

# PROTEIN FOLDING, MOLECULAR DOCKING, DRUG DESIGN

## *The Role of the Derivative “Drift” in Complex Systems Dynamics*

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**Keywords:** Protein folding, Complex systems dynamics, Traditional Differential Calculus (TDC), Incipient Differential Calculus (IDC), Molecular docking, Drug design.

**Abstract:** The relevance of Protein Folding is widely recognized. It is also well-known, however, that it is one of the dynamic problems in TDC considered as being intractable. In addition, even in the case of solutions obtainable in reasonable computation time, these always present a “drift” between the foreseen behavior of the biological system analyzed and the corresponding experimental results. A drift which is much more marked as the order of the system increases.

Both the “intractability” of the problem and the above-mentioned “drifts”, as well as the insolubility of the problem in explicit terms (or at least in a closed form), can be overcome by starting from a different gnoseological approach. This suggests a new definition of derivative, the “incipient” derivative.

The solution to the “Three-body Problem” obtained by means of IDC, and its extension to any number of bodies, allows us to assert that the folding of even a macroscopic protein, such as dystrophin for example, made up of about 100,000 atoms, can be carried out in a few minutes, when the model is run on next generation computers (1 Petaflop).

The same methodology can also be applied to both Molecular Docking and computer-aided Drug Design.

## 1 INTRODUCTION

Mathematical models of Complex Systems sometimes result as being intrinsically insoluble, such as the famous “Three-body Problem” (Poincaré, 1889).

In other cases they may result as being insolvable “in practice” or, as usually referred to, as being “intractable” (such as, for instance, Protein Folding). This is because, although these problems are thought of as being theoretically solvable in principle, the time required in practice to be solved may range from hundreds to some thousands of years, even when run on the most updated computers. Furthermore, even if they were solvable in reasonable time, they would always present a “drift” between the foreseen behavior of the system analyzed and the corresponding experimental results. A characteristic which is shared by all the other mathematical models which result as being solvable both in theory and in practice. A drift which, in addition, is generally much more marked as the order of the system increases.

This substantially depends on the fact that mathematical models of Complex Systems are generally formulated in terms of Traditional Differential Calculus (TDC), that is by means of linear and non-linear differential equations based on the well-known concept of derivative. TDC, however, often shows its limits, particularly when describing biological Systems and, even more, social Systems.

These in fact present such a richness of characteristics that are, in the majority of cases, much wider than the description capabilities of the usual differential equations. In particular, because all these Systems are habitually modeled as they were mere “mechanisms”.

Such an aspect became particularly evident during the research (Giannantoni, 2001b, 2002) for an appropriate formulation of Odum’s Maximum Emery-Power Principle (proposed by the same Author as a possible Fourth Thermodynamic Principle (Odum, 1994a,b,c)).

The original concept of Emery, in fact, introduces a profound novelty in Thermodynamics, that is: there are processes which cannot be

considered as being pure “mechanisms” (Odum, 1988). This is equivalent to say that they are not describable in mere functional terms, because their outputs show an unexpected “excess” with respect to their inputs. “Excess” that can be termed as Quality (with a capital Q) exactly because it is no longer understood as a simple “property” or a “characteristic” of a given phenomenon, but it is recognized as being any emerging “property” (from the considered process) never ever reducible to its phenomenological premises or to our traditional mental categories.

This evidently suggests a different gnoseological approach with a correspondingly associated new formal language, now represented by the definition of a new concept of derivative, the “incipient” derivative (see Appendix).

This enabled us to reformulate the Maximum Em-Power Principle in a more general form, that is, as the Maximum Ordinality Principle.

The successful application of such a Principle to some decisively “critical points” of various Disciplines, now enables us to assert that both the “intractability” of the problem and related “drifts”, as well as the insolvability of the problem in explicit terms (or at least in a closed form), can be overcome by starting from the above-mentioned new gnoseological approach.

## 2 THE M. EM-P. PRINCIPLE

The Maximum Em-Power Principle asserts that: “Every System reaches its Maximum Organization when maximizing the flow of processed Energy, including that of its surrounding habitat”.

It thus suggests we focus our attention on those processes which can be considered as more specifically generative. Among them (as the same Odum points out) there are three fundamental processes (Co-production, Inter-action, Feed-back) in which such an aspect is particularly evident. These processes, in fact, when analyzed under steady state conditions, can more appropriately be described by means of a particular non-conservative Algebra (Brown and Herendeen, 1996). This leads to the introduction of the concept of Transformity, which allows us to define Energy as

$$\text{Energy} = \text{Energy Quality (Tr)} \times \text{Energy quantity (Ex)} \quad (1)$$

that is as the product of a given quantity of available Energy (represented by Exergy), by the product of its corresponding Quality (expressed by Transformity).

The M. Em-P. Principle, through the introduction of the new concept of derivative (given in Appendix), can be reformulated in an extremely more general form, by replacing the concepts of Emergy and Transformity with the concept of Ordinality (Giannantoni, 2008a).

The corresponding verbal enunciation then becomes: “Every System tends to Maximize its own Ordinality, including that of the surrounding habitat”. In formal terms, this can be expressed as

$$(\tilde{d}/\tilde{d}t)^{(m/n)} \{\tilde{r}\} = 0 \quad (m/n) \rightarrow \text{Max} \quad (2)$$

where:  $(m/n)$  = the Ordinality of the System, which represents the Structural Organization of the System in terms of Co-productions, Inter-actions,

Feed-backs, while  $\{\tilde{r}\}$  = the proper Space of the System.

Such a more general formulation was thus assumed as the preferential guide to recognize the most profound physical nature of the basic processes which particularly characterize self-organizing Systems (such as Co-production, Inter-action, Feed-back).

In such a perspective, we can now consider the solutions to the “Two-body Problem”, to the “Three-body Problem”, and to the more general “N-body Problem”, respectively, in order to apply the latter solution to the case of Protein Folding.

## 3 THE TWO-BODY PROBLEM

The new concept of derivative appeared as rather surprising from the very beginning. In fact, although originating from the description of self-organizing systems, it seemed also valid when describing non-living systems, such as those analyzed in Celestial Mechanics. Let us think of, for example, Mercury’s Precessions, the Three-body Problem, etc..

The initial idea of adopting IDC, to reconsider such problems in a new light, originated from the subsisting difference between the derivatives of the exponential function  $e^{\alpha(t)}$  obtained on the basis of the two distinct concepts of derivative (see Table 1). In this respect it is worth noting that the assumption of the exponential function as a reference function does not represent a limitation, because any function  $f(t)$  can always be structured in the form

$$f(t) = e^{\ln f(t)} = e^{\alpha(t)} \quad (3)$$

Table 1: Comparison between traditional and incipient derivatives for the exponential function  $e^{\alpha(t)}$ , where the traditional derivative of order  $n$  is expressed by Faà di Bruno's formula (Oldham & Spanier, 1974, p. 37).

$\frac{de^{\alpha(t)}}{dt} = \dot{\alpha}(t) \cdot e^{\alpha(t)}$	$\frac{\tilde{d}e^{\alpha(t)}}{\tilde{d}t} = \overset{\circ}{\alpha}(t) \cdot e^{\alpha(t)}$
$\frac{d^2e^{\alpha(t)}}{dt^2} = [\dot{\alpha}(t)]^2 \cdot e^{\alpha(t)} + \ddot{\alpha}(t) \cdot e^{\alpha(t)}$	$\frac{\tilde{d}^2e^{\alpha(t)}}{\tilde{d}t^2} = [\overset{\circ}{\alpha}(t)]^2 \cdot e^{\alpha(t)}$
$\frac{d^n e^{\alpha(t)}}{dt^n} = e^{\alpha(t)} \cdot \sum \frac{n!}{k_1! k_2! \dots k_n!} \cdot \left(\frac{\dot{\alpha}}{1!}\right)^{k_1} \left(\frac{\ddot{\alpha}}{2!}\right)^{k_2} \dots \left(\frac{\alpha^{(n)}}{n!}\right)^{k_n}$	$\frac{\tilde{d}^n e^{\alpha(t)}}{\tilde{d}t^n} = [\overset{\circ}{\alpha}(t)]^n \cdot e^{\alpha(t)}$

Such a choice, in addition, simplifies the exposition of the basic concepts we are going to present.

As Table 1 clearly shows, the traditional derivatives present "additional" terms (from the second order on) with respect to the incipient derivatives. Such a specific "difference" suggested the possibility of re-interpreting, by means of incipient derivatives, the "failure" of Classical Mechanics in foreseeing Mercury's Precessions, without modifying, in any form, the space-time concepts, as vice versa happens in General Relativity (Giannantoni, 2004b).

In fact the "Two-body Problem", as traditionally modeled in Classical Mechanics, is strictly equivalent to solving a second order homogeneous differential equation with variable coefficients (Landau and Lifchitz, 1969, p. 46). At the same time it is also well known that Classical Mechanics underestimates the value of Mercury's Precessions, by foreseeing an angular anomaly of "zero", with respect to  $42.6 \pm 0.9$  sec/cy, obtained by astronomical measurements (ib.). It was precisely this "discrepancy" which led us to think that such an effect could be directly related to the "drift" of the second order traditional derivative with respect to the corresponding second order "incipient" derivative. In fact, we obtained an estimation of the angular anomaly of 42.45 sec/cy, which represents a satisfactory agreement with the most recent available data (Giannantoni, 2004b).

#### 4 THE THREE-BODY PROBLEM

The Three-body Problem was proved to be intrinsically insoluble in Classical Mechanics

(Poincaré, 1899). In fact it is described by an 18th-order system of ordinary differential equations which, however, admits only 2 first order closed form integrals (energy and areas). The concept of "integral", in this case, is not understood according to the traditional sense of "solution", but as a "function of solutions" (ib., p. 8) structured in the form

$$F_i[x_1(t), x_2(t), \dots, x_n(t)] = \cos t \quad (4)$$

where  $x_1(t), x_2(t), \dots, x_n(t)$  represent the generic unknown variables of the considered problem. (ib., vol. 1, p. 253).

Vice versa, when faced in terms of incipient derivatives, the problem becomes perfectly solvable, in the sense that: i) there exists at least one solution in a closed form, as explicitly desired by Poincaré (ib.); ii) such a solution, in addition, can be obtained (always in a closed form) at there different hierarchical levels of Ordinality, according to the initial model adopted (Giannantoni 2007b, pp. 49-60): a) as System made up of three distinct bodies; b) as System made up of three "binary-duet" sub-systems, c) as one sole "ternary" System made up of three "binary-duet" sub-systems (see also Appendix).

The fact that the "Three-body Problem", even in its most general form, admits at least one solution in a closed form when reformulated in IDC, is substantially due to the intrinsic and specific properties of the incipient derivatives (see Appendix). In fact such a solution can be obtained on the basis of the following: i) the Fundamental Theorem of the Solving Kernel (Giannantoni, 1995), which gives the general solution of any linear differential equation with variable coefficients in

terms of the sole Solving Kernel; ii) such a solution, in particular, is already structured in a closed form (according to Poincaré's definition) and can directly be transposed to the case of incipient derivatives (Giannantoni 2007a, ch. 5); iii) in addition, since the Solving Kernel is generally a function of function, such a transposition can be directly obtained by means of Faà di Bruno's formula (ib., ch. 3); iv) this in fact, being in turn structured in a closed form, can directly be transposed to the derivatives of functions of function when the latter are expressed in incipient terms (the only difference is that, in such a case, there are no longer "partitions" and, consequently, related "sums"); v) finally, any traditional non-linear differential equation in TDC can always be transformed into a linear Ordinal differential equation in IDC, with the same methodology as already shown, for example, with reference to Riccati's Equation (ib. ch. 2).

On the other hand, such a general procedure, already adopted in other papers and books (e.g., Giannantoni, 2004a,b, 2006a), is the same which enabled us to sustain the general validity of a Differential Calculus (namely IDC), which contemporaneously operates in terms of Ordinality and cardinality (Giannantoni 2007a, ch. 3).

These solutions, however, are still affected by another form of "drift", related to the supposed independence of the space variables (x,y,z) from each other. A hypothesis which, in reality, is merely an aprioristic assumption about the geometrical nature of the proper Space of the System.

If, vice versa, the proper Space of the System is considered as being essentially "unum", that is to say the three coordinates (x,y,z) are so strictly related to each other so as to form one sole thing of Ordinal nature (ib., ch. 6), the problem admits an extremely elegant solution in explicit terms and in an Ordinal exponential form (ib.).

In such a case, the cardinal structure of the System is nothing but the formal reflex of its Ordinal nature, and it can be obtained through an adherent reduction process (ib.).

## 5 THE N-BODY PROBLEM

The results obtained in the case of the Three-body Problem can easily be generalized to the "N-body Problem" (Giannantoni, 2008b, ch. 22), so as to get an explicit solution in an Ordinal exponential form (ib.). This solution is not affected by any form of "drift", either due to the "step by step" derivation or to the supposed reciprocal independence of

coordinates, because the System analyzed is always referred to its proper Space of generative nature.

On the other hand, such an extension can easily be understood on the basis of what has been previously said: any non-linear differential equation, written in terms of incipient derivatives, can always be transformed into a linear differential equation (Giannantoni, 2007a, ch. 2).

This enables us to assert that the simulation of Protein Folding, even in the case of a macroscopic protein, such as dystrophin (made up of about 100,000 atoms), can be obtained in a few minutes, when run on the next generation computers (1 Petaflop).

## 6 CONCLUSIONS

The solution to the "Three-body Problem", thought of as being a self-organizing system, and thus modeled in the light of the Maximum Ordinality Principle, after having been successfully extended to the case of "N-body Problem", enables us to assert that any Protein Folding can be modeled as a "tractable" problem. This can be solved by means of appropriate computer code (in progress), to firstly analyze biological systems made up of a limited number of atoms (e.g. sugars and their monochirality), before modeling the smallest proteins (about 2.000 atoms).

The computer time strictly required for its solution (some minutes) evidently refers to the sole availability of the three-dimensional space configuration of the considered protein, given by an appropriate set of data in the computer memory. The subsequent analysis of the various parts of the folded protein, however, could require much longer times. In all cases, the analysis will always result as being feasible and practicable.

What has been previously said about Protein Folding can clearly be applied to Molecular Docking, as well as to computer-aided Drug Design.

In this respect we have also analyzed the possibility of adopting the same methodology when analyzing the so-called "Phase 0", recently defined by US Food and Drug Administration (Shivaani K. et al. 2009).

Clearly it is worth pointing out that the mathematical procedure [code] here proposed should not be considered as being reducible to a mere mathematical "tool", that is as simply being able to solve the above-mentioned problems in a more efficient way. This is because it represents a radically new methodology, precisely because it is



based on IDC. This new differential calculus, in fact, "translates" into an adherent formal language a gnoseological approach which is completely different from the traditional one. This difference resides on the three new basic presuppositions: Generative Causality, Adherent Logic, Ordinal Relationships (see also Appendix).

This an entirely different approach also enabled us to recognize the reason for the mono-chirality of proteins (Giannantoni, 2007a., ch. 18). That very aspect which, really surprisingly, is ever present, even in non-living Systems. For example, in the motion of the planets in the Solar System. Albeit mono-chirality is characterized in this case by some "genetic" properties which, by keeping "memory" of the generative process of the System, always reveal the different nature of mono-chirality with respect to biological systems (such as proteins, for instance) (ib.).

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## APPENDIX

The analysis of Generative Processes under dynamic conditions suggests the introduction of a new concept of "derivative". This is because the same adoption of the traditional derivative (d/dt) is nothing but the formal reflex of three fundamental pre-assumptions when describing physical-biological-social systems: i) efficient causality; ii) necessary logic; iii) functional relationships.

It is then evident that such an aprioristic perspective excludes, from its basic foundation, the possibility that any process output might ever show anything "extra", with respect to its corresponding input, as a consequence of the intrinsic (supposedly) necessary, efficient and functional dynamics of the system analyzed.

Consequently, such a theoretical approach will never see any "output excess", exactly because it has

already excluded from the very beginning (but only aprioristically) that there might be “any”. In this sense it is possible to say that such an approach describes all the phenomena as they were mere “mechanisms”.

Generative Processes, on the contrary, suggest we think of a different form of “causality”, precisely because their outputs always show something in “excess” with respect to their inputs. This “causality” may be termed as “generative” causality or “spring” causality or whatsoever. In all cases the basic concept is rather clear. In fact, any term adopted is simply finalized at indicating that it is worth supposing a form of “causality” which is capable of giving rise to something “extra” with respect to what it is usually foreseen (and expected) by the traditional approach.

The same happens for Logic. In fact, a different Logic is correspondently needed in order to contemplate the possibility of coming to conclusions much richer than their corresponding premises. This new form of Logic, in turn, could correspondently be termed as “adherent” Logic, because its conclusions are always faithfully conform to the premises. The conclusions, however, could even be well-beyond what is strictly foreseen by the same premises when interpreted in strictly necessary terms.

As an adherent consequence of both previous concepts, the relationships between phenomena cannot be reduced to mere “functional” relationships between the corresponding cardinal quantities. In fact, they always “vehicle” something else, which leads us to term those relationships as “Ordinal” relationships. The term “Ordinal”, which might appear as being simply adopted only to make a difference with respect to its corresponding “cardinal” concept, has in reality a much more profound meaning (as shown later on).

At this stage we can clearly assert that the new concept of derivative is nothing but the adherent “translation”, in formal terms, of the three newgnoseological concepts: Generative Causality, Adherent Logic, Ordinal Relationships.

Such a new derivative was termed as “incipient” (or prior derivative) because it describes the processes in their generating activity or, preferably, because it focuses on their pertinent outputs in their specific act of being born. Its mathematical definition is substantially based on the reverse priority of the order of the three elements that constitute the traditional definition:

$$\lim_{\Delta t \rightarrow 0} \frac{\Delta}{\Delta t} f(t) \tag{5}$$

that is: i) the concept of function (which is assumed to be a primary concept); ii) the incremental ratio (of the supposedly known function); iii) the operation of limit (referred to the result of the previous two steps). It is thus defined as follows (for further details see also (Giannantoni, 2001a, 2002)):

$$\frac{\tilde{d}^q}{\tilde{d}t^q} f(t) = \tilde{Lim}_{\tilde{\Delta}t:0 \rightarrow 0^+} \circ \left( \frac{\tilde{\delta}-1}{\tilde{\Delta}t} \right)^q \circ f(t) \tag{6}$$

where: i) the symbol  $\tilde{Lim}$  now represents a sort of “window” or “threshold” (= Limen in Latin), from which we observe and describe the considered

phenomenon, whereas  $\tilde{\Delta}t:0 \rightarrow 0^+$  indicates not only the initial time of our registration, but also the proper “origin” (in its etymological sense) of something new which is being born; ii) the

“operator”  $\tilde{\delta}$  registers the variation of the property  $f(t)$  analyzed, not only in terms of quantity, but also, and especially, in terms of Quality (as indicated by the symbol “tilde” specifically adopted); iii) thus

the ratio  $\left( \frac{\tilde{\delta}-1}{\tilde{\Delta}t} \right)$  indicates not only a quantitative

variation in time, but both the variation in Quality and quantity. That is, the Generativity of the considered process or, in other terms, the output “excess” (per unit time) characterized by both its Ordinality and its related cardinality; iv) the sequence of symbols in Eq. (6) is consequently interpreted according to a direct priority (from left to right); v) the sequence is also interpreted as a generative inter-action (represented by the symbol “o”) between the three considered concepts; vi) the definition is valid for any fractional number  $q$ . This enables us to represent the three basic processes (Co-production, Inter-action, Feed-back) in terms of fractional derivatives of order  $1/2$ ,  $2$ , and  $\{2/2\}$  respectively. In such a case the order of derivation is termed as Ordinality, because the corresponding resulting “functions” (“binary”, “duet”, and “binary-duet” functions, respectively) are structured in such a way as to show an “excess” of Information, which is never ever reducible to its sole phenomenological

premises or to our traditional mental categories (Giannantoni, 2004b).

On the basis of such a definition, by always referring to a generic function structured in the exponential form  $e^{\alpha(t)}$  (for the same reason previously specified), the incipient derivative of order  $n$  is given by

$$\left(\frac{\overset{\sim}{d}}{\overset{\sim}{dt}}\right)^n e^{\alpha(t)} = [\overset{\circ}{\alpha}(t)]^n \cdot e^{\alpha(t)} \quad (7)$$

where  $\overset{\circ}{\alpha}(t)$  represents the first order incipient derivative of the function  $\alpha(t)$ . The symbol of a little circle adopted to denote the incipient derivative was evidently chosen in analogy to classical Newton's "dot" notation, which usually indicates a first-order derivative.

The different symbology is here justified by the fact that the former should now remind us the conceptual difference between the incipient derivative and the traditional one.

In fact, even if  $\overset{\circ}{\alpha}(t)$  and  $\dot{\alpha}(t)$  coincide from a pure cardinal point of view, they are, on the contrary, radically different from a Generative point of view. The former in fact represents the specific exit of a Generative Process, whereas the latter is always understood as the result of a necessary process (thought of as being a "mechanism" or a set of "mechanisms").

Such a quantitative coincidence, however, is strictly valid only for  $n = 1$ . The right hand side of Eq. (7), in fact, reveals an extremely important property: a sort of "persistence of form", which is even more marked when the derivative is of fractional order ( $m/n$ ). This is precisely because it represents an "adherent" consequence of a Generative Process, characterized by specific generation modalities. In other words, any "generating process" (modeled by the left hand side of Eq. (7)) gives origin to an output which corresponds to a multiple structure functions (multiple "binary" functions or multiple "duet" functions (or both)), characterized by the Ordinality ( $m/n$ ) and described by the right hand side of Eq. (7). (Giannantoni, 2006, 2007b). These functions are similar to harmonic evolutions always in "resonance" (as in a "musical chord") with the original function and at the same time with each

other, and they reach their maximum harmony in the case of a perfect Ordinal Feed-back  $\{n/n\}$ . (ib.)

Such a more general modeling capacity of incipient derivatives, associated with the aforementioned property that any Ordinal dynamic model always presents a solution (at least) in a closed form (Giannantoni 2007a, ch. 5), confers to the Incipient Differential Calculus much wider potentialities with respect to the Traditional Differential Calculus, both of integer and fractional order (ib.). This is also confirmed by the fact that such a new mathematical approach not only led us to the solution of the famous "Three-body Problem" (ib.), but also paves the way to the solution to the well-known "Three-good Problem" which, on the other hand, remains still unsolved in Neo-Classical Economics.