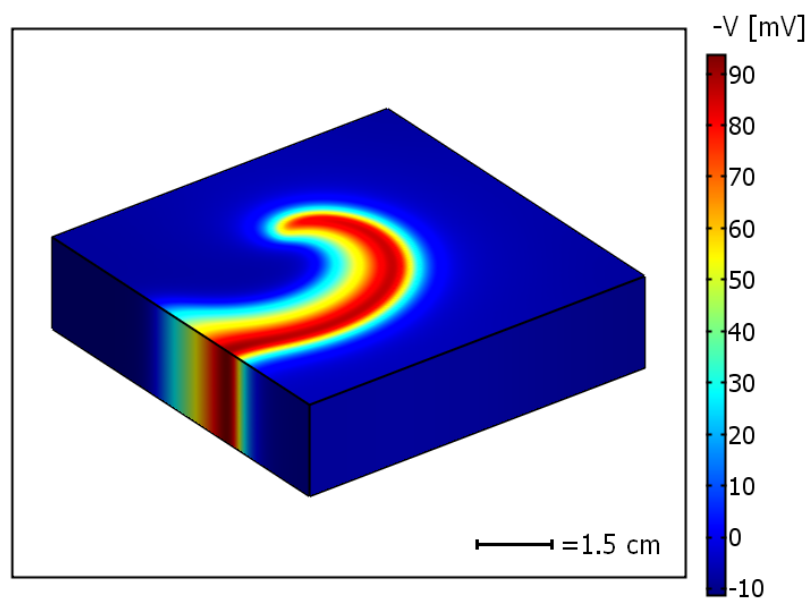


Figure 0.8: 3D scroll wave of action potential

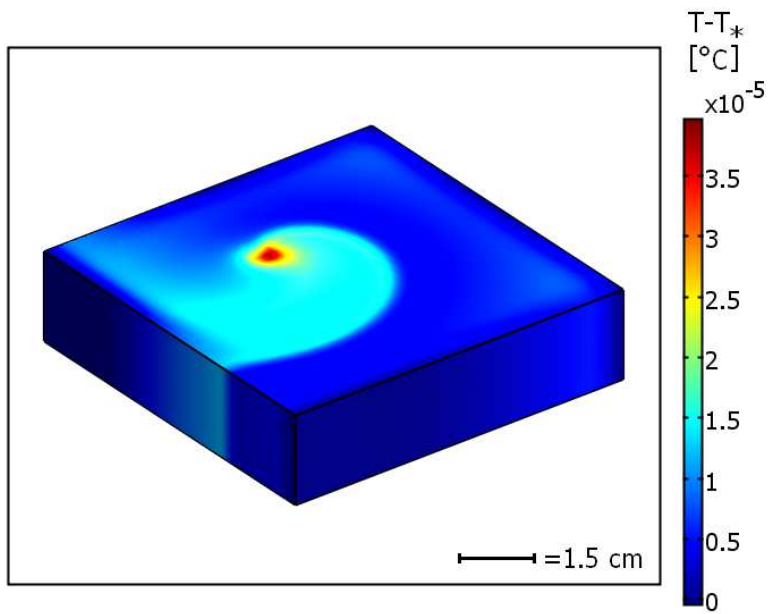


Figure 0.9: 3D thermal pattern associated with the electric scroll wave of the previous figure.

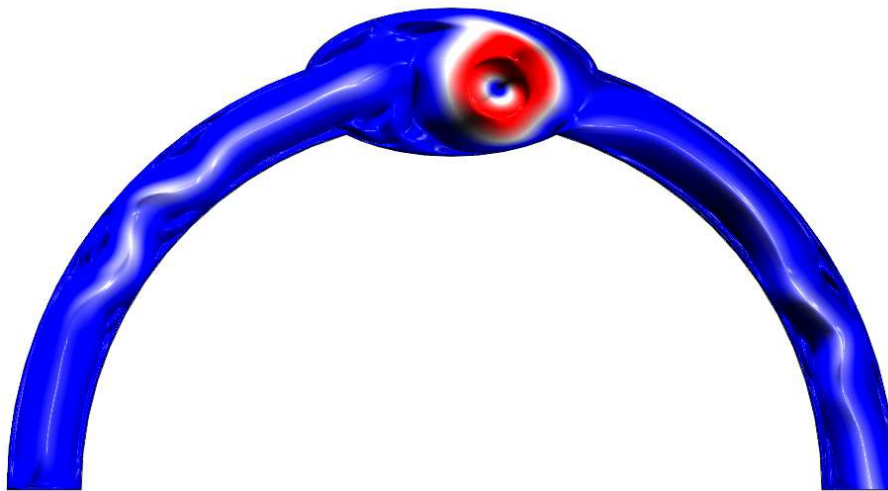


Figure 0.10: Snapshot at a given time of the velocity amplitude in the domain adopted to simulate a viscous hemodynamical flow.

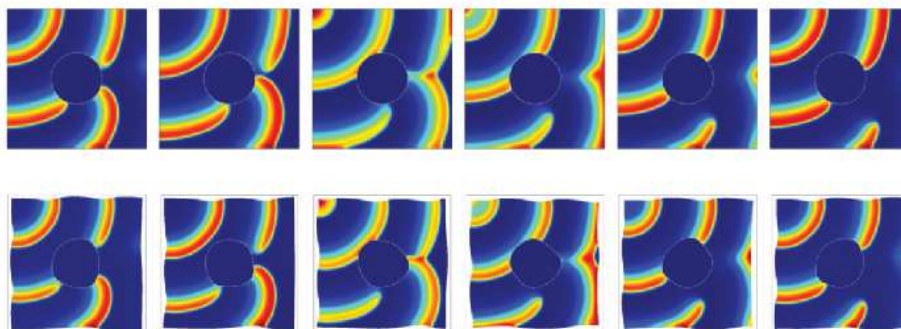


Figure 0.11: Defibrillation protocol for a pinned vortex shown at different times. On the first row electro-elastic feedback is inactivated, while on the lower one this effect is switched on. Coloring here denotes different values of action potential.

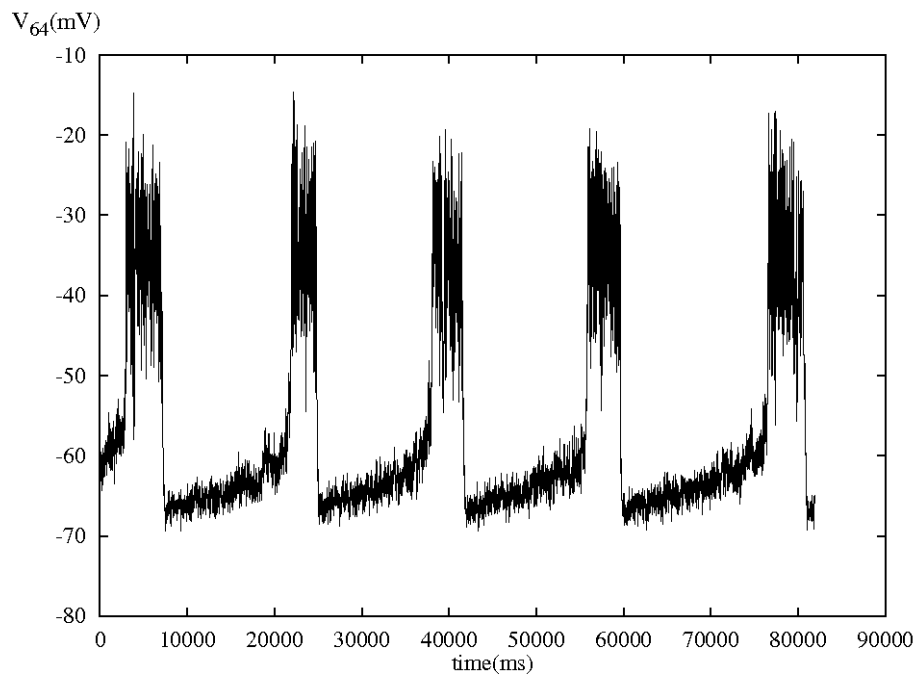


Figure 0.12: Typical action potential stochastic pattern for a beta cell embedded in a connected cluster sufficiently stimulated by glucose presence.

scroll waves. The introduction of heat transfer necessary on physical ground provides 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 Nth's 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 AlievRichardsWikswio 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/extinction 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-cartilaginous 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.

16. C. Cherubini S. Filippi and A. Gizzi, "Electroelastic unpinning of rotating vortices in biological excitable media", *Phys. Rev. E*, vol.85, 031915 (2012)

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 car-

diac contraction in the preexisting theoretically modeled defibrillation scenarios. Based on a two-dimensional minimal 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.

17. R. Portuesi, C. Cherubini, A. Gizzi, R. Buzzetti, P. Pozzilli and S. Filippi . "A stochastic mathematical model to study the autoimmune progression towards type 1 diabetes." *Diabetes/Metabolism Research and Reviews*, vol. 29, p. 194-203, S (2013)

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 (insulinitis), by modelling the disruption of pancreatic islet anatomy as a consequence of insulinitis 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 Ca^{2+} 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 Ca^{2+} 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

Abstract: 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 stim-

ulation 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), 31(3):259-83 (2014)

Abstract: We investigate the interaction of intracellular calcium spatio-temporal variations with the self-sustained contractions in cardiac myocytes. A consistent mathematical model is presented considering a 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 variables 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.

22. S. Filippi, A. Gizzi, C. Cherubini, S. Luther. and F H. Fenton "Mechanistic insights into hypothermic ventricular fibrillation: the role of temperature and tissue size" *Europace* 16, 424434 (2014)

Aims: Hypothermia is well known to be pro-arrhythmic, yet it has beneficial effects as a resuscitation therapy and valuable during intracardiac surgeries. Therefore, we aim to study the mechanisms that induce fibrillation during hypothermia. A better understanding of the complex spatiotemporal dynamics of heart tissue as a function of temperature will be useful in managing the benefits and risks of hypothermia. **Methods and results:** We perform two-dimensional numerical simulations by using a minimal model of cardiac action potential propagation fine-tuned on experimental measurements. The model includes thermal factors acting on the ionic currents and the gating variables to correctly reproduce experimentally recorded restitution curves at different temperatures. Simulations are implemented using Web GL, which allows long simulations to be performed as they run close to real time. We describe (i) why fibrillation is easier to induce at low temperatures, (ii) that there is a minimum size required for fibrillation that depends on temperature, (iii) why the

frequency of fibrillation decreases with decreasing temperature, and (iv) that regional cooling maybe an anti-arrhythmic therapy for small tissue sizes however it may be pro-arrhythmic for large tissue sizes. Conclusion: Using a mathematical cardiac cell model, we are able to reproduce experimental observations, quantitative experimental results, and discuss possible mechanisms and implications of electrophysiological changes during hypothermia.

23. Dupraz, M, Filippi, S, Gizzi, A, Quarteroni, A., Ruiz-Baier, R, "Finite element and finite volume-element simulation of pseudo-ECGs and cardiac alternans", *Mathematical Methods in the Applied Sciences*, (2014) in press, DOI: 10.1002/mma.3127

Abstract: In this paper, we are interested in the spatio-temporal dynamics of the transmembrane potential in paced isotropic and anisotropic cardiac tissues. In particular, we observe a specific precursor of cardiac arrhythmias that is the presence of alternans in the action potential duration. The underlying mathematical model consists of a reaction-diffusion system describing the propagation of the electric potential and the nonlinear interaction with ionic gating variables. Either conforming piecewise continuous finite elements or a finite volume-element scheme are employed for the spatial discretization of all fields, whereas operator splitting strategies of first and second order are used for the time integration. We also describe an efficient mechanism to compute pseudo-ECG signals, and we analyze restitution curves and alternans patterns for physiological and pathological cardiac rhythms.

24. Loppini A., Capolupo A., Cherubini C., Gizzi A., Bertolaso M., Filippi S., Vitiello G. "On the coherent behavior of pancreatic beta cell clusters" *Physics Letters A* Volume 378, Issue 44, Pages 32103217 (2014)

Abstract: Beta cells in pancreas represent an example of biological oscillators which via communication pathways, are able to synchronize their electrical activity, giving rise to pulsatile insulin release. In this work we numerically analyze scale free self-similarity features of membrane voltage signal power density spectrum, through a stochastic dynamical model for beta cells in the islets of Langerhans fine tuned on mouse experimental data. Adopting the algebraic approach of coherent state formalism, we show how coherent molecular domains can arise from proper functional conditions leading to a parallelism with phase transition phenomena of field theory.

25. Giuliani, A , Filippi, S, Bertolaso, M, "Why network approach can promote a new way of thinking in biology" *Frontiers in Genetics* Volume 5, (2014), Article number Article 83, (2014),

Abstract: This work deals with the particular nature of network-based approach in biology. We will comment about the shift from the consideration of the molecular layer as the definitive place where causative process start to the elucidation of the among elements (at any level of biological organization they are located) interaction network as the main goal of scientific explanation. This shift comes from the intrinsic nature of networks where the properties of a specific node are determined by its position in the entire network (top-down explanation) while the global network characteristics emerge from the nodes wiring pattern (bottom-up explanation). This promotes a "middle-out" paradigm formally identical to the time honored chemical thought holding big promises in the study of biological regulation.

26. Altomare, A., Gizzi, A., Guarino, M.P.L., Loppini, A., Cocca, S., Dipaola, M., Alloni, R., Cicala, M., Filippi, S., "Experimental evidence and mathematical modeling of thermal effects on human colonic smooth muscle contract", *American Journal of Physiology - Gastrointestinal and Liver Physiology* Volume 307, Issue 1, 1, Pages G77-G88 (2014)

Abstract: It has been shown, in animal models, that gastrointestinal tract (GIT) motility is influenced by temperature; nevertheless, the basic mechanism governing thermal GIT smooth muscle responses has not been fully investigated. Studies based on physiologically tuned mathematical models have predicted that thermal inhomogeneity may induce an electrochemical destabilization of peristaltic activity. In the present study, the effect of thermal cooling on human colonic muscle strip (HCMS) contractility was studied. HCMSs were obtained from disease- free margins of resected segments for cancer. After removal of the mucosa and serosa layers, strips were mounted in separate chambers. After 30 min, spontaneous contractions developed, which were measured using force displacement transducers. Temperature was changed every hour (37, 34, and 31C). The effect of cooling was analyzed on mean contractile activity, oscillation amplitude, frequency, and contraction to ACh (10-5 M). At 37C, HCMSs developed a stable phasic contraction (0.02 Hz) with a significant AChelicited mean contractile response (31% and 22% compared with baseline in the circular and longitudinal axis, respectively). At a lower bath temperature, higher mean contractile amplitude was observed, and it increased in the presence of ACh (78% and 43% higher than the basal tone in the circular and longitudinal

axis, respectively, at 31°C). A simplified thermochemomechanical model was tuned on experimental data characterizing the stress state coupling the intracellular Ca^{2+} concentration to tissue temperature. In conclusion, acute thermal cooling affects colonic muscular function. Further studies are needed to establish the exact mechanisms involved to better understand clinical consequences of hypothermia on intestinal contractile activity.

27. Cherubini C., Filippi S., Gizzi A., Loppini, A. "Role of topology in complex functional networks of beta Cells" *Physical Review E*, Volume 92, Issue 4, 5 October (2015), Article number 042702.

Abstract: The activity of pancreatic cells can be described by biological networks of coupled nonlinear oscillators that, via electrochemical synchronization, release insulin in response to augmented glucose levels. In this work, we analyze the emergent behavior of regular and percolated cells clusters through a stochastic mathematical model where functional networks arise. We show that the emergence and robustness of the synchronized dynamics depend both on intrinsic and extrinsic parameters. In particular, cellular noise level, glucose concentration, network spatial architecture, and cell-to-cell coupling strength are the key factors for the generation of a rhythmic and robust activity. Their role in the functional network topology associated with cells clusters is analyzed and discussed.

28. Bertolaso M., Capolupo A., Cherubini C., Filippi S., Gizzi A., Loppini A., Vitiello G, "The role of coherence in emergent behavior of biological systems" *Electromagnetic Biology and Medicine* Volume 34, Issue 2, 1 June (2015), Pages 138-140.

Abstract: In his research activity, Emilio Del Giudice explored the possibility to move towards a unified view of some long-range dynamics in nature, ranging from quantum field theory in physics up to biology. Such a view is adopted in this contribution by discussing a mathematical model for synchronized electrical behavior of pancreatic beta cells. The stochasticity is a fundamental component of the physiological synchronized behavior of this system. On the contrary, in a pathological type I diabetes scenario, the cells are destroyed by the autoimmune system and their coherent behavior is lost. This phenomenology conceptually links to ideas of coherent dynamics in quantum physics. Possible implications both for physical sciences and for the epistemology of life sciences are outlined.

29. Cherubini C., Filippi S., Gizzi A., Nestola M.G.C., "On the Wall Shear

Stress Gradient in Fluid Dynamics” Communications in Computational Physics, Volume: 17, (2015) Issue: 3 Pages: 808-821.

Abstract: The gradient of the fluid stresses exerted on curved boundaries, conventionally computed in terms of directional derivatives of a tensor, is here analyzed by using the notion of intrinsic derivative which represents the geometrically appropriate tool for measuring tensor variations projected on curved surfaces. Relevant differences in the two approaches are found by using the classical Stokes analytical solution for the slow motion of a fluid over a fixed sphere and a numerically generated three dimensional dynamical scenario. Implications for theoretical fluid dynamics and for applied sciences are finally discussed.

30. Gizzi A., Cherubini C., Filippi S., Pandolfi A., “Theoretical and Numerical Modeling of Nonlinear Electromechanics with applications to Biological Active Media”, Communications in Computational Physics Volume 17 (2015) Issue 1 Pages: 93-126

Abstract: We present a general theoretical framework for the formulation of the nonlinear electromechanics of polymeric and biological active media. The approach developed here is based on the additive decomposition of the Helmholtz free energy in elastic and inelastic parts and on the multiplicative decomposition of the deformation gradient in passive and active parts. We describe a thermodynamically sound scenario that accounts for geometric and material nonlinearities. In view of numerical applications, we specialize the general approach to a particular material model accounting for the behavior of fiber reinforced tissues. Specifically, we use the model to solve via finite elements a uniaxial electromechanical problem dynamically activated by an electrophysiological stimulus. Implications for nonlinear solid mechanics and computational electrophysiology are finally discussed.

31. Nestola M.G.C., Gizzi A., Cherubini C., Filippi S. and Succi S., “Novel risk predictor for thrombus deposition in abdominal aortic aneurysms” EPL (Europhysics Letters), 112, Number 2, 28001

Abstract: The identification of the basic mechanisms responsible for cardiovascular diseases stands as one of the most challenging problems in modern medical research including various mechanisms which encompass a broad spectrum of space and time scales. Major implications for clinical practice and pre-emptive medicine rely on the onset and development of intraluminal thrombus in which effective clinical therapies require synthetic risk pre-

dictors/indicators capable of informing real-time decision-making protocols. In the present contribution, two novel hemodynamics synthetic indicators, based on a three-band decomposition (TBD) of the shear stress signal, are introduced. Extensive fluid-structure computer simulations of patient-specific scenarios confirm the enhanced risk-prediction capabilities of the TBD indicators. In particular, they permit a quantitative and accurate localization of the most likely thrombus deposition in realistic aortic geometries, where previous indicators would predict healthy operation. The proposed methodology is also shown to provide additional information and discrimination criteria on other factors of major clinical relevance, such as the size of the aneurysm.

32. Gizzi A., Ruiz-Baier R., Rossi S., Laadhari A., Cherubini C., Filippi S. "A three-dimensional continuum model of active contraction in single cardiomyocytes" *Modeling, Simulation and Applications* Volume 14, (2015), Pages 157-176.

Abstract: We investigate the interaction of intracellular calcium spatio-temporal variations with the self-sustained contractions in cardiac myocytes. A 3D continuum mathematical model is presented based on a hyperelastic description of the passive mechanical properties of the cell, combined with an active-strain framework to describe the active shortening of myocytes and its coupling with cytosolic and sarcoplasmic calcium dynamics. Some numerical tests of combined boundary conditions and ionic activations illustrate the ability of our model in reproducing key experimentally established features. Potential applications of the study for predicting pathological subcellular mechanisms affecting e.g. cardiac repolarization are discussed.

33. Loppini, A., Braun, M., Filippi, S., Morten Gram Pedersen, "Mathematical modeling of gap junction coupling and electrical activity in human β -cells" (2015) *Physical Biology* 12 (6), 066002,

Abstract: Coordinated insulin secretion is controlled by electrical coupling of pancreatic cells due to connexin-36 gap junctions. Gap junction coupling not only synchronizes the heterogeneous cell population, but can also modify the electrical behavior of the cells. These phenomena have been widely studied with mathematical models based on data from mouse cells. However, it is now known that human cell electrophysiology shows important differences to its rodent counterpart, and although human pancreatic islets express connexin-36 and show evidence of cell coupling, these aspects have been little investigated in human cells. Here we investigate theoretically, the gap junction coupling

strength required for synchronizing electrical activity in a small cluster of cells simulated with a recent mathematical model of human cell electrophysiology. We find a lower limit for the coupling strength of approximately 20 pS (i.e., normalized to cell size, 2 pS pF⁻¹) below which spiking electrical activity is asynchronous. To confront this theoretical lower bound with data, we use our model to estimate from an experimental patch clamp recording that the coupling strength is approximately 100-200 pS (10-20 pS pF⁻¹), similar to previous estimates in mouse cells. We then investigate the role of gap junction coupling in synchronizing and modifying other forms of electrical activity in human cell clusters. We find that electrical coupling can prolong the period of rapid bursting electrical activity, and synchronize metabolically driven slow bursting, in particular when the metabolic oscillators are in phase. Our results show that realistic coupling conductances are sufficient to promote synchrony in small clusters of human cells as observed experimentally, and provide motivation for further detailed studies of electrical coupling in human pancreatic islets.

34. Dupraz M., Filippi S., Gizzi A., Quarteroni A., Ruiz-Baier R., "Finite element and finite volume-element simulation of pseudo-ECGs and cardiac alternans", *Mathematical Methods in the Applied Sciences* (2015) Volume 38, Issue 6, 1 April (2015), Pages 1046-1058.

Abstract: In this paper, we are interested in the spatio-temporal dynamics of the transmembrane potential in paced isotropic and anisotropic cardiac tissues. In particular, we observe a specific precursor of cardiac arrhythmias that is the presence of alternans in the action potential duration. The underlying mathematical model consists of a reaction-diffusion system describing the propagation of the electric potential and the nonlinear interaction with ionic gating variables. Either conforming piecewise continuous finite elements or a finite volume-element scheme are employed for the spatial discretization of all fields, whereas operator splitting strategies of first and second order are used for the time integration. We also describe an efficient mechanism to compute pseudo-ECG signals, and we analyze restitution curves and alternans patterns for physiological and pathological cardiac rhythms.

35. Nestola, M.G.C., Gizzi, A., Cherubini, C., Filippi, S., "Three-band decomposition analysis in multiscale FSI models of abdominal aortic aneurysms", (2016) *International Journal of Modern Physics C* 27 (2), 1650017.

Abstract: Computational modeling plays an important role in biology and medicine to assess the effects of hemodynamic alterations in the onset and development

of vascular pathologies. Synthetic analytic indices are of primary importance for a reliable and effective a priori identification of the risk. In this scenario, we propose a multiscale fluid-structure interaction (FSI) modeling approach of hemodynamic flows, extending the recently introduced three-band decomposition (TBD) analysis for moving domains. A quantitative comparison is performed with respect to the most common hemodynamic risk indicators in a systematic manner. We demonstrate the reliability of the TBD methodology also for deformable domains by assuming a hyperelastic formulation of the arterial wall and a Newtonian approximation of the blood flow. Numerical simulations are performed for physiologic and pathologic axially symmetric geometry models with particular attention to abdominal aortic aneurysms (AAAs). Risk assessment, limitations and perspectives are finally discussed.

36. Nestola, M.G.C., Faggiano, E., Vergara, C., Lancellotti, R.M., Ippolito, S., Antona, C., Filippi, S., Quarteroni, A., Scrofani, R. , "Computational comparison of aortic root stresses in presence of stentless and stented aortic valve bio-prostheses", (2016) *Computer Methods in Biomechanics and Biomedical Engineering*, in press.

Abstract: We provide a computational comparison of the performance of stentless and stented aortic prostheses, in terms of aortic root displacements and internal stresses. To this aim, we consider three real patients; for each of them, we draw the two prostheses configurations, which are characterized by different mechanical properties and we also consider the native configuration. For each of these scenarios, we solve the fluidstructure interaction problem arising between blood and aortic root, through Finite Elements. In particular, the Arbitrary LagrangianEulerian formulation is used for the numerical solution of the fluid-dynamic equations and a hyperelastic material model is adopted to predict the mechanical response of the aortic wall and the two prostheses. The computational results are analyzed in terms of aortic flow, internal wall stresses and aortic wall/prosthesis displacements; a quantitative comparison of the mechanical behavior of the three scenarios is reported. The numerical results highlight a good agreement between stentless and native displacements and internal wall stresses, whereas higher/non-physiological stresses are found for the stented case.

37. Cherubini C., Filippi S., Gizzi A., Ruiz-Baier R. , "A note on stress-driven anisotropic diffusion and its role in active deformable media", (2017) *Journal of Theoretical Biology*, 430, p.221-228.

Abstract: We introduce a new model to describe diffusion processes within active deformable media. Our general theoretical framework is based on physical and mathematical considerations, and it suggests to employ diffusion tensors directly influenced by the coupling with mechanical stress. The proposed generalised reaction-diffusion-mechanics model reveals that initially isotropic and homogeneous diffusion tensors turn into inhomogeneous and anisotropic quantities due to the intrinsic structure of the nonlinear coupling. We study the physical properties leading to these effects, and investigate mathematical conditions for its occurrence. Together, the mathematical model and the numerical results obtained using a mixed-primal finite element method, clearly support relevant consequences of stress-driven diffusion into anisotropy patterns, drifting, and conduction velocity of the resulting excitation waves. Our findings also indicate the applicability of this novel approach in the description of mechano-electric feedback in actively deforming bio-materials such as the cardiac tissue.

38. Gizzi A., Loppini A., Ruiz-Baier R., Ippolito A., Camassa A., La Camera A., Emmi E., Di Perna L., Garofalo V., Cherubini C., Filippi S., "Non linear diffusion and thermo-electric coupling in a two-variable model of cardiac action potential", (2017) *Chaos*, 27, p.093919 – 1 – –093919 – 11. Abstract: This work reports the results of the theoretical investigation of nonlinear dynamics and spiral wave breakup in a generalized two-variable model of cardiac action potential accounting for thermo-electric coupling and diffusion nonlinearities. As customary in excitable media, the common Q10 and Moore factors are used to describe thermo-electric feedback in a 10 range. Motivated by the porous nature of the cardiac tissue, in this study we also propose a nonlinear Fickian flux formulated by Taylor expanding the voltage dependent diffusion coefficient up to quadratic terms. A fine tuning of the diffusive parameters is performed a priori to match the conduction velocity of the equivalent cable model. The resulting combined effects are then studied by numerically simulating different stimulation protocols on a one-dimensional cable. Model features are compared in terms of action potential morphology, restitution curves, frequency spectra, and spatio-temporal phase differences. Two-dimensional long-run simulations are finally performed to characterize spiral breakup during sustained fibrillation at different thermal states. Temperature and nonlinear diffusion effects are found to impact the repolarization phase of the action potential wave with non-monotone patterns and to increase the propensity of arrhythmogenesis.

39. Gizzi A. Loppini A., Cherry E.M., Cherubini C., Fenton F.H., Filippi S. , "Multi-band decomposition analysis: application to cardiac alternans as a function of temperature", (2017) *Physiological Measurement*, 38, p.833-847.

Abstract: OBJECTIVE: It has long been known that variations in temperature can facilitate the development of cardiac arrhythmias. Here, we aim to quantify the effects of temperature on cardiac alternans properties. APPROACH: in this work, we use optical mapping recordings of canine ventricular epicardial preparations to demonstrate that hypothermia can promote the formation of alternans, which is an important precursor to potentially lethal arrhythmias like fibrillation. We then present a novel quantification of alternans properties for a broad range of cycle lengths under different thermal states. Specifically, we apply the recently developed multi-band-decomposition analysis (MBDA) in the context of cardiac action potential dynamics. MAIN RESULTS: We show that the MBDA offers several advantages compared with traditional analysis of action potential durations. First, MBDA allows a depiction and quantification of the magnitude of alternans at all threshold values simultaneously and thus offers more information about how alternans relates to the action potential morphology while also removing the necessity of choosing a single threshold value. Second, the MBDA technique offers simple ways for assessing action potential amplitude alternans. Finally, MBDA provides a quantification of signal quality without any additional processing. SIGNIFICANCE: We find that the MBDA technique shows promise in leading to a deeper understanding of cardiac alternans properties.

40. Gizzi A., Giannitelli S.M., Trombetta M., Cherubini C., Filippi S., De Ninno A., Businaro L., Gerardino A., and Rainer A. "Computationally Informed Design of a Multiaxial Actuated Microfluidic Chip Device", (2017) *Scientific Reports*, 7, p.5489-1–5489-11.

Abstract: This paper describes the computationally informed design and experimental validation of a microfluidic chip device with multi-axial stretching capabilities. The device, based on PDMS soft-lithography, consisted of a thin porous membrane, mounted between two fluidic compartments, and tensioned via a set of vacuum-driven actuators. A finite element analysis solver implementing a set of different nonlinear elastic and hyperelastic material models was used to drive the design and optimization of chip geometry and to investigate the resulting deformation patterns under multi-axial loading. Computational results were cross-validated by experimental testing of

prototypal devices featuring the in silico optimized geometry. The proposed methodology represents a suite of computationally handy simulation tools that might find application in the design and in silico mechanical characterization of a wide range of stretchable microfluidic devices.

41. Boccia E., Gizzi A., Cherubini C., Nestola M.G.C., Filippi S., "Viscoelastic computational modeling of the human head-neck system: Eigenfrequencies and time-dependent analysis" (2018), *Int J Numer Meth Biomed Engng.* 34:e2900.

Abstract: A subject-specific 3-dimensional viscoelastic finite element model of the human head-neck system is presented and investigated based on computed tomography and magnetic resonance biomedical images. Ad hoc imaging processing tools are developed for the reconstruction of the simulation domain geometry and the internal distribution of bone and soft tissues. Material viscoelastic properties are characterized point-wise through an image-based interpolating function used then for assigning the constitutive prescriptions of a heterogenous viscoelastic continuum model. The numerical study is conducted both for modal and time-dependent analyses, compared with similar studies and validated against experimental evidences. Spatiotemporal analyses are performed upon different exponential swept-sine wavelocalized stimulations. The modeling approach proposes a generalized, patient-specific investigation of sound wave transmission and attenuation within the human head-neck system comprising skull and brain tissues. Model extensions and applications are finally discussed.

42. Loppini A., Cherubini C., Filippi S., "On the emergent dynamics and synchronization of β -cells networks in response to space-time varying glucose stimuli" (2018), *Chaos, Solitons and Fractals*, 09 p.269 – 279

Abstract: Recent findings based on calcium fluorescence imaging of pancreatic islets, also combined with optogenetic techniques, showed that β -cells synchronization underlie a small-world and scale-free functional organization, where specified hubs are responsible of the emergent coordination in electrical activity. Despite these features were suggested to be linked to an efficient spreading of information and calcium waves, it is still unclear from what they emerge, if they can still be observed when different dynamical variables are used to build functional networks, and how they vary upon changes in control parameters. In this work we investigate this aspect with a novel hybrid discrete-continuum mathematical model, coupling the stochastic electrical dy-

namics of β -cell clusters to nonlinear reaction-diffusion of glucose. By analyzing cells activity with the use of dynamical functional networks computed on the correlations between cells membrane voltage signals, we recover functional features in accordance to experimental observations. We further show that such properties are observed during specific phases of the complex electrical bursting oscillation, and are affected by glucose diffusion. These results suggest that functional properties derived from experimental calcium signals, on a time scale on the order of tens of seconds, are also recovered at a much faster time scale, i.e., on the order of hundreds of milliseconds. We finally describe how such functional features are strongly linked to synchronization patterns, in which coordinated sub-clusters of cells naturally emerge from the underlying dynamics.

43. Loppini A., Gizzi A., Ruiz-Baier R., Cherubini C., Fenton F.H. and Filippi S., "Competing Mechanisms of Stress-Assisted Diffusivity and Stretch-Activated Currents in Cardiac Electromechanics" (2018), *Frontiers in Physiology*, Volume 9, article 1714

Abstract: We numerically investigate the role of mechanical stress in modifying the conductivity properties of cardiac tissue, and also assess the impact of these effects in the solutions generated by computational models for cardiac electromechanics. We follow the recent theoretical framework from Cherubini et al. (2017), proposed in the context of general reaction-diffusion-mechanics systems emerging from multiphysics continuum mechanics and finite elasticity. In the present study, the adapted models are compared against preliminary experimental data of pig right ventricle fluorescence optical mapping. These data contribute to the characterization of the observed inhomogeneity and anisotropy properties that result from mechanical deformation. Our novel approach simultaneously incorporates two mechanisms for mechano-electric feedback (MEF): stretch-activated currents (SAC) and stress-assisted diffusion (SAD); and we also identify their influence into the nonlinear spatiotemporal dynamics. It is found that (i) only specific combinations of the two MEF effects allow proper conduction velocity measurement; (ii) expected heterogeneities and anisotropies are obtained via the novel stress-assisted diffusion mechanisms; (iii) spiral wave meandering and drifting is highly mediated by the applied mechanical loading. We provide an analysis of the intrinsic structure of the nonlinear coupling mechanisms using computational tests conducted with finite element methods. In particular, we compare static and dynamic deformation regimes in the onset of cardiac arrhythmias and address other potential

biomedical applications.

44. Cherubini C., Loppini A. and Filippi S., "Chapter 10. Systems Biology Modeling of Nonlinear Cancer Dynamics" (2018) in "Systems Biology", (Mariano Bizzarri ed.), *Methods in Molecular Biology*, vol. 1702, Abstract: Systems Biology represents nowadays a promising standard framework for natural and human sciences to attack complicated problems involving Life. Here a particular application of such a program is discussed in the case of Cancer, by using a basic toy model for solid tumor spread for framing together two apparently different conceptual leading paradigms of Oncogenesis.

45. Loppini A., Gizzi A., Cherubini C., Cherry E.M., Fenton F.H. and Filippi S. "Spatiotemporal correlation uncovers characteristic lengths in cardiac tissue", *Phys. Rev. E*, vol. 100 , 020201(R) 5 pages (2019)

Abstract: Complex spatiotemporal patterns of action potential duration have been shown to occur in many mammalian hearts due to period-doubling bifurcations that develop with increasing frequency of stimulation. Here, through high-resolution optical mapping experiments and mathematical modeling, we introduce a characteristic spatial length of cardiac activity in canine ventricular wedges via a spatiotemporal correlation analysis, at different stimulation frequencies and during fibrillation. We show that the characteristic length ranges from 40 to 20 cm during one-to-one responses and it decreases to a specific value of about 3 cm at the transition from period-doubling bifurcation to fibrillation. We further show that during fibrillation, the characteristic length is about 1 cm. Another significant outcome of our analysis is the finding of a constitutive phenomenological law obtained from a nonlinear fitting of experimental data which relates the conduction velocity restitution curve with the characteristic length of the system. The fractional exponent of $3/2$ in our phenomenological law is in agreement with the domain size remapping required to reproduce experimental fibrillation dynamics within a realistic cardiac domain via accurate mathematical models.

46. Loppini A., Filippi S. and Stanley H. E. "Critical transitions in heterogeneous networks: Loss of low-degree nodes as an early warning signal", *Phys. Rev. E*, vol. 99, 040301(R) 5 pages (2019)

Abstract: A large number of real networks show abrupt phase transition phenomena in response to environmental changes. In this case, cascading phenomena can induce drastic and discontinuous changes in the system state and lead to collapse. Although complex network theory has been used to investigate these drastic events, we are still unable to predict them effectively. We here analyze collapse phenomena by proposing a minimal two-state dynamic on a complex network and introducing the effect of local connectivities on the evolution of network nodes. We find that a heterogeneous system of interconnected components presents a mixed response to stress and can serve as a control indicator. In particular, before the critical transition point is reached a severe loss of low-degree nodes is observed, masked by the minimal failure of higher-degree nodes. Accordingly, we suggest that a significant reduction in less connected nodes can indicate impending global failure

47. Ruiz-Baier R, Gizzi A, Loppini A, Cherubini C, Filippi S. "Modelling Thermo-Electro-Mechanical Effects in Orthotropic Cardiac Tissue". *Communications in Computational Physics*, vol. 27, p. 87-115, (2020)

Abstract: In this paper we introduce a new mathematical model for the active contraction of cardiac muscle, featuring different thermo-electric and nonlinear conductivity properties. The passive hyperelastic response of the tissue is described by an orthotropic exponential model, whereas the ionic activity dictates active contraction incorporated through the concept of orthotropic active strain. We use a fully incompressible formulation, and the generated strain modifies directly the conductivity mechanisms in the medium through the pull-back transformation. We also investigate the influence of thermo-electric effects in the onset of multiphysics emergent spatiotemporal dynamics, using nonlinear diffusion. It turns out that these ingredients have a key role in reproducing pathological chaotic dynamics such as ventricular fibrillation during inflammatory events, for instance. The specific structure of the governing equations suggests to cast the problem in mixed-primal form and we write it in terms of Kirchhoff stress, displacements, solid pressure, dimensionless electric potential, activation generation, and ionic variables. We also advance a new mixed-primal finite element method for its numerical approximation, and we use it to explore the properties of the model and to assess the importance of coupling terms, by means of a few computational experiments in 3D.

48. Loppini A, Gizzi A, Cherubini C, Fenton F H, Filippi S. "Temperature ef-

fects and correlation analysis in cardiac tissue". In: 2014 8th Conference of the European Study Group on Cardiovascular Oscillations (ESGCO) . p. 1-2, Institute of Electrical and Electronics Engineers Inc., Pisa, doi: 10.1109/ESGCO49734.2020.9158021, (2020).

Abstract: Cardiac dynamic is characterized by complex spatiotemporal phenomena, including alternans and arrhythmias. A deep understanding of these phenomena is required for an effective prediction of pathological regimes, and, to this aim, mathematical modeling represents a necessary tool to be used in combination with experiments. In this contribution, we present a mathematical framework able to reproduce endocardium spatiotemporal dynamics, including temperature feedback on the electrophysiological response. The model correctly reproduces action potential shape, duration, and conduction velocity modulations upon thermal variations, as observed in experiments. Besides, simulations and experiments show similar spatiotemporal correlation properties at varying pacing frequencies. Our outcomes suggest the use of a novel indicator of alternans development and arrhythmias onset.

49. Loppini A, Cherubini C, Bertolaso M, Filippi S., "Breaking down calcium timing in heterogenous cells populations". *Biosystems*, vol. 191-192, p. 1-7, (2020)

Abstract: Calcium controls a large number of cellular processes at different scales. Decades of studies have pointed out the importance of calcium signaling in regulating differentiation, apoptosis, mitosis and functions such as secretion, muscle contraction and memory. The space-time structure of calcium signaling is central to this complex regulation. In particular, cells within organisms behave as clocks beating their own biological time, although in several cases they can synchronize across long distances leading to an emergent space-time dynamics which is central for single cell and organ functioning. We use a mathematical model built on published experimental data of hepatic non-excitable cells, analyzing emerging calcium dynamics of cells clusters composed both of normally functioning cells and pathological aggregates. Calcium oscillations are investigated by varying the severity of dysfunction and size of pathological aggregate. We show how strong and localized heterogeneity in cellular properties can profoundly alter organized calcium dynamics leading to sub-populations of cells which create their own coordinated dynamical organization. Our simulations of Ca^{2+} signals reveal how cell be-

haviors differ and are related to intrinsic time signals. Such different cells clusters dynamically influence each other so that non-physiological although organized calcium patterns are generated. This new reorganization of calcium activity may possibly be a precursor of cancer initiation.

50. Loppini A., Barone A., Gizzi A., Cherubini C., Fenton F.H., Filippi S., "Thermal effects on cardiac alternans onset and development: A spatiotemporal correlation analysis", *Phys. Rev. E* vol. 103, L040201 (2021)

Abstract: Alternans of cardiac action potential duration represent critical precursors for the development of lifethreatening arrhythmias and sudden cardiac death. The system's thermal state affects these electrical disorders requiring additional theoretical and experimental efforts to improve a patient-specific clinical understanding. In such a scenario, we generalize a recent work from Loppini et al. [*Phys. Rev. E* 100, 020201(R) (2019)] by performing an extended spatiotemporal correlation study. We consider high-resolution optical mapping recordings of canine ventricular wedges' electrical activity at different temperatures and pacing frequencies. We aim to recommend the extracted characteristic length as a potential predictive index of cardiac alternans onset and evolution within a wide range of system states. In particular, we show that a reduction of temperature results in a drop of the characteristic length, confirming the impact of thermal instabilities on cardiac dynamics. Moreover, we theoretically investigate the use of such an index to identify and predict different alternans regimes. Finally, we propose a constitutive phenomenological law linking conduction velocity, characteristic length, and temperature in view of future numerical investigations.

51. Luchetti N., Filippi S, and Loppini A., "Multilevel synchronization of human β -cells networks", *Front. Netw. Physiol.*, Volume 3 - (2023)

Abstract: β -cells within the endocrine pancreas are fundamental for glucose, lipid and protein homeostasis. Gap junctions between cells constitute the primary coupling mechanism through which cells synchronize their electrical and metabolic activities. This evidence is still only partially investigated through models and numerical simulations. In this contribution, we explore the effect of combined electrical and metabolic coupling in β -cell clusters using a detailed biophysical model. We add heterogeneity and stochasticity to realistically reproduce β -cell dynamics and study networks mimicking arrange-

ments of β -cells within human pancreatic islets. Model simulations are performed over different couplings and heterogeneities, analyzing emerging synchronization at the membrane potential, calcium, and metabolites levels. To describe network synchronization, we use the formalism of multiplex networks and investigate functional network properties and multiplex synchronization motifs over the structural, electrical, and metabolic layers. Our results show that metabolic coupling can support slow wave propagation in human islets, that combined electrical and metabolic synchronization is realized in small aggregates, and that metabolic long-range correlation is more pronounced with respect to the electrical one.

52. Luchetti N., Loppini A., Matarrese M.A.G., Chiodo L. and Filippi S. "Structural controllability to unveil hidden regulation mechanisms in Unfolded Protein Response: The role of network models", *Physica A: Statistical Mechanics and its Applications* Volume 617, 128671 (2023)

Abstract: The Unfolded Protein Response is the cell mechanism for maintaining the balance of properly folded proteins in the endoplasmic reticulum, the specialized cellular compartment. Although it is largely studied from a biological point of view, much of the literature lacks a quantitative analysis of such a central signaling pathway. In this work, we aim to fill this gap by applying structural controllability analysis of complex networks to several Unfolded Protein Response networks to identify crucial nodes in the signaling flow. In particular, we first build different network models of the Unfolded Protein Response mechanism, relying on data contained in various protein-protein interaction databases. Then, we identify the driver nodes, essential for overall network control, i.e., the key proteins on which external stimulation may be optimally delivered to control network behavior. Our structural controllability analysis results show that the driver nodes commonly identified across databases match with known endoplasmic reticulum stress sensors. This potentially confirms that the theoretically identified drivers correspond to the biological key proteins associated with fundamental cellular activities and diseases. In conclusion, we prove that structural controllability is a reliable quantitative tool to investigate biological signaling pathways, and it can be potentially applied to networks more complex and less explored than Unfolded Protein Response.

