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КВАНТОВАЯ ХИМИЯ, ФИЗИЧЕСКАЯ ХИМИЯ, МОЛЕКУЛЯРНАЯ ДИНАМИКА, ФТП (ФУНКЦИОНАЛЬНАЯ ТЕОРИЯ ПЛОТНОСТИ) И МЕТОД ОГРУБЛЕННОГО ОСРЕДНЕНИЯ, ИСПОЛЬЗУЕМЫЕ В СТРУКТУРНОЙ, КЛЕТОЧНОЙ БИОЛОГИИ, НАУКЕ О ПОЛИМЕРАХ, И ПРИМЕНЕНИЕ ДЛЯ ПЕРЕНОСА ПО МАСШТАБАМ

В.С. Травкин[1], Н.Н. Болотина[1, 2]

[1]Hierarchical Scaled Physics and Technologies (HSPT), Los Angeles, CA, USA
E-mail: travkin@travkin-hspt.com
[2]University of Applied Sciences, Rheinbach, Germany

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В известной нам вселенной не существует веществ с физическим объемным содержанием, которое одновременно не являлось бы гетерогенным. Вопрос заключается в том, на каком масштабе (уровне) вещество становится таковым – на атомном, планетарном, звездном, уровне субчастиц или на каком-либо другом известном масштабе? Нынешняя тенденция состоит в том, что почти все технические дисциплины (науки) утверждают, что описывают физические проблемы на разных масштабах. Среди множества научных методов, используемых в настоящее время, мы рассматриваем лишь следующие техники как учитывающие разные масштабы: 1) квантовая химия; 2) ФТП (функциональная теория плотности); 3) физическая химия; 4) моделирование в молекулярной динамике (МД); 5) метод огрубленного осреднения; 6) многомасштабные и многофазные методы в клеточной биологии. В общем, эти области должны предусматривать несколько пространственных и временных масштабов, физических моделей, которые могут соответствовать друг другу на стыке смежных масштабных пространств. Методика переноса по масштабам была введена несколько лет назад в качестве способа определения средств и процедур для прямого и строгого «преобразования» данных или модели на одном масштабе к данным на соседнем верхнем или нижнем масштабе. Эти связи между масштабами, масштабные преобразования данных происходят в основном не посредством формул, а чаще всего с помощью масштабных управляющих уравнений для данных явлений. В данном обзоре мы учитываем одномасштабные особенности вышеупомянутых теорий, методов и их потенциала для переноса по масштабам на соседних уровнях.

Ключевые слова: биополимеры, органические полимеры, биовещества, клеточная биология, гетерогенный, многомасштабный, полимасштабный, биологическое моделирование, многомасштабное моделирование, огрубленное осреднение, физическая модель, теорема Гаусса-Остроградского, теории осреднения, теорема WSAM, перенос по масштабам.

QUANTUM CHEMISTRY, PHYSICAL CHEMISTRY, MOLECULAR DYNAMICS SIMULATION, DFT (DENSITY FUNCTIONAL THEORY), AND COARSE-GRAINING TECHNIQUES APPLIED IN STRUCTURAL, CELLULAR BIOLOGY, POLYMER SCIENCE AND IMPLICATION FOR SCALEPORTATION

V.S. Travkin[1], N.N. Bolotina[1, 2]

[1]Hierarchical Scaled Physics and Technologies (HSPT), Los Angeles, CA, USA
E-mail: travkin@travkin-hspt.com
[2]University of Applied Sciences, Rheinbach, Germany

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There is no substance of physical volumetric content in our known universe that is not a heterogeneous one. The thing is to determine at which scale it becomes as that, at the atomic, planetary, stellar, sub-particle, or other known scale? The current trend is that almost all technical fields can be characterized by attention and claims to the physically multiscale description of problems. Among many scientific techniques used nowadays we consider the following as scale depending: 1) Quantum Chemistry; 2) Density Functional Theory (DFT); 3) Physical Chemistry; 4) Molecular Dynamics (MD) Simulation; 5) Coarse-Graining

Techniques; 6) Polyscale Polyphase Needs for Cellular Biology. Totally, these fields must provide for the ladder of spatial and temporal scales, physical models that could match one another at the interface between the neighboring scale fields. Scaleportation was introduced some years ago as a definition for the means and procedures of the direct and strict "transformation" of data, model at one scale to the data of the neighboring Upper or Lower Scale. These interscale communications, scale transformations of data are mainly not by formulae, but most often using the scaled governing equations for the phenomena. In this review, we take into consideration one scale features of the above mentioned theories, methods and their potentials for the scaleportation to the neighboring scales.

Keywords: Biopolymer; Organic polymers; Biomedia; Cellular biology; Heterogeneous; Multiscale; Polyscale; Biology modeling; Multiscale modeling; Coarse-Graining; Physical model; Gauss-Ostrogradsky theorem; WSAM theorem; Averaging theories; Scaleportation.

Introduction

1. Some definitions of scaling related to the subject of sub-continuum and continuum physics and modeling of biopolymers, biomedia as scaled media

There is a great need for creation or explanation of biological components, biomedia properties. The current trend is that almost all technical fields can be characterized by attention and claims to the physically multiscale description of problems. Among many scientific techniques used nowadays we consider the following as scale depending or becoming used for scaling studies. We would like to scrutinize the following:

1) Quantum Chemistry;
2) Density Functional Theory (DFT);
3) Physical Chemistry;
4) Molecular Dynamics Simulation;
5) Coarse-Graining Techniques;
6) Polyscale Polyphase Needs for Cellular Biology, Biophysics, etc.

Totally, these fields are thought to be able to provide for the ladder of spatial and temporal scales, physical models that could match one another at the interface between the neighboring scales fields. In reality it is a long way before meeting this goal. At the same time we will be dealing with the problems of multiscale, heterogeneous, nonlocal and nonlinear character that are discussed now in printed literature. We should be concerned about the drawbacks within the techniques themselves along with the proper, correct communication of the different scale fields. Having this in mind, we shall try to maintain a balance between the methods employed at this time while demonstrating what arrays of possibilities can be explored in the future studies.

In each technique mentioned above there has been developed through the periods from their conceptions a number of assumptions and adjustments that are so convenient in use that workers consider them as laws, nevertheless now they must be challenged while making improvements to these techniques; and an upgrade or a change of the physical model will follow.

Most of these improvements can be referred to the proper, stricter treatment of collective, interactive phenomena while taking heterogeneous matters for study. To this kind of phenomena/changes we can relate almost any action or process more complicated than collision of "mathematical" ball onto the "mathematical" wall, or movement and collisions of two "mathematical" balls, meaning particles, atoms or molecules in MD.

In all other nature prescribed cases the physical matters are of scaled or multiscale character by existence. ***There is no substance of physical content in our known universe that is not a heterogeneous one.*** The question is at what scale down the matter is still homogeneous? That answer we don't know yet. And taking the scale an Upper or Lower one, then we will have the Heterogeneous matter anyway. The volume of the earth can be considered as homogeneous at the galaxy mean scale, meanwhile for our human experiences the earth scale is a huge heterogeneous object. Another sample – water which we can obviously consider as a homogeneous matter? While it is not, at an atomic and lower scales. As always, we need taking into account these physical characteristics of matter description that always hold and are promoted for future quality improvements, and sometimes for quality change. For the better one, of course.

Also, there is no action or process that we can name a local one, unless we want to. Otherwise, we have to look into the point and what it means more strictly. Obviously, many actions or processes can be separated from their less important, at the moment or case, surroundings or/and forces. But that is always more or less an artificial choice. Also we don't know yet – what is or is not the collective influence of the Lower Scale forces, because up to now physicists have been connecting the scales by approximations with the help of appropriate coefficients. We want the issues to be open for the inquiries and we ourselves have the right to inquire.

In these notes we won't be concerned with the multiscale, heterogeneous, nonlocal and nonlinear properties related to scales that are smaller, than what is allegedly used here as of the atomic scales group $\sim(10^{-11} \div 10^{-10})m$. We leave it for the future texts. We would look at the works and critically analyze the molecular to $\leftrightarrow$ continuum $(10^{-3} \div 10^{-2})m$ range of scales and techniques used to tackle the intra- and interscale transport tasks of physical nature.

In these ~8 orders of decimal magnitude the mentioned physical theories provide mostly for the approximate or even ad-hoc adjusting mechanisms for the two-scale

Bottom-Up scale communication, and that mode is to be re-entered in the current review from the Bottom-Up and Top-Down interscale transport (communications) point of view. This says that the connections of the scale inherited fields are of great significance/importance. The reviewed here studies often have as results of their task solutions the weakly conjugated to the next on scale (Up or/and Down) initial data values.

The strictest definition for the different scale related fields communication - transformation we suggested in 2004 as the ***Scaleportation***. Scaleportation is the means and procedures of the direct and strict "transformation" of data at one scale to the data of the neighboring Upper or Lower Scale. These interscale communications, scale transformations of data are performed mostly not by formulae, but via using the scaled governing equations for the phenomena. When more than 2 neighboring scales of physical fields are involved, we have introduced the definition of a Scaleleaping (or Leapscaling).

For example, we never think that the temperature of 1 $mm^3 = 10^{-9}$ m^3 and then of the same volume part of 10^{-9} (10^{-9}) m^3 = 10^{-18} m^3 = 1μm^3 or then of the 10^{-9} μm^3 = = 10^{-27} m^3 =1ηm^3 volume part are different, even if that 1mm^3 is at the thermodynamic equilibrium. But they are different. Depending on the type of boundaries and particular phenomena of subscales for scales n_{ss} that means of $10^{-15}[m,Sc] \geq n_{ss}$ $[m,Sc]$ (Sc – Scale spatial). Which is usually out of the picture.

We start with a short outline in which some definitions of a few scales physics and a developed volume of results that is used in the contemporary physics will be introduced. The specific attributes of complex materials, biomedia and tissue engineering are hardly to be achieved without polymer-based constituents. That is of interest in promoting the understanding of multiscale studies. We consider the existing and in use–as well as the new techniques of "multiscaling" that allegedly connect properties of polymers and polymer-based or hold media, biomedia mostly. At the same time, we compare and describe in some detail the true multiscaling mechanisms stemmed from the heterogeneous analogs of Gauss-Ostrogradsky theorem and scaled exact governing equations and solutions for classical homogeneous physical problems in different physical discipline fields that are under stable development path for more than 40 years.

At the moment here we need to confirm that, yes, all interatomic forces can be explained by electromagnetic forces. That means the attractive interactions named as the Van-der-Waal forces (dipole-dipole and London) and hydrogen bonding, as well as Coulomb long range collective forces, in principle can be evaluated (and will be probably in the near future) via the field generating scaled (two scales [Sc]) governing equations that are much more depicting and are of much more accurate description. Thus, and much more difficult in simulation than the use of any kind of potentials, – Lennand-Jones forces, for example.

We won't count in the present review on the aether potential relating actions and forces, it might be suggested in [1] among many others publications. That restriction is obvious at the beginning of polyscale language established in biology via the undeniable examples, problem considered solutions, etc., and controversy of the aether ("active" vacuum) theory now which was, as it is known, quite favorably commented on by Einstein at one time. And that is not common knowledge. We will touch this topic lately in the review when concerning the MD techniques.

We would follow so far in this review the conventional classical set of Maxwell-Heaviside-Lorenz-Lorentz's (MHLL) EM homogeneous governing equations and based on them observed results. We won't discuss here their validity and meaning. Nevertheless, we ought to say that the near future of many phenomena discussed in the reviewed areas is in an uncertainty state, just because of the evidences of a severe trouble of conventional classical and quantum electrodynamics related to basics of mathematical formulations for governing modeling equations.

It might help with the understanding of our approach to the more strict mathematical and physical description of many biological subjects, which mostly are of Heterogeneous, Scaled, and Hierarchical character, made by nature itself when some knowledge of HSP-VAT (Hierarchical Scaled Physics – Volume Averaging Theory) can be obtained. To look through, one might browse our previous analytical reports in other areas where the Heterogeneous, multiphase, scaled media and phenomena are in the core of subject matter, while this data should help in the estimation of the present review – http://www.travkin-hspt.com/fundament/03.htm Why is it Different from Homogeneous and other Theories and Methods of Heterogeneous Media Mechanics/(other Sciences) Description?

http://www.travkin-hspt.com/fundament/04.htm Are there any other Methods and Theories available?

http://www.travkin-hspt.com/fundament/pseudo.htm Pseudo-Averaging (Scaling, Hierarchy), Quasi-Averaging, Ad-hoc Averaging, and other "Averaging" (Scaling, Hierarchy) Type Claims

http://www.travkin-hspt.com/urbp/turbpart/Turbpart.htm Turbulent and Non-Linear Transport in Heterogeneous and Porous Media Including the URL

http://www.travkin-hspt.com/urbp/meteoaver.htm Modeling and Averaging in Meteorology of Heterogeneous Domains - Follow-up the NATO PST.ASI.980064

http://www.travkin-hspt.com/urbp/exper.htm Experiments, Experimental Data Reduction and Analysis; Numerical Experiment (Simulation) Data Mining

http://www.travkin-hspt.com/elastic/whatsupf/whatsup.htm What is in use in Continuum Mechanics of Heterogeneous Media as of Through ~1950 - 2005?

http://www.travkin-hspt.com/elastic/ivorytower/ivorytower.htm Who Are in the Continuum Mechanics

Continuing to Dwell in an Ivory Tower? Who Tries to Re-Invent the Wheel? What Are the Damage and Financial Loss?

http://www.travkin-hspt.com/fundament/scaleport/scaleport.htm Reductionism and/versus Holism in Physics and Biology - are Both Defective Concepts without Scaleportation

http://www.travkin-hspt.com/acoustics/02.htm Linear Acousto-Elasticity in Porous Medium

http://www.travkin-hspt.com/acoustics/litreview.htm More of Acoustics in Heterogeneous Media Current Work Reviews

http://www.travkin-hspt.com/atom/01.htm Solid State Plasma Models

http://www.travkin-hspt.com/nanotech/right.htm Nanotechnologies - General Concept for Pretty Large Amount of Pretty Small Gadgets Embedded Into Something and Consequences for Design and Manufacturing

http://www.travkin-hspt.com/optics/optscattering.htm Scattering Modeling in Optics using One Scale

http://www.travkin-hspt.com/thermph/heatconstruc/heatconstruc.htm Pseudo-Science of Constructal Theory (Hierarchy) in Heat Transfer Modeling

http://www.travkin-hspt.com/fluid/03.htm Classical Problems in Fluid Mechanics.

The same procedures we have been applying for analyzing the situation, trends and tools that are used in Theoretical Biology, Systems Biology, Cellular Biology, Tissue Engineering and in any other field in Biology and Biosciences that need an implementation of Heterogeneous, Scaled, Hierarchical theoretical tools, concepts, physical and mathematical modeling and simulation. We have selected a few of the upper quality and broad on subject and its consequences articles, reports that also have a good conceptual, physical and mathematical basis to discuss under our subject angle.

So far, in almost all contemporary physics fields, but Fluid Mechanics and part of Thermal physics, the tools and math used for Heterogeneous, Scaled, Hierarchical description are of the 30-50 years old, from the particle physics, statistical mechanics and quantum mechanics when the spatial scales used are of $(10^{-5} \div 10^{-15})m$ and less range. All these tools of the one scale, homogeneous physics and math, are just examples [2-6] we have found – with the governing equations that have been derived with the homogeneous Gauss-Ostrogradsky theorem. Which is incorrect.

2. The scales within a biological cell related to specific physical phenomena (processes) in a cell

Approximately (because of the different sizes of cells) we would distinguish and we can take for simplicity three different scales participating differently in the smallest of considered cell functions:

a) a scale of a separate molecule (as amino group, for example) in a macromolecule, protein, or in a solvent, or etc. – ~0.2 [*nm,Sc*]);

b) a scale of a single protein – 1-5 [*nm,Sc*]; which is not "walking" alone, but imbedded into a polyphase solvent, or docked to other protein(s), or is a part of an assembly;

c) and a scale of constitutive protein complexes – ~10-50 [*nm,Sc*].

Afterwards, we would like to deal with the subject of organelles, which can get to the upscale of ~100-200 [*nm,Sc*]. Finally, we understand that all bottom scale phenomena are organized with polyphase, polyphysics processes, phenomena into a concerted, controlled functioning unit – a cell of ~1-5 [*μm,Sc*] scale.

3. The need to connect the scale phenomena, actions and their physical and mathematical models

The review paper [7] tells us a lot with regards to how experimentalists understand the matter of scaled, hierarchical organization of human (and not only human) biomedia, tissue. From the abstract one can read: "It is increasingly clear that the function of tissues is determined by their hierarchical architecture. Understanding of such natural hierarchical nanofibril structures can lead to new design and fabrication concepts for use in tissue engineering. The ability to create hierarchical synthetic nanocomposites ... creates the potential to engineer better tissue construct for repair and...."

That is a good acknowledgement of the situation with hierarchy of tissue morphologies. Reflecting this paper's content – and within our effort to advance the quantitative aspects of Biology and Medicine technologies, we would like to mention again that the only existing nowadays tools for understanding, modeling, simulation and design of hierarchical, heterogeneous structures and materials are grown within the HSP-VAT. No other method exists, but the HSP-VAT, that has more than 40 years of advancement from the commencement with the first publications in 1967 [8, 9] and reasonable modeling value results starting from the 80s of the last century.

The most important answers we can get with the HSP-VAT hierarchical heterogeneous modeling and simulation to the following questions:

How can we present and study polyscale biomedia, biopolymers starting from within the cell organelles or cytosol?

Why does nature do this or that for/with this biomaterial, tissue?

Why do the sizes of these pores or morphology of this scale medium have these characteristics?

What should be the properties of this or that constituent part, a phase in this material?

Can we improve or substitute the design and features of a specific biomaterial?

How do you do better in the interphase between artificial and natural tissues?

What are the extracellular momentum and mass transport (calculated with a reasonable model but not by balance equalities)?

What are the bone tissue strength components? Not as of a homogeneous material which it is not.

What are the intracellular – extracellular exchange transport if it is modeled via the scaled phenomena? Not on a just verbal atomic scale level.

All these and other alike questions can not be answered by experimental only work or by conventional one scale homogeneous physics modeling and simulation.

As authors of [7] mentioned in the paper:

"Understanding of such natural hierarchical nanofibril structures can lead to new design and fabrication concepts for use in tissue engineering. The ability to create hierarchical synthetic nanocomposites using self-assembly … and electrospinning methods creates the potential to engineer better tissue construct for repair and incorporation."

That will remain to be seen. Without the ability to characterize and model the hierarchical structure this is hardly possible to deliver, while patients won't buy the promises of good performance based on only experiments of a short time scale or even going through the long time set up.

It would be appropriate to remind for young readers, that similar to present "multiscaling" campaign happened in the 80-90s of the last century. Then professionals in numbers went into public conferences with claims for a near or almost solved problem of so called "structure-properties" relation. That could not happen, because there was no base for even structure-properties phenomenology. Actually there was, because the VAT had started in 1967, nevertheless, the true scaling VAT techniques, advanced mathematics and solved hierarchical problems appeared only in the 80-90s. With not much of interest from few professionals funded in the US and engaged at that time with HSP-VAT research.

That is why the "fashion" for "structure-properties" developments went away with no results.

Introductory to polyscale description in physics and technologies

Hierarchy of phenomena and morphologies in biological media given as qualitative verbal concept

There is a sufficiently large number of publications where authors declare understanding and even describe with some formulae the overall picture of hierarchical scale dependent phenomena and processes in biology. None of them were able to address the issues of scale dependency with rigor, physical and mathematical rigor. As in the paper [7] the authors sometimes openly speak on the subject of hierarchy and scale dependency in tissue engineering, which to some extent becomes more and more recognized. So far that is in the verbal, qualitative mode within the biotechnologies.

Even the close familiarity with many concepts and presentations in biology media models, tissue modeling that will make a temptation to lay down a theoretical approach, models, which would correctly reflect the heterogeneity and polyscaling nature of biological subjects would bring in the status in the field that can be declared as a long shot unsatisfactory. That is because of the scale description invalidity, while with the homogeneous GO theorem the theory grounds were developed. Many issues even have not been raised in studies yet – no sense to fantasize about the questions that belong to the beyond the horizon picture? The main thing is – What is the connection between the exact interactive communications in properties (mechanical, chemical, biocompatible) for structures of biopolymer composites at various scales?

It was of interest reading in [7] on the fact of acknowledgment of scale interaction and interdependency. Unfortunately, it is done as in most of similar acknowledgements in the way of verbal statements, hindering the means that without that kind of knowledge – researchers will not get closer to their aim as alchemists without the periodic table had no guidance to work with.

A few of the initial concepts and mathematics we depict here, while for most of readers these are not the conventionally known and accepted since the 30s of the last century conventional averaging mathematical definitions. Those are incorrect for heterogeneous scaled media, physical problems. There are serious differences in mathematical techniques and theorems for ground physical and mathematical governing field equations.

Hierarchical Scaled Volume Averaging Theory (HSVAT) introductory concepts and theorems

Further we need a few basic statements from the hierarchical description of heterogeneous media, so far the only mathematically strict one. The basic idea of hierarchical medium description is that the physical phenomena, mathematical presentation of those phenomena, and their models can be very different and in most of situations are different even if phenomena itself are similar or looking as identical, but the scales are different and the lower scale features should be transported to the upper level of description (or Bottom-Up scaleportation) – Fig. 1 is in such a mode that the useful information would be added to the characteristics on the upper level.

The volume average value of one phase in a two phase composite medium $<s_1(x)>$ in the REV and its fluctuations in various directions, its main physical and mathematical needs, definitions are determined [8-18] by at first looking simple formula

$$s_1(\vec{x}) = \langle s_1(\vec{x}) \rangle + \hat{s}_1(\vec{x}), \quad \langle s_1 \rangle = \frac{\Delta\Omega_1}{\Delta\Omega}.$$

Five types of two-phase medium averaging over the REV (Fig. 1) function f are defined by the following averaging operators arranged in the order of seniority [14, 16, 19]

$$\langle f \rangle = \langle f \rangle_1 + \langle f \rangle_2 = \langle s_1 \rangle \tilde{f}_1 + (1 - \langle s_1 \rangle) \tilde{f}_2,$$

where the phase averages are given by

$$\langle f \rangle_1 = \langle s_1 \rangle \frac{1}{\Delta\Omega_1} \int\limits_{\Delta\Omega_1} f(t,\vec{x})\, d\omega = \langle s_1 \rangle \tilde{f}_1;$$

$$\langle f \rangle_2 = \langle s_2 \rangle \frac{1}{\Delta\Omega_2} \int\limits_{\Delta\Omega_2} f(t,\vec{x})\, d\omega = \langle s_2 \rangle \tilde{f}_2,$$

and the internal phase averaged functions are given by

$$\{f\}_1 = \tilde{f}_1 = \frac{1}{\Delta\Omega_1} \int\limits_{\Delta\Omega_1} f(t,\vec{x})\, d\omega;$$

$$\{f\}_2 = \tilde{f}_2 = \frac{1}{\Delta\Omega_2} \int\limits_{\Delta\Omega_2} f(t,\vec{x})\, d\omega,$$

where $\tilde{f}_1$ is an average over the space of phase one $\Delta\Omega_1$ in the REV, $\tilde{f}_2$ is an average over the second phase volume $\Delta\Omega_2 = \Delta\Omega - \Delta\Omega_1$, and $\langle f \rangle$ is an average over the whole REV. There are also important averaging theorems for the averaging of the spatial ∇ operator – heterogeneous analogs of Gauss-Ostrogradsky theorem. Those are plenty already since 70-80s [10, 11, 16-21]. The first few of them needed to average the field equations are the WSAM theorem (after Whitaker-Slattery-Anderson-Marle) and the one is for the intraphase ∇ averaging. The differentiation theorem for the intraphase averaged function reads

$$\{\nabla f\}_1 = \nabla \tilde{f} + \frac{1}{\Delta\Omega_1} \int\limits_{\partial S_w} \hat{f} \vec{ds}_1;$$

$$\hat{f} = f - \tilde{f}, \quad f \forall \Delta\Omega_1,$$

where ∂S_w is the inner surface in the REV, $\vec{ds}_1$ is the second-phase, inward-directed differential area in the REV ($\vec{ds}_1 = \vec{n}_1\, dS$). The WSAM theorem sets the averaged operator ∇ in accordance with

$$\langle \nabla f \rangle_1 = \nabla \langle f \rangle_1 + \frac{1}{\Delta\Omega} \int\limits_{\partial S_{12}} f \vec{ds}_1.$$

Meanwhile, the foundation for averaging made, for example, by Nemat-Nasser and Hori [22] (and many others) is based on conventional homogeneous Gauss-Ostrogradsky theorem (see pp.59-60 in [22]), not on its heterogeneous analogs as the WSAM theorem.

The following averaging theorem has been found for the **rot** operator

$$\langle \nabla \times \mathbf{f} \rangle_1 = \nabla \times \langle \mathbf{f} \rangle_1 + \frac{1}{\Delta\Omega} \int\limits_{\partial S_{12}} \vec{ds}_1 \times \mathbf{f},$$

and as a consequence, the theorem for the intraphase average of ($\nabla \times \mathbf{f}$) is found to be

$$\{\nabla \times \mathbf{f}\}_1 = \nabla \times \{\mathbf{f}\}_1 + \frac{1}{\Delta\Omega_1} \int\limits_{\partial S_{12}} \vec{ds}_1 \times \mathbf{f}.$$

More detail on the non-local VAT procedures and governing equations for different physical problems modeled in homogeneous media by linear mathematical physics equations can be found in many publications [10-13, 17, 18, 20, 21] and many other. Meanwhile, features depicting closure, nonlinear theory, polyphysics applications, polyscale developments, exact solutions, etc. can be found only in works like [14-16, 19, 23-26] and other studies.

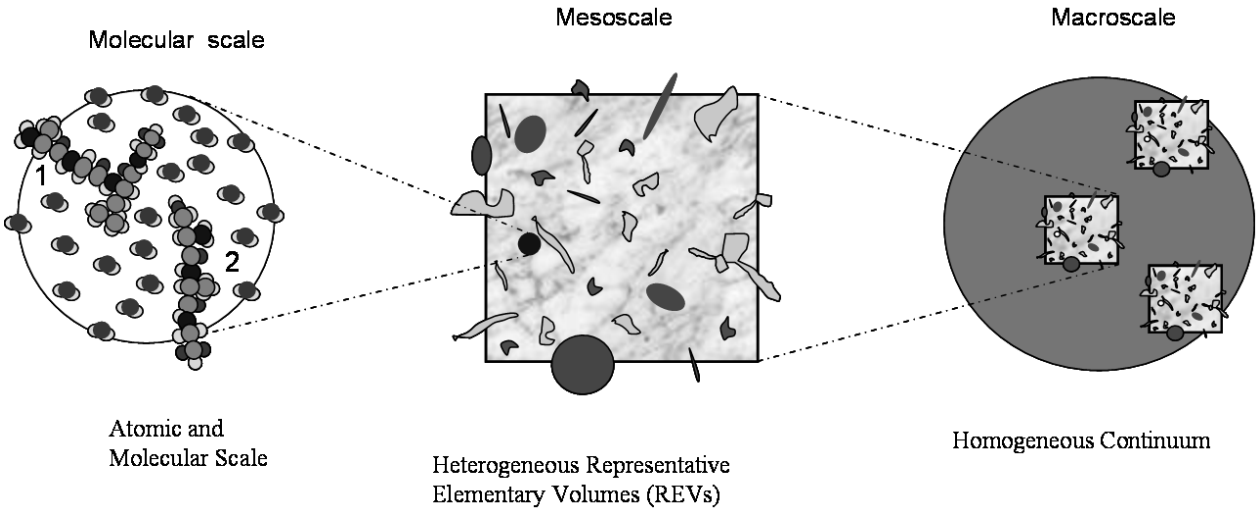

Рис. 1. Упрощенная схема «снизу вверх» (телескопического) последовательного ряда представительных элементарных объемов (ПЭО) в 3 масштабах от молекулярного (один из ПЭО представлен в водном растворе) до масштаба сплошной среды
Fig. 1. Simplified draft of Bottom-Up consecutive series of Representative Elementary Volumes (REVs) at three scales from a molecular one (one of the REVs is in an aqueous solution) to continuum scales

Quantum chemistry scaling

The qualitative notes regarding the intention to include in a scaling research the smallest reasonably performable physical models at sub-atomic size scales of $\sim <(10^{-11} \div 10^{-10})m$ can be short or long ones. The issue is that at present the connections as well as validation of sub-atomic scales physical models of matter are vague, despite that particle physicists would insist on the contrary opinion. Among many arguments that filled-up some books on uncertainties tied with the contemporary physics, while more on the same will be written on down the road, we present only a couple of points.

One is that the Schroedinger equation raised many questions in the past decades and it will be appropriate to mention that what is taught at schools regarding this equation is just a compendium of adjusted through the time agreements. As an example, we can remind readers that this equation can not be used for more or less complicated atoms. Not talking on the multi-atomic modeling and simulation, etc.

Another strong argument not in a favor of sub-atomic involvement into the polyscale modeling and simulation at this time is that the theory of Electromagnetic phenomena (EM) (Maxwell-Heaviside-Lorenz-Lorentz governing equations for EM) as it has been revealed through the last 10-15 years (but what is known to many workers for much longer time, more than a century of closed door debates, citing just N.Tesla and the Longitudinal EM waves topic would be enough) experiences great difficulties laying ground for physics and technologies.

This will be resolved in the near future with more and more theories of electromagnetism, even of scaled nature, that would lay down more stable ground for particle and atomic physics, later hopefully with the added polyscale biomedia modeling and simulation.

Density functional theory (DFT) used for hierarchical description

Again, one might consider the Density Functional Theory (DFT) as the one of “ab initio” tools, while it is just a method created for the more precise local characteristics of some simple atomic structures. Following that the atomic, molecular modeling and simulation can not have complete scaleported characteristics at the larger (Upper) scale. And the DFT technique gives positions of atoms.

At the meantime, as usual, the DFT was created not on the empty space and, of course, it needs for its own performance again some already agreed functions (functionals, approximate, as usual). Which are the assumption and adjustment techniques.

Even so, given the note that the DFT is itself an approximate tool with the attached issues of validity of these or those quantum mechanics statements and understandings, this is not to be applied even for a whole macromolecule simulation. Even for a single one.

That determines the must need for the generalization method which would combine the specific databases raised with the DFT algorithms along with the Upper scale modeling applications.

Physical chemistry scaling techniques

Methods in use general one scale

In the past, multiple methods were used, for example, [27] for a parameterization of a complicated arithmetical empirical function. It was used in the XX century for approximation of empirical interaction energy in physical chemistry, biochemistry. Among the parameters selected were atomic charges, which were used along with the internal (bonding) and interaction (nonbonding) terms of the force field and among the solvent-solvent, solvent-solute, and solute-solute interactions.

We would comment on the works of this kind of the study as following:

These are the remnants of the old mid-XX century techniques with the intention and belief that everything might and can be parameterized. These beliefs are powerful because of the generations’ heritage transmitted to each next generation of students and graduate students because they have been taught as that.

Authors wrote that “Ab initio Hartree-Fock calculations were performed with various versions of Gaussian,…” If these techniques are named as “ab initio”, that means the 50-60s years of the XX century have left a powerful memory in physical chemistry, biochemistry.

Meanwhile, all these molecular physical chemistry techniques are hardly to be communicated to a multiscale modeling of polymer components, biopolymers (Fig. 2, for example) and polyphase polymers matter.

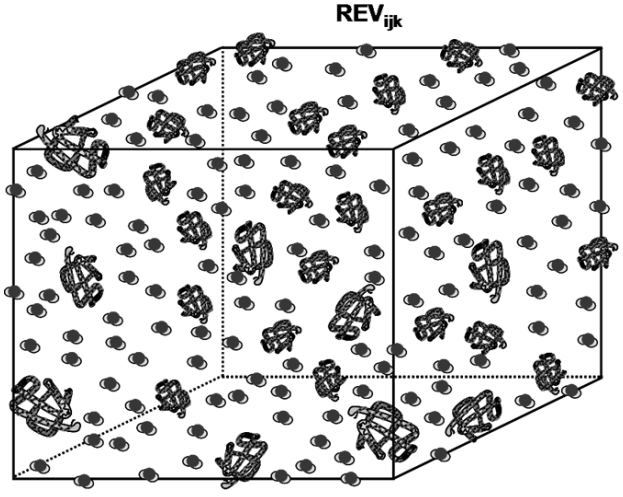

Рис. 2. Трехмерная структура ПЭО (представительных элементарных объемов). На рисунке показана крупнейшая белковая молекула биомономер (миоглобин) в водном растворе; размеры молекул воды не масштабируются
Fig. 2. Three-dimensional structure REV with shown only the largest biomonomer (myoglobin) protein molecules in aqueous solution; water molecules size is not scaled correctly

Further it might be interesting to mention the study [28] where one can find a great variety of modeling techniques that might be questionably related to a polyscale description of polymers and biomedia particularly. The methods were used to support the need for performing the current time molecular modeling via kinetic molecular atomic scale simulation plus dynamic simulation via the Brownian dynamics modeling.

In p.12098 we can read that: "One way to investigate the effects of nonspecific macromolecular interactions is to study the behavior of concentrated protein solutions: the measured translational diffusion coefficients,[3] second virial coefficients,[4] and scattering intensities of protein solutions can all provide important information regarding transient interactions between protein molecules." That means at present time the level of advancement in molecular dynamics is not up to modeling of the atomic scale dynamics with a full collective interaction, while scaleporting that modeling results in the fields up to the microscale continuum mechanics characteristics.

The methodology used admits that some continuum mechanics coefficients must be modeled for the Upper scale (of around 1000 or more than 10000 macromolecules could be considered) as still of a special one phase medium while not of the liquid two-phase medium with special properties of the one phase of macromolecules and another phase of a solvent. Meanwhile, techniques for the atomic -> microscale continuum medium modeling and simulation are developed within the HSP-VAT. Those techniques might not be applied yet to those specific tasks, albeit they are ready for deployment.

In the same page: "…a working molecular model of a protein must meet the following criteria: 1) it must be sufficiently sophisticated that it provides an accurate and predictive description of protein – protein interaction thermodynamics, 2) it must provide an easy route to calculation of intermolecular forces so that it can be incorporated into dynamic simulations, .. " This piece of the text explains to a reader that there is no way to find out the worthwhile "dynamic modeling" that can be useful or used for the next upscale physical model of the same "dynamic class".

And further: "…available computational resources are sufficiently restricted that it is currently infeasible to simulate the dynamics of concentrated protein solutions with all atoms of the solvent treated explicitly; instead, it is necessary to employ a simplified treatment of the solvent." Meanwhile, it is a common practice to have not only an implicit solvent's model, but also the model of a protein itself has the voided volume-features, and thus stimulates the adjustments in the protein kinetic model.

One of the techniques explored is that the interactions between proteins are modeled as a sum of electrostatic and van der Waals/hydrophobic interactions. For this task "a simple combined model of van der Waals and hydrophobic interactions between the carbon and sulfur atoms of neighboring proteins, - a Lennard-Jones potential was used:

$$U(r) = 4\varepsilon_{LJ}\left[\left(\sigma_{LJ}/r\right)^{12} - \left(\sigma_{LJ}/r\right)^{6}\right],$$

where the potential energy, $U(r)$, depends on the distance, r, between atoms, σ_{LJ} is the distance at which $U(r)$ changes from being favorable to unfavorable, and ε_{LJ} is the well depth of the energy minimum." With other combinations of atoms only one type of interaction potential was used assuming that there is no significant net contribution other than those modeled by the electrostatic term

$$U(r) = 4\varepsilon_{LJ}\left[\left(\sigma_{LJ}/r\right)^{12}\right].$$

When atomic interactions "...in which only interactions between hydrophobic atoms are energetically rewarded, was used by us recently to model ligand-receptor interactions.[37]"

One must accept the note that all these formulae and this approach as such are from the rather simplified assumption of a pairwise interaction. If we ourselves recall that all the talks about electrostatic modeling are compromised at all as soon as the electrodynamics of matter is at great dependency of what was simplified by Lorentz from the Maxwell's equations more then a hundred years ago (in 1893), that might raise the interest to the modeling subject to another level of strictness.

We can find that the second virial coefficient B_{22} was calculated via

$$B_{22} = -\frac{2\pi}{M_W^2 \mathrm{N_A}}\int_0^\infty \left(g(r)-1\right)r^2 dr,$$

where $g(r)$ is taken as the radial distribution function, r is the protein-protein distance, and M_W is the molecular weight of the protein, while $\mathrm{N_A}$ is the Avogadro number. This resulting formula is also from the kinetic point-like consideration and hardly can be useful for scaled physics.

We might conclude this analysis with the following notes:

1) The whole area of physical chemistry molecular modeling still preserves the route (the procedures) for only particulate kinetic model of a group of molecules on the lower scale modeling. What is used as for electrostatic interaction of macromolecules (proteins) is the almost hundred years old model of Debye-Hückel for liquid solutions – which is the Poisson-Boltzmann (PB) equation for one phase.

2) We can testify following this thorough study that the whole route of the two-"phase" molecular simulation for the solution of macromolecules within the solvent (water) consists of the theoretical physics algorithms of compromise between theoretical presentation of molecules as point particles with related final formulae for characteristics and powerful (still limited) computing simulation procedures for the macromolecules presented

already as the volumetric physical subject. That inconsistent methodology is not for application that can be in compliance with a scaled physics concept.

"Multiscaling" artificial in homogeneous one-scale physics for theoretical, structural, cellular biology modeling and simulation

We disassemble here the claims on "multiscaling" coming from the conventional one-scale Homogeneous physics studies published on behalf of the structural, cellular biology topics. The issue is that the traditional orthodox one-scale-for-all (OSFA) methodologies for a few years have been employed as the "multiscale" techniques in biological studies. Following the same move as the claims in Nanotechnology applications.

As one of the typical studies with the claims regarding "mutiscaling" used among the methods of research we can comment on a very solid paper [29]. One can read in the abstract: "We report a computational study of membrane bending by BAR domains at four levels of resolution, described by:

1) all-atom molecular dynamics;

2) residue-based coarse-graining (resolving single amino acids and lipid molecules);

3) shape-based coarse-graining (resolving overall protein and membrane shapes);

and

4) a continuum elastic membrane model."

In p. 2806 one can read that: "To overcome the limitations of atomistic MD simulations, we utilize coarse-grained modeling and a multiscale approach at four levels of resolution, which allows us to reach timescales up to several microseconds." Meanwhile, we have to remark that there are scales for the problems with biological media domains as from ~0.2 [*nm,Sc*], for one atom-one residue scale and up to ~10-50 [*nm,Sc*] for the scale of a constitutive protein complex.

In the p. 2807 one can find the figure caption: "FIGURE 2 Arrangements of BAR domains studied. The systems studied by simulations are periodic; the simulation box is highlighted as a solid square, and a few periodic images are shown in dimmed color; boundaries of periodic cells are marked by dotted lines. (A) Non-staggered one-row arrangement. (B) Staggered two-row arrangement."

We would note that this figure and the caption show incorrect simulation of scaling approach and algorithms. It is visibly an adjusting technique. In the same p. 2807 one can read that: "For all three levels, MD simulations ...The fourth level of our description involves a continuum elastic membrane model. The models, at each level, are parameterized based on properties from the higher-resolution models, as well as from experimental data."

Here in each scale method a variety of techniques for simulation is used – while communication between the models and results is done via parameterization "based on properties from the higher-resolution models," and from some experiments it can be seen – that this is adjusting or "coupling" of neighboring scales modeling effort. Meaning, that the data have been brought to some compliance with each other using the adjusting algorithms with specific coefficients, which is a legitimate way to do a scientific investigation – at the same time, it is not at all the Scale Justified Communication. This is not a Scaleportation, a connection of models and their data via interscale strict physical and mathematical modeling. This is not a Multiscaling either; the methodology might be named rather as the "multi-resolution" method to simulate the physical task.

In conclusions to this study it can be said that: 1) The methodology suggested in the work is not touching the subjects of biology itself. This characterized as a "multiscale" study, the modeling methods, as well as the "multiscale" results we would confirm as pseudo-multiscaling techniques, that not using the HSP-VAT methods, and can not develop unified, strictly communicating physical and mathematical polyscale biological models. Do At Least Two Scales, that can show features of Scaleportation. 2) These frivolous algorithms used in computational chemistry, biology, materials science as the "multiscale" ones are in essence the adjusting techniques to make ends meet while using the different scales physics for one physical problem. Starting with the Quantum Chemistry simulation.

Molecular dynamics simulation

What Molecular Dynamics (MD) consists of and its historical and methodological routes

The Molecular Dynamics (MD) approach is based on the two hundred, at least, years of understanding of kinetics and dynamics of shapeless (and with hidden size) cloud of particular matter in classical Theoretical Mechanics. Mostly it was meant to be used for gaseous mixture or even real particular arrays without the second phase interactions. All of that additional known or unknown interaction phenomena have been attributed to take action through the experimental or ad-hoc derived energy potential functions.

It would be appropriate to count and shortly comment in this review on the assumptions or even conjectures that are freely neglected by the computer simulation professionals.

1) We do not need to forget that in MD systems there is an array of N particles of the same spherical shape and size. Well, the shape and size might be frivolously adjusted, that does mean nothing as soon as everything is played via functions of energy potentials.

2) There is vacuum only in between the molecules – that is the false premises. This medium is the "active vacuum", at least consisting of the cosmic relict radiation field – Cosmic Microwave Background (CMB) radiation and more on that. With ~400 photons of it in each [cm^3] and with the influx of those photons as of ~10^{12}[$1/(s \cdot cm^2)$]. That means, there is an additional and powerful "phase" present at this scale.

3) The description of forces, energies, moments does not include the electrodynamics (yes, electrodynamics not only electrostatics) of molecules, macromolecules and of "active" vacuum.

4) For all the schemes in MD the algorithms need to be derived, mostly by fitting, using the interaction potentials as a magic "bullet".

5) Modeling equations are the point-like particle dynamics set of equations – those ideas are from the XVIII century. That is because there were no such things as the field models, field governing equations in the XVIII century. Because these models by MD don't use any field equations – that means there is the simplistic modeling of the two-"phase" at least, molecular ensembles.

6) In this type of modeling, because there are no mechanisms of field interactions within the model's statement, there is a need for the added various (often experimental) energy potentials. And this is quite an adjusting route, allowing anything to exist.

7) The final assessment procedures when characteristics of alike "continuum" are being simulated based on MD solution, the serious drawback hinders the validity and value of these estimations. The matter is that averaging of dynamic characteristics, properties is being calculated with the Gauss-Ostrogradsky theorem (GOT) for heterogeneous media. And that is wrong; the proof for this exists since 1967.

8) One more from the number of other notes regarding the space periodicity with translated unit cell is about interaction potentials using the periodic translated images of the simulation unit cell. For example, see Figs. 3-5, 7 in [4]. The suggested mechanisms and algorithms for translated molecules interactions are incorrect as they are for the space related near- and long range interactions. Many reasons and lengthy comments are presented in our tedious analysis in – http://www.travkin-hspt.com/elastic/ivorytower/ivorytower.htm Who Are in the Continuum Mechanics Continuing to Dwell in an Ivory Tower? Who Tries to Re-Invent the Wheel? What Are the Damage and Financial Loss?

9) It seems that during the last several decades specifically, the MD techniques have transformed into the MD science, so vast are the resources and publication topics concentrating on this theory. Meanwhile, it should be all clear, that all these "quasi"-molecular simulations are done only for the one real goal – to make assessments about scaleportation for characteristics and fields at molecular and continuum mechanics scales.

Bottom-Up theoretical, structural, cellular biology "multiscaling" via MD

This understanding of the MD theory and method is neglected for the approximations that communities of scientific experts rely on in an attempt to deal with the polyscale description of polymeric materials, and biopolymers which are among the highest positions in the priority list. One of these tactics is a complicated multimethod approach set up in [30] for dealing with polyscale mathematical (not of physics) account of cellular biomechanics, cell culture or biotissue. From the abstract: "We introduce a model for describing the dynamics of large numbers of interacting cells. The fundamental dynamical variables in the model are subcellular elements, which interact with each other through phenomenological intra- and intercellular potentials. ...We present here a detailed description of the model, and use successive ***mean-field approximations*** to connect it to more ***coarse-grained approaches***, such as ***discrete cell-based algorithms*** and ***coupled partial differential equations***..." Outlined by reviewers.

In the further development the author introduces algorithms for modeling multicellular systems which are designed as for simulation of large numbers of cells, and also allow for adaptive cell-shape dynamics and the accommodation of successive degrees of intracellular biology. "This framework uses subcellular elements" (defined below) "...as the fundamental dynamical variables..." The author considers a system with a constant number N of cells in 3D, with each cell being composed of M elements. The chemical signaling is absent from the system where $\rho_i(x,t)$ is the average density of cell elements in a cell.

This is the many-body approach with the point objects which, even when at the scales of many orders of magnitude difference, still have the volumetric physical properties. A great attention should be paid to these words of initial statement basic definitions – that means, the author has just substituted by a graph (diagram construction), by a classical Theoretical Dynamics Mechanics scheme – a set of nodes (points) and the connecting them edges (bonds) with their properties. Here is finite mathematics, discrete mathematics schematics for the Continuum mechanics subject. This is the XVIII century approach. And all of that for the Continuum mechanics described objects – which is much more accurate and exact in the depiction of the phenomena tool.

The author writes in p. 613: "In this case, the position vector of element α_i is taken to change in time according to three processes:

(i) a weak stochastic component, which mimics the underlying fluctuations in the dynamics of the cellular cytoskeleton;

(ii) an elastic response to intracellular biomechanical forces; and

(iii) an elastic response to intercellular biomechanical forces. We assume further that the elements' motion is over-damped, so that inertial effects can be ignored. The equation of motion for the position vector of element α_i takes the form:

$$\dot{\mathbf{y}}_{\alpha_i} = \eta_{\alpha_i} - \nabla_{\alpha_i} \sum_{\beta_i \neq \alpha_i} V_{intra}\left(\left|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_i}\right|\right) - \\ -\nabla_{\alpha_i} \sum_{j \neq i} \sum_{\beta_i} V_{inter}\left(\left|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_i}\right|\right). \qquad (1)$$

On the right-hand side, the noise term η_{α_i} is a Gaussian-distributed random variate with zero mean and correlator

$$\left\langle \eta^m_{\alpha_i}(t)\eta^n_{\beta_i}(t')\right\rangle = 2\nu\delta_{i,j}\delta_{\alpha_i,\beta_i}\delta^{mn}\delta(t-t'), \qquad (2)$$

where *m* and *n* are vector component labels in the three-dimensional space. The second and third terms on the right-hand side of equation (1) represent, respectively, intra- and intercellular interactions between the elements. These interactions are completely characterized by the phenomenological potentials V_{intra} and V_{inter}. At this level of description, all relevant biological detail must be encoded into these two potentials." In the above equations and of below depictions the numbers of the equations presented are from their respected texts.

Reading further: "...We have assumed that "two-body" potentials are sufficient to describe the dynamics." "For given biological applications of this modeling framework, one must intuit (or, better, derive) reasonable forms for V_{intra} and V_{inter} . For illustrative purposes,.."

In p. 614 one can read: "...consider a population of cells which are weakly adhesive to one another. Subcellular elements both within and between cells will be mutually repulsive if their separation is below the equilibrium size of an element. For separations larger than this size, the elements will be mutually attractive, but with the strength of attraction falling off rapidly with separation. These properties can, for example, be conveniently encoded via a generalized form of the Morse potential, which is commonly used in physics and chemistry to model inter-molecular interactions [24]

$$V(r) = U_0 \exp(-r/\xi_1) - V_0 \exp(-r/\xi_2). \qquad (3'')$$

Further is more on this: "...one can use Morse potentials for both *V*_{intra} and *V*_{inter}, with parameters chosen to ensure that the former has stronger inter-elemental adhesion than the latter. This condition is necessary, in this simplest version of the model, to maintain the mechanical integrity of the cells."

We need to comment on this development that:

1) These tools of "statistical mechanics, many-body physics" – they don't work well for many-body field and for particle physics as a whole, and they are obsolete and in part are incorrect because of the fundamental assumptions put in the derivation of the governing equations (using definitions of point-like particles, homogeneous GO theorem, and incorrect averaging procedures – coarse graining).

Over again – mostly because of the two reasons (there are others), but most mortal mathematically (and physically) – they represent the objects as the point-like phenomena which they are not, and they represent in deductions every aspect as of the use of the Homogeneous GO theorem for the definitely Heterogeneous fields and objects of interest. Also, they represent the fields of interest – particles as if they would be hanging out in vacuum. While we know that the vacuum is actually very "active" vacuum. The vacuum is the subject where the many particle physics phenomena occur.

2) All the fields and forces in this study are artificial; all of them have appeared as a result of imaginary interactions without a field of interaction.

3) What is the intracellular interaction potential V_{intra}? Morse potential? What is this? And what are its parameters? Just numbers. Is it electrical potential? What a potential we can have, if the model (phases, media, more strictly) performs interacting via the known fields (physical) and this is essential?

4) What is the extracellular interaction potential V_{inter} ? What are the connections of these potentials to the continuum fields of extracellular space or other cells' environment?

5) What is the field of noise (a Gaussian distribution field)? Exactly, what is it?

6) What determines the concentration field?

All these and myriad of other questions have only perhaps adjustable connections to the fields ascribing the biophysical behavior of a cell and a tissue. Meanwhile, in the HSP-VAT this kind of effect has the precise calculable nature.

Practically in all studies published in the fields of microbiology, cellular biology, structural biology, systems biology, the subject matter is taken as of the "anthropogenic" point of view - what is available and seems important to us should be taken for the persuasion on our goals and results. Here we talk about the perception of sizes in cellular biology that all "need" to bent to our understanding of size in physics as from our world which we can touch, assess, make an opinion about, etc. And all that can be, of course, of the one scale perception – after all, we all have only Cartesian 3D world with the one scale measure – the meter. One ruler for all – just some factor to take. This perception drives everything right now in structural biology. Any tool uses the one scale physics, and even when people spell out the words on the "multiscaling" as, for example, in Biophysical Journal, it's just the description of different scales physics phenomena.

Without Scaleportation – because, what is used in the studies for connection of each scale models and their results is the parameterization "based on properties from the higher-resolution models," and from some experiments, which is the adjusting or "coupling" of neighboring scales modeling effort. But not a Scaleportation – http://www.travkin-hspt.com/fundament/scaleport/scaleport.htm Reductionism and/versus Holism in Physics and Biology - are Both Defective Concepts without Scaleportation.

That lack of understanding and segmentation in science are probably the reasons for the "coupling" mode scale modeling happening. Also important is the stance on – What kind of scales is usually spoken about, worked with, and probably understood to some degree in biology, especially in structural biology? Exclusively, or

almost exclusively it is down to the atoms? And we are not talking about subatomic scales principles that physical instruments are based on. Why is that, if an ocean of subatomic scales particle physics, nuclear physics phenomena are relevant to the biology effects? Subtle effects as biologists say? Not correct. Is that the boundary of workers' knowledge base, or what?

In some fields of biomechanics study the Bottom-Up sequence of scales is so unusual that it is named as an "Inverse" method or Modeling? This is strange. From this kind of standing, we would consider researches in the cellular biology multiscale topics.

The first one we would look at is about the recent findings on macromolecular assemblies published in "Nature" [31, 32]. Among the notes on the study's peculiarities, we would comment on the following:

1) This is a gigantic job done for the determination of the morphology of a specific protein complex in a cell. At the same time, our goal is to discuss the methods used for this (and any other) Polyscale Heterogeneous (PH) microbiology, structural biology, cellular biology, and other definitely PH biology field studies.

2) The problem, the main issue of this analysis is about the scaled description of the evidently scaled collective interaction of many hundreds of proteins in the Nuclear Pore Complex (NPC). Roughly talking, we have, we can take for simplicity three different scales participating differently in NPC function:

a) the scale of a separate molecule (as amino group, for example) in a macromolecule, protein, or in a solvent, or in a soft tissue as the NPC is, or etc. – ~0.2[*nm,Sc*];

b) the scale of a single protein – 1-5[*nm,Sc*]; which is not walking alone, but imbedded into a polyphase solvent, or docked to other protein(s), or is the part of an assembly;

c) and the scale of constitutive protein complexes – ~10-50[*nm,Sc*];

in the known and much studied nuclear pore complex assembly NPC only 456 proteins are known.

3) In no way we would like to diminish the result, the great result in the paper. We have to set up a tone to discuss the features, the insufficiencies that surely preclude the future research over this and other assemblies of macromolecules, proteins, etc. The problem is with the function of the macromolecular assembly. . The discussed result is actually establishing bounds for measurements, the analysis of experimentations, but not the explanation of morphology, NPC function and its peculiarities. Those attributes are of Collective Macromolecular Interactions (CMI) and we can not get to that area using the same mathematical and physical tools of the one scale narrative.

What are the mathematical models for the behavior of macromolecules in an assembly?

If that is the conventional MD for macromolecules, then we can not get the assembly's morphologies (structures) correctly without specifics of protein-to-protein interactions as of the collective pattern, entity. Because the conventional MD uses many just adjusting conjectures and parameters, the basis of MD is questionable, not to mention the macromolecular particles collective interactions. That was actually one of the reasons why in the presented study the authors were not able to satisfy their needs for modeling of macro-assemblies using just the MD.

4) In Fig. 2 is given an incomplete Top-Down hierarchy, whereas the Bottom-Up sequence is in need to be performed for the scaled reconstruction of spatial assembly with the reasonable justification.

5) Pretty important is that what is shown, for example, in Fig. 5b looks as a craving for attempting to combine protein-to-protein interaction in the vicinity of the Nup84-complex in the NPC which is of high doubt, as long as for the description of the combination and attraction of proteins inappropriate tools were used – yes, what authors could get at their disposal. And that can be said about any assembly recognized in the work.

6) Authors write in p. 686: "we also need information on the interactions between nucleoporins. We obtained this information from a large number of overlay assays and affinity purification experiments." As we see, the data are just of approximate nature – taken from observation, which in no way explain to us – Why these nucleoporins are sticking to each other with this spatial morphology? Yes, there is a number of hypotheses an experienced biologist can produce, but what is the justification for that? According to the conventional physics – homogeneous one, using the adjustable MD, linear local interactions of point particles, traditional many-body (many-point) problem statements and their approximate solutions (even for point particles), etc., etc.? That means, the Fig. 5b visual version is, well, so far a fiction. In p. 687 we can find in a figure's caption – "b, The mutual arrangement of the Nup84-complex-associated proteins as visualized by their localization volumes. The localization volumes, obtained from the final NPC structure (Fig. 9), allow a visual interpretation of the relative proximities of the proteins."

7) It is also interesting to read about what was used in the study to approach the findings of explainable proteins interaction – the famous protein – protein (P-P) interaction. In p. 689 we can read in this regard: "This composite implies that at least three of the following six possible types of interaction must occur: blue-red, blue-yellow, blue-green, red-green, red-yellow and yellow-green…" "These considerations can be encoded through a tree-like evaluation of the conditional restraint. At the top level, all optional bead-bead interactions between all protein copies are clustered by protein types. Each alternative bead interaction is restrained by a harmonic upper bound on the distance between the beads; these are 'optional restraints', because only a subset is selected for contribution to the final value of the conditional restraint."

This is the combinatorial mathematics arguments for the physical fields' problem. Well, whatever authors had

at their disposal – still, that is not the protein – protein interaction especially in a collective mode. Authors even introduce out of distraction just the statistical value as "protein contacts," p. 690:

"Protein contacts. The proximities of any two proteins in the structure can be measured by their relative `contact frequency', which is defined by how often the two proteins contact each other in the ensemble (Fig. 10b)…" "Notably, few high-contact frequencies are seen between proteins of the same type, indicating that the NPC is held together primarily by heterotypic interactions."

These descriptions taken from p. 690, fully reveal the available today mathematical approaches for P-P interaction – which is often straight to the combinatorial study of the possible interactions – no chemistry, no physics; and the math is from another universe. Regarding the MD application we have made a few remarks in the above texts for other studies using the MD, generally it is a too simplistic tool to be considered for this task in the cellular biology.

Concluding we can note that:

1) The outstanding result given in this paper should not divert us from the discussion about the homogeneous tools that were used in the study.

2) Also, the suggested spatial structure of Nuclear Pore Complex (NPC) can not be verified and studied further regarding its function in a nuclear-cytoplasm exchange because of the inadequate one scale homogeneous structural molecular biology modeling tools only known to the authors. Other authors would find any possibility to encroach into the suggested morphology – and probably this morphology is close to or even the reality. Nevertheless, its fundamentals would definitely preclude the functional studies of the present assemblies.

Coarse-graining techniques

The computer simulating studies used for specific polymers are mostly using the atomic scale initial simulation techniques. Meanwhile, this modeling is not sufficient either for quantitative studying of polymers or for a real scaling and scale resolving picture, analysis of polymer, polymer composites. The rude computational force would not work even in 15-20 years when computing power will be unimaginable comparing to today's situation.

That is why, probably, a number of the united by idea techniques have found a way into researchers' armory for scale dependent calculations - named as "coarse-graining" (CG) techniques (many of them) – Fig. 3. Mostly they are based on the kinetic mechanics with the original definition of the Hamiltonian for a chosen polymer, macromolecular system or solution.

The main problem concerned with these methods is that despite their attractiveness as the working tools, they are actually adjusting methods, not justified and working by comparison with the experiment or already known properties of similar macromolecules. These are the contemporary XXI century "alchemistry" methods.

Nevertheless, the goal is a noble one and while we argue below on features of CG methods, at the same time we would like to point out that the scale transport of properties is achievable with the true scaling techniques using not only the kinetic, but also dynamic models, "fields" relying on methodology with the HSVAT. These methods have a most powerful feature, which is the ability to make a true Scaleportation.

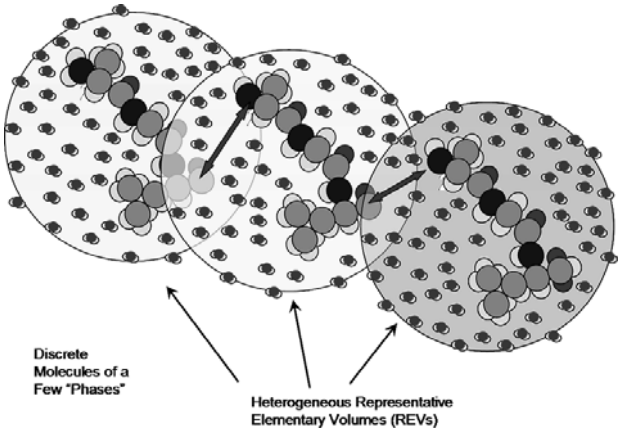

Рис. 3. Полипептидные цепочки из аланина, глицина и валина в водном растворе. Идея переноса по масштабам «снизу-вверх» в HSVAT является одним из основных понятий масштабного физического и математического моделирования, основанного в 60-х. Вот почему эта последняя разработка с предложением алгоритмов огрубленного осреднения «суператомов» взята из иерархической масштабной методологии, разработанной в VAT механике жидкости и физике теплопереноса, но при этом используются только химические однородные методы

Fig. 3. Polypeptide chains between alanine, glycine and valine in aqueous solution. The idea of Bottom-Up Scaleportation in HSVAT is one of the main concepts of scale dependent physical and mathematical modeling started in the 60s. That is the recent design of coarse-graining sequence algorithms of "Superatoms" is taken from the hierarchical scaled methodology (HSVAT) developed in Fluid Mechanics and Thermal physics VAT while using only the chemical homogeneous techniques

A hypothesis coming from the idea is in the abstract: "Mechanical oscillations are important for many cellular processes, e.g. the beating of cilia and flagella or the sensation of sound by hair cells. These dynamic states originate from spontaneous oscillations of molecular motors..." served for the biological model [33] for exceptionally difficult, polyscale and polyphysics process in muscles. Here in this paper, one can see also the Hydrodynamic model for a Visco-Elastic heterogeneous polyscale biomedium of muscle. In p. 419: "In general, the system is subdivided into volumes that are small compared to the large-scale structures of interest and that are, at the same time, large enough to allow for a thermodynamic (equilibrium) description."

In p. 420: "Under the assumption of local thermodynamic equilibrium, changes in the system's free energy can be expressed as

$$\frac{d}{dt}F = -\int_{\Delta\Omega}(\sigma\partial_x\upsilon + r\Delta\mu)dx\,, \qquad (3'')$$

where under the integral sign in each product formed by a generalized flux that multiplied by its conjugate generalized force – "the fluxes are taken to be the stress σ and the rate of ATP-hydrolysis *r*. The force conjugate to σ is the rate of strain $\partial_x\upsilon$, the force conjugate to *r* is the difference Δμ in chemical potentials of ATP and its hydrolysis products ADP and P_i, $\Delta\mu = \mu_{ATP} - (\mu_{ADP} + \mu_P)$."

This is the basic heaviest brick by the authors in the lump-sum foundation of the energy depiction as in the Homogeneous Thermodynamics. The trick in this approach for the description of the energy changing the form and undergoing transport via the space is that the numerous phenomena – polyscaled by nature, could be in this way lumped altogether into the one or more terms with very simple (and sometimes good for linear phenomena) procedures – while the effect is being declared with some knowledge of its nature and then mathematically inserted in the form of some flux and its coefficient as always done in homogeneous hypothesis in thermodynamics of homogeneous matter. Here the phenomena description for the energy process is of the highest scale of generalization – at the largest continuum level accepted in the model. Just from the beginning. That means also that the all phenomena taken further in an explanation should be of the same scale as the energy process stated – as of the bulk homogeneous matter.

Nevertheless, many observations that were put into the model further are of the much lower scale in their description, for example, of motor proteins. In p. (417+5): "The motor filament as well as the polar filament are effective structures that result from averaging the parallel filaments in a sarcomere in the direction perpendicular to the sarcomere extension. The whole structure is immersed in a fluid of viscosity μ." The authors are recognizing the "averaging" necessity in this regard. Nevertheless, the averaging should be extended and provided out by mathematically correct procedures as HSP-VAT in two dimensions for the current problem.

Concluding comments on this study:

1) In the paper [33] is given an attempt to describe mathematically clear the scaled phenomena in muscle fibers as via the homogeneous physics one-scale kind of coarse-graining, models for mass, momentum and energy of volumetric presentation of muscle fibers ensemble.

2) In page 417-4 (417+3) are given the balance equations of homogeneous medium based on the assumption of local thermodynamics equilibrium.

3) Synchronization of sarcomeres in muscle fibers is probably due to a collective effect of Bottom-Up local-non-local movements of adjacent protein molecules – actin, myosin, together with the interconnecting titin macromolecules. For example, the authors wrote: "In the following, we will use a mean-field approximation, which consists of assuming that all motors in the half-sarcomere have the same spring extension,…"?

4) The elasticity of muscle fiber as given in the equations (9) – (11) (p. 417-7 (417+6)) is obviously heuristic by nature, because the scaled local-non-local phenomena are lumped together by just mechanistic conjectures. In order to move upward to the continuum mechanics muscle fiber model authors got to the stage of artificial reasoning in pages 417-10 – 417-11.

5) To have an ability to talk about and get some continuum mechanics conceptual analysis the authors invented the "continuum limit" algorithm in pages 417-10 – 417-11, purely frivolous by nature. They are referring to their own definitions of volumes and sub-volumes to get to the desired for homogeneous equilibrium thermodynamics: "In general, the system is subdivided into volumes that are small compared to the large-scale structures of interest and that are, at the same time, large enough to allow for a thermodynamic (equilibrium) description." That volumetric exercise is not a volumetric heterogeneous averaging, as one might imagine. This is the homogeneous medium averaging used in the thermodynamics of one scale.

6) In conclusion we might emphasize that this kind of scaled biological subject – the extremely complex multiphase, multiscale mechanics of muscle fibers can not be submitted to and treated as the one scale homogeneous physics and mathematics field, if the aim is serious scrutiny. With the consecutive modeling by the means of conventional one-scale hydrodynamics mathematical models?

Well, of course everyone can do whatever the professional experience advises him/her to do, but still there exist the natural features and reasons for that or this approach, to make the object under consideration either closer to the original or just bent into the sought form. This is one of the examples of - How not to do such a theory and modeling for polyphase polyscale matter.

We might return to the paper [30] where subsequently the author after MD techniques was changing still a small scale (unspecified) formulated model to a coarse-graining methodology. In p. 615 we can read: "In the first of these coarse-graining steps, we replace the element model by a subcellular density model, in which the discrete elements within a given cell *i* are replaced by a smooth average density field $\rho_i(\boldsymbol{x},t)$. We stress that a separate density field exists for each cell in the system, and that these density fields are strongly correlated to one another. To proceed, we first recast the subcellular element model in terms of the probability distribution of individual elements. We define the probability distribution of element α_i by $P_{\alpha_i}(\mathbf{x},t) = \langle\delta^3(\mathbf{x} - \mathbf{y}_{\alpha_i})\rangle$, where the angled brackets denote an average over the noise η. Starting from equations (1) and (2) we use standard methods [19, 27] to derive an equation of motion for..."

All of this construction is taken for the statistical treatment of still underdeveloped physical model, instead of just setting up the Lower scale multiphase,

multiphysics continuum model for a cell – which is still the continuum media even many scales down the sequence until we might get to the atomic scale. Then we can make the phenomena of the subjected separate homogeneous fields taken within the classical homogeneous mathematical physics that has been done for more than a century.

In p. 616 we can find a main governing equation developed by using yet the particle physics notations and definitions: "P_{α_i}, which takes the form

$$\frac{\partial P_{\alpha_i}(\mathbf{x},t)}{\partial t} = \nu\nabla^2 P_{\alpha_i}(\mathbf{x},t) + \\ +\nabla\bullet\int d^3x'\left[\nabla V_{intra}\left(\left|\mathbf{x}-\mathbf{x}'\right|\right)\right]\sum_{\beta_i\neq\alpha_i} P_{\alpha_i,\beta_i}(\mathbf{x},t;\mathbf{x}',t) + \\ +\nabla\bullet\int d^3x'\left[\nabla V_{inter}\left(\left|\mathbf{x}-\mathbf{x}'\right|\right)\right]\sum_{j\neq i}\sum_{\beta_i} P_{\alpha_i,\beta_j}(\mathbf{x},t;\mathbf{x}',t), \quad (4)$$

where P_{α_i,β_j} is the "two-element" distribution function. The equation of the motion for this two-element distribution will involve the three-element distribution, and so on.

The simplest truncation scheme to break the hierarchy of equations is the mean-field approximation (MFA), in which the statistical correlations between elements are discarded. Within this MFA we have $P_{\alpha_i,\beta_j}(\boldsymbol{x},t;\boldsymbol{x}',t) = P_{\alpha_i}(\boldsymbol{x},t)\, P_{\beta_j}(\boldsymbol{x}',t)$."

Further one can find that: "imposing the MFA, we find a closed equation for this subcellular density function, which takes the form of an advection-diffusion equation:

$$\frac{\partial \rho_i(\mathbf{x},t)}{\partial t} = \nu\nabla^2\rho_i(\mathbf{x},t) + \nabla\bullet\rho_i(\mathbf{x},t)\nabla\Phi_i(\mathbf{x},t), \quad (5)$$

where the velocity potential experienced by the density field of cell *i* is given by

$$\Phi_i(\mathbf{x},t) = \int d^3x' V_{intra}\left(\left|\mathbf{x}-\mathbf{x}'\right|\right)\rho_i(\mathbf{x}',t) + \\ +\int d^3x' V_{inter}\left(\left|\mathbf{x}-\mathbf{x}'\right|\right)\sum_{j\neq i}\rho_j(\mathbf{x}',t). \quad (6)$$

The MFA used to derive this density equation will typically be good when the number of elements used to define the cell is very large."

Here $\rho_i(\boldsymbol{x},t)$ is the average density of cell elements in a $\rho_i(\mathbf{x},t) = \sum P_{\alpha_i}(\mathbf{x},t)$; ν is the parameter seen in eq. (2); and $\Phi_i(\mathbf{x},t)$ is the velocity potential in a whole problem's domain, or simply the 3D space as long as the spatial integrals used in this deduction are undetermined.

In pp. 617-618 we can read about further and final deductions: "We can use the density equation (5) to coarse-grain to another scale – where now only gross properties (which we refer to loosely as "moments") of the subcellular density field are used to characterize the cell. This coarse-graining step is analogous to a multipole expansion in electromagnetism."

"We omit the details here and simply give the final result:

$$\frac{\partial n(\mathbf{x},t)}{\partial t} = D\nabla^2 n(\mathbf{x},t) + \nabla\bullet n(\mathbf{x},t)\nabla\Psi(\mathbf{x},t), \quad (10)$$

where the coarse-grained velocity potential Ψ for the cell density has the form

$$\Psi(\mathbf{x},t) = \int d^3x' V_{inter}\left(\left|\mathbf{x}-\mathbf{x}'\right|\right) n(\mathbf{x}',t). \quad (11)"$$

"Finally, after three levels of coarse-graining, we have arrived at a partial differential equation for the cell density, as given in equations (10) and (11). As mentioned in the introduction, this level of description has been widely used to describe the large-scale dynamics of cell populations. However, as should be clear from this analysis, a great deal of statistical information and smaller-scale biomechanics must be discarded at this scale." Here $n(\mathbf{x},t)$ is the global density of cells $n(\mathbf{x},t) = \sum\langle\delta^3(\mathbf{x}-\mathbf{x}_i(t))\rangle$.

We would comment on this three-step coarse-graining with interest. These equations (5) – (11) especially (5),(10) are of pure speculative nature based on the procedures developed in many-body and statistical mechanics for the point-like indistinguishable particles arrays. While using the invalid for heterogeneous media truncations rules for the Mean-Field Approximation (MFA) governing equations. We can not get equations (5),(10) with the heterogeneous GOT which is the WSAM theorem. What determines the "concentration fields" in (5), (10)? The GO theorem application.

Well, but the GO theorem can not be used for a particulate medium Upper scale (averaging), or coarse graining as it is customary used in statistical mechanics. All those functions as V_{intra}, V_{inter}, noise term η_{α_i}, and their numerous parameters are just pure speculative adjusting functions and constants, baring nothing or very little of the real physics related to the collective interactions of fields, phases, biochemical characteristics of a cell, extracellular environment, etc.

Also, these final like equations for the global density of cells $n(\mathbf{x},t)$ bare nothing useful for the problem stated. Because we at any moment now know that this number of cells exists and they are within the assigned medium, that's it. Regarding their redistribution, that has no sense to consider seriously because a great number of adjusting parameters can force cells move in any direction even with the speed of light. Their motilities and shapes are nothing to do with the pure mathematical speculations for the point representations of them, if those are only applied for the model deduction.

In concluding remarks for this paper it can be said that:

1) This paper is a misleading one for workers in the field of theoretical biology, for the biologists who are not theoreticians it gives wrong knowledge, while regarding the students it is misleading their education due to misrepresentation of the subject matter. The poor

understanding and the old fashioned traditional approaches from particle physics that people, mostly physicists, apply to concepts and model development for biological subjects are not surprising. Researchers, those who have never thought of scaling or averaging issues, have started responding to the challenge with the same 50-60-year-old tools, as used for statistical physics and particle physics in the first half of the XX century. Where particles were thought as of objects with the point-like features, while other methods were nonexistent.

Most of physicists who do the "statistical mechanics (SM) for biology work" are familiar with these discussions on the validity of point particles – no volume, no features apart of those researchers would like to assign to. Unfortunately, workers-physicists prefer to work with biological matters – those are polyscaled, in the same way as particle physicists work with the volumeless particles. Meanwhile, considering that the biological objects are point-like items is the idealization used in physics in the middle and beginning of the XX century, when they did not have vision and mathematics for the scale dependent problems.

That construction of order parameters and coarse grain procedures are simplifying (not simplistic) tools and designed for well adjusting to some averaged experimental results. Physicists in biology might know that the multibody problems are the Two Scale problems, as such by nature of the statement. The point is that researchers are looking for some "bulk" averaged characteristics and fields – and those are from the Upper scale. Nevertheless, it is really treated in multibody field as for a singular scale, because all the parameters and characteristics are adjusting, as it was set-up by the nature of their definitions and determinations.

Being within the concept of the one scale for the entire scaled problem is not helpful to solve the multibody task, even the understanding and correct statement is impossible. We would be in the same situation as it was for centuries, when multibody problems were considered unsolvable. Also, the most known techniques in traditional statistical mechanics many-body problem are approximate by nature.

2) Meanwhile, using the consequences of Heterogeneous Gauss-Ostrogradsky theorems (WSAMTs), not a homogeneous GOT of the XIX century, every science, where the tools of polyscale physics and mathematics of HSP-VAT were applied, was having advances throughout the last 20-25 years to the new level of stature. Even some textbooks' problems had been solved on two scales as they should be for the scaled problems in physics, for the first time and exactly, for example in – http://travkin-hspt.com/eldyn/WhatToDo2.htm "When the 2x2 is not going to be 4 - What to do?" and others in the same website. While these results have been obtained without any fashion of many-body theory and procedures, homogeneous physics and mathematical pseudo-multiscaling models and algorithms.

Polyscale polyphase good wishes for cellular biology

This is a great by its content review [34] with the appeal for tools needed for structural biology – the workers should understand and keep in mind. It's a rather seldom situation when the request for instrument of need is openly published in spite of the fact that the research in this arena is going on for decades! In the p.1 one can find the current state of affaires in the structural biology modeling as well as the recognition that: "However, none of these computational approaches are always accurate, applicable on all time and size scales of interest, capable of describing all properties of interest, and able to include all available experimental data and theoretical considerations. Such an integrative approach still needs to be developed."

We won't be talking much on the content other than the following. In the p.4 a reader can find the outstanding Table 1, with specific needs for structural cellular biology wellbeing. People with sufficient background in math and natural sciences and their history reading this table can suspect that we are in the era of the second part of the XVII century when the need for infinitesimals was evident and the Differential Calculus was developed by G.Leibniz and I.Newton.

In other words – this is the request for a Differential Heterogeneous Scaled (at least two scales) Governing Equation(s) to study, know, control and for an experimental design for the Heterogeneous Scaled (at least two scales) biological systems under investigation.

Authors did not know that it is already done (we have informed them lately). Summarizing the thoughts regarding this paper it can be said:

1) This is the work of profound professional insight into the set of features that are available right now at one side – the Homogeneous biomedia characterization and the necessity for those with Heterogeneous Scaled techniques should be found and developed for a successful study, dynamic modeling of macromolecular assemblies, structures in cellular biology. With great interest, we have read this paper and the issues drafted in the Table 1, p. 4.

2) In the Table 1 there is given the most striking list of features desired or better to say "dreamed of" for a full scale or complete resolution of "structural dynamics" modeling of cell macromolecular processes. The matter of fact is that the authors of this paper not knowing the more general point of view have drafted the "wish list" for a thing not less than the "Scaled Heterogeneous Physical and Mathematical Differential Calculus" for the Two-scale (at least) description of transient macromolecular processes in a cell.

3) Thus, we have witnessed the appearance of the pretty seldom phenomenon when the need for the theory is so high (strong) that workers created the draft outlined feature – the table in which the number of the first priority characteristics needed for a process modeling and observation in experiments are being published in a professional journal. The authors do not know that those

features, tools and theoretical fundamentals have been already worked out in the other scientific fields. We would like to mention, that the present days science is the broad endeavor indeed.

4) We would make a few statements related to the points in the Table 1, not for the every point in the table, which is understandable.

In the characteristic wish **No. 1** in the table, one can find that the desirable feature is described as: "**State**: A state is described by a three-dimensional structure of an assembly at some resolution. The structure may be flexible and its description may be incomplete."

Meanwhile, in the HSP-VAT language it is the Upper scale formulation of the problem's dependencies for the given "phase" or "species," macromolecular assembly (MA) characteristic state in its phase and spatial manifold.

5) The number **two** point in the Table 1 reads as:

"**Key state**: The set of key states and transitions between them capture the essence of the process. Key states need not be stable and can correspond to transition states."

In the HSP-VAT language this is the set of consecutive solutions (values, field's mathematical meaning's) of the Upper scale governing equations in the phase field's of the Upper scale physics.

6) The number **three** point in the table reads as:

"**Transition**: A transition occurs between a pair of key states that can interconvert directly without passing through other key states."

In the HSP-VAT language, this is the transition between the two points on the phase space Upper scale solution curve and these points are obtained in accordance with the HSP-VAT Upper scale governing equations (GE) and their solutions.

7) For all the other left issues **No. 4-9** in the Table 1 (p. 4) we have developed the corresponding classifications and exact descriptions and mathematical formulations in the field and language of the HS physics and biology, which have been applied so far to many sciences. Among them in the website are presented:

7.1) http://travkin-hspt.com/acoustics/index.htm "Acoustics"

7.2) http://travkin-hspt.com/agrom/index.htm "Agro-Meteorology"

7.3) http://travkin-hspt.com/atom/index.htm "Atomic and Subatomic Scales Description of Matter with HSP-VAT"

7.4) http://travkin-hspt.com/bio/index.htm "Biology and Ecology as Hierarchical, Heterogeneous, Multiscale Sciences and their Applications"

7.5) http://travkin-hspt.com/coldlenr/index.htm "Cold Fusion or LENR is the HSP-VAT Science"

7.6) http://travkin-hspt.com/compos/index.htm "Composite Engineering"

7.7) http://travkin-hspt.com/elastic/index.htm "Continuum Mechanics of Heterogeneous (Ht) Media; Elasticity, Plasticity"

7.8) http://travkin-hspt.com/eldyn/index.htm "Electrodynamics"

7.9) http://travkin-hspt.com/fluid/index.htm "Fluid Mechanics"

7.10) http://travkin-hspt.com/thermph/index.htm "Thermal Physics"

7.11) http://travkin-hspt.com/med/index.htm "Medicine Heterogeneous, Multiscale Applications"

and other sciences and technologies.

Conclusions

In conclusion we note that it would be nice if the authors of the commented up here last study [34] will understand the essence and the implication for their own work and goals while they might be doing efforts to implement some working, proven tools that already exist and were suggested to them according to their own "wish-list" specification via the HSP-VAT that has been in a public domain so far for a number of years – more than 25 approximately.

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