The Tool Biologists Have Been Craving For Does Exist. The Issue Is Who Can Use It?

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Abstract:

The present paper has partly originated after summarizing the few inquires that some review paper was devoted to [1]. The issues discussed in the review are evidencing that the current state of the art in biology theory, modeling of the cellular related processes is of the outdated base. At the beginning we formulate principles and concepts that help to establish the fundamental theories, techniques of Heterogeneous Polyphase Polyscale (HPP) idea of biological media, tissue, etc. Among functions "in vivo" in a cell we recognize the transport of momentum, energy, mass, electrodynamics in cell media, force resistance (elasticity), wave mechanics presence, exchange at the boundaries, interphase and interface transport exchange. All these physical phenomena are acting in the heterogeneous (polyphase, polyscale) medium of a cell. Up to now, in conventional, one-scale homogeneous concepts in biology and physics all those fields and processes have been treated and modeled by the known for ~(100-150) years models developed in physics for media being homogeneous ones. But biological media and a cell itself are heterogeneous and polyscale matter.

Addressing this issue with correctly developed physical and mathematical concepts and formulation gives a chance for starting the modeling and simulation of polyscale heterogeneous biological functions in a cell not via use of adjusting coefficients, but with the polyscale sets of correct modeling Heterogeneous governing equations. It is well accepted idea that experimental methods alone in biology disciplines are not sufficient to discover or explain or forecast the complexity and interaction of many processes. We outline as well on this path the peculiarities of derivation of governing equations for biological floating and soft solid media. Those media while consisting of a few more scales to reasonably consider as components of the bulk soft elastic and/or viscoelastic body, have natural components that dictate the physics of the Upper scale(s). It is only now the scaled, at least for two-three scales, biophysical and biochemical phenomena can be described, modeled and possibly simulated as they exist in nature - polyscaled, with their pertinent morphologies and peculiarities of physics at each scale and between the scales. All these tasks until recent time have been treated with the help of adjusting parameters, each scale and interscale coefficients and conjectures.

Key words: 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

1. Introduction to Description of the Heterogeneous (Ht) Media of Soft Solids, Soft Solids and Fluids, Polyfluids, Soft Particles in Fluid, Scaled Fluids in a Cell

Considering the processes within a cell as those to be between objects of different size and physical properties we should naturally come to and embrace the picture where the atoms and small molecules to be seen - as the components (ingredients) of some different water soluble species - fluids as the continuum media.

In its turn, the macromolecular species are the separate phase species ("phases") each. As long as they are different in their interactions between themselves and with the continuum phases - as water and water solutions.

We have in this way numerous continuum phases (this is much better consideration than taking all of them to the lump sum as a "mixture") and soft elastic particulate phases within a cell.

The particulate phases, as organelles, can be considered also, while Down-scaled, as complex polyphase volumetric objects.

As long as the number of that species is great ~n(10^3) and their interactions are mostly either unknown, while in some instances are homogeneously described in with the present biology methods, it would be perfectly reasonable to admit and use a concept of partial auto-regime performance (metabolism) of this or that subsystem in a living cell.

Commencing only by the impulse of already performing quite complicated interaction of different systems in a cell.

Partial formulation is taken as long as we can not and don't know the complete path for starting the living process as a phenomenon. The principle of Redi "omne vivum e vivo" - "all the living are born from the living," is the part of the guessed now biogenesis pathways.

Within this concept of Partial Autoregime Performance (PAP) (metabolism) we will be working over a program to explain, model and simulate the subsystems in a living cell standing on the position of Hierarchical Scaled Physics - Volume Averaging Theory (HSP-VAT) in biology.

As always at the beginning of some complicated conceptually new theory, methodology it is reasonable to choose to follow the sample of events, phenomena with an aim to set-up a pattern for treatment of similar problems in the past and future.

We would like to have as an example of challenged here problem description that was given seems at first in conventional homogeneous biology with such an obvious and semantically grounded position as it was done in publication [1] with regard of inadequate, poor (and wrong, by us) tools used in contemporary cell biology (we may say in a whole biology) for description, modeling of dynamics of macromolecular processes.

It can be said with assurance that any single process and the whole class of these processes as depicted in Fig. 1 of the review [1], are fairly treatable with application of the HSP-VAT techniques that have been already developed throughout the last ~30 years.

Meanwhile, as it appeared from the paper, authors completely standing on the position of traditional homogeneous physics and mathematics taught in universities for biologists, and used by biologists with the true belief that it is the last word in physics and math.

In the p.1 one can find the current state of affaires in the structural biology modeling as well as the recognition that:

"To understand the processes that maintain and replicate a living cell, we need to describe the structural dynamics of a few hundred core macromolecular processes [1] (Figure 1), "Thus, a key challenge is to integrate different kinds of static and dynamic characterizations at different resolutions to obtain a comprehensive description of a process. ....."

As we already pointed out onto the statement in the p.1(online) [1] one can find the current state of affaires in the structural biology modeling:

"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. "

It should be answered that yes, ***it is already has been created. That is, please everyone welcome to use this biophysics new tool (methods of HSP-VAT) in cell biology, other biological sciences.***

2. Fundamentals of the Theory

2.1 Some principal provisions, conceptual definitions, concepts of scaling matter related to the subject of sub-continuum and continuum physics and modeling of *cellular and sub-cellular biomedia as scaled media with physical and mathematical rigor.*

Principles of the Theory.

1) Principle - Recognition of the fact - that at any scale the biological substance, a cell in the present theory, is the Polyphase Polyscale Heterogeneous medium. At atomic scale, or at some of continuum scales.

2) Principle - Recognition of the information - that the structure and the specific "phase" content in a cell are the fundamental facts controlling the function of the cell along with the environmental (boundary) conditions.

3) Principle - Recognition or knowledge that - in this consideration the polyphase, polyscale studying of the subject - the cell sample, or the sub-cellular structure, organelle, for example, is the most accurate and revealing way of obtaining the facts, conclusions. This was and is one of the main methods (the reductionism) to study the nature by physical methods by far for many centuries.

4) Principle - Recognition or knowledge of the fact - that for studying the polyphase matters, media the only correct way is to use the discovered in 60s - 80s methods, theorems of Hierarchical physics and mathematics: Hierarchical Scaled Physics - Volume Averaging Theory, those specifically were created and tuned throughout the last 40+ years for polyphase polyscale physical, biological matters. Of many other methods suggested for the Heterogeneous media theorizing, modeling and understanding, up to this time there is no one more fundamental and/or correct.

We won't discuss or comment on numerous schemes suggested for heterogeneous, physical, biological polyphase media in the last ~100 years, as the mixture theory, for example, because they openly use an inadequate or truly simplified physical and mathematical description of the problem. We also published numerous analytical texts in hard copy and the web publications on this issue.

This fact is not objected or disputed by any professional, openly at least, for the last ~30 years. The complexity and educational policies are preventing professionals to acquire and employ the tools of HSP-VAT.

One of the examples, is the use of Gauss-Ostrogradsky (GO) theorem for deduction of governing equations for nearly 200 years in physics and other sciences. This theorem is valid only for a Homogeneous matter, that most of biologists even do not know and acknowledge. In hierarchical mathematics there are many alike theorems for the same purposes that have been developed and used during the last 40 something years.

5) Principle of Physical "Holism" (PPH): A living entity (cell, etc.) should be considered as a system of no "open" physical omission. Meaning - THAT NO ONE FUNCTION, PHYSICAL MECHANISM, PHENOMENON MAY BE OMITTED FROM THE SET OF PROCESSES, PHYSICAL PHENOMENA THAT ARE PRESENT AND VITAL FOR FUNCTIONING OF THIS LIVING ENTITY - MAMMALIAN CELL, PROCARIOTIC CELL, PROTOZOA, SUB-CELLULAR STRUCTURE, A TISSUE WITH LIVE SUPPORT EXCHANGE, ORGAN, ORGANISM.

According to this principle, biologists may not omit in their research, theoretical reasoning, modeling for the reasons of convenience, resource availability, any "reasonable" grounds to save money and/or labor, any known and important for functioning of live entity physical mechanism. As - no omission of phenomena occurring with soft solids, solids and fluids, polyfluids, particles in fluid, scaled fluids, elasticity of solid and soft solid biomedia, mass, energy, heat, momentum, electromagnetism describing phenomena, wave mechanics while studying, modeling, experimenting with the live systems.

Simply because all of the physics mechanisms of known character are participating in functions of the live subject and inseparable from the other functions or mechanisms.

The only admissible path in studying is to substitute the omitted phenomena by the simulating part of the same physical character with principally the same effectual action.

Hierarchical Polyphase Polyscale Concepts for Cell and Cellular Media Modeling.

1) Any mammalian, plant, prokaryotic cell or other bacterial live cell in reality is a polyscale constantly with continuous transport processes physical volumetric (averaged at some point, not a "point") object (entity), that constitutes a challenge for modeling its biological functions.

2) It is not correct to study, model and make valuable definitive conclusions about the cell function when using only the one scale physical and biological phenomenon(a) in a cell taken into account. This is the situation now in biology and medicine. Contemporary experimental biological, medical investigations lack ground and fundamental science, while applying the chemical reactions examination. Chemistry is itself of low understanding of integrative biomolecular mechanisms in a cell, tissue, etc.

3) The scale models constitute the separate spatial and temporal physical and mathematical models describing the functions of transport on the scale dependent phenomena in a cell.

4) Scale dependent physical (biophysical), mathematical models are inherently communicative Up-and-Down the scales. The scale communication of physical properties has been named as a scaleportation of properties and characteristics in HSP-VAT.

5) It is possible to commute the physical models and medium's properties at the neighbouring scales in a cell with mathematical strictness using methods developed in HSP-VAT.

6) Each scale developed Homogeneous models in a Ht medium based on Homogeneous presentation of this scale physical definitions and the field's governing equations can be connected more or less mathematically strictly to the neighbouring next Up-scale or Down-scale models only (most strictly) via using the interscale mechanisms of HSP-VAT.

7) The polyscale depiction of cell's functions, transport, models is the only correct approach for theoretical modeling and simulation, for experiments data reduction when the subject of analysis, theory, model, experiment is the polyscale physically object with the nature prescribed polyscaling of function - as the biological cell.

8) Any Homogeneous biomedium substance, cellular, or cell sample is in reality also of the two scale, at least, the physical entity that have molecular, atomic, sub-atomic and continuous description of transport, physical field processes of a physical volumetric character. The averaging and scaleportation of molecular scale transport and phenomena Up- to the Continuum (one of the continuum) scale phenomena and Down- to the molecular, atomic scale, should be used with application of correct Hierarchical mathematics of discontinuous "broken" physical fields.

9) At present, in the last approximately 27-29 years all the main physical fields, definitions and homogeneous governing equations have been reformulated and upgraded using methods of HSP-VAT for acting in the heterogeneous subject matters, for Heterogeneous media of solids, solids and fluids, polyfluids, particles in fluid, scaled fluids, elasticity of solid and soft solid media, mass, heat, momentum, electromagnetism describing phenomena, wave mechanics, acoustical fields. That is now making available the polyscaling in the description and modeling the most obvious and important transport (live) phenomena in a biological cell.

10) Advancements in the last 25 years in Hierarchical Scaled Physics - Volume Averaging Theory allowed to surpass inadequate, incomplete one scale homogeneous theories for averaging (mixing), "bulk" representing theories in almost every field of physics and biology. Now we can formulate the true polyscale Dynamics theories and models for biological objects and processes, polyscale by nature and fact.

11) None of the concepts written above is on the lists of "advanced" programs formulated in the recent and earlier years (and in "new" formulations of disciplines) in academic, university, government programs. And that is a signal of misleading development in the contemporary conventional Cellular Biology.

2.2. The Local, Non-Local, and Scaled Metrics, Physical Fields, and Their Mathematical Formulation

We know that each and every mathematical physics field governing equation started from the use of the Gauss-Ostrogradsky theorem. That means, we already included implicitly in the development of these equations the definitions of the two spaces and the two coordinate systems at each of the spaces agreed for consideration.

One is the scale that we perform the spatial integration - it theoretically can collapse into the point? But what is the point? What this point is representing?

The point is the subject without dimension in any direction, if in Cartesian coordinates, other 3D systems of spatial coordinates.

The lower scale (actually the same scale, but non-local) physics variables and properties then silently declared as irrelevant, unimportant - hereby we do not use, mention and mean that the point in our mathematical homogeneous formulation is actually the volume used in the GO theorem to obtain the current equation of interest. This approach is justified as soon as the matter assumed as of a homogeneous nature, because there are the mathematical theorems showing that the limit transitions when the size of a spatial domain collapses to an infinitely small one are presenting the properties of this domain in the selected internal point into which it collapses.

Meanwhile, we know that physics give us the very small objects - that constitute the body of any material - all these objects consist of atom and molecules.

That means, this conjecture for deduction of governing fundamental equations in physics via using the GO theorem where the volume should collapse to the volumeless point is defective.

And this precludes acceptance of the GO theorem for really applying to any physical matter, materials consisting of the atoms and molecules.

Because the GO theorem is mathematically valid for only Homogeneous matter - no atomic and molecular spatial Heterogeneity is accepted.

This surprised "discovery" actually "known" for many decades, since XIXth century, when this approximation was starting to be used in Atomic era physics and chemistry at the beginning of XX century.

There were voices of awareness of this approximation, incorrect for any heterogeneous, polyphase media and materials.

Unfortunately, physicists (leading figures) in the past preferred not to notice this mathematical fact. Chemists followed the path.

Because it was convenient and because this "ignorance" gave the only chance to cover with some mathematical strictness of XIXth century the whole body of physical consideration, more or less strict "proof" of mathematical deductions related to Continuum Media (CM) mechanics.

And most of the media have been accepted as continuum ones, even in chemistry - when it is "known" that any chemical substance, and biological substance and material are discontinuous matters due to existence of their atomic structure.

More correctly is to say that in reality the more precise path for mathematical conventional deductions in physics was and is the way to consider the discontinuous function of physical substance of interest, when it is no way to do otherwise, because of the atomic structure of a matter.

And at the same time, when any mathematical operations need to be performed for that physical material - the tool of operation is the Continuum conjecture - this matter, material is accepted as a continuous one.

Following that premises physicists use the Homogeneous matter GO theorem and alike up to now in almost any physical theory. While this is incorrect.

The most influential and important forces acting on all atomic and Upper scales of physical matter, material are the electromagnetic (EM) forces.

We would accept with precautions in this paper the conventional classical set of Maxwell-Heaviside-Lorentz's (MHL) EM homogeneous matter governing equations and based on them observed results that brought in and were justified in the HCM. We won't discuss here their validity and meaning.

Nevertheless, we have a prove that the electromagnetic phenomena mathematical expression governing equations used and discussed in many research areas of continuum media is an approximation of valid averaged sub-atomic MHL governing equations - http://www.travkin-hspt.com/eldyn/maxdown/maxdown.htm "What's Wrong with the Pseudo-Averaging Used in Textbooks on Atomic Physics and Electrodynamics for Maxwell-Heaviside-Lorentz Electromagnetism Equations".

It would be appropriate, meanwhile, to mention that at present exist a few points of view regarding the alternative systems of electromagnetic phenomena developed by different researchers.

There are also the non-local homogeneous media properties. Those also use the basis of integration, or averaging. Integration is taken as for the continuous functions. This legitimate base allows us to approach the variety of media, materials, but only the Homogeneous ones.

For Heterogeneous media and materials there are exist the Heterogeneous Whitaker-Slattery-Anderson-Marle (WSAM) type of theorems reminding the origin from the GO theorem. And the reason for the definitions of at least two scale spaces and physics became the pivotal one.

This, in turn brings the problem of definitions for the point-like Lower and the point-like Upper scale physical fields. Consecutively, we need to define the non-local, averaged fields for stated Heterogeneous problems at their corresponding scales.

We should obey to this original set of reasoning that was done two centuries ago in Physics and in Mathematics for the homogeneous media and translate it onto the heterogeneous, scaled media.

The great issue in all of this is the connection, communication between the physics and properties of each of the two spaces.

While for the homogeneous medium this question is seems never surfaced and discuses with application of the atomic scale discontinuous matter fields, for Heterogeneous media we need to specify these definitions with the greater detail.

After all, this is the key issue of scaling heterogeneous physics as it must work. Thus, we start with the definition of a point, a dot used in the mathematical formulation of physical problems.

Definition 1

> At the known and assigned previously system of coordinates the point is the object with no dimension in any of the three coordinates, and this object has the descriptive features, which determine the location of that point in the assigned system of coordinates. The point located physical property of the material has this spatial point determined value.

Following the GO theorem we now know that - if at any point with the coordinates inside of the problem's domain is known the functional dependency for a physical field, which in the most of physical sciences right now is the partial differential or just differential equation(s), then we imply that the domain which served for the derivation of this equation via the GO theorem was the domain of the Lower subspace - because in that theorem we start doing an integration over the finite volume and the finite surface(s).

Now - this principle can be applied to the heterogeneous media, which means - that after the averaging provided according to the one of the WSAM theorems - we get the mathematical equation (dependency) of the higher (another) space. With the corresponding spatial dependencies and the topology of the physical spatial fields.

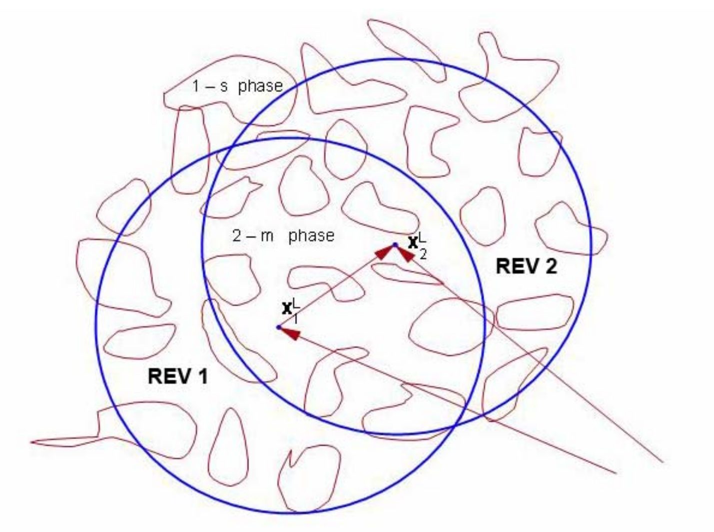

Figure 1. Representative Elementary Volumes (REVs) REV_1 and REV_2 in a heterogeneous medium with the assigned points of representation (x_1, x_2) at the Upper scale physical spatial

space. Here presented the two-phase and two scales Heterogeneous medium. The shape of the REVs can be not only a spherical one. Mathematical modeling and simulation are supposed to be performed on both scale spaces with the mathematical statements that complicate formulation and numerical (analytical) calculation of the physical field distributions.

With the one substantial different feature - it cannot infinitely be reducing the size, the volume of this domain - because this volume needs to be kept with the most of descriptive features of the both (or more) phases inside of our spatial integration domain.

Definition 2

The Upper Space point when connected to the Lower Scale Domain might reflect, determine, and establish the features of communications between the both space physics. These features can be of different physical description in accordance to their respected space physics definitions. And vise versa - the Higher Space point physics might control, govern, reflect, and determine in some ways the properties of the Lower Scale physical Domain.

It is easier to discuss and argue in favor of these definitions right now - after the number of problems in various disciplines of physics were solved in the said mode - when the Lower and Upper scale HSP-VAT governing equations were connected directly before and during their respected solutions - it has been shown by means of the two-scale solutions, especially with the exact two-scale solutions of some common textbooks known classical problems, see in -

"Classical Problems in Fluid Mechanics" http://www.travkin-hspt.com/fluid/03.htm; "Classical Problems in Thermal Physics" http://www.travkin-hspt.com/thermph/02.htm; "Globular Morphology Two Scale Electrostatic Exact Solutions" http://www.travkin-hspt.com/eldyn/glob1.htm; "When the 2x2 is not going to be 4 - What to do? http://www.travkin-hspt.com/eldyn/WhatToDo2.htm"; "Two Scale EM Wave Propagation in Superlattices - 1D Photonic Crystals Two Scale Exact Solution" http://www.travkin-hspt.com/eldyn/photcrys1.htm; "Two Scale Solution for Acoustic Wave Propagation Through the Multilayer Two-Phase Medium" http://www.travkin-hspt.com/acoustics/supercross.htm; "Effective Coefficients in Fluid Mechanics" http://www.travkin-hspt.com/fluid/04.htm; "Effective Coefficients in Electrodynamics" http://www.travkin-hspt.com/eldyn/edeffectivecoeff.htm.

The solutions of these problems have not been obtained for many decades since the first half of the XX century by other methods (given in textbooks the Lower Homogeneous scale "solutions" are wrongly attributed to the Upper Heterogeneous scale averaged fields).

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

There is the great need for creation or explanation of biological components, biomedia properties definitions for mathematical integration of these definitions into the scaled, hierarchical structure of bio-objects within the scaled bio-systems in this subject that we name the Scaled Hierarchical Cell Modeling (SHCM).

2.3.1. Existence and relations between the different scale phenomena in a living cell

Totally, the applied physical, biophysical tools (fields) are thought be able to provide for the ladder of spatial and temporal scales, physical models that could match one to another at the interface between the neighbouring scales fields. In reality it is a long way before meeting this goal.

At the same time we will be dealing in biological applications 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.

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.

<u>There is no substance of physical content in our known universe that is not a heterogeneous one.</u>

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 - the 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 not the collective influence of the Lower Scale forces, because up to now we connect 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 this paper 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 and critically analyze the features usually pertained to 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 (biophysical) nature.

For 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.

That says the connections of the scale inherited fields are of great significance.

Reviewed here studies have as results of their task solutions often 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***).

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.

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 through the more than 40 years.

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 use of any kind of potentials, - Lennand-Jones forces, for example.

It might help with the understanding of our approach to the more strict mathematically and physically description of many biological subjects, those mostly are of Heterogeneous, Scaled, and Hierarchical nature, made by nature itself when some knowledge of 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 should help in estimation of the present article outcomes - [2 - 18].

The same procedures we have been applying for analyzing the situation, trends and tools in Cellular Biology can be applied and to Theoretical Biology, Systems 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.

So far, as usual, in almost all the 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, just examples are in [19-21], we have found - with the governing equations that have been derived with the homogeneous Gauss-Ostrogradsky theorem for decades ago and inadequate for polyscale media, problems.

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

Approximately (because of the different sizes of cells) we would distinguish, we can take for simplicity the 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 the part of an assembly;

c) and the 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 the bottom scale phenomena are organized with polyphase, polyphysics processes, phenomena into a concerted, controlled functioning unit - a cell of ~1-5 [μm,Sc] scale.

As an example of understanding of hierarchical structure of biomedium we might mention the work [22] experimentalists' appreciate 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 to 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 correct and strict method exists, but the HSP-VAT, that has a more than 40 years of advancement from the commencement with first publications in 1967 [23,24] and a 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 the within the cell organelles or cytosol?

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

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

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

2.4. Introductory to Polyscale Description in Biophysics and Biotechnologies

2.4.1. Hierarchy of phenomena and morphologies in biological media

There are 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 [22] the authors sometimes openly speak on the subject of hierarchy and scale dependency in tissue engineering, which is to some extent becomes more and more recognized. So far that is in the verbal, qualitative mode within the biotechnologies.

Many issues even have not been raised in studies yet. The main is - What is the connection between the exact interactive communications in properties (mechanical, chemical, biocompatible) for structures of biomedium at various scales?

A few of the initial concepts and mathematics we depict here, while for most of readers these are not the conventionally known and excepted since 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.

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

We need further 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 (Bottom-Up, and vice-versa by Top-Down) -

Figure 2, is in such a mode that the useful information would be added to the characteristics on the upper level.

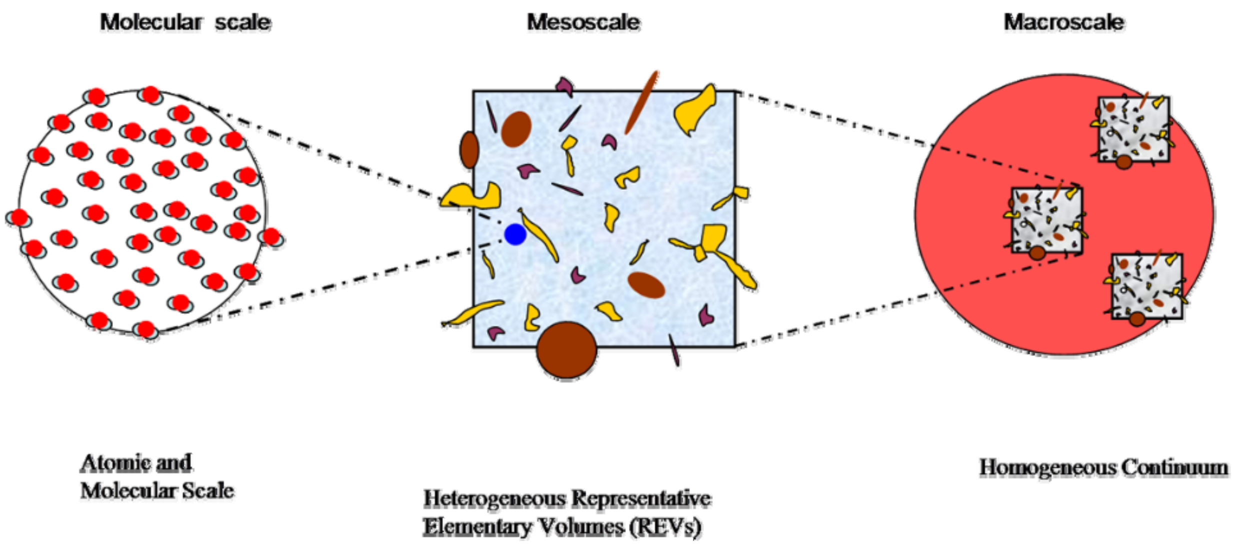

Figure 2. Simplified draft of Bottom-Up consecutive series of Representative Elementary Volumes (REVs) at three scales from a molecular one (one of the REVs is in an aqueous solution) to continuum scales. Note, that the bounding REVs surfaces do not belong to only the one singled out phase. There are only 3 scales in the physical (biological) description of the matter (biomedium, intracellular environment, tissue, etc.) depicted here in this figure. Each scale has its own physical/biochemical formulation of the problem related to the specified problem of any of these scales. The final polyscale formulation of the mathematical statements for each scale task to be more realistic should be of communicative physical nature, but not of the so-called "coupling" when the interactions between physics/biochemistry of each scale problems formulated with semantics and some coefficients following the common sense knowledge of the overall discipline peculiarities. Water molecules are depicted in a mode that is taught in GOHP, while this is erroneous atomic physics image.

The volume average value of one phase in a two phase composite medium $\langle s_1(\mathbf{x})\rangle$ in the REV and its fluctuations in various directions, its main physical and mathematical needs, definitions are determined [23-34] at first looking simple

$$s_1(\vec{x}) = \left\langle s_1(\vec{x})\right\rangle + \widehat{s}_1(\vec{x}), \qquad \langle s_1\rangle = \frac{\Delta\Omega_1}{\Delta\Omega}.$$

The three types of two-phase medium averaging over the REV (Figure 1) function f are defined by the following averaging operators arranged in the order of seniority

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

where the phase averages are given by

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

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

and the two internal phase averaged functions are given by

$$\{f\}_1 = \tilde{f}_1 = \frac{1}{\Delta\Omega_1}\int_{\Delta\Omega_1} f\left(t,\vec{x}\right)d\omega,$$

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

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 <f> is an average over the whole REV. There are also important averaging theorems for averaging of the spatial ∇ operator - heterogeneous analogs of Gauss-Ostrogradsky theorem. Those are plenty already since 70-80s [25, 26, 31-36]. 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

$$\{\nabla f\}_1 = \nabla\tilde{f} + \frac{1}{\Delta\Omega_1}\int_{\partial S_w}\hat{f}\,\vec{ds}_1\ ,$$

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

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

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

It can be shown that for the invariable morphology (<m>=const) of the medium the operator $\{\nabla f\}_1$ can be presented also as

$$\{\nabla f\}_1 = \nabla\{f\}_1 + \frac{1}{\Delta\Omega_1}\int_{\partial S_w} f\,\overrightarrow{ds}_1,$$

when <m>=const. Meanwhile, the foundation for averaging made, for example, by Nemat-Nasser and Hori [37] (and many others) is based on conventional homogeneous Gauss-Ostrogradsky theorem (see pp.59-60 in [37]), not of its heterogeneous analogs as the WSAM theorem.

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

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

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

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

The averaged time derivative according to transport theorem forms in the heterogeneous medium the following mathematical equation for a phase one, for example,

$$\left\langle \frac{\partial f}{\partial t} \right\rangle_1 = \frac{\partial}{\partial t} \langle f \rangle_1 - \frac{1}{\Delta\Omega} \int_{\partial S_{12}} (\mathbf{V}_s f) \cdot \vec{ds}_1,$$

where vector $\mathbf{V}_s$ is the velocity of the interface surface ∂S_{12}.

At present models of transport phenomena in heterogeneous when using the HSP-VAT allow to treat media with the following features: 1) multi-scaled media; 2) media with non-linear physical characteristics; 3) polydisperse morphologies; 4) materials with phase anisotropy; 5) media with non-constant or field dependent phase properties; 6) transient problems; 7) presence of imperfect interface surfaces; 8) presence of internal (mostly at the interface) physical-chemical phenomena, etc.

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 [25-28, 32-36] and many other. Meanwhile, features depicting closure, nonlinear theory, polyphysics applications, polyscale developments, exact solutions, etc. were first advanced and can be found only in works like [29-31, 34, 38-41] and other studies.

The REV of one of the shapes (could be numerous) applicable for a two-scale (multiscale) modeling of biomedia, cytosol components,(Figure 3, for example) and other cytoplasm polyphase matter.

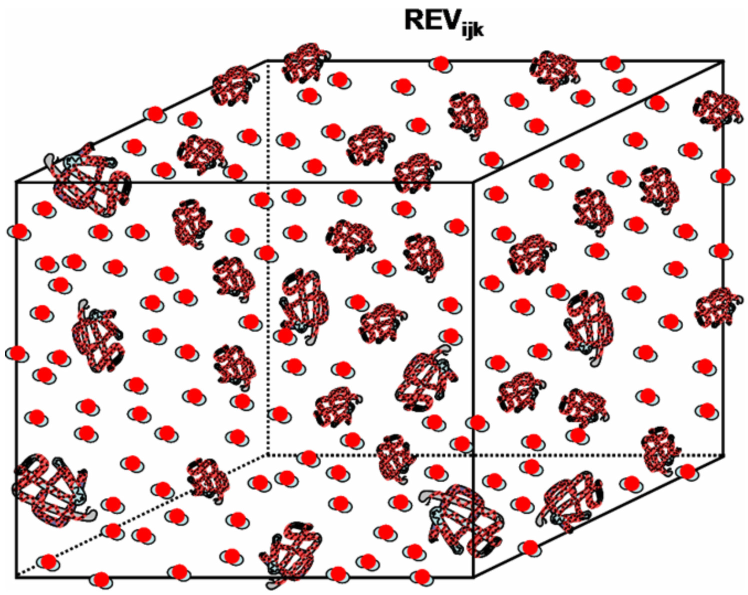

Figure 3. Three-dimensional structure REV with shown only the largest biomonomer (myoglobin) protein molecules in aqueous solution; water molecules size is not scaled correctly (they should be much smaller by scale). Presented in the figure are only the two species of the medium, cell, tissue sample, inside/around of the REV. That does not preclude the real polyphase statement of physics and mathematical nature when much more phases could be present and accounted for. The objects of different phases (molecules, molecular complexes, particles, homogeneous phases, etc.) are shown with the key morphological feature which is that the phase particle (parts) are being intersected by the REV's bounding surfaces (REVBS). That does not matter that these bounding surfaces could be of any specified and determined for the task/problem shape. Anyway, the REVBS should go (theoretically) throughout any object, part of the phase in the problem while this distinguishes the Heterogeneous and Homogeneous mathematical operations and theorems. Also, the water molecules are depicted in accordance with the COH chemistry, and this picture is incorrect. We return to this issue later on.

From this kind of standing, we would consider researches on the cellular biology multiscale topics.

2.5. Averaging, Scale Statements and Scaling Metrics in Homogeneous and Heterogeneous Media Applications

When one would write the recognized in many sciences the convective diffusion equation in a homogeneous medium $\Delta\Omega_f$

$$\frac{\partial C_f}{\partial t} + V \bullet \nabla C_f = D_f \nabla^2 C_f, \tag{1}$$

and the following one obtained in HSP-VAT as for the Upper scale averaged physical properties convective diffusion equation in the same phase $\Delta\Omega_f$ that is the $\Delta\Omega_f = \Delta\Omega - \Delta\Omega_s$

$$\langle m\rangle \frac{\partial \widetilde{C}_f}{\partial t} - \frac{1}{\Delta\Omega} \int_{\partial S_w} (\mathbf{V}_s C_f) \bullet \vec{ds} + \langle m\rangle \widetilde{U}_i \nabla \widetilde{C}_f = -\nabla \left\langle \widehat{C}_f \widehat{U}_i \right\rangle_f + \tag{2}$$

$$+ D_f \nabla \bullet \left(\nabla \langle m\rangle \widetilde{C}_f \right) + D_f \nabla \bullet \left[\frac{1}{\Delta\Omega} \int_{\partial S_w} C_f \, \vec{ds} \right] +$$

$$+ \frac{D_f}{\Delta\Omega} \int_{\partial S_w} \nabla C_f \bullet \vec{ds},$$

until relatively recent times (80s) it was hardly to be noticed that these equations are perfectly connected and by not only similar notations for concentration and velocity fields, but through the physical scales interaction mainly.

Comparison of Eq. (1) and one of the perfectly legitimate upper scale HSP-VAT heterogeneous medium mass transport Eq. (2) gives a ground for a number of observations which are critical for understanding and proper application of HSP-VAT scaled mathematical models. When one analyzes, for example, Eqs. (1) and (2) it should be up front a clear understanding of what does the global dependence through the interface of coefficient D_f mean ?

1) Is this the piece-wise constant in each of the phase function? Is the jump condition present on an interface?

2) Is this the piece-wise constant function with the relatively smooth but very thin transition layer of interface?

3) The most important question is - Are those interface physics phenomena so important qualitatively or quantitatively that their influence should be found in the governing modeling equations ?

The answers to these questions are laying mostly in the physics of another (smaller) scale and they are not ready for analysis in most of the problems.

Studies of the two-scale problems in HSP-VAT [23, 29, 31, 34, 38-41, etc.] concerning the thermal macroscale physics and fluid mechanics in capillary and globular heterogeneous (porous) medium morphologies demonstrated that even when interface transport has no openly declared physical special features as, for example, surficial transport - longitudinal diffusion or adsorption, etc., the input of additional surficial and fluctuation terms in the upper scale VAT equations solutions can be significant, reaching the same order in magnitude in balance, as traditional diffusion, heat exchange or friction resistance terms input.

That means - the another non-traditional scaled physical effects are exist and we need to take this into consideration when building the two (or more) scale physical model, experiment, optimize the structure.

More importantly is to have the lower scale physics of the interface included in the upper scale governing equations when this physics is somehow different from physics of upper scale. In electrodynamics those are, for example, effects of polarization on interface surface, surficial longitudinal waves or current, surface plasmons, etc.

Meanwhile, there is no other theory or approach which could include within itself the governing equations formulations of the physical phenomena from neighboring lower or upper scale description. We are not talking here about source terms inclusion. The source term inclusion provided usually in the form of some analytical formulae to describe an effect when there is the lack of knowledge or resources, or no vital necessity in analyzing the coupled phenomena of different scales.

The most sought after characteristics in heterogeneous media transport which are the effective transport coefficients, can be correctly determined using the conventional definition as for the steady-state solid two-phase effective diffusivity D^*, for example, with the one of possible formulae

$$-\langle \mathbf{q}_m \rangle = D^* \nabla \langle C \rangle = D_2 \nabla \langle C \rangle + (D_1 - D_2) \frac{1}{\Delta\Omega} \int_{\Delta\Omega_1} \nabla C \, d\omega,$$

but only in the fraction of problems, even while employing the Detailed Micro-Modeling -- Direct Numerical Modeling (DMM-DNM) exact solution that evidently requires the volumetric correct averaging (VAT averaging). The issue is that in a majority of problems, as for inhomogeneous, nonlinear coefficients, for example, and in many transient problems having the two-field, two-phase DMM-DNM exact solution is not enough to find effective coefficients, because the formulation of correct formulae is beyond the homogeneous physics method tools.

Thus, returning to Eqs. (1) and (2) it should be clear understanding that the representative point (RP) of physical field component in Eq. (1) is the dot point of approximate size ~10^3[ηm^3]

(for our range of scales), which includes $\geq 0(10^6)$ atoms for a substance with the low molecular mass. Then the reasonable representative elementary HSP-VAT volume (REV) at the upper scale for the Eq. (2) can be about $\gtrsim(1\div10)[\mu m^3]=(10^9\div10^{12})[\eta m^3]$, including within itself the thousands of lower scale RP volumes together with their structural elements, etc.

This REV volume would contain $\sim0(10^6)\times(10^9\div10^{12}) \simeq 0(10^{15})$ atoms, which is even for today's upper end high power supercomputers not a solvable MD problem. The important thing is that the algorithms of homogeneous MD techniques are integrating these volumetric effects incorrectly because of using the homogeneous GO theorem [42]. That means in a traditional homogeneous MD the Upper scale characteristics won't be analyzed properly anyway.

Still, the main reason, why Eq. (2) together with the lower level micromodel (1) is the more correct tool to model the heterogeneous medium transport, is because it has the mechanisms (additional terms) which clear role is to connect physics of lower scale transport, often different from the upper scale, and morphology of the two-phase (or more) medium to its bulk effective properties and upper scale fields.

It is essential to take into consideration the qualitative transformation of homogeneous conventional formulation of a process under investigation as, for example, the wave propagation problem into heterogeneous scaled (at least on two scales) problem as soon as the numerous structural objects which separate the phases are introduced by nature to the medium for any good reason.

3. Polyscale Polyphase Good Wishes for Cellular Biology

In the substantial contribution to the analytical observation in structural cellular biology review [1] a reader would recognize 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 are openly published in spite of the fact that the research in this arena is going on for decades.

We won't be responding to the much on the content of the paper [1], but only to the issues concerned the polyscale polyphase methods with regard to the stated in the paper good wishes on desirable tools (methods) for biological needs.

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 - in this paper is written the request for a Differential Heterogeneous Calculus with ability to account for Scaled (at least two scales) Governing Equation(s) to study, know, control and experimental design for the Heterogeneous Scaled (at least two scales) biological systems under investigation, cell processes.

Heterogeneous Scaled methods can be used now for Heterogeneous biomedia scaled characterization and have been already developed for a successful study, dynamic modeling of macromolecular assemblies, structures in cellular biology, etc.

With great interest, we have read this paper and the issues drafted in the Table 1, p. 4.

In the Table 1 of work [1] is given the most striking list of features desired for a full scale or complete resolution of "structural dynamics" modeling of cell macromolecular processes, as understood by authors.

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.

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.

We would make the statements and explanations related to the questions in the Table 1.

1) In the characteristic wish No. 1 in the table, one can find that the desirable feature 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.

What does it mean "structure"? Here we have insufficient wording regarding "structure"?

We can give a guessing description - with the word "structure" here it means a geometrical, topological arrangement of a substance or substances in space, its spatial localization.

So, we can write that (might be intuitively) a "state" is the 3D volumetric object, sometimes it might be of "composite" nature - or, it is always multicomponent within its boundaries. Also, the full description, or precise by this or that moment is not achievable. Mostly this situation can be explained via attraction of a term of the "scale".

We don't know for sure, or more exactly saying we have only approximate vision and physical understanding of atomic and subatomic world.

That is why we should better have taken our scales of a "state" 3D object along with its physical model(s) to be more or less precise within boundaries of our knowledge and current days understanding of bio-phenomena. It is not a secret, that many (most of) phenomena in bioworld are not understood with their connections, communication - not of verbal conjecture suggestions, but of their biophysical nature. While these phenomena are having some biological explanation nevertheless, it can be drawn an analogy to Ptolemeus solo planetary system explanation and understanding. Finally, our "state" or multi-"phase" 3D objects of interest are mathematically not simply connected regions (subjects), they are multi-phase, multiply-connected domains.

2) 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.

We would like to specify more exactly - the "key states" are the series of consecutive physical and geometrical objects (3D bio-objects) are meant to be defined as via the temporal or/and spatial realization, objectivity. This is the scale and physics involving definition. Otherwise, we need to say as in classical point mechanics, that we have points with mass and their trajectories. But we are not in such a simple situation in biology regarding this point.

3) 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 to the HSP-VAT Upper scale governing equations (GE) and their solutions.

Transition - "a transition occurs between a pair of key states......". Professionals who have happiness to be trained/taught strongly and fundamentally on the subject of basics, appearances and phenomenology of differential and integral calculus might instantly recall the fundamentals of differentials. Yes, it is the difference between the objects (two of them) and their positions interpretation. It is a scaling issue - because any object in biology, biophysics must be characterized first of all by its size (scale) and shape, location (and what is the location of objects with different inheriting scales), and function. That is why, there is no sense to determine the exact location and shape of macromolecule (even macromolecule) and a cell holding this macromolecule and compare them. But for what reason? All the pictures and semantic analysis provided for a macromolecule, ribosome floating in cytosol or exiting from organelles or making its function are mostly the exercises in molecular biology until we would like to take into consideration other biological objects that at the same time are acting, performing their function at the same geometrical location(s) and interfering with both - a macromolecule and its and their host - a cell.

4) Trajectory - "A trajectory is a detailed sequence of states describing a transition between two key states, like frames in a movie."

Any trajectory is determined via and by the center of mass of an object. In our case - the center of mass of object of what scale? And of which homogeneous or heterogeneous density distribution? When answering to this question we inevitably come to the scale determination of density and nature of our biological object(s). The better and more exact treatment brings us to the heterogeneity of our objects and their scale.

5) Rate of transition - "Transition rates can be expressed in a variety of ways such as the probability of moving from one state to another in a given period of time or rate constants."

Among simplest scale dependent physical and mathematical definitions is the fundamental definition of a derivative of the location dependent function of our biological object(s).

This can be of 1D, or 3D derivative. This can be a directional derivative. Rates of transition can be of integral nature as well. Obviously, scale-dependent definition and determination of transition rate mathematical formulations have been developed in physics for numerous occasions.

6) Conformational heterogeneity - "Conformational heterogeneity implies that multiple states exist in a single sample of the system. Such heterogeneity complicates bulk experimental measurements, often requiring single-molecule experiments."

Well, if this was the homogeneous biological object of 3D volume - we would need to say and determine only the 3D variety of the forms. That's it. Meanwhile, silently authors mean by this term, that the specifics of internal poly-"phase" scalable nature of biological object precludes this simple interpretation of conformational diversity.

As soon as we agree to realize that the biological object(s) is of complicated heterogeneous poly-"phase" (volume) nature and we cannot simply imagine and operate it as of a "homogeneous" unknown internal substance volumetric entity, or by "mixture" theory developed and used in chemistry, then we should accept the idea that to the internal structure and its physics should be applied its scale-defined consideration of already known but of smaller scale physical concepts and models. And that would mean the scale dependency consideration, study and modeling of physics and biological function of our object(s).

7) Kinetic heterogeneity - "Kinetic heterogeneity results from different copies of the system following different transitions. For example, different parts of the secondary structure of a protein can form independently and asynchronously before the tertiary structure forms [110] and, during ribosome assembly, different interactions between proteins and RNA can stabilize independently of one another [13]. "

Indeed, that means we need to read the previous concept scalable physics disclosure. They both are of the same scalable nature to answer.

8) Restraint - "A restraint restricts geometric and/or temporal properties of an assembly, such as the distance between two components, the overall shape of the complex, or the time interval between two key states. A restraint is a scalar function that quantifies the agreement between a restrained feature and the data."

Yes, the obvious explanation of reasons for appearance of this consideration that it is out of physics, actually.

Restraints are the natural features of the Lower (Lowest) level of scale, or for the Top-Down sequence of scale consideration, of the Upper scale. When a problem for a Lower scale has been formulated physically and mathematically correct - that means also that the molecules won't be flying out of a macromolecule or that the macromolecule itself can't be conformed to a size less than of its one of thousands molecules, etc.

9) Process representation - "A process is represented as a set of key states connected by transitions with associated trajectory and rate information."

Yes, indeed, a process is and has to be represented via the process' dynamics scalable model. That is not recognized in homogeneous biology. That means, at each scale of interest, a given process, pertained to this scale, should be represented by its own scale physical and mathematical model and that means the major point concept.

Meanwhile, in homogeneous biology used the common way to address this issue that is the introduction of various coefficients, which is so familiar from physics modeling.

Because these concepts and various scale models should be different in their mathematical modeling formulations, as long as even of the same physical process, for example, of momentum or diffusion nature at neighbouring scales taking place, their mathematical formulations are different, if correct.

It is an interesting reading how authors, using their terminology, language characterizing their own conceptual writings.

In p.4 authors are explaining the method of catching a "key state" right - "to provide structural information........."

The methods used are only of experimental nature. And that is explainable for conventional homogeneous biology. The modeling methods used by conventional physics are of the same only known homogeneous mode. And that is an inappropriate methodology biologists are guessing and arguing with specifics of their trade.

Regarding the experimental methods used for heterogeneous biological systems we can read (p.4) - "Disentangling conformationally heterogeneous states

Methods that measure average properties of the system are typically comparatively easy to apply, but their precision is limited by conformational and kinetic heterogeneity in the sample."

"Conformational and kinetic heterogeneity" that is the question.

While reading our previous notes above regarding these issues, we can add hopefully - that while these "heterogeneities", that should be called more correctly as spatial and dynamic non-linear problem specifics of the Lower scales, addressed as they should be at the Lower scales, then these features just mean knowing the features of solutions at the Lower temporal and spatial scales. That is the natural outcome.

In p.8 [1] we can find that: "**Conclusions**

Understanding macromolecular processes requires a wide range of experimental and computational techniques. As a result, we expect that integrative approaches will be critical, even more so than in the static structure case. Most existing models of dynamic processes have been the result of ad hoc integration of experimental results via simple models or mental constructions. But moving to higher accuracy, precision, coverage, and efficiency through incorporating all the available information will require novel computational approaches."

In the following sections in this paper we try to explain with the more simple portrayal the already existing tools, mechanisms in the polyscale hierarchical biology that were suggested firstly in 90s, continued to be under development throughout the present time.

4. Polyscale Physical Phenomena in a Cell and the HSP-VAT Methods Describing Them

We provide in the below section the main ideas and general governing equation - mostly for the Upper scale physics (while the Lower scale physics and governing equations are the Homogeneous statements known in COHP for a long time), that have been advanced throughout the last ~30 years in HSP-VAT. Within this mathematical framework there were numerous problems had been formulated and solved with the HSP-VAT applied for rather many physical disciplines - see the website http://www.travkin-hspt.com with information structured for various fields of physics, engineering and biological sciences.

4.1. Mass, Energy, Heat, Momentum Transport in Heterogeneous Media of a Cell

In homogenous media the physical and mathematical models used by theoretical biologists and workers from all over medical sciences are taken from conventional Homogeneous physical disciplines. Those studies exist of many thousands. We would be concerned here only with a few well known in heterogeneous physics methods for description of these enumerated above transport phenomena for biomedia, which is simply more complicated media and phenomena in those, but the basis of modeling should be the same for any heterogeneous processes because mathematics is the universal science.

We have done substantial research and writing in 80-90s in these disciplines for HSP-VAT clarification. The theoretical developments were suggested and some problems were solved firstly as the two-scale ones, even analytically [17, 43-49]. Summaries and further ideas with progress in theories and solutions while communicating to other physical sciences and can be found in our http://travkin-hspt.com/index.htm.

We bring up here, as examples, a few equations to demonstrate how far are the statements for Homogeneous and Heterogeneous Continuum Mechanics models and their mathematical embodiment. The scaleportation between molecular (macromolecular) scale levels and the meso-continuum mechanics in a cell is the area of research and development at present.

For example, when the linear equation of mass transport in water solution "fluid" phase of interior of a cell

$$\frac{\partial C_f}{\partial t} + V \bullet \nabla C_f = D_f \nabla^2 C_f + S_{C_f}, \qquad (3)$$

S_{C_f} is the Lower scale phenomena including the molecular scale reaction rates, while the second q (should be many) phase, particular phase the diffusion equation in its simplest form with the Lower scale reaction terms S_{C_q} would be

$$\frac{\partial C_q}{\partial t} = D_q \nabla^2 C_q + S_{C_q}. \tag{4}$$

The Upper scale, also of continuum mechanics governing equations take the form (one of possible) where the full averaged concentration integral term "fluid" equation yields (with the constant volume fraction of the "fluid" phase <m>)

$$\langle m \rangle \frac{\partial \widetilde{C}_f}{\partial t} - \frac{1}{\Delta\Omega} \int_{\partial S_w} (\mathbf{V}_s C_f) \cdot \vec{ds} + \langle m \rangle \widetilde{U}_i \nabla \widetilde{C}_f -$$

$$- \frac{\widetilde{C}_f}{\Delta\Omega} \int_{\partial S_w} U_i \cdot \vec{ds} + \nabla \left\langle \widehat{C}_f \widehat{U}_i \right\rangle_f + \frac{1}{\Delta\Omega} \int_{\partial S_w} C_f U_i \cdot \vec{ds} =$$

$$= D_f \nabla \cdot \left(\nabla \langle m \rangle \widetilde{C}_f \right) + D_f \nabla \cdot \left[\frac{1}{\Delta\Omega} \int_{\partial S_w} C_f \vec{ds} \right] +$$

$$+ \frac{D_f}{\Delta\Omega} \int_{\partial S_w} \nabla C_f \cdot \vec{ds} + \langle m \rangle S_{C_f}, \; U_i \equiv V, \tag{5}$$

while the shorten version with an impermeable interface is

$$\langle m \rangle \frac{\partial \widetilde{C}_f}{\partial t} - \frac{1}{\Delta\Omega} \int_{\partial S_w} (\mathbf{V}_s C_f) \cdot \vec{ds} + \langle m \rangle \widetilde{U}_i \nabla \widetilde{C}_f = -\nabla \left\langle \widehat{C}_f \widehat{U}_i \right\rangle_f +$$

$$+ D_f \nabla \cdot \left(\nabla \langle m \rangle \widetilde{C}_f \right) + D_f \nabla \cdot \left[\frac{1}{\Delta\Omega} \int_{\partial S_w} C_f \vec{ds} \right] +$$

$$+ \frac{D_f}{\Delta\Omega} \int_{\partial S_w} \nabla C_f \cdot \vec{ds} + \langle m \rangle S_{C_f}. \tag{6}$$

Similarly, in the particular phase q (with an impermeable interface), a second form equation when the full averaged concentration function under the integral is the following

$$\langle q\rangle \frac{\partial \widetilde{C}_q}{\partial t} - \frac{1}{\Delta\Omega}\int_{\partial S_w} (\mathbf{V}_s C_q)\cdot \vec{ds}_q = D_q \nabla\cdot\left(\nabla\langle q\rangle \widetilde{C}_q\right) + D_q\nabla\cdot\left[\frac{1}{\Delta\Omega}\int_{\partial S_w} C_q\, \vec{ds}_q\right] +$$

$$+\frac{D_q}{\Delta\Omega}\int_{\partial S_w} \nabla C_q\cdot \vec{ds}_q + \langle q\rangle S_{C_q}. \tag{7}$$

The transport momentum equations within the separate cell's region is based on a creep flow using the fluid dynamics laminar flow equations with the permeable interface surface ∂S_{w} between the phases (for the two phases), or a number of interface surfaces ∂S_{wq} for multiple phases accounted for.

The modified momentum linear equations for the each "fluid" phase at the Lower still continuum scale have the form

$$\nabla V = 0, \tag{8}$$

$$\varrho_f\left(\frac{\partial V}{\partial t} + V\cdot\nabla V\right) = -\nabla p + \mu\nabla^2 V, \tag{9}$$

where μ is the dynamic viscosity, the nonlinear term $(V\cdot\nabla V)$ can be easily dropped in the momentum equation for most of cases except some blood flow in a larger vasculature networks.

Now, one can write down the Upper scale "fluid" dynamics equations. The first is

$$\nabla\langle V\rangle_f + \frac{1}{\Delta\Omega}\int_{\partial S_w} U_i\cdot \vec{ds} = 0, \tag{10}$$

with the second filtration term; while the momentum equation for the "fluid" phase (cytosol)

$$\varrho_f\left(\langle m\rangle \frac{\partial \widetilde{V}}{\partial t} - \frac{1}{\Delta\Omega}\int_{\partial S_w} (\mathbf{V}_s V)\cdot \vec{ds} + \langle m\rangle \widetilde{V}\cdot\nabla\widetilde{V} - \widetilde{V}\frac{1}{\Delta\Omega}\int_{\partial S_w} V\cdot \vec{ds} + \right.$$

$$\left. +\nabla < \widehat{U}_i\widehat{U}_i >_f + \frac{1}{\Delta\Omega}\int_{\partial S_w} VV\cdot \vec{ds}\right) =$$

$$= -\nabla(\langle m\rangle \widetilde{p}) - \frac{1}{\Delta\Omega}\int_{\partial S_w} p\, \vec{ds} + \mu\nabla\cdot\nabla\left(\langle m\rangle \widetilde{V}\right) +$$

$$+\mu\nabla \bullet \left[\frac{1}{\Delta\Omega} \int_{\partial S_w} V \bullet \vec{ds} \right] + \frac{\mu}{\Delta\Omega} \int_{\partial S_w} \nabla V \bullet \vec{ds}. \tag{11}$$

Of course, to these two-scale equations one must add ones for energy and heat transport for each of the "phase", whatever is more relevant to the studied task.

These types and great number of modeling mathematical equations do not known for use in biology. Unfortunately, the education and other obvious reasons hinder the penetration of these modeling concepts to knowledge base of biological and medicine practices.

The old and of good mathematics solution of mathematical statement that was developed for the like filtration process at the pretty important place - through the capillary walls presented in [50] where the filtration equation for capillary wall

$$\langle\nabla p\rangle = -\left(\frac{3\mu_{eff}}{B^2}\right)\langle U\rangle,$$

where < > brackets denote the averaging, but what type of averaging is not specified (authors probably know the only one type of averaging), we can guess it is the internal phase average value. This "pseudo-averaged" equation is incorrect. The procedure for calculation of the effective drag coefficient $\mu_{eff\_}$ in page 134 is incorrect either.

One of the latest example is the series of models suggested and studied in the monograph [51] where in the first most realistic and advanced chapter by Nakayama et al. [52] one can find the sets of governing equations that can not be found as the correct modeling equations also, by the way, the modeling equations for heterogeneous (porous) media in the whole book chapters.

4.2. Elasticity of Solid and Soft Solid Heterogeneous Media of a Cell

The widely used by most of researchers in biophysics, biomechanics fields the homogeneous theories (as in examples, taken from hundreds of publications), by studies of [53-55] that embrace the concept that the biomedia are the homogeneous mixture of different substances, we do not analyze and observe here as soon as this approach to the biomedia description is out of correct, appropriate physics even of homogeneous physics. Too many of assumptions and conjectures are used [8,9,18,42]. We take the polyphase polyscale approach in this field.

It is known to Continuum Mechanics, Biophysics researchers that the any physical field's within Continuum Mechanics governing equations deduction has been started with application of the GO theorem to the piece, volume of a material, matter under investigation.

Meanwhile, the mathematical fact that this theorem is justified for only Homogeneous media mostly overlooked in applications. This brings the situation when many features of

Heterogeneous media are not seen in the models, governing equations for a bulk properties of the medium. For example, defects, irregularities, interface characteristics, fluctuations of different origins are being missed from the models, and only spoken about as of features that might be taken into account after the "bulk" properties are somehow known or measured, or approximated. We have been researched intensively on this subject in http://www.travkin-hspt.com/elastic/whatsupf/whatsup.htm. The hard copy publication [56] summarizes shortly the problematic (simply wrong) physics and mathematics of homogeneous elasticity theory used for heterogeneous materials, media.

Regarding the very important issue of the Upper scale medium effective coefficient bounds we need to recognize that by using the homogeneous concepts and theoretical constructions we inevitably are developing the same kind of useless characteristics on bounds.

The matter is that the methods of HSP-VAT give the ability to model, simulate and make calculation practically of an exact nature, as long as we are able to figure out the morphology features (that is now accepted as a solvable task) and willing to invest into the much larger then the usual mathematical physics project that is the two scale (at least) HSP-VAT mathematics simulation.

When the correct polyphase HSP-VAT applied to this problem we will have the equation for the averaged over the Upper scale medium stress tensor $\langle \sigma_{ij} \rangle$ as

$$\langle \sigma_{ij} \rangle = C^m_{ijkl}\left[\nabla \langle \mathbf{V} \rangle_m + (\nabla \langle \mathbf{V} \rangle_m)^T \right] + \tfrac{1}{2} \sum_{q=1}^{N} C^q_{ijkl}\left[\nabla \langle \mathbf{u} \rangle_q + \left(\nabla \langle \mathbf{u} \rangle_q \right)^T \right] +$$

we can not write here the strain tensor as averaged $\langle \varepsilon_{kl} \rangle_q$ already over the phase q, because the averaged $\langle \varepsilon_{kl} \rangle_q$ means the existence of additional surficial terms

$$+C^m_{ijkl}\left[\frac{1}{\Delta\Omega} \int_{\partial S_{wm}} \mathbf{V} \overrightarrow{ds}_m + \left(\frac{1}{\Delta\Omega} \int_{\partial S_{wm}} \mathbf{V} \overrightarrow{ds}_m \right)^T \right] +$$

$$+\tfrac{1}{2} \sum_{q=1}^{N} C^q_{ijkl}\left[\frac{1}{\Delta\Omega} \int_{\partial S_{wq}} \mathbf{u} \overrightarrow{ds}_q + \left(\frac{1}{\Delta\Omega} \int_{\partial S_{wq}} \mathbf{u} \overrightarrow{ds}_q \right)^T \right], \qquad (12)$$

here we used only the deviatoric part of the stress tensor in the fluid phase, where $\mathbf{V}$ is the velocity. while $C^m_{ijkl} = \mu$ (dynamic viscosity) and C^q_{ijkl} are the stiffness tensors for phases q, m is the subscript designating the liquid "matrix" or water solution (cytosol) medium volume all over the selected part within the biocell, that is taken here for simplicity as the Newtonian fluid, which is not, but to take into account the polyphase nature of cytosol there should be taken one more scale down physics model; N is the number of macromolecular complexes (or organelles, etc.).

We have here the 2(N+1) additional surficial terms - that is the correct averaging for Heterogeneous media that substantially different from the homogeneous elasticity equations - http://travkin-hspt.com/elastic/index.htm "Continuum Mechanics of Heterogeneous (Ht) Media; Elasticity, Plasticity".

For further we need to turn to the elasticity equation (Elastostatics as of the simplest form elasticity mathematical equation) for the selected part within the biocell

$$\nabla \cdot \sigma_{ij} = 0, \tag{13}$$

as in a polyphase medium. The modeling elasticity phenomena for the heterogeneous part of a cell demands the elastodynamics governing equations, that has been developed also in 90s. The Upper scale equilibrium averaged over the two-phase m and p where the perfect BC for a displacement at the interface has been applied (just an example) to the Nuclear Pore Complex (NPC) biomedium will be in its simplest form $\langle \nabla \bullet \sigma_{ij} \rangle = 0,$ which becomes after using the above derived averaged fields of stress via the displacement field in soft solids and velocity field in a fluid phase as

$$\mu\nabla \bullet \left[\nabla\langle \mathbf{V}\rangle_m + (\nabla\langle \mathbf{V}\rangle_m)^T\right] + \tfrac{1}{2}C^p_{ijkl}\nabla \bullet \left[\nabla\langle \mathbf{u}\rangle_p + \left(\nabla\langle \mathbf{u}\rangle_p\right)^T\right] +$$
$$+\mu\nabla \bullet \left[\frac{1}{\Delta\Omega}\int_{\partial S_{wm}} \mathbf{V}\overrightarrow{ds}_m + \left(\frac{1}{\Delta\Omega}\int_{\partial S_{wm}} \mathbf{V}\overrightarrow{ds}_m\right)^T\right] +$$
$$+\tfrac{1}{2}C^p_{ijkl}\nabla \bullet \left[\frac{1}{\Delta\Omega}\int_{\partial S_{wp}} \mathbf{u}\overrightarrow{ds}_p + \left(\frac{1}{\Delta\Omega}\int_{\partial S_{wp}} \mathbf{u}\overrightarrow{ds}_p\right)^T\right] -$$
$$-\nabla\langle p\rangle_m - \frac{1}{\Delta\Omega}\int_{\partial S_{wm}} p\overrightarrow{ds}_m = 0. \tag{14}$$

We need to remember that this model is working for the NPC assembly as of the array of complicated shape continuum mechanics elastic volumes within the cytosol.

To introduce the Lower scale physics of atomic, molecular interactions we need to agree with addition of this Lower scale physics phenomena with its physical and mathematical scale models. And this can be done with the substantial effort for simulation performing for the needs of the upper mesoscale simulation.

The phenomena of viscoelasticity that are truly pertained to the some parts – that are the subvolumes of interior of a cell like cell's skeleton, to the cell itself, to the cytoplasm as a whole for certain microorganisms and for locomotion, the pretty studied and failed in these studies viscoelastic properties of blood, blood flow, other biomedia, are also the subject of scaled, polyphase, polyphysics concepts modeling which should be followed by the scaled simulation. The basic concepts and viscoelastic governing equations for heterogeneous media via HSP-VAT also have been developed in 90s.

4.3. Electromagnetism Describing Phenomena in Heterogeneous Media of a Cell

We would shortly give a few basic formulations for Heterogeneous biological media electromagnetism modeling within the wildly used Maxwell-Heaviside-Lorentz (MHL) Continuum Mechanics electromagnetism. Among some first time polyphase correct formulation of physical and mathematical models for heterogeneous two-scale electrodynamics (http://www.travkin-hspt.com/eldyn/index.htm) we cite just the following [57-59].

The non-local HSP-VAT based electrodynamic equations for heterogeneous media used here have coefficients that can be inhomogeneous or nonlinear functions and the interface surface is taken to be immobile. Inhomogeneity is assumed in a form that involves space-function dependent smooth coefficients. The electrodynamic equations for an inhomogeneous nonferromagnetic substance are the Gauss's law equation

$$\nabla \cdot (\varepsilon \mathbf{E}) = \rho, \tag{15}$$

here, according to conventional nomenclature of electrodynamics, we designate also ε as the dielectric permittivity. The conservation of magnetic flux equation in homogeneous medium

$$\nabla \cdot (\mu \mathbf{H}) = 0, \tag{16}$$

here μ is usually the magnetic permeability in electrodynamics. Faraday's law of induction equation

$$\nabla \times \mathbf{E} = -\frac{\partial}{\partial t}(\mu \mathbf{H}), \tag{17}$$

the Maxwell - Ampere's law equation

$$\nabla \times \mathbf{H} = \frac{\partial}{\partial t}(\varepsilon \mathbf{E}) + \mathbf{j}, \ \mathbf{j} = \sigma \mathbf{E}, \tag{18}$$

(without induced by external field current density vector $\mathbf{j}^{(e)}$ with the constitutive relations

$$\mathbf{B} = \mu\mathbf{H},\ \mathbf{D} = \varepsilon\mathbf{E},\ \mathbf{j} = \sigma\mathbf{E}, \tag{19}$$

where σ is the electric conductivity coefficient. The equation of conservation of electrical charge ρ in a homogeneous medium is

$$\frac{\partial\rho}{\partial t} + \nabla\cdot(\sigma\mathbf{E}) = \mathbf{0}. \tag{20}$$

Averaging for the Upper scale of the first and third equations (15, 17) will be done using the left hand side as the nonlinear operator.

In this work we publish the simplified version of the electrodynamics - elasticity physics two-scale HSP-VAT governing equations, with the interface surfaces ∂S_{ij} movement admitted to having the negligible effect onto the some physics and governing equations.

Taking into account the all "phases" complimentary interfaces we have after averaging over the phase one (matrix) using $\langle\ \rangle_1$ equation (15) becomes

$$\nabla\cdot\left[\langle m_1\rangle\tilde{\varepsilon}_1\tilde{\mathbf{E}}_1\right] + \nabla\cdot\left[\langle m_1\rangle\left\{\hat{\varepsilon}_1\hat{\mathbf{E}}_1\right\}_1\right] +$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{12}}(\varepsilon_1\mathbf{E}_1)\cdot d\vec{s}_1 +$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{13}}(\varepsilon_1\mathbf{E}_1)\cdot d\vec{s}_1 + \sum_{i=4}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{1i}}(\varepsilon_1\mathbf{E}_1)\cdot d\vec{s}_1\right] = \langle\rho\rangle_1, \tag{21}$$

and the second electric field equation averaged is (used here are with the immobile interface notations)

$$\nabla\times\left(\langle m_1\rangle\tilde{\mathbf{E}}_1\right) + \frac{1}{\Delta\Omega}\int_{\partial S_{12}}d\vec{s}_1\times\mathbf{E}_1 + \sum_{i=3}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{1i}}d\vec{s}_1\times\mathbf{E}_1\right] =$$

$$= -\frac{\partial}{\partial t}\langle\mu_1\mathbf{H}_1\rangle_1. \tag{22}$$

Meanwhile, the Upper scale equations for magnetic field are averaged as following

$$\nabla\cdot\left(\langle m_1\rangle\tilde{\mu}_1\tilde{\mathbf{H}}_1\right) + \nabla\cdot\left[\langle m_1\rangle\left\{\hat{\mu}_1\hat{\mathbf{H}}_1\right\}_1\right] +$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{12}}(\mu_1\mathbf{H}_1)\cdot\vec{ds}_1+$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{13}}(\mu_1\mathbf{H}_1)\cdot\vec{ds}_1+\sum_{i=4}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{1i}}(\mu_1\mathbf{H}_1)\cdot\vec{ds}_1\right]=0, \tag{23}$$

and

$$\nabla\times\left(\langle m_1\rangle\widetilde{\mathbf{H}}_1\right)+\frac{1}{\Delta\Omega}\int_{\partial S_{12}}\vec{ds}_1\times\mathbf{H}_1+\sum_{i=3}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{1i}}\vec{ds}_1\times\mathbf{H}_1\right]=$$

$$=\frac{\partial}{\partial t}\langle\varepsilon_1\mathbf{E}_1\rangle_1+\left[\langle m_1\rangle\widetilde{\sigma}_1\widetilde{\mathbf{E}}_1+\langle m_1\rangle\left\{\widehat{\sigma}_1\widehat{\mathbf{E}}_1\right\}_1\right]. \tag{24}$$

The HSP-VAT based transient charge conservation equation in heterogeneous media obtains the form

$$\frac{\partial\langle\rho\rangle_1}{\partial t}+\nabla\cdot\left[\langle m_1\rangle\widetilde{\sigma}_1\widetilde{\mathbf{E}}_1\right]+$$

$$+\nabla\cdot\left[\langle m_1\rangle\left\{\widehat{\sigma}_1\widehat{\mathbf{E}}_1\right\}_1\right]+\frac{1}{\Delta\Omega}\int_{\partial S_{12}}(\sigma_1\mathbf{E}_1)\cdot\vec{ds}_1+$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{13}}(\sigma_1\mathbf{E}_1)\cdot\vec{ds}_1+\sum_{i=4}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{1i}}(\sigma_1\mathbf{E}_1)\cdot\vec{ds}_1\right]=0. \tag{25}$$

Analogous Upper scale averaged equations result for the 2nd and other phases, for example, in the second phase

$$\nabla\cdot\left[\langle m_2\rangle\widetilde{\varepsilon}_2\widetilde{\mathbf{E}}_2\right]+\nabla\cdot\left[\langle m_2\rangle\left\{\widehat{\varepsilon}_2\widehat{\mathbf{E}}_2\right\}_2\right]+$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{21}}(\varepsilon_2\mathbf{E}_2)\cdot\vec{ds}_2+$$

$$+\frac{1}{\Delta\Omega}\int_{\partial S_{23}}(\varepsilon_2\mathbf{E}_2)\cdot\vec{ds}_2+\sum_{i=4}^{n}\left[\frac{1}{\Delta\Omega}\int_{\partial S_{2i}}(\varepsilon_2\mathbf{E}_2)\cdot\vec{ds}_2\right]=\langle\rho\rangle_2. \tag{26}$$

As one can observe, the most appealing features of heterogeneous medium electrodynamics equations is the inclusion of terms reflecting phenomena on the interface surface(s) ∂S_{12},which will be used to incorporate morphologically precisely polarization phenomena as well as tunneling into heterogeneous electrodynamics.

One of the immediate consequences of adopting the correct governing equations in heterogeneous medium is that the problem of effective coefficients appears in clear formulation where the only serious challenges are computational difficulties see [31,34] and references therein.

There are also quite a bit of theoretical constructions that were suggested for the hierarchical medium description and effective characteristics, as electrical conductivity σ_{eff}, thermal conductivity k_{eff}, dielectric permittivity $\varepsilon_{\mathrm{eff}}$, and magnetic permeability μ_{eff} in heterogeneous media. The "cross-physical" analogies are often the basis for experimental analysis and data reduction. It can be seen that there are physical phenomena that are ignored making these analogies incomplete or not possible. Most obvious are the interface surface charge distribution, weak actual current in dielectrics and surface current distribution, as well as surface diffusion phenomena, which greatly complicate the description. The usefulness of an analogy between momentum transport (via Darcy's law) $\langle \mathbf{V} \rangle = -(k_{dc}/\mu)\langle \nabla p \rangle$ and Ohm's law $\langle \mathbf{j} \rangle = \sigma^*_{ij} \langle \mathbf{E} \rangle$ in porous media can be determined by a comparison of conductivity equation in fluid phase one, for a dc applied field,

$$\nabla^2\left(\sigma_1 \langle m_1 \rangle \widetilde{\Phi}_1\right) + \nabla \cdot \left[\frac{\sigma_1}{\Delta\Omega} \int_{\partial S_{12}} \Phi_1 \, d\vec{s}_1 \right] + $$

$$+ \frac{\sigma_1}{\Delta\Omega} \int_{\partial S_{12}} \nabla \Phi_1 \cdot d\vec{s}_1 = 0, \tag{27}$$

and the creeping transport momentum equation in the same phase [34]

$$\mu_f \nabla \cdot \left(\nabla \langle m \rangle \widetilde{\mathbf{V}}\right) + \mu_f \nabla \cdot \left[\frac{1}{\Delta\Omega} \int_{\partial S_{12}} \mathbf{V} \, d\vec{s}_1 \right] +$$

$$+ \frac{\mu_f}{\Delta\Omega} \int_{\partial S_{12}} \nabla \mathbf{V} \cdot d\vec{s}_1 = \nabla \langle p \rangle_1 + \frac{1}{\Delta\Omega} \int_{\partial S_{12}} p \, d\vec{s}_1 \ , \tag{28}$$

where μ_f here is the fluid dynamic viscosity, and Φ is the potential in the phase's medium in the system. Observation and analysis of these equations [40,41,57-60] shows some similarity in the appearance of mathematical operators in the left hand side of statements, but for media with permeable interface. The pressure loss right hand side terms in (28) allows similarity only for medium with homogeneous morphologies, when the right hand side becomes constant. This kind of comparison is not possible when the two homogeneous equations of electrostatics (for each of the phase) written with their corresponding boundary conditions.

4.4. Wave Mechanics, Acoustical Fields in Heterogeneous Media of a Cell

We will present here also as an example of the developed technology (physical models, mathematics, techniques, methods of analysis and solution, etc.) of acoustics in Heterogeneous media within the HSP-VAT. This example is for demonstration of the available theoretical approach and methods for treatment of biomedia, which is always Heterogeneous, acoustical phenomena studies. This area of biomedia treatment is hardly of the first order of interest while study, for example, the Nuclear Pore Complex physics and mechanics. Nevertheless, for other of upper scale biological problems the wave mechanics is the vital part of medical techniques, we remember that the blood flow, for example, is the periodic phenomenon. Apart of tasks that realistically are fallen into the category of elasticity issues in biomedia, there are the large area of bioacoustics that is demanding for proper media based treatment, solutions.

Following the linearized hydrodynamics equations in a cell's interior water solution

$$p = p_0 + p', \; \varrho = \varrho_0 + \varrho',$$

$$\frac{\partial p'}{\partial t} + (\varrho_0 c^2)\nabla \cdot \mathbf{V} = 0, \; \frac{\partial \mathbf{V}}{\partial t} + \frac{1}{\varrho_0}\nabla p' = 0, \tag{29}$$

where c is the sound velocity in a medium, it is known the equation of acoustical wave to be derived as the simplest form wave equation for homogeneous medium without absorption

$$\frac{\partial^2 F(x,y,z,t)}{\partial t^2} = c^2 \Delta F(x,y,z,t), \tag{30}$$

where F is, for example, the pressure fluctuations $p'(x,y,z,t)$.

In inhomogeneous media (still without discontinuous interfaces), one of the acoustic final equations in the time-harmonic form is

$$\nabla \cdot \left(\frac{1}{\varrho(\mathbf{x})} \nabla p \right) + \frac{k^2}{\varrho(\mathbf{x})} p = 0, \; k^2(\mathbf{x}) = \frac{\omega^2}{c^2(\mathbf{x})}, \quad p \equiv p'. \tag{31}$$

This equation for further transformation as by the HSP-VAT methods might be easier to hold as

$$\nabla \cdot (a(\mathbf{x})\nabla p) + b(\mathbf{x})p = 0, \quad a(\mathbf{x}) = \frac{1}{\varrho(\mathbf{x})}, \quad b(\mathbf{x}) = \frac{\omega^2}{\varrho(\mathbf{x})c^2(\mathbf{x})}, \tag{32}$$

which we have shown is not a correct form for the scaled analysis, when the upper scale physics is dependent on the heterogeneous effects form of the lower scale physics - http://travkin-hspt.com/acoustics/index.htm.

For a polyphase medium the non-local two-scale averaged acoustic equations can be obtained in the following mathematical form, for example, for the first phase (might be the cytosol) as

$$\frac{\partial^2 F_1(x,y,z,t)}{\partial t^2} = c^2 \Delta F_1(x,y,z,t), \tag{33}$$

$$\frac{\partial^2 \langle F_1 \rangle_1}{\partial t^2} - \frac{\partial}{\partial t}\left[\frac{1}{\Delta\Omega} \int_{\partial S_{12}} (\mathbf{V}_s F_1) \cdot d\vec{s}_1 \right] - \frac{1}{\Delta\Omega} \int_{\partial S_{12}} \left(\mathbf{V}_s \left(\frac{\partial F_1}{\partial t} \right) \right) \cdot d\vec{s}_1 =$$

$$= c_1^2 \Delta(\langle F_1 \rangle_1) + c_1^2 \nabla \cdot \left[\frac{1}{\Delta\Omega} \int_{\partial S_{12}} F_1 \, d\vec{s}_1 \right] + \frac{c_1^2}{\Delta\Omega} \int_{\partial S_{12}} \nabla F_1 \cdot d\vec{s}_1 . \tag{34}$$

This surface for a polyphase medium (q+1) is the poly-part surface $\partial S_{12} = \sum_{q=1}^{N} \partial S_{1_q}$. It is obvious that, while observing acoustic equations for the lower homogeneous scale (32,33) and for upper scale averaged presentation equation (34) one would have to deal with and naturally include into description, modeling and simulation the new interface based physically understandable 4 (four) more terms in the governing upper scale acoustics equation (34).

As soon as these above heterogeneous acoustics modeling equations are only an example of the two-scale acoustics description for heterogeneous, scaled media, we can suggest for more detail to address to the website section http://travkin-hspt.com/acoustics/index.htm, where much more details and some classic problem solution had been made (presented) for educational purposes. This information can be found so far only in this and associated with it websites.

Now we can state, that to the all issues No. 1-9 in the Table 1 (p. 4) of [1] are existing the HSP-VAT corresponding classifications and exact descriptions and mathematical formulations in the field and language of the HS physics, which have been applied so far to many sciences.

Among them in the website presented:

1) http://travkin-hspt.com/acoustics/index.htm "Acoustics"
2) http://travkin-hspt.com/atom/index.htm "Atomic and Subatomic Scales Description of Matter with HSP-VAT"
3) http://travkin-hspt.com/bio/index.htm "Biology and Ecology as Hierarchical, Heterogeneous, Multiscale Sciences and their Applications"
4) http://travkin-hspt.com/compos/index.htm "Composite Engineering"
5) http://travkin-hspt.com/elastic/index.htm "Continuum Mechanics of Heterogeneous (Ht) Media; Elasticity, Plasticity"
6) http://travkin-hspt.com/eldyn/index.htm "Electrodynamics"
7) http://travkin-hspt.com/fluid/index.htm "Fluid Mechanics"
8) http://travkin-hspt.com/thermph/index.htm "Thermal Physics"
9) http://travkin-hspt.com/med/index.htm "Medicine Heterogeneous, Multiscale Applications"

and other sciences and technologies.

5. Conclusions

We have shown in this material that the ability at present time to approach thus complicated area as the theoretical modeling of most of existing physical processes in the polyphase environment of biological cells does exist. The cells, if to apply with the appropriate scales are extremely complex media from any objective point of view.

Obtained models are also extremely complex, demanding for modeling and simulation effort the resources allocation comparable to the biggest projects ever encountered throughout the human history.

A separate each kind physical phenomena studying as of momentum, heat, elasticity, electromagnetism, wave mechanics, bio-chemical reactions, as this is the way of doing research now in cellular, structural biology, are in no way explain and can point out to the reasons and consequences as long as the whole functioning of the cell is the tightly interactive process where all known to people physics is interwoven altogether.

Here it is presented as the two-scale at least models interconnected narrative (can be more scales included, albeit and more complicated physics and math with), where the Lower scale models are of familiar from the major physical textbooks description with the homogeneous fields that are formulated as homogeneous mathematical statements. Meanwhile, the upper second scale modeling formulation for the physical processes mentioned above have been developed for many years already, used for studies, and obtained the results unattainable with the one scale homogeneous physics.

Now the tools and methods of HSP-VAT are available as the polyscaling tools for description and modeling of the most obvious and important transport (live) phenomena in biological cells. The many details of transforming these rather general mathematical models, governing equations have been already given in specific physical disciplines worked out in the hard copy and web publications. Of course, the practical value biophysical theories and modeling capabilities should find the further devoted effort and financing.

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