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0.1 Topics

- Reaction-diffusion equations
- Turbulence in vortex dynamics
- Heat Transfer in excitable tissues
- Mechano-electric Feedback
- Computational Cardiology
- Mathematical Models of Tumor Growth
- Fluid Dynamics
0.2 Participants

0.2.1 ICRANet participants
- Donato Bini (IAC, CNR, Rome, Italy)
- Christian Cherubini (University Campus Bio-Medico, Rome, Italy)
- Simonetta Filippi, project leader (University Campus Bio-Medico, Rome, Italy)

0.3 External Collaborations
- Valentin Krinsky (INLN, CNRS, Nice, France)
- Alain Pumir (INLN, CNRS, Nice, France)
- Flavio Fenton and Elizabeth Cherry (Biosciences Department, Cornell University, USA)

0.3.1 Postdocs and students
- Alessio Gizzi (Postdoc, University Campus Bio-Medico, Rome, Italy)
- Edda Boccia (PhD student, University Campus Bio-Medico, Rome, Italy)
- Giuseppina Nestola (PhD student, University Campus Bio-Medico, Rome, Italy)
- Alessandro Loppini (Granted scientific collaborator, University Campus Bio-Medico, Rome, Italy)
- Nicola Pomella (Granted scientific collaborator, University Campus Bio-Medico, Rome, Italy)
0.4 Brief description

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

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

\[
\begin{align*}
V_t &= D_1 \nabla^2 V + f(U, V) \\
U_t &= D_2 \nabla^2 U + g(U, V),
\end{align*}
\]

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:

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

(0.2)

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

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

(0.3)

\[
\rho c_p \frac{\partial T}{\partial t} = \nabla_i (k_{il} \nabla_l T) + \sigma_{ik} \nabla_i V \nabla_k V + w_s(T_s - T),
\]

(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

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

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

\[
\frac{\partial \psi_2}{\partial t} = -D_1 \nabla^2 \psi_2 + \frac{\partial S}{\partial \psi_1} (C_1 - \psi_2) + \frac{\partial H}{\partial \psi_1} (C_2 - \psi_4)
\]

\[
\frac{\partial \psi_4}{\partial t} = -D_2 \nabla^2 \psi_4 + \frac{\partial S}{\partial \psi_3} (C_1 - \psi_2) + \frac{\partial H}{\partial \psi_3} (C_2 - \psi_4)
\]

\[
\frac{\partial \psi_1}{\partial t} = D_1 \nabla^2 \psi_1 + S(\psi_1, \psi_3)
\]

\[
\frac{\partial \psi_3}{\partial t} = D_2 \nabla^2 \psi_3 + H(\psi_1, \psi_3), \] (0.6)

Noether’s theorem then can be adopted to obtain conserved quantities. The group has published in the past also a chapter devoted on mathematical modelling of cardiac tissue dynamics on a monograph on Mechano-sensitivity in biological cells [9]. In 2010 the group has investigated the spiral wave solutions of the diffusion equation through mathematical physics methods [10]. Moreover a study in cardiac dynamics [11] has been published discussing the electrical arrhythmias suppression in portions of cardiac tissue. In the heart in fact an action potential vortex pinned by an obstacle can be removed through defibrillation protocols fine-tuned theoretically by using electrophysiological nonlinear mathematical models. Finally similar mathematical methods have been implemented to analyse the nonlinear electrophysiological dynamics of intestinal tissue in the case of strong thermal gradients as experienced during surgery [12]. In this case it has been predicted that in these situations unstable behaviors similar to cardiac electrical turbulence can occur. This formulation has been linked to the clinical problem of postoperative paralytic ileus. In 2011 the group has analyzed problems of fluid dynamics in biology [13]. Specifically space-time patterns of Wall Shear Stress (WSS) resulting from the numerical simulation of pulsating hemodynamic flows in semi-coronal domains have been analyzed, both in the case of regular semi-coronal domains and semi-coronal domains with bumpy insertions (see Fig. 10), with the aim of simulating aneurysm-like geometries. These studies have been obtained by numerically integrating via Finite Elements Techniques the equations for a viscous Newtonian incompressible fluid. New
cardiovascular risk indicators, named Three-Band Diagrams (TBD) have been introduced extending the ones already existing in the literature. These indicators allow a quick visual assessment of the risk level to individual fluctuations of the physiological risk thresholds. Due to its generality, such a new mathematical tool is expected to be useful for several problems of Physics, Chemistry, Engineering and Biomedicine. In 2012 the group activities have been focused on cancer dynamics and biomechanics modelling. The authors have adopted partial differential equations to model cancer spread [14], a dynamical process occurring in time but also in space which, for solid tumors at least, can be modelled quantitatively by reaction and diffusion equations with a bistable behavior. Tumor cell colonization happens in a portion of tissue and propagates, but in some cases the process is stopped. The authors have then extended this formulation by using the highly nonlinear porous medium equation

\[
\frac{\partial C}{\partial t} = \sigma^{-m} \nabla \cdot (C^m \nabla C) + F(C) \tag{0.7}
\]

with the aforementioned nonlinear reaction bistable dynamics

\[
F(C) = aC(1 - C)(C - \alpha) \tag{0.8}
\]

Here C stands for cancer cell concentration, while \(m, a, \alpha, \sigma\) 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).

0.5 Publications (2005-2012)


Abstract: An extended FitzHugh-Nagumo model coupled with dynamic al heat transfer in tissue, as described by a bioheat equation, is derived and confronted
Figure 0.1: Spiral wave in the temperature domain at a given time.

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


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

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

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

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

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

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


Abstract: This article discusses the RMN import of a brain geometry in Consol Multiphysics via an interpolating function. The physical property associated with the grayscale is the diffusivity tensor, assumed here to be isotropic but inhomogeneous. Applications to antitumoral drug delivery and cancer growth processes are discussed.

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.

Abstract: An extension of the HodgkinHuxley mathematical model for the propagation of nerve signal which takes into account dynamical heat transfer in biological tissue is derived and fine tuned with existing experimental data. The medium is heated by Joules effect associated with action potential propagation, leading to characteristic thermal patterns in association with spiral and scroll waves. The introduction of heat transfer necessary on physical grounds 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.


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


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 results are discussed.


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.


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


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
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.


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.


Abstract:Spiral waves in excitable biological media are associated with pathological situations. In the heart an action potential vortex pinned by an obstacle has to be removed through defibrillation protocols fine-tuned theoretically by using electrophysiological nonlinear mathematical models. Cardiac tissue, however, is an electroelastic medium whose electrical properties are strongly affected by large deformations. In this paper we specifically investigate the electroelastic pinning-unpinning mechanism in order to include cardiac contraction in the preexisting theoretically modeled defibrillation scenarios. Based on a two-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.