COMPUTATIONAL BIOPHYSICS (CB_23_24)
INAUGURAL LECTURE

Physics vs biology vs mathematics

To set the stage, let me revisit in these notes the themes I have introduced, starting this course, in the previous academic years.

Let me start with a big picture question: when science started? A kind of canonical ostensive answer would be – when the transition from *natural philosophy* to science took place: that is when the approach based on systematically collecting curiosity driven observations evolved by including explanatory/predictive mathematical models. In a nutshell, *from stamp collection and surprise to newtonian science*. It is nice that very recently a translation of a beautiful book appeared in Italian: Richard Holmes, *The Age of Wonder: How the Romantic Generation Discovered the Beauty and Terror of Science* (Published by HarperPress in 2008 ISBN 978-0-00-714952-0)[I]. A full-body narrative book illustrating the laborious and vivid passage from the naturalistic approach passageUn corposo libro narrativo che celebra il passaggio ancora romanticamente faticoso, a cavallo tra diciottesimo e diciannovesimo secolo, dalle scienze empiriche osservative alla scienza teorica.

Let us do now some word analysis about *Computational Bio-physics*. Let us pay attention, initially, to the suffix *physics.* As all of you know, physics is an *operational* (empirical, reductionist) activity. In physics, most concepts and every physical quantity (e.g. mass, force, electrical charge, voltage, currents…) are defined through protocols, finite sequels of concrete, empirical *operations*[i]. In a nutshell, through *recipes*. This is the humble, anti-metaphysical but powerful setting of our job, at least since the times of Galilei. Humble (from the latin humus) attitudes, inspired, indeed, by great visions[ii]. One can have an initially vague, intuitive or narrative idea of a physical quantity, which becomes clear once the "one" above prescribes, with reasonable, understandable, precision the set of operations you should proceed with in measuring that quantity. At least for the strict operationists, if you change the protocol you change the physical meaning of the quantity. This point is scholarly illustrated e.g. by the history of the concept of inertial mass as distinct from that of gravitational mass[iii].

Physics then, is an empirical activity, but, since at least the second part of the XIX century, is also a theoretical one, based on mathematical *models*. Through *correspondence rules* one associates mathematical objects with physical quantities and the empirical laws with theorems and lemmas that constitute the properties of the mathematical objects entering in the models[iv]. Physics has been, historically, a reductionist activity; looking for the simplest. Modelling is traditionally based on throwing out the inessential. The talented theoretician is a gal/guy who is not seduced by the the baroque tastes of formalisms, one who gets to the point with the simplest methematics that is needed to express a solid *physical intuition*[v] (…a quite hard to define concept, operationally speaking). As examples of successful reductionist models let us just mention the harmonic oscillator (classical and quantum (e.g. based on creation and annihilation operators)) and the Drude model for the electrical conductivity of metals, which evolved in the quantum mechanical free electron model. From the previous courses you have attended, you surely know what I mean. Technically speaking, a reductionist attitude searches for the minimum number of effective degrees of freedom to be entered in the model in order to mirror with the mathematics what is observed experimentally.

Complexity

P.W. Anderson has been one of the heralds of modern theoretical condensed matter physics (the study of collective quantum phenomena, e.g. superfluidity and superconductivity). In the early seventies Anderson published a paper that, with broad consensus, is considered the manifesto of a new way of doing physics: "More is different"[vi]. In that paper, Anderson points out that each scale of description and assessment of reality let emerge its own laws, that can hardly be deduced from the laws established at a lower scale. In the

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[I] R. Holmes, L' Età della Meraviglia, trad. Rita Topi, Orville Press, 2023.

language we have made precise in the classroom: the "meso", e.g., is more than the "micro". Precisely, the physics of living systems emerges at the integration of the microscopic molecular behaviours with the mesoscopic fluctuating regimes that take place within a cell. Elaborating on these considerations we could say, in simple terms, that the physics of complex systems is integrative, not reductionist. What does integrative means? Sensibly, it means that in dealing with complex systems (e.g. multi-factorial pathologies such as cancer, diabetes, auto-immune diseases) one has to retain in the models the "right" level of complexity. The one that should be retained to get a reasonable simulation (possibly predictive) of the observed collective behaviours.

Networks

After several years of practice in complex systems one can plainly say that networks are the simplest paradigmatic theoretical models associated to a complex system. A network is made by interacting objects (nodes, vertices); that can be associated, correlated, linked. Then, the model is a graph made by points that are linked pairwise. To a net is associated an adiacency matrix, that captures the basic structure of the integration levels of the system. From the knowledge of the adjacency matrix several quantities characterizing statically and dynamically the states of the network can be evaluated[vii]. Recently, an interesting approach, based on modelling layers of connected networks, "networks of networks", emerged as a theoretical construct of potential impact in the study of biological systems[viii].

Computing

Computational sciences exploded when the computer era started (trivial statement, indeed). The computer era started, in a socially recognizable form, in the late seventies, early eighties of the last century. When acces to computer centers was granted to an increasing number of researchers[ix]. The age of *computationals* was definitely established when personal-computers invaded the scene, a transition largely due by the invention and commercialisation of microprocessors, an achievement of Federico Faggin, a remarkable character still full of highly imaginative, questionable ideas on the theme of artificial vs natural intelligence and consciousness (see e.g. the website of his foundation: http://www.fagginfoundation.org/). The age of *computationals*: e.g. computational physics, computational chemistry, computational humanities, computational music,...What does it mean computational? It basically means: based on computations, that is transformations of numbers (of representations of numbers). It has been brilliantly argued that the basic living systems, cells, do perform computations by chemically transforming molecules in networks of chemical reactions[x]. In a more standard view, computation means *computation using computers*, implementing algorithms (methods) to compute the solution of a problem, of an equation (the general form of a model is in form of equations, but also in the form of transformation rules, as in the case of cellular automata[xi]. It is also interesting to point out that inspired physicists (I think here either to Roger Penrose, recent Nobel prize winner for the seminal works he did on black-holes and the structure of space-time together with the late S. Hawking, or Brian D. Josephson, also a Nobel prize for the effect that bears his name) have been speculating on the *non-computable* nature of bio-processes of mental type; this year we shall only allude to those topics[xii]. So, for us, computational biophysics means: *a branch of general physics aimed at the study of living systems, which is based on technologically advanced experimental procedures and on probabilistic and deterministic modelling*. The study is computational, made by using computers (in silico), through *algorithms* and *simulations*, like in atomistic molecular dynamics or in the numerical solution of the chemical master equations based on the stochastic Gillespie algorithms.

Indeed, algorithms can be divided into two broad classes: *deterministic* and stochastic (the ones that require the use of random number generators). This distinction between algorithms basically refers to the treatment of noise[xiii] and uncertainty in modelling. Whenever uncertainty (bounded predictability) either cannot be neglected or is constitutive of what is under study one should rely on probabilistic modelling (examples of probabilistic models are master equations for the evolution of the probabilities for a system to be in a set of

states, Hidden Markov Models associated to families of homologous proteins, the statistical mechanical setting behind pairwise, max-ent modelling of effective pair-wise interactions in complex systems).
In the probabilistic perspective it is important to state two classes of problems: *direct* and *inverse* problems. The *direct* problems refer to the efficient numerical sampling of given probability distributions that directly constitute the model (as in the Boltzmann-Gibbs statistical mechanics, sampled (e.g.) either through Molecular Dynamics or via Monte Carlo sampling). *Inverse problems* refer to the inference of the form or of hidden parameters of unknown probability distributions, through the combination of the constraints set by empirical data and heuristic principles (such the maximum entropy principle, or the maximum likelihood principle).

AI and Learning
It is worth mentioning that in recent years we are looking at an emerging new paradigm, that points to the overcoming of theoretical schemes based on models. In this line of thinking, modelling is a consequence of the limits of the human mind in dealing with high dimensional spaces of data. In the era of artificial intelligence we can manage a predictive science of data by a pragmatic combination of algorithms and big data, avoiding the use of models and of theories. To set the a time scale for the emergence of this tendency we can refer to an epoch making article by Chris Anderson (...nomen omen) appeared in Wired, in 2008[xiv].
Recently, we had a major advance in the learning approach to biophysics. It has been claimed tht the long standing protein folding problem has been solved through Artificial Intelligence, deep learning methods[xv].
As some of you may have heard of, we had recently kind of a revolution in computational biophysics, through the emergence of the Alphafold deep learning algorithm (https://alphafold.ebi.ac.uk/) that, though still in a black-box approach, appears to have solved the challenging problem of ab-initio predicting 3D protein structures. On that we shall possibly elaborate along the course.

Modern biophysics as Systems Biology
Speaking about biophysics it is important to locate our biophysics in the XXI century. As the integrative *physics of living systems*, that incorporates darwinian evolution, whereas the biophysics of the last century has been definitely a molecular biophysics, based on the explicative, analytic paradigm of molecular biology. Of course, this distinction is definitely just a methodological one; no fine-minded person would take it as definitive or discriminating. I would like to add, just for the sake of igniting some more reflexions, that contemporary integrative biophysics has reached the status of a definite broad area of research named Systems Biology, that I would like to introduce to in this year course.

Bio
Now, after *physics* and *computational,* let as further allude at the *bio* aspects. There is a nice, albeit deceivingly naive, definition of living system tht you can find in one of the suggested text books of this course[xvi]. *Life is a self-sustaining chemical system* [network of chemical reactions] *capable of undergoing Darwinian evolution*.
Darwinian evolution is based on a mutation/selection feed-back (reflective) mechanism, acting on *informational* biomolecules: nucleic acids (DNA & RNAs) and proteins. Evolution is a time-process that makes biology an inherently dynamical science. Someone would say that biology adds to physics and chemistry an *historical* perspective[xvii].
To me, for the sake of making a strongly opinionated statement, the biology and biophysics we are interested in is *modern* biology.
Modern biology and biophysics are integrative, look at working organisms not only at their constituents (e.g. genetic) parts. We are now looking for the laws, the principles, of living systems[xviii].
Let me conclude with a few general statements about living systems, for your consideration.

i) every living system has its own energetic scale, $K_b T_{env}$; (set by its environment);

ii) all living systems are made by cells: a cell is the basic living unit;

iii) every living system originates from a living system[xix].

Enjoy the course!

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Rome, september 25th, 2023, Physics Department, Sapienza University of Rome.

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[i] P.W. Bridgman, The Logic of Modern Physics, Macmillan, 1927. This booklet initiated the operational revision of the foundations of physics. In Italy, we had an interesting methodological movement, often referred to as La Scuola Operativa Italiana. Let me just remind here: Vittorio Somenzi (1918-2003), Silvio Ceccato (1914-1997) Giuseppe Vaccarino (1919-2016) and Mario Ageno (1915-1992). In particular of Mario Ageno, who has been one of the initiators of biophysics in Italy, i would suggest to the attention of the methodologically oriented scholar, his *La costruzione operativa della fisica*, published by Bollati Boringhieri in 1970 and the introductory chapter of his treatise *Elementi di Fisica,* also published by Bollati Boringhieri, that has been the physics textbook for several generation of medical students here in Sapienza.

[ii] …physicists are responsible from the quark to the galaxy, as used to introduce physics to freshmen our old and greatly admired teacher, the late prof. Giorgio Salvini (1920-2015).

[iii] See: M. Jammer*, Concepts of mass in classical and modern physics*, Dover, (1997) (Chap. X).

[iv] It is interesting to ask ourselves whether physics is part of mathematics or mathematics is part of physics. The latter alternative is shared by the eminent russian mathematician V. I. Arnold. See: On teaching mathematics,1998 *Russ. Math. Surv.* **53** 229, https://iopscience.iop.org/article/10.1070/RM1998v053n01ABEH000005 .

[v] Fermi and Landau, are mostly reputed as the champions of this way of doing theoretical physics**.**

[vi] P.W. Anderson, *More is different*. Science, **177**, 393 (1972)**.**

[vii] V. Latora, V. Nicosia and G. Russo. *Complex Networks, principles, methods and applications*. Cambridge University Press (2017).

[viii] G. Bianconi, *Multilayer networks*: *Structure and Function.* Oxford University Press (2018).

[ix] At the end of 2nd World War, the computational power accumulated in Los Alamos (due to the contributions of John von Neumann) was used by Fermi to explore a subtle question related to the equipartition of energy in a collective systems. Fermi is then considered as the initiator of computational physics with his study of a chain of 64 nonliner oscillators, in the early fifities of the last century. I am referring to the Fermi, Pasta, Ulam, Tsingou model, a workhorse of the teory of dynamical systems. An interesting rewiew in the nice wiki-article by Thierry Dauxois and Stefano Ruffo: http://www.scholarpedia.org/article/Fermi-Pasta-Ulam_nonlinear_lattice_oscillations

[x] See: D. Bray. *Wetware*. Yale University Press. 2011. An elegant essay of scientific English prose, by a remarkable Cambridge professor, alluding to the field of "bacterial decision making".

[xi] B. Chopard and M. Droz, *Cellular Automata Modelling of Physical Systems*. Cambridge University Press (2009).

[xii] However, see B.D. Josephson's homepage: http://www.tcm.phy.cam.ac.uk/~bdj10/ , and Penrose's: https://penroseinstitute.com. Proceed with caution…R-rated, **vietato ai minori**. A more scholarly reading on the subject is Siri Hustvedt, "*The Delusions of Certainty*", Simon & Schuster 2016 (ed. it. *Le Illusioni della Certezza*, Einaudi, 2018).

[xiii] Noise, uncertainty, limited predictability; seem to be peculiar of human intelligent behaviour. A puzzling field of research: illustrated by an essay by Daniel Kahneman (Nobel laureate in economics in the year 2002), Olivier Dibony and Cass Sunstein, *Noise, a flaw in human judgement*, recently published by UTET in an Italian translation; the English text is published by Spark.

[xiv] C. Anderson, *The end of theory: the data deluge that maked the scientific method obsolete.* Wired, june 23 issue, 2008**.** https://www.wired.com/2008/06/pb-theory/ .Let me note, however, that a wiew pointing at the overcoming of theory in statistical physics was also proposed in an unconventional paper by John Wheeler (Feynman's mentor): J. A. Wheeler, *On recognizing law without law*, American Journal of Physics **51**, 398 (1983); doi: 10.1119/1.13224**.** On the methodological and epistemological impact of the Big Data approach I would suggest the recent book by Teresa Numerico, *Big data e algoritmi, prospettive critiche*, Carocci 2021.

[xv] Extensive hands-on informations can be found at https://alphafold.ebi.ac.uk/ a database of predicted protein structures hosted at the European Bioinformatics Institute, near Cambridge,UK.

[xvi] See: Paul G. Higgs and Teresa K. *Attwood, Bioinformatics and Molecular Evolution*, Blackwell (2005), p.37.

[xvii] See: E. Zuckerkandl and L. Pauling, *Molecules as Documents of Evolutionary History*. J. Theor. Biol. **8**, 357, (1965).

[xviii] This kind of perspective is represented in Bill Bialek's book: W. Bialek, *Biophysics*. Princeton University Press (2012).

[xix] J. Craig Venter in his institute has an interesting research line on the theme of minimal cells & genomes. In 2016 they announced in the Science magazine to have synthesized a self-replicating synthetic bacterium, called JCVI-syn3.0 (see: https://science.sciencemag.org/content/351/6280/aad6253.full **We could organize in december a journal club on the follow-up of that paper I exspect that you activate on that!**)