A grand challenge for research: multimodal, multilevel and multiscale systems in medicine and biology

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Abstract

Computational modelling, nano-bioscience and information technology in biology and medicine will play a major role in the interdisciplinary attempts to elucidate structures and functions of living systems. Developing tools capable to integrate the new advances and make benefit of them is crucial: accumulation of data and knowledge base with only storage and retrieval capabilities will have a poor impact if they are not made "active" or "operational". This is where models will play a central role in offering, not only sound ways for representation or simulation, but also the appropriate frames to put the players in the right place, with intra- and inter-level coupling and multisource handling. This paper advocated that sequential observations of multiple and complex mechanisms will be of limited interest to understand the inter-relations that are occurring at the same time, and therefore, that designing multimodal, multilevel and multiscale experiments, matched with these models, are of major importance.

Key words: modelling, multimodal data, multilevel descriptions, multiscale processing.

Introduction

There is a large consensus today about the need for convergence of genomics, proteomics, metabolomics, biochemistry, biology and physiology with computer sciences, information technology, mathematics and automatic control. The wealth of new data and knowledge related to sub-cellular and supra-cellular mechanisms calls for smart warehouses allowing efficient queries. The same requirements can be found at individual and population level with the aim to improve the diagnosis decision and the therapeutic means, to better manage health care systems. They all deal with large scale, dynamically varying, non-linear complex systems.

If there is a general agreement on this situation, no clear definition on the ways to carry out such tasks are available. All disciplines are concerned and claim that they are the right places to drive this research while, at the same time, recognizing the need for multidisciplinary or interdisciplinary competences. New educational tracks are open, novel journals and conferences are launched, new attractive keywords are displayed, multiple reports are disseminated, and this does not help in clarifying the most relevant approaches to undertake. It may be more interesting sometimes to have a look back to science and to see if we are not reinventing the wheel by just creating "virtual worlds" with pseudomagic clothes. There is no doubt for instance that interface domains are existing for decades, and the "biomedical engineering" is one example, among many others. Some decline may have been observed in physiology, whose goal is to explore whore organs in their natural context. Structural biology has taken the lead for years and left functions away. Computational modelling has a long experience to share with other fields even if for a long time it has been considered by experimental scientists as a marginal and too abstract way to handle real problems.

This short paper does not pretend to bring "ready-to-use" solutions in this area. However, its goal is to point out some important issues that will be more and more important in the future. Section 2 reviews the last trends illustrating the views recently proposed under different headings and sketches a few important issues to deal with. An overall picture, organized around the multimodal, multilevel, multisource and multiscale concepts and illustrated through two examples, is provided Section 3 before concluding.

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Some trends and key paradigms

A few recent headings

"Integrative" is certainly the most popularised term today in almost all Life Sciences and particularly in Biology and Physiology [1,2]. It is opposed to the "reductionnist" approach whose goal consists to identify molecular and cellular events studied in isolated systems (like it is performed in genomics, proteomics, biochemistry and cell biology). "Integrative" is seen as the studies targeted to the understanding of physiological functions in the context of organ or organ systems. Behind these views, there is the perception that molecular biology can not provide all the answers to understand the genetic, proteomic and cellular mechanisms involved in tissue organization, growth, differentiation, etc. It is striking to see the move from structural to functional, genomics to metabolomics... However, fundamental questions are posed at the same time by this debate. One of the key point is how to derive findings or to extrapolate the observed behaviours to global, *in vivo*, organs or systems at specific life stages. The functional properties, and the structure-to-function features, are among the most concerned.

Systems Biology is another fashionable topic even if it is loosely defined. It deals with studies of intra- and intercellular dynamics, using systems and signal-oriented approaches. One of the goal is to identify structural characteristics and variables in order to derive mathematical models and to simulate the sub-cellular, cellular and supra-cellular dynamics. The emphasis is put here on regulation, prediction and control, signals and information, theoretical modelling, predictive behaviour, all terms referring to engineering and applied mathematical sciences or physics. The cell has been already widely explored: an example of the mammalian cell can be found in [3] where the main circuitry is identified with growth, differentiation and apoptosis controls. The fascinating features of such modelling, and consequently the challenges to face, are related to the sensing capabilities, catalyse reactions, switches, actuators and to the number of distinct inputs/outputs that are present, some being known, others being only approximated or assumed. Many questions for Systems Biology arise about information processing, the transduction pathways, the types of reactions, the non-linear relations involved, the robustness, the role of multiple loops, the mix of discrete and continuous components, etc. These issues are central to Systems Biology and call for advances in mathematical modelling (the recent paper by Sontag [4] argues that automatic control should, in turn, benefit of biological problems by identifying new theoretical problems).

Nanomedicine has emerged very recently and several surveys have been published to analyse their potential opportunities for health [5-8]. Nanomedicine, as defined in [8], aims at "the comprehensive monitoring, repair and improvement of all human biological systems, working from the molecular level using engineered devices and nanostructures to achieve medical benefit". The same report identified nanomaterials and devices, nanoimaging and analytical tools, novel therapeutic and drug delivery systems, as the major technological components to address. It also emphasized the importance of regulatory issues for clinical applications and the need of in-depth toxicological studies, either environmental and clinical. Taking nanoimaging as example (refer to [9] for more details), there is no clear frontiers with what is called "molecular imaging" even if the initial views where mainly directed to medical modalities. In both cases the objective is the *in vivo* measurement and characterization of biological processes at the cellular and molecular level and, beyond the standard anatomical and functional mapping, the *in vivo* detection and quantification of molecular disease markers or therapeutic agents via specific probes. It is expected that early disease manifestations will be detected by enzymes or signalling molecules. Succeeding in such challenges should take time of course and should address many faces among which patient-specific patterns and adverse drug reactions.

All these topics are of course inter-related and represent the many attempts to understand the overall levels of living bodies. The "flags" they display express the search for new paths. They lack sometimes of basic links to major theoretical disciplines and may try to rebuild them on their own, for their specific purpose. The convergence mentioned above aims at merging technology, informatics with mathematics, statistical physics to deal with the many facets to jointly address. Historically, truly pluridisciplinary fields can not be away of this effort for several reasons. First, learning or simply understanding the key concepts coming from other disciplines requires time before really bringing significant contributions. Second, these concepts are confronted to very different practices which also must be acquired. Third, the techniques already in hands may be not sufficient to face the new problems to be solved. Fourth, the amount of data and knowledge is such that it may be difficult to properly adjust the trade-off between the many elementary components and the global properties to take into account. The next section will exemplify a few points in this direction.

Basic questions

Determinist versus stochastic views

Most of the molecular mechanisms involved in gene expression and cellular processes have relied on the paradigm of determinism. In this classical view of a genetic program, a cell differentiates during embryo development upon an input signal and no variability (all cells must react identically to the stimulus) can be expected. The stochastic aspects of cell physiology have been widely discarded. However, there is more and more evidence that, instead to consider on-off schemes, stochastic behaviours have an important role. The notion of "average cell" has been recently discussed [10] and a model was proposed based on a probability for each gene of a single cell to be activated at any time, probability depending of the concentration of transcriptional regulators. Fluctuations at a macrolevel in heartbeats, in regulatory networks, in the activity of neurons or in proteins and nucleic acids, that can in certain cases look like noise, have been recognized as major features. Statistical physics point out that many stochastic processes (say stochastic disorder at the molecular level) can lead to organized structures (e.g. macroscopic level, tissues). There are many problems to be solved before capturing, describing, modelling these fluctuations and understanding how the biological entities control them during normal growth and pathological disorders. We need further

in vivo experiments to elucidate the stochastic rules governing cellular and supra-cellular mechanisms but in-silico models can provide some insights on their plausibility.

From genes to biological organizations

If it is true that genetics has brought many major highlights within the last decades, it can also be questioned. It may be important to consider, for cell differentiation, phenotypic auto-stabilization (differentiated cells stabilizing their own phenotype) and interdependence for proliferation (differentiated cells stimulating the proliferation of alien phenotypes). It has been shown in embryogenesis for instance that these two mechanisms can generate an organized cellular bi-layer structure from two cell types with finite growth, and that their imbalance leads to tissue disorganization and cancer-like growth [11]. These elements suggest that the molecular theory where cells rest or proliferate according to the input signals they receive can be challenged by other views based on quantitative equilibrium between a set of factors involved in tissue organization, including the cellular microenvironment, the tissue structure and, in other words, the whole organism is concerned. The consequence of such view is that both genomic and cellular interactions are involved in tissue organization. The assumptions about our accurate descriptions of elements are perhaps overestimated because much remains to discover at nano-, micro- and macrolevels in living systems. But, it is true, that the study of entire ensembles has to be conducted. The next challenging task is to reassemble them into global pictures in order to capture their proper roles and their key collective properties. This is the objective of the Physiome project [12,13].

Complex systems and complexity

The convergent feeling that we have to understand complex systems is not enough. Complexity must be defined in a more precise way. Von Neumann already in 1966 said about complexity that “none of this can get out of the realm vague statement until one has defined the concept of complication correctly... the simplest mechanical and thermodynamical systems had to be discussed a long time before the correct concepts of energy and entropy could be extracted from them”. Oxford dictionary defines complexity as “comprehending various parts connected together; composite, compound, involved, intricate”. Parts, that can not so easily be separated, are both distinct (large variety and heterogeneity, highly variable behaviours) and connected (with constraints, redundancy and strong dependency). Roughly speaking, we may say that complexity increases when the variety (distinction) and dependency (connection) of parts increase in space, time and function.

However, the number of parts left out the connectivity, what may be of utmost importance, “organisation” and “levels of organisation” (molecules, proteins, cells, assemblies, tissues, organs, systems, etc.). Complexity is sometimes specified as the way in which the whole is different from the composition of its parts. In other words, a complex system should show collective properties that can not be apprehended from their elementary components.

There are two approaches debated on complex systems, either by questioning a given object from multiple disciplines, or, by tackling a specific question transversal to different objects. The latter being the essence of a complex system science, its purpose is to model biological objects, ecological systems, social organizations and also the highly sophisticated man-made systems. It is very likely that both views will be continuing in the future. What is at our mathematical reach today? What can be built on our present physiological/biological knowledge? What generic questions may traverse the all fields? The answers are not much.

Mode, level, source, scale and models

This section is devoted to three major issues that should bring new highlights to undertake some of the biological and the medical problems above mentioned. They are not of course the only topics of interest to address in the future: in each area of engineering science (information processing in its wide sense), in all biomedical and clinical disciplines (understanding of disease and the underlying mechanisms), there are significant advances that may be foreseen. There is no in our mind a hierarchy that should justify to consider these problems as less important than those reported and discussed below. All are participating to the search of answers to basic questions or, equally, to better care of human beings.

Modelling, processing and sensing

The tight connection between data acquisition and data processing is well established. It includes the design of innovative sensors providing vectorial (multichannel or multilead) signals capable to provide observations at nano-, micro- or macroscales. Their main advantage is to achieve a very high time resolution, their drawback being a poor spatial sampling. Conversely, macro-imaging modalities (ranging from the new Multi Slice Computer Tomography – MSCT, high field Magnetic Resonance Imaging to Nuclear Modalities like Positron Emission Tomography – PET) lead to relatively well sampled volume data sets but with still limited time resolution (the exceptions being ultrasound techniques and perhaps the emerging optical devices). A major feature between these two sources of data remains perhaps the relative lack of innovations for devices devoted to physiological signal sensing while the imaging modalities are improving every day and can significantly change our access to pathological patterns. Another trend in clinical devices (mainly in imaging but also through the development of micro-technologies) is the emphasis put on multimodal techniques with either post-registration of data sets or a direct coupling of sources in the same system (for instance CT and PET).

When surveying the recent advances in processing techniques, it is worth noting that a number of new resources are at our disposal: wavelets, time-frequency, blind source separation, particle filtering for signal processing, Kernel methods in data mining, deformable models and level sets in image analysis are among the most well known [14]. All these tools, when applied to data to detect, separate mixture components, extract quantitative features, are aimed at improving decisions, the ultimate goal being early and better diagnosis. They belong to what I call the “surface approach” which means that no explicit

Figure 1. **The basic loop providing the capability from hypothesis generation, to design biological experiments or medical protocols, with the appropriate data acquisition resources, the most efficient information processing means in order to feed, refine and evaluate the relevance of model and the most plausible interpretations. Additional loops can be added (processing to sensing, for instance) if the analysis does not introduce formal representations of physiological knowledge)**

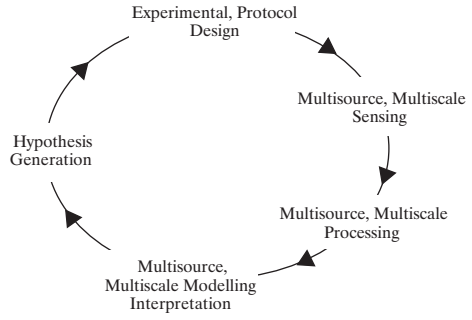
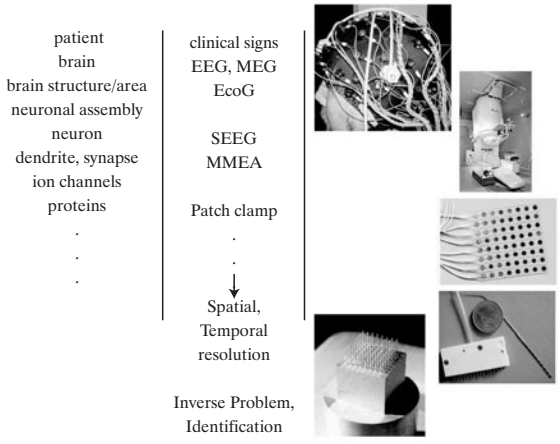


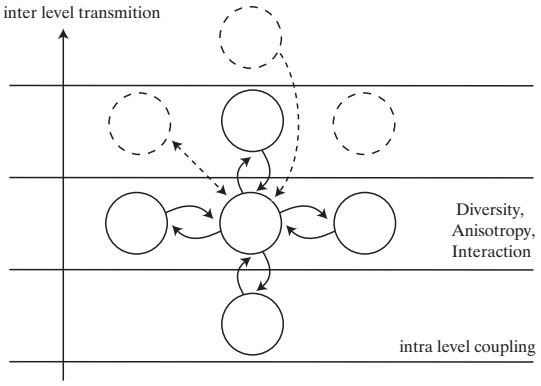
Figure 2. **The multilevel signals that can be recorded during in-vitro and in-vivo observations of cells, neuronal assemblies and main cerebral structures. Pictures from top to bottom display the dense EEG setting, a MEG platform, an electrode array in EcoG, depth electrodes for SEEG and a Multiple Micro Electrode Arrays (MMEA)**



formulation of the pathophysiological mechanisms originating the observed patterns is carried out. I oppose that to the "deep approach" which tries to establish the link, at a given detail level, between these patterns and the underlying mechanisms. The latter requires to design a model of these mechanisms, allowing a physical interpretation of the information conveyed by the data.

These remarks represent the foundation of *Fig. 1*. It is my feeling that the fundamental loop, iterated over time, must include both sensing, processing and modelling. In addition this loop has to integrate both the multimodal, multiscale, multilevel and multisource dimensions. Multimodal means that a specific object, at a given scale, must be observed simultaneously in most, if not all, the physical components (electrical, mechanical, chemical, etc.) that drive its behaviour. We are far from that and such approach requires the design, not only of the appropriate

Figure 3. **A schematic representation of the multilevel challenge. Rows depict the intra-level interactions between similar entities, columns the inter-level connections with close and distant loops**



devices, but also of new experimental protocols, either in biology or in medicine. Multilevel concerns the ability to derive relations between very elementary entities with macrosets constituted by these entities leading to different, collective behaviours (an example of that is the jump from neurons to populations of neurons, see next paragraph). Multisource refers, for instance, to the several features that can be extracted from the data: it is in some way related to multiparametric approaches or the so-called fusion problems. When dealing with image sequence, it will combine both motion information, boundary and region features, intensity-based or topology-based. Multiscale methods call for innovating views to jointly acquired and processed data at fine and large scale. It can be sometimes close to the multilevel concept but when applied to time, it discriminates the long-term dependences to the immediate responses to local events.

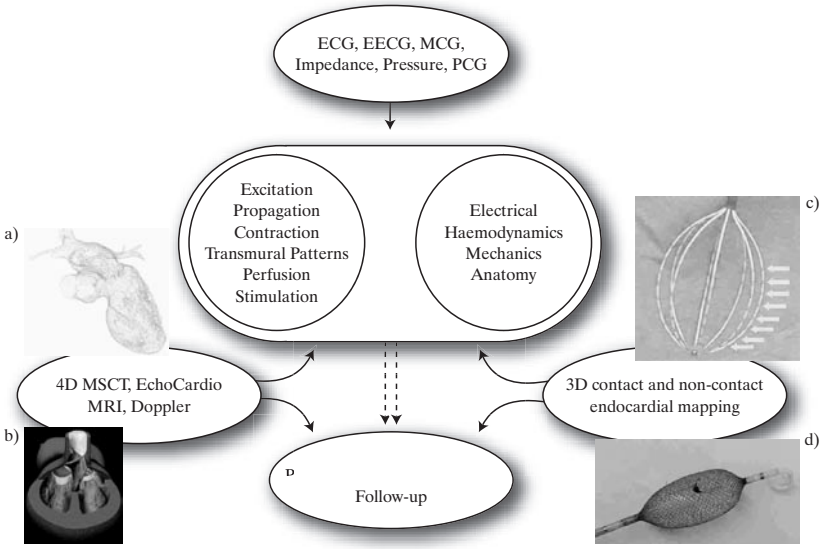
It is the conjunction of these all dimensions with the coupling to physiologically-founded models which is, in our views, very challenging.

An example of multilevel, monomodal, multitimescale system

Let us take the epilepsy case to illustrate our purpose. The data that we may access are identified *Fig. 2*. They go from membrane properties with the ion channels that can observed through patch clamp techniques, to neuronal *in vivo* characteristics available by means of multiple micro arrays (MMA), still limited populations of neurons using stereo-electro-encephalography signals (SEEG), brain structures with electro-corticography (EcoG) up to the brain activities with high density EEG and magneto-encephalography (MEG). These multilevel data represent of course important jumps over description levels, e.g. too rough and sparse to reflect the continuum we are looking for, among which synaptic delays, excitation and inhibition, afferent and efferent connections and loops, conduction paths, etc.

They remain monomodal, e.g. electrically-based mechanisms are observed. However, they provide a first step of the frame required to model and to understand the intra-level coupling and the inter-level transitions (*Fig. 3*). From the multiscale standpoint, we are also interested in short impulses (submil-

Figure 4. **Major measurements and components intervening in clinical diagnosis of cardiac disorders with focus on Cardiac Resynchronization Therapy. Picture (a) is from [Garreau, 2004]** [21]**. Picture (b) is from [Schleich, 2002]** [22]**. Pictures (c) and (d) are from [de Boer, 2000]** [23]



liseconds), potentiation effects over long-range time horizon (i.e. seconds, minutes or more) but also on the immediately adjacent interactions or very distant ones (from nanometers up to millimeters or more). Models here should play a major role to simulate and provide insights on the plausible roles of neuronal network topologies (chains, lattices, fully-connected graphs), on the mutual synchronization of cells (uniform or non-uniform pulse-coupled oscillators), on travelling waves and non-linear dynamics, etc. A lot of models have been developed to render the functional behaviours at different levels. The reader interested in this area can refer to the compartmental model [15], recently investigated in networks with axo-axonal gap junctions [16], the work of Nunez [17] putting emphasis on the delays due to axonal conduction and long-range interactions, population models [18,19] and the efforts devoted to link micro and macro behaviours by Wright and Liley [20].

An example of multimodal, monolevel approach

The key dimensions for further advances in clinical diagnosis and therapy of cardiac disorders are reported *Fig. 4*. Only a few of them, that we consider as major issues to deal with, will be discussed here. The integration of multimodal imaging data is a critical issue [24]. It starts with the diagnosis tools providing the 2D, 3D and 4D elements to capture local, regional and global characteristics required to determine the morphological and functional patterns of the heart, either normal or abnormal. The progress in ultrasound techniques, and in Multi Slice CT allows now to acquire 3D time image sequences with high contrast and spatio-temporal resolutions. The major problems, beyond spatio-temporal registration methods aimed at deriving a common coordinate system, are to extract quantitative features that can be physically and physiologically interpreted with a proper anatomical reference. Accurate and reliable segmentation methods, fulfilling the time computation constraints in clinical practice, with robust motion estimation algorithms and perfusion parameters have to be combined in a sound information processing frame in order to get a full view of the status of the heart. Electrical catheter-based mapping [25-27] is a relevant complement of the imaging sources for electrophysiological tracking but they have the inconvenient to be invasive, expensive and to increase the time duration of the exploration, and as such put more clinical demands.

The physiopathological in-silico modelling of the heart capable to fuse together the patient specific features (i.e. electrical, mechanical and perhaps more importantly the electromechanical, mechanochemical, etc.) with the corresponding anatomical structures into generic models integrating the last data obtained through *in vitro*, *ex vivo* and *in vivo* experiments is perhaps the grand challenge for tomorrow. A lot of efforts have been devoted to the restitution of the electrophysiological activity of the heart and two main model families can be distinguished (refer to [28, 29] for full references): 1. simplified models, which are limited to the simulation of an action potential waveform, without taking into account any sub-cellular process, such as the Fitzugh-Nagumo's model (which was later improved by Aliev and Panfilov) or the model proposed by van Capelle and Durrer and 2. electrophysiologically detailed models: which are based on the Hodgkin-Huxley approach for modelling ionic currents. A variety of models have been proposed for the later type, with increasing levels of detail and for specific myocardial tissues (i.e. ventricular, atrial, or Purkinje myocites). Large-scale electrical models have been developed [30,31], some being mapped to 3D anatomical data [32,33] but the key issue remains the inverse problem, i.e. the identification of the system from the current observed data. However, even if it is not out of reach, we are still far to deal with the full complexity of cardiac mechanisms. To just take an example, the excitation-contraction coupling, which refers to the physiological processes linking myocite depolarisa-

tion and contraction, involves many structural and regulatory proteins whose nature and function are just emerging [34].

Merging the multifunctional models we need to face electrical, mechanical, haemodynamic facets, at different scales, distinct supports, time dynamics with the multimodal data that we have at our disposal, would directly impact our capability to diagnose and care. Further clinical advances should rely on the design of intelligent devices, implantable or not, able to handle the several variables required, with both real-time recording, processing, stimulation capabilities.

Conclusions

The topics addressed in this paper are a few among many fields where major emerging research is carried out. They are at the exact convergence point between biology, medicine, physics, mathematics and engineering science. The future is open due to the amount of knowledge that are currently acquired and the challenging work to perform before really achieving significant breakthroughs. Engineering – with competences in computer science (database management), automatic control (modelling and control), information processing (recognition and fusion for signals and images), microtechnology (sensing devices) – must be fully part of this future. Moreover, biomedical engineering and medical informatics are key players because they are used to interdisciplinary research, to design pertinent experiments and also to take care of the all aspects involved between a research finding and its transformation into a product with an health care impact.

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