

Theories, models, simulations: a computational challenge

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In this talk I would like to illustrate with examples taken from Quantum Field Theory and Biophysics how an intelligent exploitation of the unprecedented power of today's computers could lead not only to the solution of pivotal problems in the theory of Strong Interactions, but also to the emergence of new lines of interdisciplinary research, while at the same time pushing the limits of modeling to the realm of living systems.

Prologue

The somewhat schematic partition of the last century natural science into separated fields of research, which were essentially identified with mathematics, physics and biology, is nowadays becoming less and less rigid, leading to large areas of overlapping interests.

The fundamental reason for the former *de facto* separation was the enormous amount of accumulated knowledge in each of the three areas, which resulted in an increasing, and at the end unsurmountable, degree of specialization for people working at the front-end of their research field.

Two facts have been drastically changing the situation. One was the growing evidence that methods and ideas developed in one research area could be fruitfully exported to other, even distant, fields of investigation. The second, is a related one and has to do with the sharp increase of the available computing resources (in terms of CPU-time, memory and storing capacity), which is making algorithms and general computational strategies immediately ready for use to researchers working in different areas.

In my opinion this last fact is of particular relevance in today's spectacular progress of science, because it has allowed to imagine and attack problems that were considered impossibly difficult only a few years ago. New, flexible and adaptive computational tools that can be of general help to many scientific disciplines are being implemented under the pressure of the challenges posed on the one hand by the developments of pure science and technology and on the other by the fast expanding needs of our modern societies (think to weather forecasting, stock market "surveillance", power plant control systems, distributed information network management, etc.).

Taking an example of this trend from a field which is nearer to the scientific interests of our community, it is interesting to remark that one of the most extraordinary and somewhat unexpected outcome of the long lasting interplay between Statistical Mechanics and the theory of Strong Interactions in its lattice formulation (lattice QCD - LQCD) was the decision taken within the community of theoretical physicists to build "dedicated machines" with parallel architecture^{1,2}. The aim of these machines was to provide a tool capable of efficiently dealing with the extremely hard computational task of extracting useful physical information from the simulation of QCD, when the latter is seen as

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a statistical system of interacting “coloured spins” living on the sites of a (Euclidean space-time) lattice with gauge fields sitting on the links.

Numerical and conceptual tools developed in Statistical Mechanics and in Theoretical Chemistry^{3,4} immediately found applications in LQCD, and vice-versa ideas and numerical techniques invented in LQCD were fed back in simulations of statistical systems^{5,6} as well as in the study of the more complicated situations that appear when systems of biological interest are modeled^{7,8}.

The second half of the 80’s was marked by a breakthrough in the theory of disordered systems that turned out to have a significant impact in numerous emerging fields of investigation. The replica approach was extended to spin glass systems and the notion of replica symmetry breaking was proposed as an explanation for the occurrence of the glassy phase transition⁹. In this context a new and more precise notion of complexity has emerged, suggested by the phenomenology of spin glass, that rather soon appeared to be of great relevance in the apparently distant problem of constructing mathematically sensible models of biosystems.

In fact, there is an intriguing analogy between the mathematical structure of spin glasses⁹ and certain approaches to the problem of modeling protein folding^{10,11,8}. Here the relation between the two fields is in physical terms less direct than in the case of Quantum Field Theory and Statistical Mechanics mentioned above and most importantly in the case of both spin glasses and proteins mathematical computationability is intrinsically limited by the complexity of the models one is considering. Despite these difficulties, a lot has been learned about protein structure from approaches inspired by the theory of disordered systems and, vice-versa, ideas taken from biology have spurred new strategies aimed at dealing with hard computational problems (NP-complete problems^{12,13,14}) from a novel point of view.

Indeed, the very recent discovery that the “typical” (not the worst) NP-complete problem¹² (examples of NP-complete problems are the *K*-SAT problems¹⁵) may be (almost always) solved with polynomial algorithms (like the cavity method, or the “survey inspired decimation”) seems to suggest and make us hope that similar methods could be developed and used to attack the most challenging among the theoretical problems that arise in modeling biological macro-molecule interactions, among which we might mention protein folding and aggregation, protein-protein and protein-DNA recognition, etc.

I cannot end this brief overview without recalling that the most spectacular and successful results of the generalized use of computers in pure and applied research are probably to be found in the realm of life sciences. Sequencing the human genome would have been impossible without the support of the most advanced computers of the time¹⁶. Today the big task is annotation. It is now clear that to gain a really useful understanding about the complexity of living systems, we need to record, cross-link and organize in an appropriate way the exponentially fast growing amount of biological information that is being gathered in experiments. The task is made particularly difficult by the impressive variety of data we need to store and correlate. Just to give you some examples of such an enormous variety let me recall that understanding biosystems at large will require dealing with data that go from the structure of the metabolic networks of biochemical reactions taking place in the cell to the description of the series of events by which the immunological system responds to an antigen, from the epidemiological and statistical information necessary to monitor the progression and the spreading of a disease in a population to the biochemical characterization of the complicated protein-DNA interactions

which regulate gene expression and so on.

The very same development of the micro-array technique, that so much biological information is continuously providing, was only possible thanks to the wide-spread availability of computers capable to deal with the huge outflow of data of combinatorial chemistry in an efficient, reliable and retrievable way.

1 Introduction

Personally I was introduced to the fascinating field of computers and simulations by Adriano in 1980, when we were both visiting CERN. It was the exciting time when the first attempts to extract physics from numerical simulations of QCD were just starting to produce useful results and APE was a new extraordinary scientific and technological enterprise.

Since then the increase of the computational power at disposal to research and everyday life has proceeded at a pace that only the most blunt extrapolation of the Moore law^b over more than thirty years was able to predict. This exponential explosion has radically changed not only the life style of billions of people, but also the way we scientists think about science and research. Completely new problems have appeared to be within our reach, that only few years ago would have seemed just impossible to attack or even to dream of. If appropriately used, computers represent more than a simple tool which can increase our ability to answer questions: their enormous potentiality, associated to flexibility and adaptability, has opened the way to new adventures that are only limited by our fantasy and courage.

In this talk I would like to try to underline the irreplaceable role of what might be called “intelligent computing” in certain domains of physics and biophysics, by illustrating in three significative examples of application, chosen according to my personal inclination and competences, how new ideas could be effectively implemented and made to work thanks to the power of the available computational means. Two examples are taken from the field of Monte Carlo simulations of LQCD. The first has to do with the analysis of the gluon sector of QCD (sect. 2). The second with possible ways of solving or easing the problems posed by the explicit breaking of chiral symmetry which according to the Nielsen–Ninomiya theorem¹⁸ affects any (ultra-)local lattice regularization of QCD (sect. 3). In the third example I wish to report on a somewhat innovative approach to the study of polymer structure with the methods of Statistical Mechanics (sect. 4).

2 Gluon operators

I want to start by discussing two selected topics related to the gluonic sector of QCD where “intelligent computing” has been decisive to give support to our understanding of certain properties of the Theory of Strong Interactions. I will illustrate the calculation and

^bMoore’s original statement was the observation made in 1965¹⁷ that the number of transistors per square inch on integrated circuits (we would more precisely say today the number of transistors that minimizes the cost per transistor in a chip) had doubled every year since the integrated circuit was invented. Moore, co-founder of Intel, predicted that this trend would continue for the foreseeable future. In subsequent years, the pace slowed down a bit, but transistor density has doubled approximately every 18 months, and this is the current definition of Moore’s Law, which Moore himself has blessed. Most experts, including Moore himself, expect Moore’s Law to hold for at least another two decades.

the physical relevance of two quantities: the plaquette expectation value and the topological susceptibility. The first quantity is related to the so-called gluon condensate¹⁹. The second is supposed to be responsible²⁰ for the non-vanishing of the η' mass in the chiral limit (the limit where quark masses are sent to zero).

2.1 The plaquette expectation value

The expectation value of the plaquette, $\langle P \rangle$, is an obviously relevant quantity in the study of the thermodynamic properties of lattice gauge theories. Besides, it was thought that one could extract the F^2 -gluon condensate of ref.¹⁹ from lattice data if one could subtract from the lattice data on $\langle P \rangle$ its perturbative tail²¹. In this context it was an open question to decide whether signs of renormalon effects²² and of what dimension were visible in the plaquette perturbative expansion.

At the time where we (I mean Adriano and me) started to ask ourselves such questions there was little experience about perturbative and non-perturbative definition of lattice composite operators and even less about the relation between lattice and continuum expectation values. Lacking any better strategy, we attacked by brute force the problem of defining the F^2 -operator starting from its definition in terms of the plaquette expectation value. We computed the first three terms (*i.e.* tree-level, order g^2 (1-loop) and order g^4 (2-loops)) in the perturbative expansion of the plaquette by hand. At that time ours was the most difficult perturbative lattice calculation ever attempted. It took us about six months of intense work and cross-checking until we could agree on the analytic expression of the function that we then had to integrate numerically²¹. The result was

$$\langle 1 - P \rangle = \frac{1}{4} \frac{N_c^2 - 1}{2N_c} g^2 + \frac{1}{2N_c} \frac{N_c^2 - 1}{2N_c} \left[(0.0203 \pm 0.0001) N_c^2 - \frac{1}{32} \right] g^4 + \mathcal{O}(g^6), \quad (1)$$

where N_c is the number of colours and the error in parenthesis comes from the uncertainty inherent in the numerical integration. It is amazing (should I say disappointing looking back at our effort?) to observe that the clever stochastic methods which are available today²³ allow to compute the perturbative expansion of $\langle P \rangle$ up to order $(g^2)^{16}$, with the aid of a good 32-node cluster in a few hours²⁴. From this recent knowledge indications are that a dimension four operator can indeed be seen below the computed perturbative tail, if accurate data, like those of ref.²⁵, are used in the analysis.

To tell the truth we could do something slightly better: by comparing our results to the brand new $N_c = 2$ simulation data just produced in those days by Mike Creutz²⁶, we could extract the numerical value of the coefficient of the term g^6 obtaining an estimate which, within its relatively large error, appears to be quite accurate, when compared to the successive explicit perturbative calculations of ref.²⁷.

This story is paradigmatic of the inextricable interplay between technological developments and scientific intelligence. Thanks to his scientific creativity Mike Creutz was able to exploit at their best the computational possibilities of the time, producing data that led us to ask questions whose answer had in turn to wait still a few years before one could arrive at the technical improvements and theoretical advances necessary to get a full comprehension of the underlying problems.

2.2 Topological charge density and susceptibility

Topology is a key concept in gauge theories. According to our understanding of the solution of the so-called $U(1)_A$ problem a non-vanishing topological susceptibility is responsible for providing a mass to the η' pseudo-scalar meson in the limit where up, down and strange quark masses are set to zero. As a result the η' is not the ninth Goldstone boson of chiral symmetry.

In the limit $N_f/N_c \rightarrow 0^c$ the mass of the (lightest) flavour singlet pseudo-scalar meson is given by the well-known Witten–Veneziano (WV) formula²⁰

$$m_{\eta'}^2 = \frac{2N_f}{F_\pi^2} A, \quad (2)$$

where F_π is the pion decay constant (normalized so that $F_\pi \simeq 94$ MeV for $N_f = 3$) and A is the “topological susceptibility”. A is formally defined by the equation

$$A = \int d^4x \langle Q(x)Q(0) \rangle \Big|_{\text{YM}}, \quad (3)$$

with $Q(x)$ the topological charge density, which in the formal continuum theory has the expression

$$Q(x) = \frac{g^2}{64\pi^2} \epsilon_{\mu\nu\rho\sigma} \sum_{a=1}^{N_c^2-1} F_{\mu\nu}^a F_{\rho\sigma}^a(x). \quad (4)$$

The notation $\langle \dots \rangle|_{\text{YM}}$ in eq. (3) means that the QQ -correlation function is to be computed in the pure Yang–Mills theory, *i.e.* in the absence of quarks.

The idea that the non-perturbative value of A could be measured from pure gauge lattice simulations dates back to the works of ref. ²⁸, where the first attempts to extract such a number from numerical data were made. The resulting quantity, though non-vanishing and endowed with the correct scaling behaviour, was yielding a value of the η' mass significantly smaller than phenomenologically required.

The discrepancy was due to the fact that the renormalization effects necessary to match lattice and continuum definitions of topological charge density had been completely overlooked. This mistake was corrected in the seminal paper of ref. ²⁹, where the required renormalization constant was computed to one-loop in perturbation theory. Remarkably when the perturbatively normalized and vacuum subtracted simulation data for the topological susceptibility were inserted in eq. (2), the agreement between the theoretical calculation and the experimental value of the η' mass turned out to be rather good.

In my opinion getting an agreement between theory and experiments in this corner of the theory is of especially great conceptual importance, because the η' mass issue is one of the few instances where the non-perturbative structure of QCD as a theory for Strong Interactions is at stake and can be subjected to a stringent test. For this very good reason the Pisa group (led by Adriano) has striven for some time to arrive at an accurate and fully non-perturbative definition of the topological objects relevant to this problem. Indeed they have been finally able to get a reliable non-perturbative determination of

^c N_f is the number of light (massless) quark flavours.

the renormalization constant and subtraction term necessary to construct from simulation data the proper definition of A . This was achieved relying on the clever method of cooling the gauge configurations to freeze out their perturbative fluctuations³⁰.

2.3 Topology in chiral regularizations of QCD

The situation of LQCD simulations has radically changed recently owing to the appearance on the market of exactly chiral fermions^{31,32,33,34} and the subsequent observation that the index theorem holds true as a lattice identity^{33,34} if fermions obeying the Ginsparg–Wilson (GW)³⁵ relation are employed. In this framework the WV formula can be given a rigorous non-perturbative status³⁷. In fact, after identifying the unrenormalized operator which represents the topological charge density on the lattice as the one suggested by the flavour singlet Ward–Takahashi identities of the GW-regularized theory, one can prove that eqs. (3) and (2) are valid on the lattice with no need for any renormalization or subtraction.

The trouble with this approach is that simulations where the definition of A suggested by GW fermions is employed are fairly expensive, although rather nice results have been recently obtained for it³⁸. Adriano’s recent idea in this context is surprisingly simple and effective: it consists in making use of the GW-inspired definition of topological charge density only to the extent the latter is needed to determine the non-perturbative normalization constant of the more standard gluon definition³⁹, *i.e.* only to measure the topological charge of a configuration. The interest of this strategy is obvious: it allows to get an accurately normalized topological charge density without having to pay a much too high computational price.

3 Waiting for a fully chiral simulation of LQCD

The next generation of computers may allow LQCD simulations with exactly chirally invariant fermions, *i.e.* fermions obeying the GW-condition³⁵. In the meantime a viable alternative^d could be to employ maximally twisted Wilson fermions^{40,41,42,43,44}, possibly accompanied with a judicious choice of the pure gauge action. Preliminary quenched⁴⁵ as well as unquenched⁴⁶ numerical results in this direction are quite encouraging. They confirm the theoretical expectation that correlators are $O(a)$ improved and that simulations require computational times that are of the same order of magnitude as for plain Wilson fermions (see, however, sect. 3.2 for some word of caution). Extrapolation of the present trends makes us confident that the overall computational power allocated in Europe to maximally twisted lattice QCD (Mtm-LQCD) simulations can match the CPU-time needed for a study of the full theory in physically realistic conditions, *i.e.* on a $(3 \text{ fm})^3 \times 6 \text{ fm}$ lattice with a pion mass of about 250 MeV. The computation requires an estimated power of the order of 10 Teraflop*year^e. Optimistically one may hope to get the first useful results in a little more than one year from now. In view of this remarkable and fortunate situation I think it might be worth reviewing the theoretical structure and the properties of Mtm-LQCD as developed in refs.^{41,42,43,44}.

^dStaggered fermions³⁶ have also offered a successful computational scheme.

^eI wish to thank I. Montvay for correspondence on this issue.

3.1 A cheap proposal

Soon after noticing that to avoid exceptional configurations in Wilson fermion simulations one should introduce quarks in flavour pairs and have the Wilson term rotated with respect to the quark mass term by an axial rotation in iso-spin space, it was realized that an especially useful choice for that angle is to set it at its maximal value, $|\omega| = \pi/2$, because in such a situation $O(a)$ (actually $O(a^{2k+1})$, $k \geq 0$) improvement of physical quantities is automatic with no need to introduce the “clover term”⁴⁷ in the action.

It was then shown in⁴² that the nice improvement properties enjoyed by Mtm-LQCD, which were derived for pairs of mass degenerate quarks in⁴¹, can be immediately extended to the more interesting case of non-degenerate quarks, without losing the positivity of the corresponding fermion determinant. The last property is obviously crucial if one wants to be able to set up workable Monte Carlo-like simulation algorithms for LQCD.

With the above ingredients and exploiting the flexibility offered by the freedom of regularizing different valence flavours with different values of the Wilson parameter, it was shown in⁴³ that it is possible to construct a hybrid theory, where sea quarks are introduced as pairs of non-degenerate particles and valence quarks are regularized as Österwalder–Seiler⁴⁸ fermions, such that no “wrong chirality” mixing⁴⁹ affects the computation of the matrix elements of the \mathcal{CP} -conserving $\Delta S = 1, 2$ effective weak Hamiltonian. Of course the same result would hold if GW fermions were used as valence quarks. Absence of wrong chirality mixing makes Mtm-LQCD a more appealing regularization of QCD than the one offered by the use of standard (clover) Wilson fermions.

From what we said above about improvement, it turns out that Mtm-LQCD correlators that are not trivially vanishing in the continuum limit can be affected by lattice artifacts described by a Symanzik expansion⁵⁰ with only even powers of a . Among these terms there are lattice contributions which tend to become large as the quark mass is lowered. They originate from the breaking of parity and iso-spin induced by the presence of the twisted Wilson term in the action. These effects have been discussed both in chiral perturbation theory^{51,52}, as well as in the language of the Symanzik expansion⁴⁴ where they appear as terms of the form $(a/m_q)^{2k}$, $k \geq 1$. The general conclusion of the theoretical analysis is that such lattice artifacts can be reduced to a numerically tolerable level (precisely down to order $a^2(a^2/m_q)^{k-1}$, $k \geq 1$) if the clover term⁴⁷ is introduced in the action⁴⁴ (with its non-perturbatively determined c_{SW} coefficient⁵³) or, alternatively, if the critical mass is chosen in some “optimal way”^{51,52,44}. Actually it turns out⁵⁴ that, at least up to $O(a)$ included, the optimal critical mass coincides with the critical mass one would get from the vanishing of the pion mass (or the PCAC mass) within the standard Wilson fermion regularization.

The previous discussion about chirally enhanced discretization artifacts affecting Mtm-LQCD correlators is rather important because it shows that the strong (order of magnitude) inequality

$$m_q > a\Lambda_{\text{QCD}}^2, \quad (5)$$

invoked in ref.⁴¹ in order to have the phase of the chiral vacuum driven by the quark mass term and not by the (twisted) Wilson term, can be relaxed to the more favourable

relation

$$m_q > a^2 \Lambda_{\text{QCD}}^3, \quad (6)$$

before large cutoff effects are possibly met when the quark mass is lowered at fixed a . The bound (6) is fairly weak as it permits simulations in a region of quark masses that correspond to rather light pions (with masses around 200 MeV for typical present-day lattice spacings).

3.2 Where is the catch?

All this sounds good, perhaps too good to be true. So the natural question to ask is: is there a catch in the twisted mass approach to LQCD and where is it?

To tell the truth there is one little catch. It has to do with the observation^{55,56,57} that at too coarse lattice spacing meta-stabilities are seen to affect unquenched data⁴⁶ which prevent their extrapolation to the chiral limit. Such meta-stabilities are the consequence of the explicit breaking of chiral symmetry induced by the presence of the Wilson term in the action. They appear at sufficiently low quark mass when the latter is progressively lowered at fixed a and cause the statistical system one is dealing with not to reach equilibrium. For recent reviews on these and related questions and an updated assessment of the present status of quenched and unquenched Mtm-LQCD simulations see ref.⁵⁸.

A safe way-out of these difficulties is obviously to work at sufficiently small lattice spacing: something which, however, may turn out to be computationally too expensive. Actually there is another, more clever solution to the existence of meta-stable phases (and to the other dangerous flavour breaking effects⁵⁹ that in this regime plague the theory) which will work even on coarse lattices. It consists in tuning the pure gauge action so as to set to zero (in the chiral limit) the matrix element of the dimension six operator of the Symanzik low energy action of LQCD taken between pion states with vanishing three-momentum, *i.e.* the quantity $c_2 \propto \langle \pi(\mathbf{0}) | \mathcal{L}_6 | \pi(\mathbf{0}) \rangle$. It can be shown that this particular matrix elements controls the magnitude of all the unwanted cutoff effects described above^{60,51,52}, making them to vanish as soon as $c_2 = 0$.

This strategy has been already partially implemented by working with a gluon action other than the standard plaquette action^{46,58}. One finds that meta-stabilities are avoided in this way as soon as $a \leq 0.1$ fm and for pion masses down to (at least) 300 MeV.

4 Structural properties of polymer chains

Lacking at the moment in most cases mesoscopic, functionally useful, descriptions of biological systems, theoretical models aimed at understanding the dynamic and/or the thermodynamic properties of molecular aggregates of biological interest are based on a detailed atomistic description of the compound. The physico-chemical behaviour of the resulting model and its compatibility with the available experimental information is then investigated by numerical simulations. The deterministic approach of Molecular Dynamics (MD) or the stochastic methods of Monte Carlo type^{61,7,8} are employed either classically or with quantum corrections injected *à la* Car-Parrinello⁶².

The need for a numerical approach appears to be even stronger if the problem of predicting the folded configuration of a protein, solely from the knowledge of its linear amino-acidic composition, is considered. The interest of investigating the folding

problem rests on the experimental observation that the biological functionality of a protein crucially depends on the nature of its folded configuration⁶³. Misfolding is, in fact, known to lead to malfunctioning and in certain cases to severe pathologies, such as Creutzfeld–Jacobs disease and human variant of BSE⁶⁴, Alzheimer disease⁶⁵, cystic fibrosis⁶⁶ and probably also to other neuro-degenerative processes.

Understanding the nature of folding is expected to be a formidable task: already the classical problem of finding the absolute minimum of the free energy of atomistic models of long polymer chains has a computational complexity which bears close resemblance to that of instances belonging to the class of problems technically called NP-complete¹². Furthermore the problem may not have a unique solution: the recent studies on misfolding induced diseases have shown that proteins may live in more than one (meta-)stable state. It is remarkable that the simple model of ref.¹¹ can yield some understanding for this behaviour.

In the following sections I shall discuss merits and limitations of some interesting research lines and computational strategies that have been recently put forward to deal with the problem of folding or, more modestly, with the problem of predicting the structure of a polymeric chain from its chemical composition. For a review of approaches of different nature see, for instance, ref.¹⁰.

4.1 *State of the art*

The study of Statistical Mechanics of polymers, *i.e.* long chains consisting of monomers of specific nature, is becoming more and more important in chemical technologies and biological applications. Polymers like proteins⁶⁷, nucleic acids⁶⁸, polysaccharides⁶⁹ and synthetic materials⁷⁰ display features that strongly depend on their detailed physico-chemical properties like, for instance, the degree of flexibility of certain chemical bonds, the charge density at monomer atoms, the structure of the hydrogen bond network between monomers either close or far away in the sequence, and so on.

As we said, the enormous complications associated, even within classical physics, with the atomistic description of the specific interaction among the elementary components of the polymer can only be handled by numerical simulations. Clever algorithms have been devised to explore the configuration space available to the system and different types of *ensembles* have been invented and numerically implemented, starting from molecular dynamics (MD) and Monte Carlo (MC) methods⁶¹. As is well known, MD and MC simulations explore the *micro-canonical* ensemble and the *canonical* ensemble of the system, respectively. Other kinds of ensembles, which may be collectively indicated by the name of *generalized ensembles*⁷¹, have also been introduced and employed for the study of thermodynamic properties at equilibrium. In principle, under standard ergodicity assumptions, all these *ensembles* should yield equivalent physical information. Indeed the use of *generalized ensembles* within MD and MC simulation strategies resulted in a rather powerful approach capable of predicting the statistical properties of atomistic models of fluids and other compounds of chemical and/or biological interest in a wide range of temperatures and order parameter values⁷².

The crucial limitation that is encountered in numerical simulations of systems with many relevant degrees of freedom is related to the inadequate and strongly biased sampling of the configurational space occurring when the temperature is lower than the criti-

cal temperature of the model. By “critical temperature” we generically mean the temperature above which the system is in the disordered phase. Below the critical temperature the system remains trapped in local minima, within energy barriers that are rarely (or never) overtaken by thermal fluctuations.

Many strategies have been proposed over the years aimed at trying to overcome this difficulty. Among them we may recall simulated annealing^{73,74}, stochastic tunneling⁷⁵ and many variants of genetic algorithms⁷⁶. The problem with these approaches is that they do not always permit the calculation of statistical averages in well defined *ensembles* (i.e. in the *ensembles* that are statistically representative of the desired experimental conditions).

Vice-versa, algorithms designed to access *ensembles* of the *multi-canonical* type, i.e. the kind of *generalized ensembles* that exploit the information on the (potential) energy density of states^{7,8}, are well assessed and made rather effective if used in conjunction with the replica-exchange method^{77,8,74}. In many interesting instances it is possible to computationally monitor order parameters of geometrically constrained molecular models of polymers in a fairly large temperature range.

However, even within these approaches problems arise when all the many degrees of freedom of realistic models, including the high-frequency vibration modes, are taken into account⁷⁸, as it is necessary to do in order to treat condensed phases and explicit solvents. In fact, large variations of the potential energy are observed associated with such stiff terms in the Hamiltonian even for tiny configurational changes. Such large potential energy changes cause very low acceptance in the exchange of temperatures between replicas and lack of convergence in the *multi-canonical* weight computation^{7,78}.

4.2 A proposal for a new approach

The main lesson one learns from the previous discussion is that energy is not the best variable to label configurations because on the one hand configurations that are only slightly different in their atomic spatial arrangement may have largely different potential energies and on the other configurations with similar energy can be structurally very different. This is the main reason why, within the standard *multi-canonical* approach, introducing the temperature through the modulation of the energy density of states by the Boltzmann factor does not yield sufficiently satisfactory results, as soon as the number of degrees of freedom of the polymer is too large and/or the temperature is above the order-disorder phase transition.

In order to overcome this type of problems it was proposed in⁷⁹ to work in a *generalized ensemble* where configurations are generated according to the density of states associated to some configurational quantity (or some set of configurational quantities), rather than energy. These configurational quantities can be the mean value of some bond or dihedral angle along the polymer chain, the value of the α -helicity of the polymer, the head-to-tail distance of the chain or any other variable which may serve to characterize the geometrical structure of the system.

A problem with this approach may be considered the fact that it is not clear how to introduce the notion of temperature, because the fundamental statistico-mechanical relation between the energy of the system and its temperature is put at stake. Actually, for the purpose of studying, say, biopolymers, which after all are neither isolated systems, nor do they work at equilibrium, this state of affairs is not really a problem and can be

dealt with along the lines described below in sect. 4.3 (see also the Appendix).

In brief the idea of ref. ⁷⁹ is to start by working in the *micro-canonical ensemble* associated to some configurational variable, A , rather than energy, and then pass to the associated *canonical ensemble* by the “constrained maximal entropy method” (CMEM) imposing that A assumes some preassigned value, \bar{a} . The latter can be either taken from experiments or can be known from some exact theoretical calculations in particularly simple models. The scheme can be extended in an obvious way to the case of more than one configurational variable.

The passage from the standard *micro-canonical/canonical ensembles* to the *configurational ensembles* introduced in ref. ⁷⁹ is schematically illustrated in the steps 1. to 4. outlined below (in the formulae that follow we generically indicate with r the whole set of variables necessary to describe the degrees of freedom of the system).

1. Make the replacement

$$\begin{aligned} U(r) &\rightarrow A(r) \\ \omega_U(E) = \int dr \delta(E - U(r)) &\rightarrow \omega_A(a) = \int dr \delta(a - A(r)) \end{aligned}$$

2. From seeds at random temperatures (see Appendix) collect configurations according to a Metropolis test with *multi-canonical* weight

$$[\omega_U(E)]^{-1} \equiv e^{-S(E)} \rightarrow [\omega_A(a)]^{-1} \equiv e^{-Q(a)},$$

obtaining the configurational distribution (which may or may not be further elaborated)

$$\tilde{P}_U(r) \rightarrow \tilde{P}_A(r)$$

3. Determine the best configurational distribution, P , satisfying the constraint

$$\langle U \rangle = \int dr U(r) P_U(r; \bar{\beta}) = \bar{E} \rightarrow \langle A \rangle = \int dr A(r) P_A(r; \bar{\lambda}) = \bar{a}, \quad (7)$$

using the CMEM, which yields

$$\begin{aligned} P_U(r; \bar{\beta}) = \frac{1}{Z_U(\bar{\beta})} \tilde{P}_U(r) e^{-\bar{\beta}U(r)} &\rightarrow P_A(r; \bar{\lambda}) = \frac{1}{Z_A(\bar{\lambda})} \tilde{P}_A(r) e^{-\bar{\lambda}A(r)} \\ Z_U(\bar{\beta}) = \int dr \tilde{P}_U(r) e^{-\bar{\beta}U(r)} &\rightarrow Z_A(\bar{\lambda}) = \int dr \tilde{P}_A(r) e^{-\bar{\lambda}A(r)} \end{aligned}$$

with the Lagrange multiplier implicitly fixed by (7)

$$\bar{\beta} = \beta(\bar{E}) \rightarrow \bar{\lambda} = \lambda(\bar{a}).$$

4. The expectation value of $F = F(r)$ is computed by means of the re-weighting formula

$$\langle F \rangle = \frac{\sum_{i=1}^{N_{conf}} [\omega_U(E_i)]^{-1} e^{-\bar{\beta}E_i} F_i}{\sum_{i=1}^{N_{conf}} [\omega_U(E_i)]^{-1} e^{-\bar{\beta}E_i}} \rightarrow \langle F \rangle = \frac{\sum_{i=1}^{N_{conf}} [\omega_A(a_i)]^{-1} e^{-\bar{\lambda}a_i} F_i}{\sum_{i=1}^{N_{conf}} [\omega_A(a_i)]^{-1} e^{-\bar{\lambda}a_i}}, \quad (8)$$

where

$$E_i = U(r_i), \quad F_i = F(r_i) \rightarrow a_i = A(r_i), \quad F_i = F(r_i),$$

and N_{conf} is the number of collected configurations.

Roughly speaking we may say that the computational strategy displayed in the left column is fine for energy related quantities, but not so much for structural quantities. On the contrary the new strategy outlined in the right column is expected to work appreciably well for structural quantities, but not as well for energy related quantities. To appropriately deal with them temperature must be brought back on stage.

4.3 Introducing temperature

Introducing the notion of temperature for a complex (fully flexible) system, like a polymer, is a delicate issue, because of the observation we already made that configurations only slightly different in their atomic spatial arrangement may have largely different (potential) energies. Consequently, as it turns out, it becomes more and more difficult to get the correct (Boltzmannian) energy distribution of the total available energy among the many degrees of freedom of the system as the temperature increases (despite the fact that at high temperature overcoming energy barriers may become easier).

Actually, in the scheme we have just discussed there is room for the introduction of a sensible notion of temperature. This is done in two separate, but complementary steps. Temperature can be injected in the configurational probability distribution, P_A , if we know how the expectation values of the configurational variable we have chosen to fix (*i.e.* \bar{a}) depend on T . This dependence will in turn induce a T dependence in the values of the Lagrange multipliers that are obtained by solving the constraint equation (7). Through eq. (8) this dependence is then passed to the expectation value of any other configurational quantity one wishes to compute. It is important to remark that in a similar way dependence upon other environmental parameters can be introduced in the study of the physico-chemical properties of the system.

The temperature dependence induced through the method described above is not enough, however, to produce the correct T behaviour of quantities that require an accurate thermalization of all the degrees of freedom of the system for their calculation. Examples of such quantities are the moments of the (potential) energy distribution. In these cases a local, extra thermalization step has to be carried out. This can be accomplished in the following way. Starting from each one of the recorded configurations, one performs a number of hybrid MC steps with velocities extracted from a Maxwell–Boltzmann distribution at the desired temperature. At the end of each MD block of moves configurations are subjected to a standard Metropolis test with acceptance/rejection probability given by $\exp(-\beta H)$, where H is the total (kinetic plus potential) energy of the system. In this way configurations are smoothly thermalized at the desired temperature and can be used to compute the *ensemble* averages (8).

4.4 An application to oligopeptides

A first step in the study of protein folding properties can be the determination of the local propensity of the amino-acid chain to form α -helix, β -sheet or other more or less structured arrangements. As an application of the considerations previously illustrated in this section, I would like to briefly report on the interesting example considered in ref.⁷⁹, where the propensity to form α -helix structures of two simple oligopeptides, *viz.* Gly₁₂ (a chain formed by 12 Glycine amino-acids) and Ala₁₂ (a chain formed by 12 Alanine amino-acids), was studied. The result of comparing data from the simulations of the two oligopeptides was that the order (folded) to disorder (unfolded) critical temperature is lower for Gly₁₂ than for Ala₁₂, implying that the propensity of Gly₁₂ to form α -helix

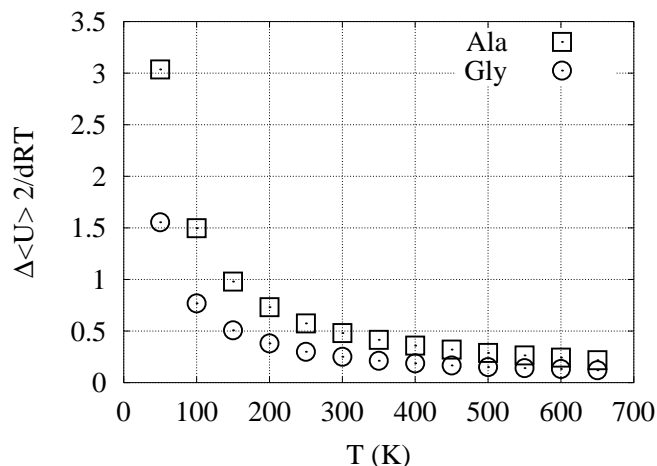


Figure 1: Difference of average potential energy between disordered ($\bar{n}_\alpha = 0$) and ordered ($\bar{n}_\alpha = 12$) states for Ala₁₂ (squares) and Gly₁₂ (circles) as function of temperature.

is lower than for Ala₁₂. The conclusion $T_c(\text{Gly}_{12}) < T_c(\text{Ala}_{12})$, which is in agreement with experimental evidence, follows from Fig. 1 by identifying T_c as the temperature at which the energy difference between the ordered and the disordered phase equals the equipartition energy. For completeness I give in the Appendix some detail on how the data of Fig. 1 are obtained following the strategy described in sect. 4.2.

I wish to end this section with two remarks. First of all the result one gets is rather robust and does not depend on the precise definition of critical temperature one decides to employ, as Ala₁₂ data all lie higher than Gly₁₂ data. Secondly and, most importantly, the possibility of determining such a non-trivial physico-chemical property of these systems should be regarded as a methodologically rather remarkable result because it is based on a first principle computation. It only relies, in fact, on the topology of the systems and the detailed properties of the atomistic model we took to describe the force field of the two oligopeptides.

5 Conclusions

It was my intention in this talk to convey to you the idea that the enormous computational power we have today at our disposal has been a crucial ingredient for the spectacular advances we have been witnessing in many research areas as well as in every-day-life applications and technological developments. I tried to do so by showing in a few significant examples, belonging to my field of competence, how the cultural layout upon which new ideas and methods have emerged have been appreciably influenced by the easy access to large-scale computing facilities and vice-versa.

In recent years a sort of mini-cultural revolution has been taking place. The radically reductionistic paradigm, that so successful had proved to be in our quest for the fundamental laws of micro-physics, is appearing not to be fully adequate to deal with the challenge posed by the physics of, say, dynamical (non-linear) systems or the conceptual

problems of modeling biological objects. Chances are that in these emerging fields of investigation notions like chaos or complexity will be going to play a central role. These notions have rapidly evolved from the initial physico-mathematical frameworks where they have been first introduced (non-linear dynamics and the physics of disordered systems). They have grown to the status of conceptual interpretative schemes under the stimulating pressure of the many successes they have led to in difficult numerical problems and the beneficial effect of the vast diversification of their field of application.

Outlook

Let me conclude with a personal note. I started my career as a student of Bruno Touschek who, as you certainly know, was the inventor of $e^+ - e^-$ colliders and the leader of the group of scientists that in Frascati built the first working storage ring, christened AdA, for “Anello di Accumulazione”. A large fraction of theoreticians and students in Rome and Frascati were at that time (from 1966 to 1970) busy with computing cross-sections for all sorts of $e^+ - e^-$ processes. Computers were not based on transistors or chips, but on electronics tubes, and people were still busy with punching cards. So you were expected to carry on your calculations as much analytically as possible and only at the very end come up with some sensible approximation that one could work out numerically. Nevertheless Touschek was fond of electronic computers. He had clear in his mind their enormous potential in many strategic applications and he immediately suggested that computers should be used to simulate statistical systems with the idea of checking theory against actual numerical data.

To a large extent this the same competent and inspired vision I found in Adriano’s attitude towards research. One can identify a clear and consistent line of development in Adriano’s scientific activity which, starting from his innovative studies on the role of topology in gluon-dynamics at finite and vanishing temperature, has naturally brought him in his more recent papers to attack the most difficult problem of all in QCD, the problem of understanding the mechanism underlying colour confinement (for a recent review see, for instance, ref.⁸⁰).

I’m pretty sure that for many years to come Adriano’s enthusiasm for research will still be a stimulating example for all of us: his ideas and intellectual ingenuity have had an enormous impact in lattice QCD, and more broadly in the whole field of high energy physics.

Collaborating with Adriano was a privilege for me which has strongly influenced my approach to physics and shaped my scientific interests in research. I wish to thank him for that, but most of all for his invaluable and sincere friendship.

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Appendix

The definition of ordered and disordered thermodynamical states is given within the context of the strategy described in sect. 4 by going through the following steps.

1) Configurations (seeds) are initially generated by sequential MD moves of fixed length by taking as starting system coordinates the coordinates of the last stored configuration and, as starting particle velocities, vector components extracted from a Maxwell–Boltzmann distribution at a random temperature, uniformly chosen at each MD step within zero and a high-temperature limit (1000 K in the case at hand). This procedure can be proved to obey the detailed balance principle and generates a time independent (stationary) conditional probability, P_c . Although unknown, P_c is perfectly well defined and gives rise to an acceptable probability distribution, $\tilde{\mathcal{P}}^{(0)}$.

2) As a configurational variable relevant for the problem one is studying the average molecular α -helicity, N_α , is naturally taken. N_α is defined as the number of amino-acids with the two dihedral angles, C($i-1$)-N(i)-C α (i)-C(i) (ϕ_i) and N(i)-C α (i)-C(i)-N($i+1$) (ψ_i) within appropriately chosen bounds, which were taken to be $260^\circ \leq \phi_i \leq 320^\circ$, $i = 2, \dots, 12$, and $293^\circ \leq \psi_i \leq 353^\circ$, $i = 1, \dots, 11$.

3) The initial probability distribution, $\tilde{\mathcal{P}}^{(0)}$, is improved by *multi-canonical* iterations leading from $\tilde{\mathcal{P}}^{(k)}$ to $\tilde{\mathcal{P}}^{(k+1)}$ by generating configurations that are accepted or rejected according to a Metropolis test based on the current α -helicity number of states of the system, $\omega_{N_\alpha}^{(k)}(n_\alpha)$. The iterative procedure is stopped when some stability criterion is fulfilled and the last probability distribution, $\tilde{\mathcal{P}}_{N_\alpha}$, is recorded.

4) For each oligopeptide the configurational probability distributions corresponding to the ordered and disordered phases are constructed from $\tilde{\mathcal{P}}_{N_\alpha}$ by the CMEM, imposing the constraint $\bar{n}_\alpha = 12$ or $\bar{n}_\alpha = 0$, respectively.

5) At this point the two resulting probability distributions, $\mathcal{P}_{N_\alpha}(\lambda(\bar{n}_\alpha = 12))$ and $\mathcal{P}_{N_\alpha}(\lambda(\bar{n}_\alpha = 0))$, are thermalized at a set of temperatures ranging from 50 K to 650 K, in steps of 50 K. From the latter the data points of Fig. 1 are obtained.

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