Arbitrary multi-scale (AMS) systems biology and biomedical engineering effective modeling and simulation

Rodolfo A. Fiorini

Abstract—The addiction to IC (Infinitesimal Calculus), in the mathematical treatment of EM (electromagnetic) and BEM (bioelectromagnetic) biology and biomedical engineering modeling problems, is such that, since the digital computer requires an algebraic formulation of physical laws, it is preferred to discretize the differential equations, rather than considering other more convenient tools for problem mathematical description like, for instance, FDC (Finite Differences Calculus) or more sophisticated algebraic methods. Unfortunately, even traditional FDC, FDTD, etc., approaches are unable to conserve overall system information description. As a matter of fact, current Number Theory and modern Numeric Analysis still use mono-directional interpretation for numeric group generator and relations, so information entropy generation cannot be avoided in current computational algorithm and application. Furthermore, traditional digital computational resources are unable to capture and to manage not only the full information content of a single Real Number R, but even Rational Number Q is managed by information dissipation (e.g. finite precision machine, truncating, rounding, etc.). CICT PG approach can offer exact arithmetic and an effective and convenient "Science 2.0" universal framework, by considering information not only on the statistical manifold of model states but also on the combinatorial manifold of low-level discrete, phased generators and empirical measures of noise sources, related to experimental high-level overall perturbation. We present an effective example; how to unfold the full information content hardwired into Rational OpeRational (OR) representation (nano-microscale discrete representation) and to relate it to a continuum framework (meso-macroscale) with no information dissipation. This paper is a relevant contribute towards arbitrary multi-scale systems biology and biomedical engineering modeling, to show how CICT PG approach can offer a powerful, effective and convenient "Science 2.0" universal framework to develop innovative, antifragile application and beyond.

Keywords—CICT, arbitrary multi-scale systems, systems biology, biomedical engineering.

I. INTRODUCTION

THERE is no doubt that the IC (Infinitesimal Calculus) has played in the past and will play in the future a major role in the mathematical treatment of EM (electromagnetic) and BEM (bioelectromagnetic) biology and biomedical

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engineering modeling problems. Nevertheless, we must be aware that its addiction specifically on multi-scale system modeling hides some fundamental features of the natural phenomenon being represented, such as both its intrinsic invariant features (ontological, topological, geometric, etc.) and its extrinsic interaction with observer, to get overall phenomenon formal observation, description and representation by humans. The addiction is such that, since the digital computer requires a finite formulation of physical laws, it is preferred to discretize differential equations, rather than considering other more convenient tools like FDC (Finite Differences Calculus), Finite Difference Time Domain (FDTD) or more sophisticated algebraic methods. FDC and FDTD deal especially with discrete functions, but they may be applied to continuous function too and to continuum problems, with no loss of generality. They can deal with both discrete and continuum problem categories conveniently. Unfortunately, even traditional FDC, FDTD and more sophisticated and advanced algebraic approaches are unable to conserve overall system information description in a multi-scale modeling environment. As a matter of fact, current Number Theory and modern Numeric Analysis still use LTR (Left-To-Right) mono-directional interpretation for numeric group generator and relations, so information entropy generation cannot be avoided in current computational algorithm and application [1]. Furthermore, traditional digital computational resources are unable to capture and to manage not only the full information content of a single Real Number R, but even Rational Number Q is managed by information dissipation (e.g. finite precision machine, truncating, rounding, etc.). So, paradoxically if you don't know the code used to communicate a message you can't tell the difference between an information-rich message and a random jumble of letters [2]. This is the information double-bind (IDB) problem in contemporary classic information theory and in current science [2]. Scientific community laid itself in this double-bind situation. Even the most sophisticated instrumentation system is completely unable to reliably discriminate so called "random noise" (RN) from any combinatorically optimized encoded message, which CICT called "deterministic noise," DN, for short [2]. It is a problem to solve clearly and reliably, before taking any quantum leap to more competitive and convenient, at first sight, post-human cybernetic approach in science and

technology. As a matter of fact, to grasp a more reliable representation of reality, researchers and scientists need two intelligently articulated hands: both stochastic and combinatorial approach synergistically articulated by natural coupling [3]; let's say we need a fresh "Science 2.0" approach. To get stronger solution to advanced problems, like resonant nanoparticle, nanophotonic, optifluidics structure modeling, etc., we have to look for convenient arbitrary multi-scaling (AMS) BU (bottom-up) point-of-view (POV) (from discrete to continuum view ≡ BU POV) to start from first, and NOT the other way around! We present an effective example; how to unfold the full information content hardwired into Rational OpeRational (OR) representation (nano-microscale discrete representation) and to relate it to a continuum framework (meso-macroscale) with no information dissipation. Nevertheless, to achieve that goal we have to be aware and achieve a deep understanding of a paradigm shift first.

II. PARADIGM SHIFT

An organism and all the biologically relevant processes that it experiences must have an extremely "many-atomic" structure and must be safeguarded against haphazard, "single-atomic" events attaining too great importance. In fact, we are taught that all atoms perform all the time a completely disorderly heat motion, which, so to speak, opposes itself to their orderly behavior and does not allow the events that happen between a small number of atoms to enroll themselves according to any recognizable laws. Only in the co-operation of an enormously large number of atoms do statistical laws begin to operate and to represent the behavior of these assemblies with an accuracy increasing as the number of atoms involved increases. It is in that way that the events acquire truly orderly features. All the physical and chemical laws that are known to play an important part in the life of organisms can be represented by this statistical kind. Any other kind of lawfulness and orderliness that one might think of is being perpetually disturbed and made inoperative by the unceasing heat motion of the atoms. Every particular physiological process that we observe, either within the cell or in its interaction with the cell environment, appears, or appeared a century ago, to involve such enormous numbers of single atoms and single atomic processes that all the relevant laws of physics and physical chemistry would be safeguarded even under the very exacting demands of statistical physics in respect of large numbers; this demand illustrated just by the well-known √n rule. That, the "naive physicist" tells us, is essential, so that the organism may, so to speak, have sufficiently accurate physical laws on which to draw for setting up its marvelously regular and well-ordered working.

This is the main reason why statistical and applied probabilistic theory became the core of classic scientific knowledge and engineering applications at system macroscale level. It was applied to all branches of human knowledge under the "continuum hypothesis" assumption, reaching highly sophistication development, and a worldwide audience. Many "Science 1.0" researchers and scientists up to scientific journals assume it is the ultimate language of science and it is

the traditional instrument of risk-taking. How do these conclusions, reached, biologically speaking, a priori (that is, from the purely physical point of view), fit in with actual biological facts?

Today, we know that this question is generated by an ill-posed problem and trying to find a sound answer to it requires enlarging our panorama and related worldview first of all. In fact, early biological concepts based on reductionist inference systemic and classic cybernetic approaches have been largely revisited and overshadowed by more recent molecular and pathogenetic findings for healthcare security and safety management, creating a brand new cultural approach. Incredibly small groups of atoms, much too small to display exact statistical laws, do play a dominating role in the very orderly and lawful events within a living organism. They have control of the observable large-scale characteristics of its functioning; and in all this very sharp and very strict biological laws are displayed.

The great revelation of quantum theory (QT), discovered by Max Planck (1858–1947) in 1900, is that features of a discreteness were discovered in the Book of Nature at system microscale (nanoscale) level, in context in which anything other than continuity seemed to be absurd, according to the views held until then at macroscale level. On the side of QT it took more than a quarter of a century till in 1926-7 the QT of the chemical bond was outlined in its general principles by Walter H. Heitler (1904–1981) and Fritz W. London (1900–1954). The Heitler-London theory involved the most subtle and intricate conceptions of the development of QT at that time, called "quantum mechanics" (QM) or "wave mechanics" (WM).

In the 1920s the problem of creating a QM theory of the electromagnetic field originated early quantum field theory (QFT). In particular Louis de Broglie (1892–1987) in 1924 introduced the idea of a wave description of elementary systems. In 1925, Werner Heisenberg (1901–1976), Max Born (1882–1970), and Pascual Jordan (1902–1980) constructed such a theory by expressing the field's internal degrees of freedom as an infinite set of harmonic oscillators and by employing the canonical quantization procedure to those oscillators. The first reasonably theory of early quantum electrodynamics, which included both the electromagnetic field and electrically charged matter (specifically, electrons) as quantum mechanical objects, was created by Paul Dirac (1902–1984) in 1927 [4]. Pascual Jordan and Wolfgang Pauli (1900–1958) showed in 1928 that quantum fields could be made to behave in the way predicted by special relativity during coordinate transformations (specifically, they showed that the field commutators were Lorentz invariant). The early development of the field involved Dirac, Vladimir Fock (1898–1974), Pauli, Heisenberg and Nikolay Bogolyubov (1909–1992). This phase of development culminated with the construction of the theory of quantum electrodynamics (QED) in the 1950s [5].

Parallel developments in the understanding of phase transitions in condensed matter physics led to the study of the renormalization group. This in turn led to the grand synthesis of theoretical physics, which unified theories of particle and

condensed matter physics through quantum field theory (QFT). This involved the work of Michael E. Fisher (1931-) and Leo P. Kadanoff (1937-) in the 1970s, which led to the seminal reformulation of QFT by Kenneth G. Wilson (1936–2013) in 1975 [6].

QFT has emerged from major paradigm shift with respect to Classical Physics which still provides the framework of the vision of nature of most scientists. This change of paradigm has not yet been completely grasped by many contemporary scientific disciplines and current researchers so that not all the implications of this big change have been realized hitherto, even less their related applications. So, the discreteness approach, developed under the QT "discreteness hypotesis" assumption, has been considered in peculiar application areas only. It has been further slowly developed by a few specialists and less understood by a wider audience. It is the fresh QFT approach.

Unfortunately, the above two large scientific research areas (continuum based and discreteness based) have followed separate mathematical development paths with no articulated synergistic coupling. That is the main reason why QFT is still mostly overlooked by traditional scientific and engineering researchers for system multi-scale modeling, from system microscale to macroscale. Unfortunately, the "probabilistic veil" can be very opaque computationally, in a continuum-discrete arbitrary multi-scale (AMS) environment, and misplaced precision leads to information dissipation and confusion [7].

III. THE ROOT OF THE PROBLEM

In the past, many attempts to arrive to a continuum-discrete unified mathematical formulation have been proposed, all of them with big operational compromises. The most recent ones find their roots at the beginning of the 1980s, even if their publication date records a later public release. As a practical biomedical example, let us consider both biological tissues and many biomaterials which are complex, hierarchical, and heterogeneous structures. It is well established that the mechanical properties of tissues and biomaterials are important for proper functioning of both. It is therefore important to be able to characterize the mechanical properties of tissues and biomaterials not only to understand their functional behavior, but also to diagnose any potential pathological conditions of tissues or to fine-tune the mechanical properties of synthetic biomaterials for their intended function.

Biological tissues and biomaterials are often made of several phases and components that make them highly heterogeneous. Moreover, these heterogeneous structures are often made at different scales, giving rise to certain hierarchical patterns of organization that enable tissues and biomaterials to perform certain functions. Furthermore, the macroscopic shapes of biological tissues are often complex. Mechanical characterization modeling of such complex structures at the various relevant scales is a challenging task (Fig.1) [8]. Since the measurements plotted in the final output histograms originate from very complex multi-component, heterogeneous, hierarchical structures, interpretation of such histograms requires application of classic statistical clustering

theories. Their modeling is still approached under the "continuum hypotesis." The resultant contribution of the different constituents of the characterized materials will then appear in the final histogram that shows the probability of measuring a certain range of mechanical properties.

Current trending approach is to use finite mixture models (FMMs) as a tool capable of performing such types of analysis. Finite Gaussian mixture models assume that the measured probability distribution is a weighted combination of a finite number of Gaussian distributions with separate mean and standard deviation values. Therefore, certain "objective," sharable criteria need to be available to determine the optimum number of Gaussian distributions to associate to unique constituents. For instance, FMMs are used for interpreting the probability distribution functions representing the distributions of the elastic moduli of osteoarthritic human cartilage and co-polymeric microspheres [9]. We are talking about the resultant output data of complex, hierarchical, and heterogeneous structures, which we try to infer from, through sophisticated statistical techniques, both the number and the weighted single contributes of their unique constituents, at the same time. This approach is manifestly an ill-posed problem by definition, with strong interpretative limitations by mathematical and practical point of view. Furthermore, it will never be able to exploit any advantage offered by a discreteness approach.
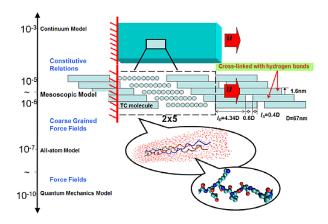

Fig.1 Example of multi-scale modeling hierarchical structure for heterogeneous system biomechanical characterization [8].

On the other hand, in the case of the construction of a full collagen fibril mechanics model, computational challenges associated with such modeling are daunting as the construction of such a model would involve billions of atoms for protein and solvent, a size that is currently out of reach for current protein simulations (Fig.2). The computational modeling challenges associated with these methods are, however, enormous. In fact, a collagen microfibril mechanics model is based on the periodic repetition of a crystallographic unit cell, necessitated by the significant computational cost associated with simulating this large molecular structure. So, collagen fibrils may feature additional interfaces and disorder between

them that could affect the overall mechanical properties. All-atom simulations of the collagen microfibril with explicit solvent are computationally very intense. As an example, the fully solvated (full-atomistic model contains ≈57,000 atoms (≈25,000 in the dehydrated [dry] model), requiring about 6 hours per nanosecond modeling on 32 CPUs on a parallel machine in [10].
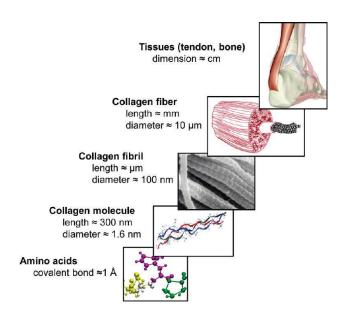

Fig.2 Example of multi-scale modeling hierarchical levels for collagen fibril bioengineering modeling [10].

From a mathematical point of view, this kind of modeling is subjected to computational combinatorial explosion quite easily (Fig.3) We need more efficient representation and convenient computational multi-scale modeling tools. We need a better modeling understanding of the physics at the core of three fundamental concepts: A) arbitrary multi-scale modeling (AMS), B) mesoscale modeling and C) quantum field theory interaction dynamics.

A. *Arbitrary Multi-Scale Modeling (AMS)*

The most fundamental concept of Mathematical Analysis is that of the function. Two sorts of functions are to be distinguished. First, functions in which the independent variable x may take every possible value in a given interval; that is, the variable is continuous. These functions belong to the domain of Infinitesimal Calculus (IC). Secondly, functions in which the independent variable x takes only given values; then the variable is discontinuous or discrete. In the same way, we talk of continuous probability distribution and discrete probability distribution. Unfortunately, to discrete variable the methods of IC are NOT applicable without information dissipation. To deal with discrete variables, we need the Finite Differences Calculus (FDC). The origin of this Calculus may be ascribed to Brook Taylor (1685–1731) [11], but the real founder of the theory was James Stirling (1692–1770) [12], who solved very advanced questions, and gave useful methods. Introducing the famous Stirling numbers, he paved the way

even to an important part of modern combinatorics. The Stirling numbers form the backbone of FDC. To find innovative solution, we just need to remember the Relativity's father inspiration quote: "We cannot solve our problems with the same thinking we used when we created them."
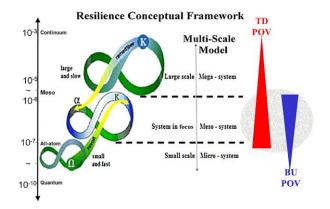

Fig.3 Top-Down (TD) and Bottom-Up (BU) scale-relative Point-Of-View (POV) in an arbitrary multi-scale (AMS) Modeling Framework.

To grasp a more reliable representation of reality and to get stronger biological and physical system correlates, researchers and scientists need two intelligently articulated hands: both stochastic and combinatorial approaches synergistically articulated by natural coupling [3]. Let's say we need a fresh "Science 2.0" approach.

Unfortunately, the previous two large mathematical research areas, discussed in present paper introduction, have followed separate mathematical development paths with no articulated synergic coupling. In the past, many attempts to arrive to a continuum-discrete unified mathematical approach have been proposed, all of them with big operational compromises, and we can go back at least to the introduction of the Riemann–Stieltjes integral, published in 1894 by Dutch mathematician Thomas Joannes Stieltjes (1856–1894), which unifies sums and integrals [13]. Every approach that uses analytical function applies a top-down (TD) point-of-view (POV) implicitly. These functions belong to the domain of Infinitesimal Calculus (IC).

From a system computational perspective, all approaches that use a TD scale-free POV allow for starting from an exact global solution panorama of analytic solution families, which offers a shallow local solution computational precision to real specific needs (in other words, from global to local POV overall system information is not conserved, as misplaced precision leads to information dissipation [3], [15], Fig.3). In fact, usually further analysis and validation (by probabilistic and stochastic methods) is necessary to get localized computational solution of any practical value, in real application. A local discrete solution is worked out and computationally approximated as the last step in their line of reasoning, that started from an overall continuous system approach (from continuum to discreteness ≡ TD POV).

Unfortunately, the IC methods are NOT applicable to discrete variable. To deal with discrete variables, we need FDC. FDC deals especially with discrete functions, but it may be applied to continuous function too. As a matter of fact, it can deal with both discrete and continuous categories conveniently.

In other words, if we want to achieve an overall system information conservation approach, we have to look for a convenient (combinatorically explosion-free solution, Fig.3) bottom-up (BU) scale-relative POV (from discreteness to continuum view ≡ BU POV) to start from first, and NOT the other way around! We need tools able to manage ontological uncertainty more effectively [14], [15]. We need a better understanding of the mesoscopic modeling level (molecular, supramolecular, etc.) related to microscopic and macroscopic system representations.

B. Mesoscale Modeling

We have to recall that among the discrete set of states of a given selection of atoms in such a state form a molecule. The point to stress here is, that the molecule will of necessity have a certain stability; the configuration cannot change, unless at least the energy difference, necessary to "lift" it to the next higher level, is supplied from outside. Hence this level difference, which is a well-defined quantity, determines quantitatively the degree of stability of the molecule. It will be observed how intimately this fact is linked with the very basis of quantum theory, viz. with the discreteness of the level scheme. This order of ideas has been thoroughly checked by chemical facts; and it has proved successful in explaining the basic fact of chemical valence and many details about the structure of molecules, their binding-energies, their stabilities at different temperatures, and so on.

We are speaking of concepts and experimentations, starting from the Heitler- London theory and arriving to QFT, which cannot be examined in detail here. We must content ourselves with examining the point which is of paramount interest for our biological modeling problem, namely, the stability of a molecule at different temperatures. Take our system of atoms at first to be actually in its state of lowest energy. The physicist would call it a molecule at the absolute zero of temperature. To lift it to the next higher state or level a definite supply of energy is required. The simplest way of trying to supply it is to "heat up" your molecule. You bring it into an environment of higher temperature ("heat bath"), thus allowing other systems (atoms, molecules) to impinge upon it. Considering the entire irregularity of heat motion, there is no sharp temperature limit at which the "lift" will be brought about with certainty and immediately. Rather, at any temperature (different from absolute zero) there is a certain smaller or greater chance for the lift to occur, the chance increasing of course with the temperature of the scale heat bath.

The best way to express this chance is to indicate the average time you will have to wait until the lift takes place, the "time of expectation" t. It is defined as:

$$t = \tau \, e^{W/kT} , \qquad\qquad (01)$$

where τ is a certain small constant of the order of 10^{-13} or 10^{-14} s, e is the usual mathematical constant reference, W the

energy difference itself that is required to effect the lift, and kT the scale characteristic energy (characterizing the intensity of the heat motion at the scale temperature in question), where T is the absolute temperature and k is a numerically known constant, called Boltzmann's constant (e.g. 3/2 kT is the average kinetic energy of a gas atom at temperature T). It stands to reason that the chance for effecting the lift is smaller, and hence that the time of expectation is longer, the higher the lift itself compared with the average heat energy, that is to say, the greater the ratio W/kT. What is amazing is how enormously the time of expectation depends on comparatively small changes of the ratio W/kT. To give an example: for W = 30 kT, the time of expectation might be as short as 1/10 s, but would rise to about 16 months when W = 50 kT, and to 30,000 years when W = 60 kT! Now, this particular exponential function is not an accidental feature. It recurs again and again in the statistical theory of heat, forming, as it were, its backbone. It is a measure of the improbability of an energy amount as large as W gathering accidentally in some particular part of the system, and it is this improbability which increases so enormously when a considerable multiple of the "average energy" kT is required. Actually a W = 30 kT is already extremely rare event (from an atomic point of view). That it does not yet lead to an enormously long time of expectation (only 1/10 s in our example) is, of course, due to the smallness of the factor T. This factor has a physical meaning. It is of the order of the period of the vibrations which take place in the system all the time. You could, very broadly, describe this factor as meaning that the chance of accumulating the required amount W, though very small, recurs again and again "at every vibration," that is to say, about 10^{13} or 10^{14} times during every second.

C. QFT Interaction Dynamics

As a practical example of complex system (hierarchical heterogeneous multi-scale system) modeling with important implications, let us consider classic relativistic electrodynamics, applied to biological system modeling (e.g. fullwave electromagnetic modeling of brain waves). Neural activity inside the human brain results in low frequency waves known as brain waves. These brain waves can be further classified into delta (0.1 to 3 Hz), theta (4 to 7 Hz), alpha (8 to 12 Hz), beta (12 to 30 Hz) and gamma (30 to 100 Hz) waves based on the rate of neural activity inside the brain. The success of neuroscience in the study of the structural and biochemical properties of neurons, glia cells, and all the biological units and cellular structures in the brain have not yet filled the gap between the behavior understood at cellular level (microscale) and the macroscopic dynamics involved in the traffic between the brain and the world which it is immersed within. There is an essential problem in the study of brain function (mesoscale dynamics) that even today, after so many years since Karl Lashley posed his dilemma [16], still waits for a solution. As recalled many times in the literature, in the mid 1940s he wrote [16]:

" .... Here is the dilemma. Nerve impulses are transmitted ...from cell to cell through definite intercellular connections. Yet, all behavior seems to be determined by masses of

excitation...within general fields of activity, without regard to particular nerve cells... What sort of nervous organization might be capable of responding to a pattern of excitation without limited specialized path of conduction? The problem is almost universal in the activity of the nervous system."

The traditional quasi-static approach is not sufficiently accurate for the head-modeling problem since the quasi-static potential differs from the full-wave potential by nearly 30 % to 50 % [17], supporting the argument that a full-wave solution should be derived even at low frequencies [18]. In fact, in Quantum Theory (QT), the space-time distribution of matter and energy has a coarse-grained structure which allows its representation as an ensemble of quanta (particle representation). The local phase invariance is shown to hold if a field exists which is connected to the space-time derivatives of the phase.

In the case of a system made up of electrically charged components (nuclei and electrons of atoms), as, for instance, a biological system, this is just the electromagnetic (e.m.) potential $\mathbf{A}_\mu$, where μ is the index denoting the usual four space-time coordinates $\gamma_0 = ct$, γ_1, γ_2, γ_3. The electric and magnetic fields are suitable combinations of the space-time derivatives of $\mathbf{A}_\mu$. In order to get the local phase invariance, we should assume that the system Lagrangian is invariant with respect to specific changes of the field $\mathbf{A}_\mu$. Thus a specific principle of invariance, named "gauge invariance," emerges; hence the name "gauge field" denotes $\mathbf{A}_\mu$. Actually it is well known that the Maxwell equations just obey the gauge invariance, which in quantum physics becomes the natural partner of the phase invariance to produce our world.

Quantum fluctuations give rise to e.m. potentials which spread the phase fluctuations beyond the system at the phase velocity. This gives an intrinsic nonlocalizability to the system and prevents a direct observation of quantum fluctuations. Through the e.m. potential, the system gets a chance to communicate with other systems. Notice that all e.m. interactions occur in a two-level way; the potential keeps the interacting particles phase-correlated whereas the combination of its space-time derivatives, named e.m. field, accounts for the forces involved. The lower level, the potential, becomes physically observable only when the phase of the system assumes a precise value. The structure of electrodynamics makes possible the presence of a potential also when both electric and magnetic fields are absent, whereas on the contrary fields are always accompanied by potentials. The above solution which stems from the mathematical formalism of QFT [19] opens the possibility of tuning the fluctuations of a plurality of systems, producing therefore their cooperative behavior. However, some conditions must be met in order to implement such a possibility. Let us, first of all, realize that in quantum physics the existence of gauge fields, such as the e.m. potential, dictated by the physical requirement that the quantum fluctuations of atoms should not be observable directly, prevents the possibility of having isolated bodies. For this reason, the description of a physical system is given in terms of a matter field, which is the space-time distribution of atoms/molecules, coupled to the gauge field with the possible

supplement of other fields describing the nonelectromagnetic interactions, such as the chemical forces. According to the principle of complementarity, there is also another representation where the phase assumes a precise value; this representation which focuses on the wave-like features of the system cannot be assumed simultaneously with the particle representation.

The relation between these two representations is expressed by the uncertainty relation, similar to the Heisenberg relation between position and momentum:

$$\Delta N \, \Delta \varphi \geq 1/2 \qquad (02)$$

connecting the uncertainty of the number of quanta (particle structure of the system) ΔN and the uncertainty of the phase (which describes the rhythm of fluctuation of the system) $\Delta \varphi$. Consequently, the two representations we have introduced above correspond to the two extreme cases:

(1) If $\Delta N = 0$, the number of quanta is well defined, so that we obtain an atomistic description of the system, but lose the information on its capability to fluctuate, since $\Delta \varphi$ becomes infinite. This choice corresponds to the usual description of objects in terms of the component atoms/molecules.

(2) If $\Delta \varphi = 0$, the phase is well defined, so that we obtain a description of the movement of the system, but lose the information on its particle-like features which become undefined since ΔN becomes infinite. Such a system having a well-defined phase is termed "coherent" in the physical jargon. We have an interaction where a common phase arises among different objects because of their coupling to the quantum fluctuations and hence to an e.m. potential. In this case there is no propagation of matter and/or energy taking place, and the components of the system "talk" to each other through the modulations of the phase field travelling at the phase velocity, which has no upper limit and can be larger than c, the speed of light.

In the phase representation, the deepest quantum features appear since the system becomes able to oscillate with a well-defined phase only when the number of its components becomes undefined, so that it is an open system and able to couple its own fluctuations to the fluctuations of the surroundings. In other words, such a coherent system, like a biological one, is able to "feel" the environment through the e.m. potential created by its phase dynamics. In conclusion, a coherent system involves two kinds of interaction:

(A) an interaction similar to that considered by Classical Physics, where objects interact by exchanging energy. These exchanges are connected with the appearance of forces. Since energy cannot travel faster than light, this interaction obeys the principle of causality (Science 1.0);

(B) an interaction where a common phase arises among different objects because of their coupling to the quantum fluctuations and hence to an e.m. potential. In this case there is

no propagation of matter and/or energy taking place, and the components of the system "talk" to each other through the modulations of the phase field travelling at the phase velocity, which has no upper limit and can be larger than c, the speed of light.

The process of the emergence of coherent structures out of a crowd of independent component particles has been investigated in the last decades and is presently quite well understood [20],[21]. The presence of this field has received experimental corroboration by the discovery of the so-called "Lamb shift," named after the Nobel prize winner Willis E. Lamb (1913–2008) [22]. He discovered as far back as in 1947 that the energy level of the electron orbiting around the proton in the hydrogen atom is slightly shifted (about one part per million) with respect to the value estimated when assuming that no e.m. field is present. Further corroboration for the existence of vacuum fluctuations is provided by the "Casimir effect" [23]. The Casimir effect and the Casimir–Polder force are physical forces arising from a quantized field. They are named after the Dutch physicists Hendrik Casimir (1909–2000) and Dirk Polder (1919–2001). Therefore a weak e.m. field is always present, just the one arising from the vacuum quantum fluctuations.

We should now pay attention to an important mismatch of the scales present in the problem we are dealing with. An atom has a size of about 1 Angstrom (Å) which amounts to 10^{-8} cm, whereas a typical excitation energy is in the order of some electron volts (eVs), corresponding to a wavelength of the associated e.m. fluctuation in the order of some thousand Å ($\approx 10^{-4}$ cm). This means that the tool (the e.m. fluctuation) able to induce a change of configuration in the atom is some thousands of times wider than the atom itself. Hence a single quantum fluctuation can simultaneously involve many atoms. In the case, for instance, of the water vapor at boiling temperature and normal pressure, the exciting e.m. mode (in this case 12 eV) would include in its volume about 20,000 molecules. Let us assume now that in the volume $V = \lambda^3$ of the fluctuation there are N atoms. Let P be the probability (calculated by using Lamb shift-like phenomena) that an isolated atom is excited by an e.m. quantum fluctuation. Therefore the probability P_N that one out of the N atoms gets excited by the fluctuation is given by:

$$P_N = PN = P\lambda^3\,(N/V) = P\lambda^3 d, \qquad (03)$$

where d is the density of atoms. We can see that there is a critical density d_{crit} such that $P_N = 1$, which means that the fluctuation excites with certainty one atom. In such conditions, the virtual photon coming out from the vacuum is "handed over" from one atom to another and gets permanently entrapped within the ensemble of atoms, being busy in keeping always at least one atom excited. According to this dynamics atoms acquire an oscillatory movement between their two configurations. In a short time, many quantum fluctuations pile up in the ensemble, producing eventually a large field which keeps all atoms oscillating between their two configurations. Moreover, the field gets self-trapped in the ensemble of atoms

since its frequency becomes smaller; actually the period of oscillation T of the free field should be extended by adding the time spent within the excited atoms. Like in the cavity of a laser, the field becomes coherent, that is, acquires a well-defined phase, in tune with the oscillations of the atoms, which therefore become coherent, too.

The more realistic case of atoms having a plurality of excited states has been also successfully addressed and needs a more sophisticated mathematics [20]. Among all the excited levels, the one selected for giving rise to the coherent oscillation is the level requiring the smallest time to self-produce a cavity. The region becomes a coherence domain (CD) whose size is the wavelength of the e.m. mode, where all atoms have tuned their individual fluctuations to each other and to the oscillation of the trapped field [24]. The size of the coherence domain cannot be arbitrary but is determined in a selfconsistent way by the dynamics underlying the emergence of coherence via the wavelength of the involved e.m. mode. A coherent system is therefore an ensemble of self-determined e.m. cavities. The fact that a biological system appears to be a nested ensemble of cavities within cavities of different sizes (organs, tissues, cells, organelles, etc.) having well-defined sizes is a strong indication for its coherence. In a CD there is a common phase, specific of the CD, which is therefore an object governed by a dynamics which eliminates the independence of the individual components and creates a unitarily correlated behavior of all of them, governed by the e.m. field.

A peculiar feature appears in the case of water. The coherent oscillation of the water molecules, which induces the formation of the CDs, occurs between the molecule's ground state and an excited state at 12.06 eV, which is slightly below the ionization threshold at 12.60 eV. The electron cloud of the water molecule oscillates between a configuration where all electrons are tightly bound (in this configuration water is an insulator and a mild chemical oxidant, since it is able to bind an extra electron) and a configuration where one electron is almost free (in this configuration water becomes a semiconductor and a chemical reducer, since it is able to release electrons). In conclusion, liquid water (which contributes about 70% of the total mass and 99% of the total number of component molecules of a living organism) exhibits a twofold inner dynamics [24]. This feature confirms the proposal of Erwin Schrödinger (1887–1961) [25] about the need of negative entropy (negentropy) for the appearance of order in living systems.

The theoretical framework outlined above has increasingly received support by a growing body of evidence. First of all, one should realize that the QFT picture satisfies the two main requirements demanded by biological evidence: the existence of selective recognition and attraction among biomolecules (organic codes) and long-range connections among biocomponents which cannot be accounted for by the very short-range interactions implied by a purely chemical dynamics. Secondly, "Science 1.0" researchers and scientists are unaware that QFT picture is already well present and hardwired in our current computational tools by rational arithmetic's Q [1]. This new awareness leads to our

exploitation of more efficient and competitive computational modeling tools.

IV. CICT RESULTS

The first attempt to identify basic principles, to synergistically articulate Computational Information Conservation Theory (CICT) by natural coupling to geometric science of information (GSI, Fig.5), for scientific research and application, has been developing at "Politecnico di Milano University" since the end of last century. In 2013, the basic principles on CICT, from discrete system parameter and generator, appeared in literature and a brief introduction to CICT was given in 2014 [9]. CICT tries to bring classical and quantum information theory together in a single formalism, by considering information not only on the statistical manifold of model states but also on the combinatorial manifold of low-level discrete, phased generators and empirical measures of noise sources, related to experimental high-level overall perturbation [2]. CICT showed that long arithmetic division minority components (Remainders, R), for long time concealed relational knowledge to their dominant result (Quotient, Q), not only can always allow quotient regeneration from their remainder information to any arbitrary precision, but even to achieve information conservation and entropy minimization, in systems modelling and post-human cybernetic approaches [28],[29]. CICT is a natural framework for arbitrary multi-scale (AMS) systems biology and biomedical engineering computational modeling in the current landscape of modern QFT [14],[15].

We have selected an example to show how leading zeros in positional notation representation system for CICT ***Q*** Arithmetic do count effectively to get coherent phased representation correctly. They can even model the quantum-classical system transition (system decoherence) quite efficiently. With no scale related coherent inner phase information, we get system decoherence, entropy generation, information dissipation and algorithmic quantum incomputability on real macroscopic machines. Our results are presented in term of classical power series to show the close relationships to classical and modern control theory approaches for causal continuous-time and discrete-time linear systems. Usually, the continuous Laplace transform is in Cartesian coordinates where the x-axis is the real axis [26] and the discrete z-transform is in circular coordinates, where the rho-axis is mapping the Real axis [27].

Traditional knowledge on significant figures of a number teaches that any 0 digit that comes before the first nonzero digit (leading zeros) can be omitted in a number string in positional notation representation system [28]. When leading zeros occupy the most significant digits of an integer, they could be left blank or omitted for the same numeric value [29]. Therefore, the usual decimal notation of integers does not use leading zeros except for the zero itself, which would be denoted as an empty string otherwise [30]. However, in decimal fractions between 0.0 and 1.0, the leading zeros digits between the decimal point and the first nonzero digit are necessary for conveying the magnitude of a number and cannot be omitted [28].

Let us introduce a convenient LTR symbolic compression operator (SCO) as SCO $\equiv$ <M│DS>, where DS is a finite digit string of length L and M is the number of times DS is repeated to get our unfolded digit string in full (e.g. (4│1) $\equiv$ 1111 or (2│123) $\equiv$ 123123). Usual symbolic string operations can be applied to SCO. Then, we can write usual rational number OpeRational Representation (OR) [1] corresponding to their Symbolic Representation (SR) as:

$$Q1 = \frac{1}{D1} = \frac{1}{9} = 0.11111111111...$$

$$Q2 = \frac{1}{D2} = \frac{1}{99} = 0.0101010101010101010101...$$

$$Q3 = \frac{1}{D3} = \frac{1}{999} = 0.001001001001001001001001001001001001... \qquad (04)$$

in a more compact RFD Q_L format as:

$$Q1 = \frac{1}{D1} = \frac{1}{9} \equiv 0. < \infty I1 >$$

$$Q2 = \frac{1}{D2} = \frac{1}{99} \equiv 0. < \infty I01 >$$

$$Q3 = \frac{1}{D3} = \frac{1}{999} \equiv 0. < \infty I001 > \qquad (05)$$

In the same way, we can write:

$$Q4 = \frac{1}{D4} = \frac{1}{7} = 0.142857142857142857142857142857... \quad \text{as}$$

$$Q4 = \frac{1}{D4} = \frac{1}{7} \equiv 0. < \infty I142857 > \qquad (06)$$

On the other hand, we have:

$$Q5 = \frac{1}{D5} = \frac{1}{142857} = 0.0000070000070000070000070000007... \quad \text{written as}$$

$$Q5 = \frac{1}{D5} = \frac{1}{142857} \equiv 0. < \infty I000007 > \qquad \text{either (first compressed form)}$$

$$Q5 = \frac{1}{D5} = \frac{1}{142857} \equiv 0. < \infty I(< 5I0 >< 1I7 >) > \qquad \text{or (second compressed form)}.$$

$$(07)$$

Now, we can realize that $Q4$ *RFD* is related by $Q5$ *RFD* and vice-versa by periodic scale relativity (precision length) $L = 6$ [1]. So, to conserve the full information content of rational correspondence between $Q4$ and $Q5$, we realize that we have to take into account not only the usual $Q4$ and $Q5$ modulus information, but even their related periodic precision length information $L = 6$ (extrinsic or external world representation phase). As far as it concerns $D5$ it comes almost automatically, but the same it is not true for $D4$ (see (06)) because we wrote digit 7 only as denominator, without its five leading zeros, according to traditional knowledge on significant figures of a number. In that way, we lose the rational correspondence intrinsic period information (coherence) which an inner or intrinsic relative phase for each RTL (right-to-left) string generator can be computed from (i.e. from their optimized exponential cyclic sequences (OECS) of R_L [2]). With no scale related coherent inner phase information, we get system

decoherence, entropy generation and information dissipation. In fact, misplaced precision leads to information opacity, fuzziness, irreversibility, chaos, complexity and confusion.

Therefore, rational information Q can be better thought to be isomorphic to vector information rather than to usual scalar one, at least. Now, from (07) second compressed form, it is immediate to verify the following phase relations:

$$QQ1 = \frac{1}{DD1} = \frac{1}{142857} \equiv 0. < \infty I(< 5I0 >< 1I7 >) >$$

$$QQ2 = \frac{1}{DD2} = \frac{1}{142857142857} \equiv 0. < \infty I(< 11I0 >< 1I7 >) >$$

$$QQ3 = \frac{1}{DD3} = \frac{1}{142857142857142857} \equiv 0. < \infty I(< 17I0 >< 1I7 >) >$$

$$\bullet\bullet\bullet \qquad \bullet\bullet\bullet$$

$$QQN = \frac{1}{DDN} = \frac{1}{< N I 142857 >} \equiv 0. < \infty I(< 5 + 6(N-1)I0 >< 1I7 >) > \quad \text{for } N = 1,2,3,...,\infty$$

$$. \tag{08}$$

Therefore, we can write the following final relation:

$$CQ4 = \frac{1}{CD4} \equiv \frac{1}{< \infty I(< \infty I0 >< 1I7 >) >} \equiv 0. < \infty I 142857 > \tag{09}$$

According to our SCO approach, the coherent representation $CD4$ emerges out of an LTR (left-to-right) infinity of symbolic structured infinite length sequences as in (09). By this point of view, traditional natural numbers, according to human common knowledge, appear as just the rightmost approximated part of those sequences. So, $CD4$ in (09) is the correct coherent relation representation of traditional scalar modulus $D4$ in (06) as denominator, while scalar modulus $D4$ in (06) can be interpreted as the decoherenced relation representation of $CD4$ denominator in (09). Leading zeros in positional notation representation system for CICT Q Arithmetic do count effectively, and can model the quantum-classical system transition quite efficiently.

Finally, our knowledge of $RFDQ_L$ and corresponding $RFDR_L$ can allow reversing LTR numeric power convergent sequence to its corresponding RTL numeric power divergent sequence uniquely [1].
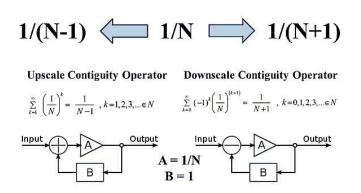

Fig.4 Egyptian fractions Q subset as the discrete continuum of connected rationals (with no loss of generality) with two basic contiguity operators for LTR (downscale) and RTL (upscale) sequencing (full information reversibility).

Reversing a convergent sequence into a divergent one and vice-versa is the fundamental property to reach information conservation, i.e. information reversibility (Fig.4). Eventually, OECS have strong connection even to classic DFT algorithmic structure for discrete data, Number-Theoretic Transform (NTT), Laplace and Mellin Transforms [2]. Scale related, coherent precision correspondence leads to transparency, ordering, reversibility, cosmos, simplicity, clarity, and, as you saw from previous discussion, to algorithmic quantum incomputability on real macroscopic machines [15]. CICT fundamental correspondence relation, relating convergent LTR to divergent RTL formal power series, with D ending by digit 9, in [2] allows to focus our attention on combinatorically optimized number pattern generated by LTR or RTL phased generators and by convergent or divergent power series with no further arbitrary constraints on elementary generator and relation:

$$\frac{1}{D} = \sum_{k=0}^{\infty} \frac{1}{10^W} \left(\frac{\bar{D}}{10^W} \right)^k \Rightarrow ... \Leftarrow Div\left(\frac{1}{D}\right) = \sum_{k=0}^{\infty} (D+1)^k \quad , \tag{10}$$

where D is the information string generator of length W, and "Div" means "Divergence of". Further generalizations of (10) related to D ending by digit 1, 3 and 7 are straightforward. Thanks to subgroup interplay and intrinsic phase specification through polycyclic relations in each solid number (SN) remainder sequence [1], word inner generator combinatorial structure can be arranged for "pairing" and "fixed point" properties for digit group with the same word length [2]. They are the low-level word properties corresponding to "correspondence" and "incidence" OECS (Optimized Exponential Cyclic Sequence) space fundamental reflections, respectively [2]. Actually, since space is limited, the discussion here will not be extended further to the subgroup interplay of the family group and polycyclic groups. We refer the interested reader to good general references on polycyclic groups [31],[32].

V. CICT PHASED GENERATORS

To conserve the full information content of rational correspondence at higher level, we realize that we have to take into account not only the usual modulus information, but even the related external or extrinsic periodic precision length information W = 6 (numeric period or external phase representation) in this case (i.e. CD4 = 000007 as base RFD). We can use Euler's formula to establish the usual fundamental relationship between trigonometric functions and the complex exponential function:

$$e^{ix} = \cos x + i \sin x \ , \tag{11}$$

where e is the base of the natural logarithm and $i = \sqrt{-1}$. It establishes the fundamental relationship between the trigonometric functions and the complex exponential function. We obtain:

$$CQ4 = \frac{1}{7} e^{i\frac{\pi(2n+1)}{3}} = \frac{1}{7}\left(\cos\left(\frac{2\pi(n+1)}{6}\right) + i\sin\left(\frac{2\pi(n+1)}{6}\right)\right)$$
(12)

and

$$CD4 = \frac{1}{CQ4} = 7 e^{-i\frac{\pi(2n+1)}{3}} = 7\left(\cos\left(-\frac{\pi(2n-1)}{3}\right) + i\sin\left(-\frac{\pi(2n-1)}{3}\right)\right) = 7\left(\frac{1}{2} - i\frac{\sqrt{3}}{2}\right)$$ p.v. (13)

for n = 1, 2, 3, …in N, where p.v. means principal value. CICT shows that any natural number D in N has associated a specific, non-arbitrary external or exterior phase relationship [2] that we must take into account to full conserve its information content by computation in Euclidean space [3]. The interested reader will have already guessed the relationship of our result to de Moivre number or root of unity (i.e. any complex number that gives 1.0 when raised to some integer power of n). In this way, we can exploit Rational numbers Q full information content to get effective and stronger solutions to current AMS system modeling problems.

VI. CONCLUSION

According to QFT, the gauge invariance in quantum physics becomes the natural partner of the phase invariance to produce our world. Quantum fluctuations give rise to e.m. potentials which spread the phase fluctuations beyond the system at the phase velocity. This gives an intrinsic nonlocalizability to the system and prevents a direct observation of quantum fluctuations. Through the e.m. potential, the system gets a chance to communicate with other systems and subsystems. The presence of this field has received experimental corroboration by the discovery of the so-called "Lamb shift," named after the Nobel prize winner Lamb [22]. He discovered as far back as in 1947 that the energy level of the electron orbiting around the proton in the hydrogen atom is slightly shifted (about one part per million) with respect to the value estimated when assuming that no e.m. field is present. Further corroboration for the existence of vacuum fluctuations is provided by the "Casimir effect" [23]. Therefore a weak e.m. field is always present, just the one arising from the vacuum quantum fluctuations. We see that the correct AMS modeling of complex system must involve two kinds of interaction:

(1)- an interaction similar to that considered by Classical Physics, where objects interact by exchanging energy. These exchanges are connected with the appearance of forces measured by their magnitude (modulus) only, in an assumed continuum manifold that may be approached and studied by traditional stochastic and probabilistic tools offered by the large arena of the Geometric Science of Information (GSI, Fig.5). Since energy cannot travel faster than light, this interaction obeys the principle of causality (Science 1.0 approach). The missing part of this worldview is usually called "system noise", "background radiation", etc... on cosmic scale by human being;

(2)- an interaction where a common phase arises among different objects because of their coupling to the quantum fluctuations and hence to an e.m. potential. In this case there is

no propagation of matter and/or energy taking place, and the components of the system "talk" to each other through the modulations of the phase field travelling at the phase velocity, which has no upper limit and can be larger than c, the speed of light (Science 2.0 approach).
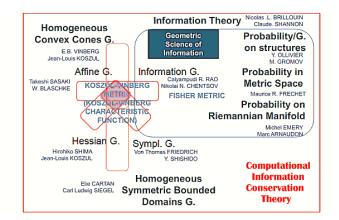

Fig.5 Computational Information Conservation Theory (CICT) is a Natural Framework for Computer Science and Systems Biology Modeling in the current landscape of modern Geometric Science of Information (GSI).

CICT PG approach can offer an effective and convenient "Science 2.0" universal framework, by considering information not only on the statistical manifold of model states but also on the combinatorial manifold of low-level discrete, phased generators and empirical measures of noise sources, related to experimental high-level overall perturbation. CICT new awareness of a discrete HG (hyperbolic geometry) subspace (reciprocal space) of coded heterogeneous hyperbolic structures [3], underlying the familiar Q Euclidean (direct space) surface representation, shows that any natural number n in N has associated a specific, non-arbitrary phase relationship that we must take into account to full conserve overall system information content by computation in Euclidean space. This awareness opens the way to system AMS information conservation by the CICT PG approach [1],[2].

The final result is CICT new awareness of a hyperbolic framework of coded heterogeneous hyperbolic structures, underlying the familiar Euclidean surface representation system. CICT emerged from the study of the geometrical structure of a discrete manifold of ordered hyperbolic substructures, coded by formal power series, under the criterion of evolutive structural invariance at arbitrary precision. It defines an arbitrary-scaling discrete Riemannian manifold uniquely, under hyperbolic geometry (HG) metric, that, for arbitrary finite point accuracy level L going to infinity under scale relativity invariance, is isomorphic (even better, homeomorphic) to classic Riemannian manifold (exact solution theoretically). In other words, HG can describe a projective relativistic geometry directly hardwired into elementary arithmetic long division remainder sequences,

offering many competitive computational advantages over traditional Euclidean approach. More generally, CICT is a natural framework for AMS biology and biomedical engineering modeling complementing the current landscape of modern Geometric Science of Information (GSI), with strength enough to dispel and wipe out the usual probabilistic veil. Specifically, high reliability organization (HRO) [33], mission critical project (MCP) system [34], very low technological risk (VLTR) and crisis management (CM) system will be highly benefitted mostly by these new techniques. The present paper is a relevant contribute towards AMS systems biology and biomedical engineering modeling and simulation, to show how computational information conservation can offer stronger and more effective system modeling algorithms for more reliable simulation.

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