BIO-INFORMATICS IN THE LIGHT OF THE MAXIMUM ORDINALITY PRINCIPLE

The Case of Duchenne Muscular Dystrophy

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Abstract: In a previous paper (presented at the Third International Conference on Bioinformatics) we have shown that Protein Folding, although considered as being an "intractable" problem that would require thousands of years to be solved, in reality can be solved in less than 10 minutes when modeled in terms of Incipient Differential Calculus (IDC). Such an evaluation was specifically made with reference to Dystrophin, precisely because, being made up of about 100,000 atoms, it represents the largest protein in a human being. Consequently it can be considered as being the most significant ostensive example in the context of such Informatics problems. The present paper aims to show that the folding of Dystrophin can also be run on a simple PC in less than two hours, as a consequence of very profound "symmetry" properties of the Ordinal Matrices that characterize the mathematical model adopted. The same happens in the case of dynamic interactions, such as Molecular Docking and computer-aided Drug Design, which can be obtained in absolutely comparable computation time. This is also why, by keeping the original reference to Dystrophin, we assumed Duchenne Muscular Dystrophy as the pertinent corresponding example. The paper will also point out that such advantages are strictly referable to a different gnoseological (and mathematical) approach based on the Maximum Ordinality Principle, which can be considered as being the most advanced Ordinal Self-organization Principle for living (and also non-living) Systems.

1 INTRODUCTION

The paper presents some Informatics advances with respect to the results shown at the Third International Conference on Bioinformatics (Giannantoni 2010b).

On that occasion we dealt with the well-known Problem of Protein Folding, which is usually considered as being one of the most important "intractable" problems. This is because, although the problem is 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.

In this respect we have shown that, by introducing a new concept of derivative (the "incipient" derivative) (ib.), the Maximum Emergy Power Principle (Odum 1994a,b,c) can be reformulated in a more general form, by replacing both Emergy and Transformity by the concept of Ordinality. The principle can be thus renamed as the Maximum Ordinality Principle (Giannantoni 2010a). Its corresponding enunciation then becomes: "Every System tends to Maximize its own Ordinality, including that of the surrounding habitat". In formal terms:

$$(\tilde{d}/\tilde{d}t)^{(\tilde{m}/\tilde{n})}\{\tilde{r}\} = 0 \qquad (\tilde{m}/\tilde{n}) \rightarrow Max \tag{1}$$

where: $(\tilde{m}/\tilde{n})$ is the Ordinality of the System, which represents the Structural Organization of the same in terms of Co-Productions, Inter-Actions, Feed-Backs (see also Appendix), while

$\{\tilde{r}\}$ = the proper Ordinal Space of the System.

At this stage, by modeling Protein Folding as a Self-organizing System which evolves in adherence to the Maximum Ordinality Principle, the problem becomes soluble in explicit terms. This enabled us to

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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).

A fortiori, any Protein Folding becomes a "tractable" problem, with a corresponding solution obtainable in even much lower computation time. This led us to think of developing a computer code, first finalized to analyze biological systems made up of a limited number of atoms (e.g. sugars), before modeling the smallest proteins (about 2.000 atoms).

In reality, during the development of the code, we discovered some additional properties of the mathematical model adopted, which enabled us to further improve the solution in terms of Informatics.

2 INFORMATICS ADVANCES

As just anticipated, the improvements here considered are directly related to some formal properties which are intrinsic to the mathematical model. Such mathematical properties (that will be dealt with in the next section) "emerged" more clearly during the development of the code and led us to recognize the possibility of some decisive advantages with respect to the previous stage presented in (Giannantoni 2010b). Namely: i) *a reduced number of computations*; ii) a *reduced need* of a high *computation power*; iii) a *reduced incidence* of *special numerical methods* to be adopted.

In order to adequately point out the relevance of the improvements obtained, it is worth recalling the present state of High Performance Computing (HPC) and its foreseeable perspectives.

The most powerful computers at present available (IBM, June 2010) have a computation power of about 1 Petaflop. Their power supply, however, is of about 500 MW. This value represents a sort of a "threshold", which seems to prevent further developments, at least in terms of the same technology. On the other hand, even in the case of a very rapid change of technology, an increase of the corresponding power of 10^6 Flops would require (according to Moore's Law) not less than 30 years.

In such a general context, the afore-mentioned advantages enable us to largely overcome the same improvements pertaining to the previous solution. This in fact, although obtainable in a few minutes, always had to be run on very advanced computers, characterized by a computation power of at least 1 Petaflof. Such an aspect would certainly limit the application (and the diffusion) of the new methodology to special cases only, as a consequence of the very high costs associated to the use of such powerful computers.

Vice versa, the possibility of obtaining the same solution by means of less powerful computers should increase the diffusion of the methodology proposed and the number of problems which can adequately be solved.

3 ORDINAL PROPERTIES OF THE MATHEMATICAL MODEL

Let us then consider the intrinsic Ordinal properties of the Model which facilitate the research for a solution, in faithful adherence to the Maximum Ordinality Principle.

These properties are related to the fact that, when a Self-organizing System, which persistently tends toward the Maximum Ordinality conditions, effectively reaches such very special conditions, it presents itself as being self-structured in a radically different way with respect to its initial Ordinality. This is because the latter has evolved according to the following Trans-formation

$$(\tilde{m}/\tilde{n}) \rightarrow \{\{\tilde{2}/\tilde{2}\} \uparrow \{\tilde{2} \uparrow\}\} \uparrow \tilde{N} \qquad (2)$$

where: $\{\tilde{2}/\tilde{2}\}$ represents a "binary-duet" coupling (see Appendix); the Ordinal power $\{\tilde{2} \uparrow\}$ indicates the "perfect specularity" of the previous "binary-duet" structure; while $\uparrow \tilde{N}$ indicates the Ordinal Over-structure of the $\tilde{N}$ elements of the System considered as a Whole (this is the reason for the "tilde" notation).

Under such conditions, the solution to Eq. (1) assumes the form of an exponential Ordinal Matrix

$$\{\tilde{r}\} = e^{\begin{Bmatrix} \tilde{\alpha}_{11}(t) & \tilde{\alpha}_{12}(t) & \dots & \tilde{\alpha}_{1N}(t) \\ \tilde{\alpha}_{21}(t) & \tilde{\alpha}_{22}(t) & \dots & \tilde{\alpha}_{2N}(t) \\ \dots & \dots & \dots & \dots \\ \tilde{\alpha}_{N1}(t) & \tilde{\alpha}_{N2}(t) & \dots & \tilde{\alpha}_{NN}(t) \end{Bmatrix}} \qquad (3)$$

in which any element $\tilde{\alpha}_{ij}$ is characterized by the Ordinality $\{\tilde{2}/\tilde{2}\} \uparrow \{\tilde{2} \uparrow\}$. Ordinal Matrix (3) in fact, as already shown in (Giannantoni 2010b), reflects the fact that the relationships between the different parts of the System cannot be reduced to

mere "functional" relationships between the corresponding cardinal quantities. This is because such quantities always "vehicle" something else, which leads us to term those relationships as "Ordinal" relationships. The term "Ordinal" would thus explicitly remind us that each part of the System is related to the others essentially because, prior to any other aspect, it is related to the Whole or, even better, it is "ordered" to the Whole. This is also the basic reason why the most important terms, when understood in such an Ordinal sense, are usually *capitalized* to expressly point out such a fundamental concept.

Given these conditions, each element of the Ordinal Matrix can be interpreted as being Inter-Acting (in Ordinal terms) with all the other elements of the System. This leads to a first simplification, because in this case the elements of the main diagonal result as being equal to zero. In addition, the afore-mentioned *perfect specularity* reveals itself as being a property which also characterizes the Ordinal Matrix as a Whole. This in turn suggests we give an equivalent representation of the System by choosing, as a preferential reference perspective, any of the N elements of the Ordinal Matrix.

Such a preferential choice introduces a further simplification, due to the fact that any preferential description adopted is "perfectly specular" to any other perspective specifically associated to each one of the remaining $N-1$ elements of the System. This evidently reduces the description to $(N-1)(N-1)/2$ distinct elements, which are coupled between them in the form of "binary-duet" structures.

However, it is also possible to show that all these distinct basic elements are so strictly related to each other (in Ordinal terms) that the description can equivalently be given by means of one sole element (assumed as a preferential reference perspective) and only $(N-1)$ correlating factors λ_i.

Clearly, all these properties are exclusively related to the concept of Ordinal Matrix. These intrinsic properties, in fact, express a much more profound concept of "symmetry" (with respect to the traditional one), which can more properly be termed as "specularity". That very aspect which offers such relevant advantages when developing a computer code based on an Ordinal Model.

More specifically, by considering the Folding of Dystrophin, the above-mentioned properties allow us to reduce the corresponding computation power of about 10^6 Flops. This means that the same Ordinal Model can also be run in less than 2 hours on a common PC, usually characterized by a computation power of about 1 Gigaflop (such as, for instance, a traditional Pentium IV processor).

4 BIO-INFORMATICS IN THE LIGHT OF THE M. O. PRINCIPLE

Mathematical Models and Ordinal Methods of solution illustrated with reference to Protein Folding are also applicable to the majority of Biological Problems usually dealt with through Informatics Methods.

Protein Folding, in fact, is only an ostensive example. In such a context the Dystrophin Folding, in addition, represents the most significant case, precisely because Dystrophin is the largest protein in a human body.

The same Ordinal Methods can also be applied to the research for the best therapy in the case of a Protein mis-Folding. This can be obtained by considering the dynamic Ordinal Inter-Action between the considered protein and any given chemical compound.

As an example, the exon skipping method, at present adopted in Duchenne Muscular Dystrophy (Aartsma-Rus et al. 2006, Wilton 2007) could surely be improved by selecting the most appropriate AONs (Antisense Oligo-Nucleotides). Their potential Ordinal Inter-Actions with the mis-folded Dystrophin, in fact, could be analyzed in advance, by modeling their potential Inter-Actions on the basis of an appropriate Ordinal Model. This would lead to a significant acceleration in such a research, by also saving time and costs associated to a reduced number of experimental tests (in vitro and in vivo).

The Ordinal Methodology here proposed could also become even more effective when finalized to Drug Design. That is, when thought of as a supporting method in the research for new compounds, precisely because exon skipping method cannot be considered, at present, as being the definitive solution to DMD (ib.).

This is even truer when considering that, as a consequence of the reduced computation power need, such a fundamental research could be diffused to all those research laboratories involved in the field and, in this way, increasing the probability of a more rapid success.

This latter aspect can be considered as being the fundamental advantage of the present Methodology with respect to that presented in (Giannantoni

2010b). In that case, in fact, the Methodology still required very high computation powers. Consequently, in that preliminary version it could only be adopted by very important Research Groups and/or big Pharmaceutical Companies.

From a more general point of view, the main aim of this paper is thus to show that, in the light of the Maximum Ordinality Principle, it is possible to realize Ordinal Models of several biological Systems, with very significantly related Informatics advantages.

In fact the adoption of the Maximum *Ordinality* Principle as reference criterion leads to minimize all the associated *cardinalities*, in all their various forms: i) a reduced incidence of computation, because the "sequence" of traditional "functional operations" (e.g. successive derivatives) is replaced by "co-instantaneous" derivatives (Giannantoni 2010b); ii) a reduction of computation power, due to always explicit solutions; iii) a substantial absence of sophisticated numerical methods for getting a solution; iv) with the additional advantage of eliminating the correlative solution "drifts" (ib.).

The relevance of these advantages could also be pointed out by considering that the Clay Mathematics Institute announced in the year 2000 that they would pay a US$ 1,000,000 prize for the first person to prove a solution to the famous P vs NP problem.

In this respect, the solution to Protein Folding previously shown seems to indicate that there are no NP problems, in any case. Obviously, this is true only when the considered Processes are analyzed in adherence to the Maximum Ordinality Principle, and consequently modeled in terms of IDC. Such an Ordinal Approach in fact does not limit its validity exclusively to the case of Protein Folding but, as already said, is also applicable to Molecular Docking and Drug Design. This is precisely because the ever-present specularity of the pertinent Ordinal Matrices always leads to solutions which can be run in absolutely comparable computation time.

However, beside the afore-mentioned advantages, it is worth emphasizing that Methods of solution based on IDC operate in terms of Ordinality, whose various forms are always represented through associated cardinalities, which are consequently always understood as "cipher-values".

Such an extremely important aspect will be gone into more in depth in the next section.

5 CONCLUSIONS

The adoption of the Maximum Ordinality Principle as reference criterion in modeling "intractable" problems in Biology (e.g. Protein Folding) led us to a preliminary result concerning their solubility in explicit terms, with a consequential significant reduction of the computation time (from thousand of years to some minutes), always evaluated, in both cases, with specific reference to the most updated computers.

Afterwards, a much deeper analysis of the emergent properties of the Ordinal Model adopted led us to recognize some profound forms of "symmetry" (thus termed as "specularity"). This enabled us to further improve the Informatics methods of solution, especially because of the extremely reduced influence of the cardinal values to be calculated. This led to: i) a reduced number of computations required to obtain the solution; ii) much lower computation powers; iii) a reduced need of electrical power supply, iv) without mentioning the higher precision achieved, because IDC always adopts "co-instantaneous" derivatives, which eliminate the "drift" associated to a "step by step" derivation, which characterizes TDC.

The generality of the approach based on the Maximum Ordinality Principle (and associated IDC) also enables us to assert that the achieved results are not limited to the specific case analyzed, but can easily be extended to other aspects, such as, for instance, Molecular Docking and Drug Design. In actual fact the results previously shown indicate that the dynamic evolutions of the above-mentioned Processes can be described in a similar way. They can consequently be run in comparable computation time and, above all, on computers of much lower computation power (1 Gigaflop).

This clearly means that, in the near future, any researcher would be able to analyze the dynamic behavior of any biological Process, by means of his/her own personal computer, simply sitting at his/her own desk. This is because the optimization of any Process could then be obtained by means of successive attempts, each one lasting a few minutes.

However, as already anticipated, all these advantages should not lead to underestimate the unavoidable "training" on behalf of the User, because the computer code operates in terms of both Ordinality and associated cardinality. This means that the code interprets cardinal inputs in terms of "cipher" values and, correspondently, furnishes cardinal outputs that must analogously be interpreted as "cipher" of their corresponding Ordinality. The

outputs of any Ordinal Model, in fact, cannot be understood as mere cardinalities, because this would alter the corresponding proper meaning, by making the solution vanish.

Such a "training" period is the essentially finalized to get familiar with such a "*com-possible*" Ordinal Approach, whose basic characteristics have already been presented in (Giannantoni 2010a,b).

In this respect, it is worth recalling what was already said on that occasion. Any Mathematical Model (and associated code) based on the Maximum Ordinality Principle should not be considered as being reducible to a mere mathematical "tool", that is as simply being able to solve "intractable" problems in a more efficient way. This is because it is the reflex of a radically new methodology, precisely because 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 (ib.).

From an even more general point of view, all the afore-mentioned results are substantially due to the independence of the Maximum Ordinality Principle from the "rigidity" of Classical Thermodynamics. The latter in fact prevents us from getting the correct solutions (Giannantoni 2010a), especially because of the Energy conservation Principle, which represents "a limitation imposed to *freedom* of complex systems" (Poincaré 1952, p. 133) and excludes the "*emergent properties* that arise through the multiple relations existing between individual components of the System" (Van Regenmortel 2001).

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APPENDIX

The basic concepts of IDC and, in particular, the concept of "incipient" derivative, have already been presented in (Giannantoni 2010b). This appendix is then finalized to recall that the three Fundamental Processes introduced by H.T. Odum (1994a,b,c), that is Co-Production, Inter-Action and Feed-Back, when formalized in terms of IDC, and analyzed under Maximum Ordinality conditions, appear as being *one sole* Generative Process.

For the sake of simplicity, we can always refer to Ordinal relationships represented by exponential functions (in the most general form $e^{\alpha(t)}$) because, as is well know, any function $f(t)$ can always be written as $f(t) = e^{\ln f(t)} = e^{\alpha(t)}$ (4) (Giannantoni (ib.)).

Co-Production Process

This Process, schematically graphed in Fig. 1, can formally be represented by means of the "incipient" derivative of order 1/2. This derivative, in fact, gives rise to a "binary" function, that is: an output made up of two distinct entities, which however form *one sole thing*. This is equivalent to say that the two "by-products", precisely because generated by the same *unique* (Generative) Process, keep memory of their common and *indivisible origin*, even if they may have, later on, completely different topological locations in time:

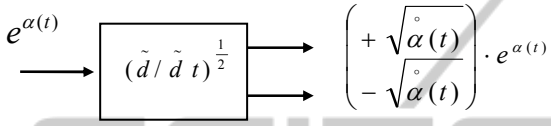

Figure 1: Representation of a Co-Production Process.

The genesis of "binary" functions (from a Co-Production Process) can formally be represented as:

$$(\frac{\tilde{d}}{\tilde{d}\,t})^{\frac{1}{2}} e^{\alpha(t)} = \begin{pmatrix} + \sqrt{\overset{\circ}{\alpha}(t)} \\ - \sqrt{\overset{\circ}{\alpha}(t)} \end{pmatrix} \cdot e^{\alpha(t)} \qquad (5)$$

where $\overset{\circ}{\alpha}(t)$ represents the first order incipient derivative (ib.), while the derivative 1/2 explicitly reminds us that the output generated is "1" sole entity, although made up of "2" parts. In other terms the output, when understood as a whole, is much more than the simple sum of its single parts. Said differently, the *uniqueness* of the Generative Process, recognized as being a specific property of a Co-Production Process, remains as being *in-divisible*, and thus also *ir-reducible* to the component parts. This is why the correspondent Ordinality should better be represented as $1/\tilde{2}$. However, in order to simplify the various formulae, the "tilde" notation indicating the Ordinality can also be omitted (even if always understood).

Inter-Action Process

This Generative Process can easily be illustrated by considering first a single input Process (see Fig. 2). In such a case the Process, modeled through the incipient derivative of Order 2, represents a *reinforcement* of the same input, so giving rise to a new entity which, however, is much more than the simple (cardinal) product of the original input by itself considered, and it can be thus represented as

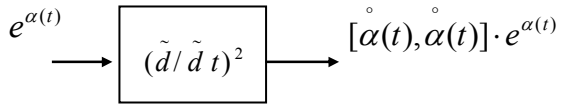

Figure 2: Representation of a "duet" Process.

This Process can be termed as "Generative" precisely because the two contributions not only reinforce each other, but are also unified in a new *one sole entity*. In other terms, they not only increase the cardinality of their joint action, but also generate an exceeding Quality, represented by the *uniqueness* and *irreducibility* of their co-operating activity, because *solidly* and *indissolubly* orientated in the same "direction". This is why the corresponding output can be termed as a "duet" function, while the Process can formally be represented as follows

$$(\tilde{d}/\tilde{d}\,t)^2 e^{\alpha(t)} = [\overset{\circ}{\alpha}(t), \overset{\circ}{\alpha}(t)] \cdot e^{\alpha(t)} \qquad (6)$$

It is then easy to recognize that Eq. (7) can never be represented in terms of TDC because, in this case, we have

$$(d/dt)^2 e^{\alpha(t)} = [\dot{\alpha}(t) + \ddot{\alpha}(t)]^2 \cdot e^{\alpha(t)} \qquad (7)$$

Accordingly, even if the term $\ddot{\alpha}(t)$ (due to the "step by step" derivation) equals zero, the Process is always understood in mere *cardinal* terms. The output reduces in fact to the traditional *scalar* product between the two quantities $\dot{\alpha}(t)$. This is because TDC, as already shown in (Giannantoni 2006, 2008, 2010b), *aprioristically* "filters" any form of Ordinality.

The True Inter-Action Process

The Inter-Action Process, in its proper definition, manifests its true essence when associated to a Co-Production Process. In such a case we can also speak of an Inter-Action Process characterized by a "subjacent" Co-Production Process (with its associated "binary" function). The Process can be then characterized by a derivative of Order 2/2 and thus represented as in Fig. 3

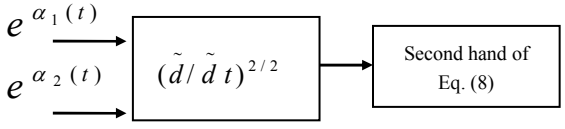

Figure 3: Representation of a true Inter-Action Process.

In such a case the two inputs not only contribute to a reciprocal reinforcement, but are also reciprocally coupled in the form of a "binary" function. The Process thus gives rise to a "duet-binary" function:

$$(\frac{\tilde{d}}{\tilde{d}t})^{\frac{2}{2}}[e^{\alpha_1(t)}e^{\alpha_2(t)}] = \left[\begin{pmatrix} +\sqrt{\overset{\circ}{\alpha}_1(t)} \\ -\sqrt{\overset{\circ}{\alpha}_2(t)} \end{pmatrix}, \begin{pmatrix} +\sqrt{\overset{\circ}{\alpha}_2(t)} \\ -\sqrt{\overset{\circ}{\alpha}_1(t)} \end{pmatrix}\right] \cdot e^{\alpha_1(t)}e^{\alpha_2(t)} \quad (8)$$

In addition, such a coupling is further enhanced by the inter-exchange (and successive coupling) of the specific "genetic" properties of the input Ordinal functions (see $\sqrt{\overset{\circ}{\alpha}_1(t)}$ and $\sqrt{\overset{\circ}{\alpha}_2(t)}$, respectively).

A significant example of this Generative Process can be represented by the generation of a living being. The formal expression (8), in fact, would be a preliminary representation of the re-composition of a *completely new* couple of chromosomes by starting from one chromosome pertaining to the father and the other pertaining to the mother. Evidently, the Process is here extremely simplified. In fact, in the human case (for instance) we should have to consider 23 couples of chromosomes deriving from the father and 23 from the mother, respectively, which give rise to a *completely new* human being, characterize by 46 new couples of chromosomes.

Ordinal Feed-back

This Process can easily be illustrated on the basis of the Inter-Action Process, by assuming that the Ordinal output of the Process contributes, together with the input, to its same genesis (see Fig. 4).

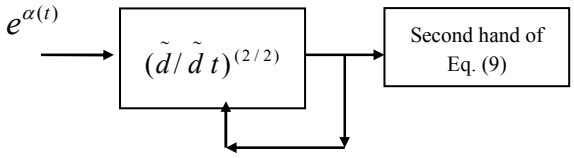

Figure 4: Representation of an Ordinal Feed-Back Process.

In such a case the output represents a reproduction of the input, although at a *higher* Ordinality level. This is why the derivative of Order (2/2) is specifically represented in brackets: to expressly point out such a *harmonic consonance* between the input and the output of the Ordinal Feed-Back Process, which can be represented in formal terms as follows

$$(\tilde{d}/\tilde{d}t)^{(2/2)}e^{\alpha(t)} = \left[\begin{pmatrix} +\sqrt{\overset{\circ}{\alpha}(t)} \\ -\sqrt{\overset{\circ}{\alpha}(t)} \end{pmatrix}, \begin{pmatrix} -\sqrt{\overset{\circ}{\alpha}(t)} \\ +\sqrt{\overset{\circ}{\alpha}(t)} \end{pmatrix}\right] \cdot e^{\alpha(t)} \quad (9)$$

We are now able to formalize the fact that, under Maximum Ordinality conditions, the three above-mentioned Processes constitute *one sole* Process, which can be represented by the Ordinality $\{2/2\}$, because characterized by a *perfect internal specularity*.

Under the same conditions the Ordinal Inter-Action between *two* distinct Processes generates a new entity of Ordinality $\{2/2\}^{\{2/2\}}$ (also represented as {2/2}↑{2↑}), where the bracket notation {2↑} remind us the *perfect internal* "*specularity*" between the two basic Processes.

Such an *internal* "*specularity*" is due to *interior harmony relationships* of the Process, whose number and typology are defined by Transformation (2). These in fact express particular "coupling conditions" between different order fractional derivatives (Giannantoni 2001, 2004). For example:

$$(\tilde{d}/\tilde{d}t)^{(1/2)}f(t) \circ (\tilde{d}/\tilde{d}t)^{(1/2)}f(t) = = f(t) \circ (\tilde{d}/\tilde{d}t)^{(2/2)}f(t) \quad (10)$$

which is always valid for any function $f(t)$, also under steady state conditions.

Additional mathematical details about such harmony conditions can be found in (Giannantoni 2009).