

Research lines of Prof. Adriano Barra (May 2023)

The research exploited by Prof. Adriano Barra has a constant underlying *leitmotif*, namely the “statistical mechanics of disordered systems and complex networks” and, at present, his core research can be split in two main -and partially correlated- branches (A, B): the branch A addresses pivotal problems in statistical mechanics of (1) neural networks and learning machines and of (2) spin glasses beyond the Parisi scenario while the research branch B focuses to (3) applying such theoretical modelling to describe and quantify highly complex biological phenomena as the instauration of cancer or the coordination of the immune response and to (4) understanding information processing within single cells via a reformulation of reaction kinetics.

Hereafter the main topics within each of these two main strands will be shortly deepened.

Note: to keep the discussion broadly understandable I avoid as much as possible the technical mathematical jargon (and I add selected references of mine where this aspect can be deepened as required, solely in the research lines already active).

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Research line A: rigorous approaches in disordered statistical mechanics

1) Rigorous mathematical modelling of Neural Networks and Learning Machines

-1.1 Neural networks able to “sleep when tired”: toward Sustainable Artificial Intelligence (SAI)

A main bottleneck in the extensive usage of Artificial Intelligence (AI) for healthcare is that training a neural network at present is still prohibitively expensive from a computational (and thus energetic) viewpoint. Several research groups worldwide are working toward a “sustainable AI” (SAI) or “Optimized AI” (OAI) and I am also involved in this research. In particular, I have already proved that, by implementing suitable stylized mechanisms of *sleeping* in neural networks, they can save -by taking suitable “naps”- up to 90% of the training set still preserving the same performances in e.g. performing pattern recognition and generalization, once learning is over. I have proved this for the random setting analytically and computationally on the MNIST, Fashion-MNIST and Olivetti datasets but these preliminary results are just “the top of the iceberg” on which I plan to investigate more.

As a sideline I highlight that the formalization of this research is entirely based on generalizations of Guerra’s interpolation, thus fairly rigorous also from a pure mathematical perspective.

This is a shared collaboration with Prof. E. Agliari (Mathematics Department, Sapienza Università di Roma).

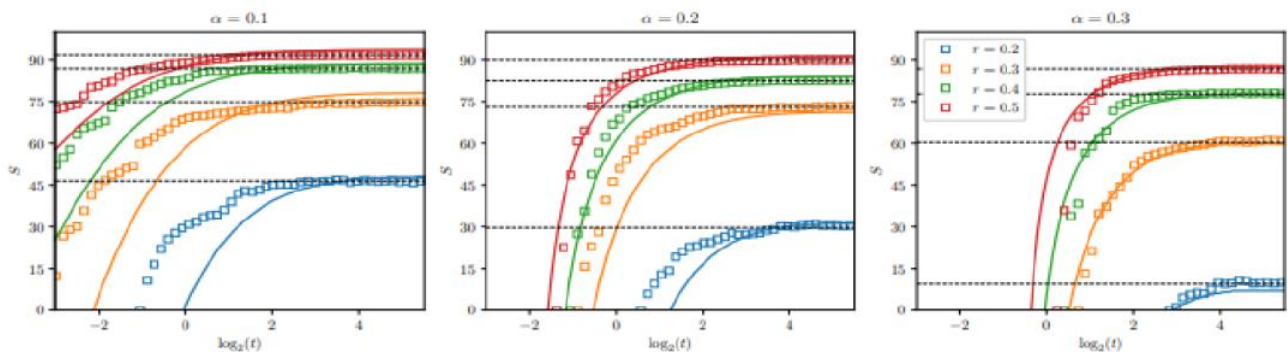


Figure One: examples of the percentage of dataset saving S versus the (logarithmic) sleeping time t for various noises in the datasets r (as shown in the legend) and various storage load α as shown in the titles. The red and green curves show a plateau at a saving percentage around 80/90% of the available datasets. The network forced to sleep here is Hopfield type.

[1] A. Barra, et al., "Outperforming RBM Feature-Extraction Capabilities by “Dreaming” Mechanism."

IEEE Transactions on Neural Networks and Learning Systems (2022).

Impact Factor = 14.25

[2] A. Barra, et al., "Dreaming neural networks: forgetting spurious memories and reinforcing pure ones."

Neural Networks 112 (2019): 24-40.

Impact Factor = 09.65

[3] A. Barra, et al. "Dreaming neural networks: rigorous results."

Journal of Statistical Mechanics 2019.8: 083503, (2019).

Impact Factor = 02.23

-1.2 Theory of neural networks performing signal detection at prohibitive signal-to-noise ratios

A central theme in modern AI is the early detection of weak signals: this is mandatory in a plethora of scenarios, ranging from army’s flaks (where the faster the recognition the prompter the response) to health-care (e.g. in early detection of skin cancer or early recognition of a heart attack). In these regards we have recently rigorously proved that dense Hebbian networks can sacrifice memory storage to lower their signal-to-noise threshold for signal detection, showing the existence of an entirely new regime (called “ultra-detection” limit) w.r.t. the standard Baldi&Venkatesh “ultra-storage” limit.

Again, this research is just started and there is a long way to go before a mature theory for this kind of performance in neural network will be robust: I plan to make progresses on this research branch too.

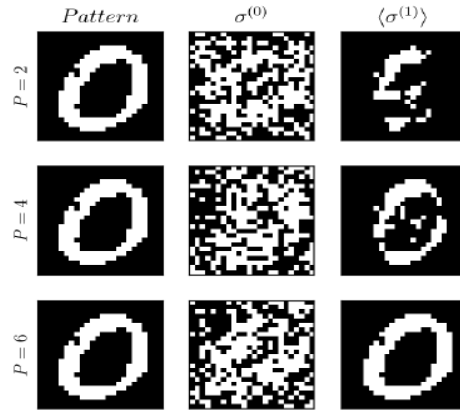


Figure Two: examples of pattern recognition by three different neural networks (one per row). The first row shows retrieval of standard Hopfield model ($P=2$), the second row focuses on a dense network with four-body interactions ($P=4$) and the last row shows recognition by a dense network with six-body interactions ($P=6$). In the first plot the true pattern is shown, in the second plot the Cauchy condition provided to the network is shown (i.e. a highly corrupted signal) and these are the same for all the networks (i.e. the first two columns are identical). In the third column the thermalization of the networks is presented: solely the dense network with $P=6$ does not fail in recognizing the pattern (further thermalization is achieved by the Hinton's prescription "1-step MCMC", thus recognition is also extremely fast, when possible).

[1] A. Barra, et al., Neural networks with a redundant representation: detecting the undetectable. *Physical Review Letters*, 124(2), 028301, (2020).

Impact Factor = 09.16

[2] A. Barra, et al., Supervised hebbian learning.

Europhysics Letters, Perspective su invito dell'Editor in Chief (2022).

Impact Factor = 01.98

[3] A. Barra, et al., From Pavlov Conditioning to Hebb Learning,

Neural Computation, MIT Press a1, 28 (2023).

Impact Factor = 03.23

-1.3 The phenomenon of replica symmetry breaking in neural networks and in Deep Learning

Despite Guerra's breakthroughs -that, coupled with Talagrand's efforts allowed a mathematical proof of the correctness of the Parisi solution for mean field spin glass- there is still a long way to go before a satisfactory broken replica-symmetry theory for neural networks will be available. In the past a rigorous generalization of the Parisi scheme to multi-specie spin glasses (i.e. as neural networks) has been proved for the overlaps: I called this new ansatz a "ziqqurat" for obvious reasons, yet a rationale for the order parameters accounting for the signals (beyond the quenched noise captured by the overlaps) is still lacking and it is expected to play a crucial role in disentangling representations of structured datasets in deep learning scenarios: I plan to deepen this research line too.

This is a shared collaboration with Prof. F. Ricci-Tersenghi (Physics Department, Sapienza Università di Roma).

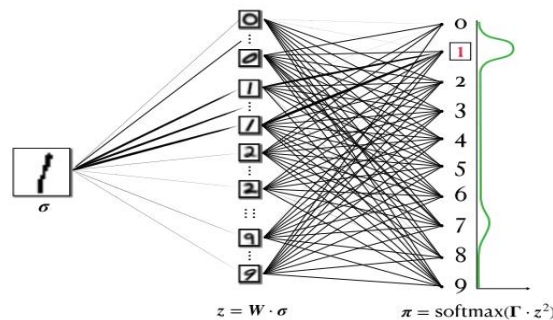


Figure Three: example of a three-layer network implementing the Parisi RSB-scheme: the input layer presents an example (leaf of the tree, full-RSB), while the middle layer frames this signal at the 1-RSB level toward its "ancestor", namely the replica symmetric archetype of the number 1 highlighted in the last layer where classification takes place.

[1] A. Barra, et al. "Replica symmetry breaking in dense hebbian neural networks." *Journal of Statistical Physics* 189.2 (2022): 24. Impact Factor = 01.24

[2] A. Barra, et al. "Replica symmetry breaking in neural networks: a few steps toward rigorous results." *Journal of Physics A: Mathematical and Theoretical* 53.41: 415005, (2020). Impact Factor = 02.13

[3] Barra, Adriano, et al. "Multi-species mean field spin glasses. Rigorous results." *Annales Henri Poincaré*. Vol. 16. Springer Basel, (2015). Impact Factor = 01.55

-1.4 Statistical mechanics of learning without planting: toward eXplainable Artificial Intelligence (SAI)

The Community of Glassy Statistical Mechanics has spent significant efforts in working within a “planted setting” to quantify learning in neural networks. This approach, relying on techniques close in spirit to “contrastive divergence” in Machine Learning, represents the “differential path”, but also an “integral path” can be developed for quantifying learning in neural networks. Making a pindaric flight, this situation resembles Analytical Mechanics, where both the differential D’Alambert and integral Hamilton principles (while giving rise to different equations, i.e. Lagrangian vs Hamiltonian equations of motion) ultimately convey roughly the same information content. I am hardly working in developing the integral representation of learning in these years and I plan to keep this branch of research open also in a near future: this research branch belongs to “eXplainable AI” (XAI).

In particular, for shallow networks, such a duality has been already constructed and we rigorously proved that the learning thresholds by restricted Boltzmann machines (achieved via, e.g., contrastive divergence, namely the differential path) are the same of its dual representation in terms of a pairwise Hebbian network (whose learning works by summations over the examples to allow the Central Limit Theorem to take place in shaping the archetypes hidden behind the examples provided to the network, hence via the integral path).

This is a shared collaboration with Prof. Fosca Giannotti (Computer Science, Scuola Normale Superiore, Pisa).

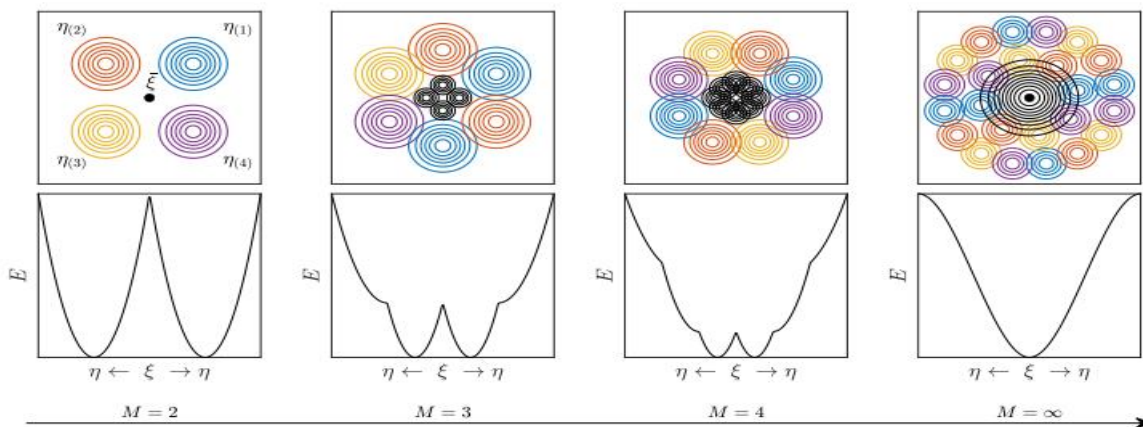


Figure Four: integral representation of learning. In these pictures, as the number of examples M provided to the network grows (here the system is a standard pairwise Hebbian network able to infer the archetypes hidden behind the noisy examples), the upper row shows how the free energy landscape evolves “from above”, while the lower row depicts a frontal snapshot of the same landscape. As the provided examples (of the same pattern) increase (i.e. “from left to right in the pots”), at first the network stores examples as different patterns (left plots), then -as examples are highly correlated and thus their corresponding minima in such a landscape rather close- once a critical threshold in the dataset volume M_c is reached, all these minima collapse into a single minimum that is the one reported by standard AGS theory of neural network.

[1] A. Barra, et al. "The emergence of a concept in shallow neural networks." *Neural Networks* 148 (2022): 232-253. Impact Factor = 09.65

[2] A. Barra, et al., "Dense neural networks: a replica symmetric theory of Supervised Learning." *Physica A: Statistical Mechanics and its applications* in press (2023). Impact Factor = 03.78

[3] A. Barra, et al., "Dense neural networks: a replica symmetric theory of Supervised Learning." *Physica A: Statistical Mechanics and its applications* in press (2023). Impact Factor = 03.78

-1.5 Parallel processing in multi-tasking neural networks and their infinite volume limit

A main reward in the mean-field approximation of neural interactions is that it allows an analytical treatment of network's model, essentially via a Parisi-like description of its low temperature free energy landscape. Yet, the price to pay for such a reward is that proving the existence of these asymptotic values (where such analytical treatments hold) is notoriously challenging for mean field models (as these are infinite-dimensional models and standard arguments as the surface-to-volume ratio do not apply). While for mean field spin glasses (e.g. the Sherrington-Kirkpatrick model) we have the Guerra-Toninelli scheme, its extension to mean field neural networks is not a trivial exercise (indeed twenty years elapsed since that milestone but no progresses have been accomplished for neural networks). Recently I started to work at a generalization of the Fekete lemma for superadditive successions by which a far-from-trivial extension of the Guerra-Toninelli scheme should be possible. As a sideline, this research branch is robust w.r.t. details of the pattern's distributions, automatically covering also modern neural networks able to cope with several patterns at once (i.e. the so-called "multitasking associative networks").

This is a shared collaboration with Prof. E. Agliari (Mathematics Department, Sapienza Università di Roma).

[1] A. Barra, et al. "Retrieval capabilities of hierarchical networks: from Dyson to Hopfield."

Physical Review Letters 114: 028103, (2015).

Impact Factor = 09.16

[2] A. Barra, et al. "Extensive parallel processing on scale free networks."

Physical Review Letters 113: 238106, (2014).

Impact Factor = 09.16

[3] A. Barra, et al. "Multitasking associative networks."

Physical Review Letters 109: 268101, (2012).

Impact Factor = 09.16

2) Rigorous results in statistical mechanics of complex systems

-2.1 Non-Linear PDE Theory: a deep bridge between Analytical and Statistical Mechanics

At the rigorous mathematical level, research on statistical mechanics of spin glasses is far from over: the state of the art is that solely the mean field fully connected limit -the Sherrington-Kirkpatrick model (SK)- is deeply understood and much efforts are still needed to study spin glasses on random topologies and, hopefully, on metric structures, namely toward a comprehension of the Edward-Anderson model.

In these regards, the plethora of techniques developed in the past four decades of research on spin glasses requires a deep revision to be able to cover also these extensions and new ideas will probably be needed: I work extensively on the mathematical aspects of the rigorous formalization of spin glasses beyond the SK picture.

In particular, I extensively worked in the duality among probabilistic-grounded techniques typical of statistical mechanics and PDE-like-driven techniques that lie at the core of analytical mechanics: by this duality it is possible to show that the free energy in statistical mechanics obeys a Hamilton-Jacobi equation in the space of the couplings (i.e. two-body and one-body interactions) hence playing as the principal Hamilton function. By this bridge it is further possible to describe phase transitions (i.e. symmetry breaking) as Hopf-Lax bifurcation, self-averaging properties as Noether invariant and depict the whole evolution of the order parameters in the space of the control parameters by a Burgers equation: paving this bridge, it should be possible in a near future to import the whole arsenal of techniques developed in Analytical Mechanics in the past two centuries into the Statistical Mechanical counterpart.

[1] A. Barra, A. Moro, "Exact solution of the van der Waals model in the critical region."

Annals of Physics 359: 290-299, (2015).

Impact Factor = 02.73

[2] A. Barra, A. Di Biasio, F. Guerra, "Replica symmetry breaking in SK through the Hamilton-Jacobi technique."

Journal of Statistical Mechanics 2010.09: P09006, (2010).

Impact Factor = 02.23

[3] A. Barra, et al., "Generalized Guerra's interpolation scheme for dense associative neural networks."

Neural Networks 128, 154, (2020).

Impact Factor = 09.65

-2.2 Construction of generalized De Almeida-Thouless lines for theories that break replica symmetry

Since the last year, I am working toward a rigorous and straightforward method to detect the onset of the instability of replica-symmetric theories in information processing systems, which does not require a full replica analysis as in the method originally proposed by Almeida-Thouless for spin glasses as understanding when a replica symmetric picture does not hold any longer is mandatory in several applied branches of disordered statistical mechanics. The method is based on an expansion of the free-energy obtained within one-step of the replica symmetry breaking scheme around the replica-symmetric value: as such, it requires solely continuity and differentiability of the free-energy and it is robust to be applied broadly to systems with quenched disorder. At present I applied the method to neural networks (i.e. to the Hopfield model and to dense associative memories with multi-node Hebbian interactions) and to spin glasses (i.e. to the Sherrington-Kirkpatrick model, the Ising P-spin and the spherical P-spin models): I recovered the AT lines known in the literature for these models, but these boundaries were derived under the assumption that the RSB order parameters depart continuously from the RS one at the onset of the RS instability while my method provides a generalization of the AT approach which can be applied even to systems with a discontinuous transition (that are proliferating day by day in the “zoology of neural networks”).

-2.3 Guerra’s interpolation as an optimal transport map in the Wasserstein metric

Since Alessio Figalli won the Fields medal for his work on Optimal Transport, the Monge and Kantorovich formulations of geodetic paths acquired a huge visibility even in fields close to pure Mathematical Analysis as Mathematical Physics. Indeed several mathematical physicists (e.g. J.L. Mourrat in Lyon) and researchers in Probability and Mathematical Statistics (e.g. E. De Vito in Genoa) have started to apply these techniques to Machine Learning with impressive results (and with a temporal derivative of their production by far positive).

In this sector I am trying to frame Guerra’s interpolation, focusing on “pattern recognition” more than “machine learning” (hence in understanding “retrieval” more than “training”): in particular the core argument of Guerra’s interpolation is to compare two probability measures, the former related to the Hamiltonian describing the problem under investigation (e.g. the SK-model, the Hopfield model, etc.) the latter a suitable one-body, whose probability structure is factorized by definition and then connecting these two measures by the Fundamental Theorem of Calculus. Trajectories in the Guerra’s framework are Galilean motions, namely geodetic in the Euclidean space hence it should be possible to prove that Guerra’s interpolation is nothing but a version of an optimal transport problem in a suitable space (e.g. equipped with the Wasserstein metric).

I just started to work in this field (and I am stuck with simpler ferromagnetic models at present) and I plan to keep working on this subject in the years to come.

Research line B: selected applications to problems in Biology & Healthcare

3) Stochastic processes and statistical inference for chemotherapy evaluation

-3.1 Toward Personalized Medicine: evaluation of the efficacy of chemotherapies

A crucial challenge in Medicine is choosing which drug (or combination) will be the most advantageous for a particular patient as, usually, drug response rates differ substantially. Consequently, it is central to classify features that contribute to the observed drug response variability and in these regards modern high dimensional inference is heavily involved.

In particular to evaluate the efficacy of chemotherapies in making cancerous cells highly recognizable by the leukocytes I am developing a unified computational protocol by which at first I inspect -via generalizations of the maximum entropy inference (i.e. techniques as those developed to tackle flocks of starlings by the Chimera Group)- how interactions among cells change in response to the administration of the drug; then, by relying upon stochastic processes, I check for dynamical coherence of these inference predictions by studying the type of

motion the various cells undergo: roughly speaking, as long as cancerous cells elude immunosurveillance, lymphocyte behave kinetically according to an unbiased Wiener process, while if cancer becomes “visible” to them -e.g., due to chemotherapies- their motion becomes ballistic (and the interactions among the two cell lines, cancer and white cells, turn out to be pronounced in the maximum entropy inference).

This research branch is expected to produce computational routines that take as input the “phase space” of the biological system under study (e.g., built of by both leukocytes and cancerous cells) and returns as output clear and useful indications to help Doctors and Clinicians in monitoring the evolution of the disease. Further I also study how the coordination within the immune response works, in particular by inspecting information processing by lymphocyte networks, in order to maximize it against selected targets (i.e. against cancerous cells).

This is a shared collaboration with Profs. G. Gigli (UniSalento) and the CNR-Nanotec experimental staff.

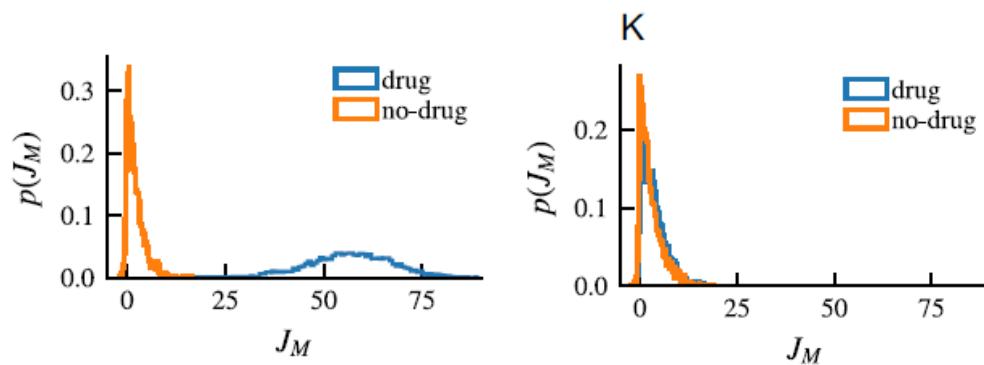


Figure Five: Examples of the inferred interactions among pancreatic cancer cells and the surrounding stroma cells (comprising leukocytes) for two different cancerous lines (at left the L3.6pl cell line and at right the AsPC1 cell line) in presence (blue curves) or absence (orange curves) of the chemotherapeutic “gemcitabine”: in the former the role of the drug is crucial as it allows enhancing motility and interactions among stroma and cancer, while for the latter the presence of gemcitabine does not alter the scenario, resulting in a possibly milder efficacy of the drug.

[1] A. Barra, et al, "Quantifying heterogeneity to drug response in cancer-stroma kinetics." *Proc. Natl. Acad. Sci. USA* 120(11), e2122352129 (2023). Impact Factor = 12.78
 [2] A. Barra, et al., "A protocol to evaluate the efficacy of chemotherapy induced anti-cancer immunity" *Nature Scientific Reports* 7, 12737, (2015). Impact Factor = 05.00
 [3] A. Barra, et al., "Cancer-driven dynamics of immune cells in a microfluidic environment." *Nature Scientific Reports* 4, 6639, (2014). Impact Factor = 05.00

-3.2 Toward Personalized Medicine: reconstruction of the pH field in LabOnChip devices

The homeostatic control of their environment is an essential task of living cells: the general belief to confirm is that, when microenvironmental pH inhomogeneities are induced by high cellular metabolic activity, diffusing protons act as signaling molecules, driving the establishment of exchange networks sustained by the cell-to-cell shuttling of overflow products such as lactate. By analyzing the mass acidification of a tumor culture (i.e. Warburg effect) it should finally be possible to investigate the hallmark of cancer almost at the single-cell level: I just started to work in this field but I plan to deepen these investigations (in particular because the experimental set-up is finally working after five years of extensive research): I do believe this as a potential cornucopia to understand carcinogenesis.

This is a shared collaboration with Dr.s Andrea & Daniele De Martino and the CNR-Nanotec experimental staff.

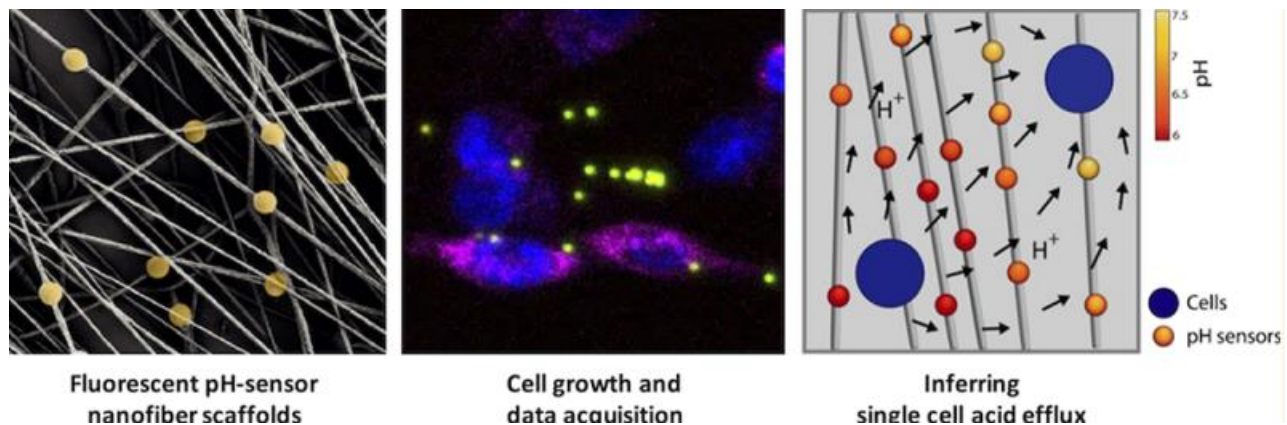


Figure Six: from left to right we show (i) the nanofiber grid where sensors (measuring pH) are stuck within a LabOnChip device. (ii) The experiment, namely cells are included in the device and they reach a dialogue at equilibrium (iii) inference of the field of fluxes and exchanges of protons among cells at the single cell level.

- [1] A. Barra, et al. "Probing Single-Cell Fermentation Fluxes & Exchange Networks via pH-Sensing nanofibers"
ACS Nano (2022). Impact Factor = 18.03
- [2] A. Barra, et al. "Automated computational approach for measuring organelle acidification by optical sensors"
ACS Applied Materials & Interfaces 14.16, 18133, (2022). Impact Factor = 09.23
- [3] A. Barra, et al., "Statistical inference to reconstruct intercellular interactions in cell migration experiments."
Science Advances 6, 11 (2020). Impact Factor = 14.14

-3.3 Coordination within underpercolated lymphocyte networks

- [1] A. Barra, et al. "Retrieving infinite number of patterns in a spin glass model of immune networks"
Europhysics Letts 117, 28003, (2017). Impact Factor = 18.03
- [2] A. Barra, et al. "Anergy in self-directed B-cells from a statistical mechanics perspective"
Journal of Theoretical Biology 375, 21 (2015). Impact Factor = 02.70
- [3] A. Barra, et al., "A thermodynamical perspective of immune capabilities"
Journal of Theoretical Biology 267, 48 (2015). Impact Factor = 02.70

4) Rigorous formalization of Reaction Kinetics within the Canonical Ensemble

-4.1 Computing with enzymes: propositional calculus and (bio)-logic gates within single cells

Reaction kinetics is already well grounded within Statistical Mechanics, but its typical exploitation happens within the Grandcanonical Ensemble as the latter is the most natural choice to describe chemical reactions (because the number of involved particles may change in time). Yet, as prototypical scenarios for Reaction Kinetics can be roughly spin into three main categories -namely "non interacting scenario" (Micaelis-Menten kinetics), "positive cooperativity" (Hill kinetics) and "negative cooperativity" (Koshland kinetics), a re-formulation of such a discipline within the Canonical Ensemble -where information processing by neural networks is typically worked out- has a potential very huge reward: it is indeed possible (and I've already done this in the reported series of selected papers) to prove that mathematically there is a one-to-one connection among the behavior of the input-output relations in reaction kinetics (where the input is the concentration of the binding molecules and the output the percentage of the saturated molecules) and the input-output relations in statistical mechanics of spin systems (where the input is the magnetic field and the output the magnetization). In particular Micaelis-Menten kinetics can be exhaustively described by the statistical mechanics of paramagnets, the Hill kinetics by the statistical mechanics of ferromagnet and the Koshland kinetics by the statistical mechanics of antiferromagnet. This translator among Biochemistry and Statistical Mechanics can be pushed forward to embrace directly electronic circuits as shown in the following picture: the ultimate goal of this research is to have a biochemical problem (e.g. ideally the Krebs cycle) and translate this into an electronic

problem by using statistical mechanics as the correct “universal translator” to see how these disciplines ultimately describe the same collective phenomena as long as their computational capabilities are investigated: should this bridge work, we could import in Biochemistry the solid knowledge collected in decades of Electronics, with all its analytical techniques (Fourier and Laplace transforms, operational methods, etc.).

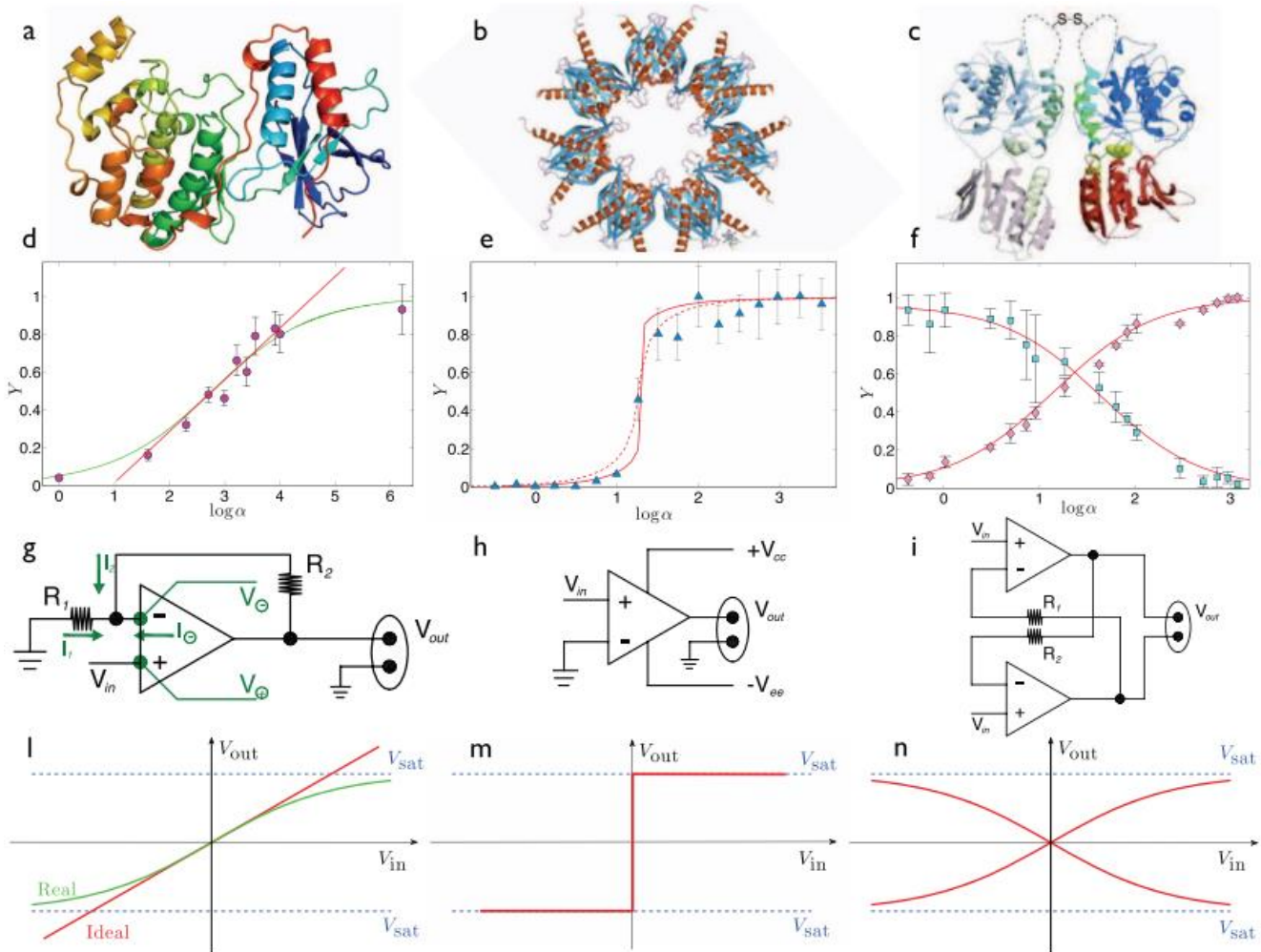


Figure Seven: In the first row, pictures of three biological systems exhibiting cooperativity, namely Mitogen activated protein kinase (positive cooperativity, panel (a)), Calmodulin dependent protein kinases II (ultra-sensitive cooperativity, panel (b)) and Synaptic glutamate receptors (negative cooperativity, panel (c)) are shown. The related input-output relations, i.e. “saturation curves” or “binding isotherms” are shown in the second row (panels (d), (e) and (f), respectively), where symbols with the relative error-bars stand for real data and lines are best fits performed through the analytical expressions obtained from statistical mechanics. The related best-fit parameters return chemical quantifiers (i.e. Hill coefficient) in perfect agreement with the Literature. In panel (d) it is possible to see clearly the “saturation” phenomenon as the first and the last experimental points are far from the linear fit (red line), while they are perfectly accounted by the hyperbolic tangent predicted by statistical mechanics (green line), whose correspondence with saturation in electronics is represented in panel (l). In the third row I sketch the cybernetic counterparts, i.e., the operational amplifier (panel (g)), the analog-to-digital converter (panel (h)) and the flip-flop (panel (i)). The (theoretical) transfer functions corresponding to the circuits are finally shown in the fourth row (panels (l), (m) and (n), respectively) for visual comparison with the second one as these are all “input-output relations”, each within its pertinence discipline.

[1] A. Barra, et al., "Complete integrability of information processing by biochemical networks" *Nature Scientific Reports* 6, 36314, (2016).

Impact Factor = 05.00

[2] A. Barra, et al., "Notes on stochastic (bio)-logic gates: computing with allosteric cooperativity" *Nature Scientific Reports* 5, 9415, (2015).

Impact Factor = 05.00

[3] A. Barra, et al., "Collective behaviours: from biochemical kinetics to electronic circuits." *Nature Scientific Reports* 3, 3458, (2013).

Impact Factor = 05.00

-4.2 Modelling heart rate variability via maximum entropy inference: the glassy heart

Heart rate variability generates time series that are typically scale free (with an obvious cut-off at high frequency) whose power spectrum is almost blank (i.e. the so-called $1/f$ noise). By setting constraints on the first and on the second moment we obtain an effective pairwise (r_n, r_m) model, whose parameters are shown to depend on the clinical status of the patient. In order to check this framework, we generate synthetic data from our model and we show that their distribution is in excellent agreement with the one obtained from experimental data. Further, our model can be related to a one-dimensional spinglass with quenched long-range couplings decaying with the spin-spin distance as a power-law. This allows us to speculate that the $1/f$ noise typical of heart-rate variability may stem from the interplay between the parasympathetic and orthosympathetic systems.

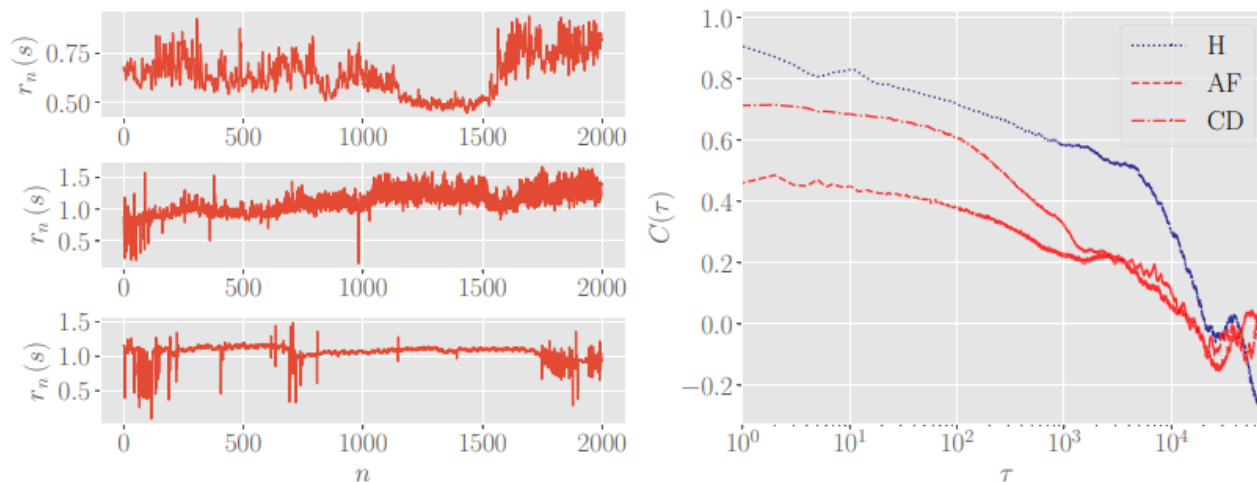


Figure Eight: Left: examples of the bare RR time series for a single patient for each class: healthy (H), atrial fibrillation (AF) and cardiac decompensation (CD). The window depicted is restricted to the first 2000 beats. Right: examples of autocorrelation functions for a single patient for each class. The dotted blue line refers to a healthy patients, while red are patients with AF (dashed curve) and CD (dashdotted line). Notice that, in any case, the autocorrelation remains positive over several orders of magnitude and this is a consequence of the scale-free behavior of the series power spectral density.

- [1] A. Barra, et al., "Analysis of temporal correlation in heart rate variability trough maximum entropy principle" *Nature Scientific Reports* 10, 15353, (2020). **Impact Factor = 05.00**
- [2] A. Barra, et al., "Detecting cardiac pathologies via machine learning on heart rate time series and related markers" *Nature Scientific Reports* 10, 8845, (2015). **Impact Factor = 05.00**
- [3] A. Barra, et al., "Application of a stochastic modelling to assess the evolution of tuberculous mycobacterial infection." *PLoS One*, 0055017, (2013). **Impact Factor = 05.00**

-4.3 Miscellanea in mathematical modeling of biologically-driven problems

What I summarized hereafter are just the principal investigation lines but the research has several further ramifications that do not deserve an item per sè, but that I quickly streamline in this last point. I just mention:

(i) ultrametric fluctuations in genomes to inspect the predictions of Kimura neutralist theory: in a nutshell, in spin glasses, there are peculiar fluctuations in the Hamming distance among replicas even after the asymptotic limits are taken (known as Ghirlanda-Guerra identities). I generalized these constraints to prove that in stochastic models of Darwinian evolution (e.g. the Peliti-Derridà, Higgs-Derridà, etc., models) similar constraints hold and they seem to be preserved even in the human genome: my work in this field is just started and there will be a long way to go because we must address at first Derridà ultrametricity beyond Parisi's one.

(ii) quorum sensing: quorum sensing is the regulation of gene expression in response to fluctuations in cell-population density and understanding its working principles is a central theme of modern Quantitative Biology. In this field I am using the weak ergodicity breaking shown by under-percolated glassy networks to provide a quantitative picture of the chaotic (re)-activations of genes (i.e. the "jumps") that are in excellent agreement with the available empirical collected data. While this may seem at a first glance a rather simple

problem, the fact that we must work “at small N” rules out much of the standard asymptotic techniques hence there is an entirely new mathematical control to be worked out for such “small systems”.

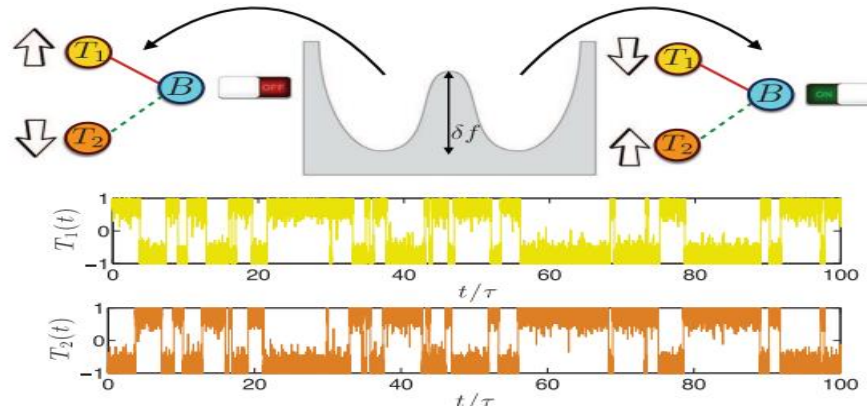


Figure Nine: in the upper plot I show a schematic representation of bi-stability induced by weak ergodicity breaking for a connected component of size $k = 3$ (a clique) in the bipartite graph whose cells are made of lymphocyte B and T . In this example the component constitutes a flip flop, where two coordinator clones (T_1 and T_2) handle the expansion of an effector clone (B), by sending inhibitory and excitatory signals (i.e. cytokines), respectively. Each clone is made of 50 cells.

[1] A. Barra, et al., "Retrieving infinite numbers of patterns in a spin glass model of immune network" *Europhysics Letters* 117, 28003, (2017). Impact Factor = 05.00

[2] A. Barra, et al., "Ultrametric identities in glassy models of Natural Evolution" *Journal of Physics A: Mathematical & Theoretical* in press (2023). Impact Factor = 02.13

[3] A. Barra, et al., "Immune networks: multitasking capabilities close to saturation." *Journal of Physics A: Mathematical & Theoretical* 46, 415003, (2013). Impact Factor = 02.13