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Research Paper

Biomechanics, computational Intelligence, and systems biology with application on vitreous dynamics using Java: An incipient discussion

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ABSTRACT

This paper proposes the simultaneous application of molecular dynamics, systems biology, biomechanics, and computational intelligence for a single aim: understanding numerically the vitreous detachment, an ophthalmologic disorder (pathophysiology). The paper is theoretical and seminar in some sense, letting for further papers the detailed labors. The paper is somehow provocative in some sense when it applies molecular dynamics to a macro-system (the vitreous), and simultaneously audacious when it proposes to associate the vitreous detachment to genotype consequences (something beyond just aging effect as in general associated). The numerical simulations are not presented herein; apart from references to incipient results. The objective is to make known the efforts of the author for reasons such as documentation or divulgation. In the biological community, the most recent challenge is how to properly link the genotype to phenotype (how to correctly make predictions starting from either of them). Further this had created two different-widely-accepted approaches in biological modeling: button-up and up-button. In the formal one starts from gene-based (or some similar level) information and strives to predict accurately some manifestations in a higher hierarchal level, such as disorders; whereas in the latter one attempts to understand the same, but from high-level pillars, most of the time physiology-based approaches. This kind of researches could have great impact in medicine and life sciences such as modeling of pharmacokinetic/pharmacodynamics systems. The author so far are not aware of any parallel work, except the ones cited, but using somehow different approaches and guiding principles. In order to simulate the virtual system, which includes mathematical models and simulations, it proposed Java™ as programming language mainly for its features. In order to cope with the complexity for correlating the genotype to the phenotype (the undesirable pathophysiology), we proposed the intriguing and state of the art computational intelligence. And finally, this work was born from the efforts of a second scientist that if it succeeds, it will be available as a discrete-continuous simulator as some defends as required in some situations. This work is relevant for correlating the most recent endeavors of applied genetics to biomechanics, something demanded in biomedical sciences.

Key words: Computational intelligence, systems biology, Eyes' disorders, biomechanics, vitreous detachment, molecular dynamics, mechanics of solids and materials, gene expression dynamics, Java.

Jorge Guerra Pires

Faculty of Applied Physics and Mathematics (Gdansk University of Technology)/Faculty of Engineering (University of L'Aquila)/ CAPES Foundation, Ministry of Education of Brazil - Brasília, DF 70040-020, Brazil. E-mail: jorgeguerrapires@yahoo.com.br, jorge.guerrapires@mathmods.eu, Tel: 0055 31 8582 6260.

INTRODUCTION

Science evolves step by step and each man depends on the work of the previous ones. Accordingly, many advances in science slept quietly for a long time until the correct approach, application and moment came up, even under the

immeasurable firmness of well-known names in science. Consequently, many of the advances in science had to wait for until a specific step had been done. An example is the final and definitive proof of the atom existence, done by A. Einstein in 1905 (Stachel, 1998) based on the work of R. Brown in 1827, a botanist; they do not just exist, rather they leave traces that we can observe and measure. In the same way, it was done with the DNA[1] structure (Double Helix) done by Crick and Watson in 1953 based on the work of previous scientists on X-ray samples (Nye, 2010; Russel, 2010)[2]

In the biological community, the most recent challenge is how to properly link the genotype to phenotype (how to correctly make predictions starting from either of them). Further, this had created two different-widely-accepted approaches in biological modeling: *button-up and up-button; those names are one way or another fuzzily used in the biological community, the preferential meaning will be explained herein. In the formal one starts from gene-based (or some similar level) information and strives to predict accurately some higher manifestations, such as disorders; whereas in the latter one attempts to understand the same, but from high-level pillars, most of the time physiology-based approaches. In accordance with Prof. P. Palumbo and Dr. A. De Gaetano (Institute of Systems Analysis and Computer Science, Italy)[4], this kind of researches could have great impact in medicine and life sciences such as modeling of pharmacokinetic/pharmacodynamics systems. Accordingly, those systems might be named "Complex Networks", once they in general are independent-coupled dynamical systems (IIComplexNet, 2013)[5]. In accordance with the literature, emergent properties are the most intriguing features such as synchronism from random-behavior systems in complex networks.

Unfortunately, those approaches presented in the last paragraph had been successful in their own domains, but failing when they need to work together (in synergy for a final-common goal) (IIComplexNet, 2013) for an interesting-and-rich set of dynamics modeling from both viewpoint. Based on this spirit, successes and failures of both approaches for biological modeling, some had proposed a middle-inspired approach (m.i.a), (Noble, 2006); moreover, Noble (2006) had to 'fix' (to propose an alternative version to) the old flowchart of 'one-direction', 'feedbacks' are predominant in the interface gene-environment in a more realistic model for phenotype-genotype biochemical pathways. In the same line, others had worked on mathematical models for biology using the same methodological approach, (Pires, 2012a; Pires, 2013a; Pires, 2013b), in which computational intelligence-based methods represents the up-button approach while the button-up approach is represented by traditional mathematical models; Pires (2013a) proposed the union of them in a biological-mathematical-modeling methodology. In order to properly understand this paper, it would be interesting that the reader is aware of those discussions in biological-mathematical modeling (Noble, 2006; Keller, 2003).

Regarding the dilemma of the opening paragraphs; how to properly study biological systems, we can identify something equal in physics, (bio) material science. Suppose you intend to study mathematically and computationally the behavior of a new material, should you apply discrete-based or continuous-based approaches? Superficially this question might sound trivial, but it is not (Figure 1). This project will have to confront this dilemma as well to succeed. In order to even start pondering on the question just presented, one needs to be aware of classical and quantum mechanics in a theoretical and practical perspective; further, in classical mechanics, continuum mechanics and particle physics (Fung, 1977; Schlick, 2002; Bulatov and Cai, 2006; Asaro and Lubarda 2006; Reddy, 1985; Rapaport, 2004; Ogden, 1943). In simple terms, when we need mathematical abstractions of (bio) materials, do we need to make use predominantly of macro- or micro-information? Some believes in continuum-discrete approaches (S. Kshevetskii, State University, Russia)[3]. More focused to real-world, when we want to treat living matter, such as tissues, do we have to make use of macro-based disciplines such as physiology or micro-based approaches such as molecular biology? This paper intends to defend the 'partnership' between those two powerful techniques. And we make use of the vitreous detachment disorder to support the theory (Repetto et al., 2010; Le Goff and Bishop, 2008, Bottega and Bishay, 2012; Pires, 2012b).

In reference to the vitreous detachment problem, this is an ophthalmological disorder; this is a pathophysiology related to the eye. As a consequence of factors associated to aging, the vitreous body starts to detach from the internal wall of the eyeball, creating a water-filled regions in the back of the eye, in front of the retina in general. The vitreous detachment might causes blindness. Further, in some cases, some 'holes' appear in the middle of the vitreous body, but due to internal pressures it moves to a single and bigger hole in the back of the eye. As defends

[1]Physical Address: Rua Timbopeba, 24, Antônio Pereira, ZIP-code: 35411-000, Ouro Preto, Minas Gerais, Brazil.

[2]Deoxyribonucleic acid is the "receipt book" of proteins, which are the "workers" in our biochemical processes in our body. For unfamiliar readers, please see for example Schoof et al. (2012) or Russel (2010).

In accordance with suggestion of Prof. C. Manes (University of L'Aquila, Italy), the best terminologies are bottom-up and top-down, respectively.

[3]100 greatest discoveries: genetics. [*Media*]: the science channel's.

[4]This is based on a set of lessons lectured by the same in Poland, Gdansk University of Technology, as part of the course in Mathematical Engineering and Technical Physics, Mathmods Programme.

Prof. A. Tatone (University of L'Aquila, Italy), this fluid – a gel-like fluid – can be modeled as a non-Newtonian fluid; the most significant point is that it is not a conventional fluid in the extreme sense, it is 'stabilized' by networks of collagen – the most abundant protein in the body– in the dimensions of 10-20 nanometers. Furthermore, Prof. A. Tatone (University of L'Aquila, Italy) believes that this biomaterial can be modeled successfully via mechanics of solids simulated using finite elements method. In Repetto et al. (2010), this hypothesis had been studied. Nonetheless, in works done by the author, we have reasons to expect that molecular dynamics might be used to model the case with some advantages compared to Prof. A. Tatone (University of L'Aquila, Italy).

The drawback that could appear when applying molecular dynamics to the vitreous dynamics is the necessity of computational power, once molecular dynamics is somehow 'heavy', and necessity of biological-collected data, which is a common bottleneck for any project. The former can be remedied with ingenious tricks, some well-known such as list of neighbors or 'cutoffs' or some designed such as "network molecular dynamics"; whereas the latter can be remedied with a proper partnership with third parties from biomedical community. Further, regarding the necessity of computational power, see that the super computer in 1998 today can be found to be purchased for less than 1000 EUR; computational power is growing significantly. According to N. Kasabov (Knowledge Engineering and Discovery Research Institute, New Zealand)[4], supercomputers such as quantum computers have been creating great expectations. In this paper we intend to present the essence of the (ongoing) project and discuss on the achieved conclusions by the author.

In accordance with Pires (2013c), with the technological advances and simultaneous paradigms shifts in science, we had rises and falls of scientific branches. One field that holds great promise of prevailing in the millennia is called systems biology (Pires, 2013c; Alon, 2006). Loosely stating, systems biology attempts to understand the workings (phenomena) of biological systems on the grounds of elements' interactions by having enough knowledge of the parts itself. One might say, as some even defends Noble (2006), that systems biology is the new generation of physiologists. For times, the so-called reductionism had prevailed as relevant approach for studying bio-matter. However, with time, the limitations appeared and a 'holistic' viewpoint as needed; these paradigm shifts were long noticed by some theoreticians in theoretical physics (Capra, 1975). As defends Noble (2006) systems biology brings all the best of the past reductionism and the achievements in science such as molecular biology; further, it also seems to fulfill the changing of accepted-truth as Keller (2003) disserts, something that changes from time to time. Systems biology is a software-dependent science (Kitano, 2001; Myers, 2010); the reasons for that is somewhat clear if one takes a look at the types of endeavors it is associated, such as understanding consequences of mutations in networks, from local to global. Networks are well-known due to complexity; those networks are called complex networks and they are everywhere (Cohen et al., 2010; IIComplexNet, 2013).

This can be asserted with certain degree of truth that amongst the future-potential cornerstones of modern applied sciences, we will have computational intelligence, biomechanics, and systems biology. They are all extremely interdisciplinary fields and correspond to the prediction delineated by Pires (2013c). Those are the cornerstones of the current work; those fields are to some extent united for making the core of the presented paper. The paper is theoretical and seminar in some sense, letting to further papers the detailed labor. The paper is somehow provocative in some sense when applies molecular dynamics to a macro-system (the vitreous), and simultaneously audacious when it proposes to associate the vitreous detachment to genotype consequences (something beyond just aging effect as in general associated).

The proposal as a whole might be considered a tough endeavor, but if completely achieved, it is something quite important for systems biology, biomechanics, and computational intelligence. For a biomechanics call for those kinds of works as the 'future' (Humphrey 2003). Some are defending the use of gene-based theory in the creation of new theories in (continuum) biomechanics instead of just classical-based models; this presents a clear-momentum for those applications, no matter how tough is the venture (Figure 8). Unfortunately, our purely mathematical models are limited in those cases, where we have many elements (sometimes even more than 1000 genes simultaneously) working for a single aim; this is where computational intelligence clearly gains momentum. A second motivation for making use of computational intelligence based methods is stochasticity. According to Wilkinson (2012), stochastic models must prevail in biology due to many reasons such as complexity or even some more well-known such as quantum mechanics. See that computational intelligence models are somewhat inherently stochastic-resilient since they model in general the "essence" of the system. However, if simulating stochasticity is essential, one could unite the models of Wilkinson (2012) with the insights of Pires (2013a), in which one applies hybrid models in the spirit of neural networks such as committee machines; for committee machines (Haykin, 1999).

In simple terms, the problem studied here can be summarized using Figure 2. The vitreous detachment was chosen due to previous concern of the author on this research, but into other context: biomechanics purely based

[5] This is based on a short-term course given by the same and talks later between the author of this paper and the same. Further, the author of this paper and the same researcher had worked on a project in quantum neural networks, still ongoing.

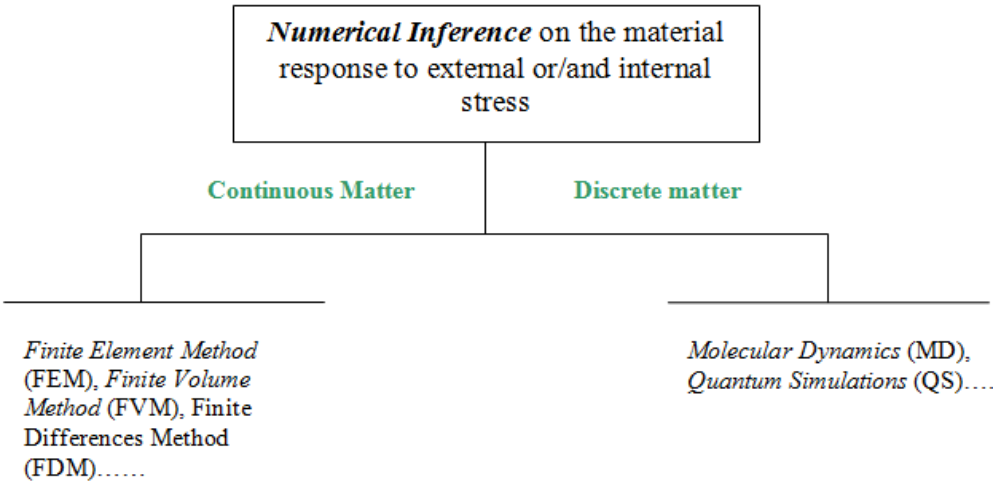

Figure 1. The 'up-button/button-up' dilemma in studies of real-material mechanics. (Since real problems are complex, we must apply computational power in order to study (bio) materials' behavior to external (such as loads) or/and internal (such as "growth") stresses. This can be done respecting one of the leaves of the scheme just presented. See that the middle-based approach would be achieved by connecting the leaves properly. Continuous stands for continuum mechanics and similar and discrete to particle physics and similar; the former treats matter using differential calculus as essential tool, while the latter makes use of discrete-driven approaches, such as molecular dynamics and/or quantum mechanics.)

on mechanics of solids theory and mathematics. Moreover, the second pillar of the work is computational intelligence. The tool is interesting for being applied in general to problems that traditional mathematics fails to solve satisfactorily, problem of complex relations or 'frightening' dimensionality, where no simple theory exists; since this is somehow a state-of-the-art-branch of science, this is not trivial to indicate didactic references (Lam et al., 2012). Conversely, the third is systems biology. This last one has been applied widely for liking gene interactions to emergent properties (a sort of phenotype hidden in the cell in most of the cases). Those three methodologies present each of them important theories and insights for achieving the final aim of the author. The fourth technology in the scheme in Figure 2 is Java. Java is a programming language launched in 1996. Initially, it supposes to serve web-pages creation, nonetheless, its power for technical calculation got eminent. Today we have systems in Java, example is seen in systems biology called "The Systems Biology Markup Language, SBML" (Dräger et al., 2011). Another example from numerical simulations in solid mechanics is the COMSOL Multiphysics Software. Many more could be listed, some even subtle. In accordance with (Deitel and Deitel, 2006; Bigus and Bigus, 1998; Pires et al., 2012; Pires, 2012a), the attractive features from Java are: a) compatibility between different platforms, 'program once, run everywhere'; b) packages easily created, this facilitates the exchange and enhancement of complex systems such as the proposed one, 'divide and conquer'; c) Multithreading as internal feature of the language, something already part of the language. Those features could make numerical simulations of complex mathematical modeling such as the one just proposed simpler either for making or launching as done project for others. Those motivations alone are reasons for preferring Java instead of others; a respectful-eminent interest for Python on those situations should be mentioned. The final system aimed here is sketched in Pires (2012b) and Pires and Palumbo (2012); (Figure 7). The main target is to make two different simulators, but later to make them running in parallel: protein production and vitreous dynamics. For example, delay in protein production in conjunction with protein degradation or destabilization might be a cause for initial damage in the vitreous body.

The manuscript is organized into discussions on each cornerstone. Again the work has theoretical and proposal nature at the current stage of the same; the information publicized herein is what we feel free to do so. Further details will come out accordingly later in the paper.

MATERIALS AND METHODS

Systems biology: transcription networks

As stated by Pires (2012a), when one aims to study the genome, two different-in-timescale modeling strategies can be identified: static and dynamics; they differ on how slow or how fast they happen respectively. Dynamics is connected to short-term activities such as seconds; whereas static is connected to long-term activities such as decades. Amongst the fields concerned with the genome such as

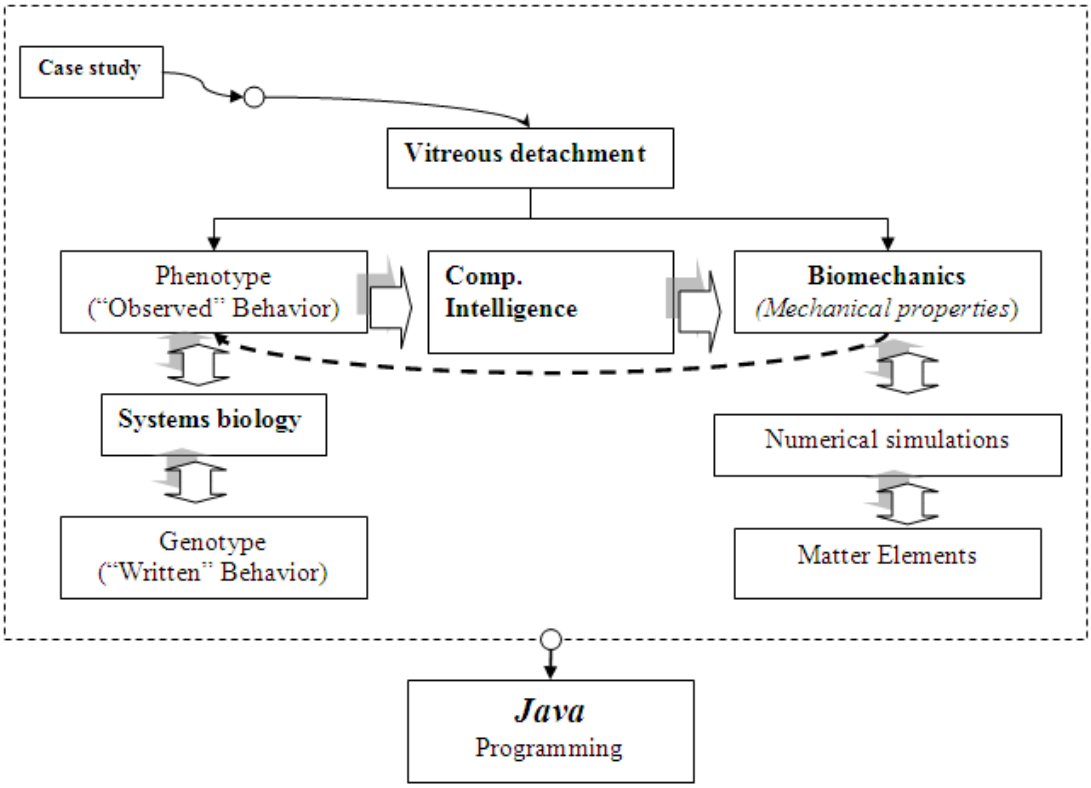

Figure 2. The vitreous detachment (case study, biomechanics), systems biology (inference-applied discipline), and Computational Intelligence (computational intelligence based tool for nonlinear mathematical modelling). (The meaning of the boxes seems trivial, but for each of them: Vitreous detachment – case study, somehow the first application of the theory proposed in case it is scientifically accepted; Mechanical properties – material science methodologies for studying material response to stresses such as loads; Genotype – gene based information, such as disorders or mutations; Phenotype – This the so-called emergent properties, what we 'see' as gene's existence and activity; Matter Elements – matter based information such the stabilization of the vitreous body by networks of collagens; Numerical Simulations – this the methods for solving complex equations such as the dynamical system from molecular dynamics or the meshes from finite elements method; Systems biology – mathematical biology based discipline for linking mathematical predictions to biological knowledge and experiments; Computational Intelligence – artificial intelligence based tool focused to mathematical modelling for modelling nonlinear phenomena, which is the case of almost any real case encountered; Java – is the programming language for simulating the theories in synergy).

molecular biology and bioinformatics, systems biology is clearly the most dynamical one. Mutations might take millennia to appear, whereas "protein communication" or protein production will take from nanoseconds to hours. Surely, this is a dynamical-systems-theory dependent field. We will not discuss too much on systems biology in spite of the fact that it could be tempting. The reader is invited to consult any of the references (Salzberg et al., 1998; Noble, 2006; Kitano, 2001; Myers, 2010; Alon, 2006; Pires, 2012a; Wilkinson, 2012). Consider the Figure 3. it presents the roots of systems biology. By making use of the theory of transcription networks from systems biology, one can understand the dynamics of genes working in synergy. Transcription networks are dynamical systems and as so might be studied using related theories, such as bifurcation theory. One might say that for successfully understanding systems biology and its methods, this is important the ingredients: differential equations, stochastic differential equations, programming skills, dynamical systems theory, bifurcation theory, graph theory with emphasis in complex networks, basic notion of biology, basic notion of molecular biology, and basic notion of bioinformatics.

Computational Intelligence: neural networks

Computational intelligence is a relatively recent field of applied sciences; therefore a precise (unchangeable) definition is not straightforward. This is a sort of "ramification" of artificial intelligence more tending to treating applied mathematics problems, problems that used to be solved by mathematics only. This cannot be considered mathematics in its strict sense as the communities that work with the techniques usually do not

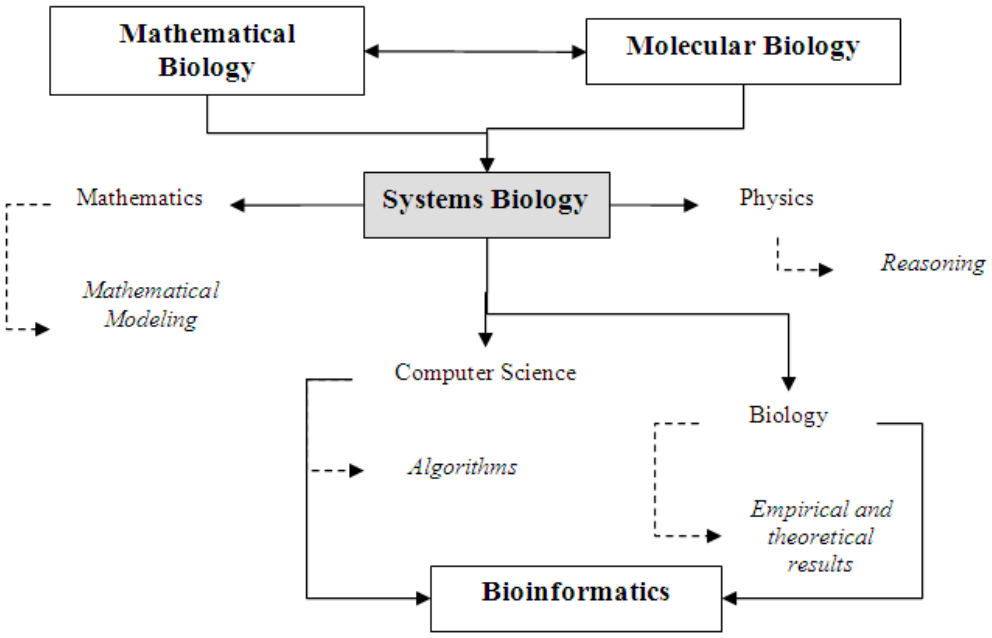

Figure 3. The "roots" of systems biology. Mathematical biology, bioinformatics, and molecular biology are the most notably, but one could as well identify others such as "physiology", mathematics, physics, and computer science. (Mathematical biology is a scientific movement mainly in the 1900s for modeling living matter; molecular biology is the biological field concerned with the genome; Systems biology is a dynamical systems driven field that makes use of other fields and some insights to understand bio-matter dynamically; bioinformatics is the biological computational driven field that concerns with dealing with complex data from the genome computationally; others: mathematics, physics, computer science, and biology; from mathematics is desired the mathematical modeling, from physics the reasoning such as laws, computer science the algorithms, from biology the knowledge of life).

require formal proofs and alike as it is in general required in mathematics. For this reason, it appeared with the advent of powerful computers and the necessity to solve complex problems. The most famous methods are natural computing and neural networks; others could be fuzzy systems or neuro-fuzzy systems. Computational intelligence and bioinformatics are recently in synergy, once the problems in bioinformatics in general are quite complex. In this project, initially, we intend to concentrate on artificial neural networks or neural networks for short (Haykin, 1999). One thing that must be pinpointed is the twofold existence of neural networks: neuroscience and applied mathematics. The former is more concerned to model neural systems, therefore complicated mathematically; the latter is simpler, once it must just solve problems though. In accordance with N. Kasabov, Knowledge Engineering and Discovery Research Institute, New Zealand, the current state of the art in neural networks are quantum inspired systems and spiking neural networks. A potential reference is Lam et al. (2012).

Biomechanics: the vitreous detachment

This is not straightforward line of attack to define biomechanics, but loosely stating and in harmony with Humphrey (2003), this is the interdisciplinary branch of applied sciences concerned with understanding, manipulating, and proposing new methods on the grounds of nature. This could be the understanding of bio-systems such as the snail movement mechanism for mimicking in mechanical version (Chan et al., 2005) or the understanding of human movement for improving human work-environment or similar to Knudson (2007) for better serving our society. Humphrey (2003) stated that biomechanics will always have as final aim in the human condition improvement. Nonetheless, we have reasons to assume a broaden definition, which would include even natural computing Eiben and Smith (2003). However, this is not important here. The vitreous detchament (vitreous dynamics) is clearly biomechanics, indepedent if modeled via mechanics of solids and materials of molecular dynamics.

Considering Figures 4 to 6, they suppose to present a schematic simplified version of the vitreous detachment, but detailed enough for the current discussions. On the current state, it seems that further anatomical details are wasteful. Figure 4 presents the simplified anatomic scheme of the eyes, Figure 5 presents the vitreous detachment, and Figure 6 presents a schematic sequence of important

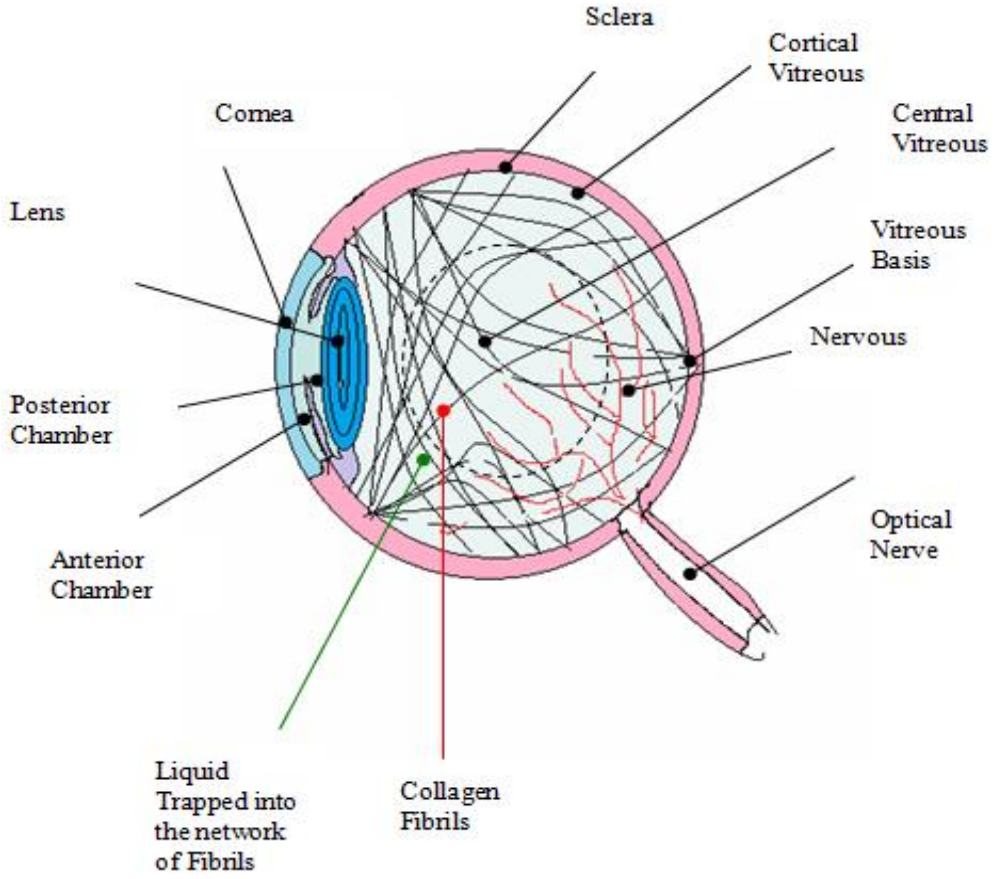

Figure 4. The eye anatomy simplified. (This simplified version shows the vitreous and some lines, hypothetically to represent the random networks of fibers of collagens) (translated from Pires (2012b) with permission). The vitreous is divided into cortical, central, and basis; besides this is not easy to see the differences in this scheme, in reality, it exists. The remaining schemes are only illustrative and explanatory.

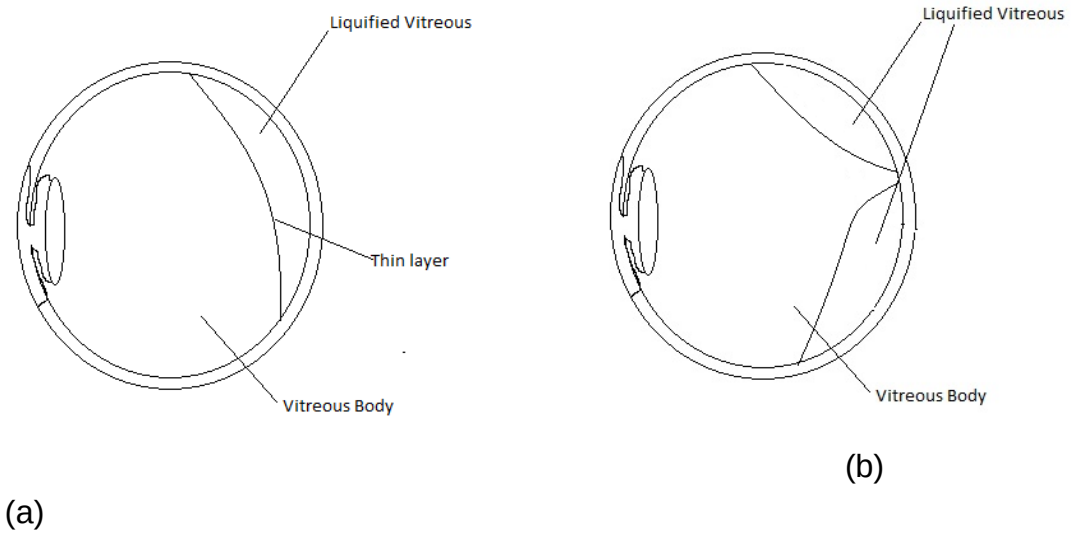

Figure 5. The simplified eye with the detached vitreous, (a) is the single chamber; whereas b) is the double chambers. In some cases holes like bubbles in water appear, but they soon evolve to one of those just presented. (translated from Pires (2012b) with permission). In scheme (a): liquefied-vitreous is the vitreous body after losing the healthy structure, thin layer is the divisor between healthy and damaged section, this thin layer was attached previously to the internal wall of the eyeball, the vitreous body is the healthy part of the vitreous, with the internal network still conserved. The scheme (b) is similar to (a), but that the double section is represented.

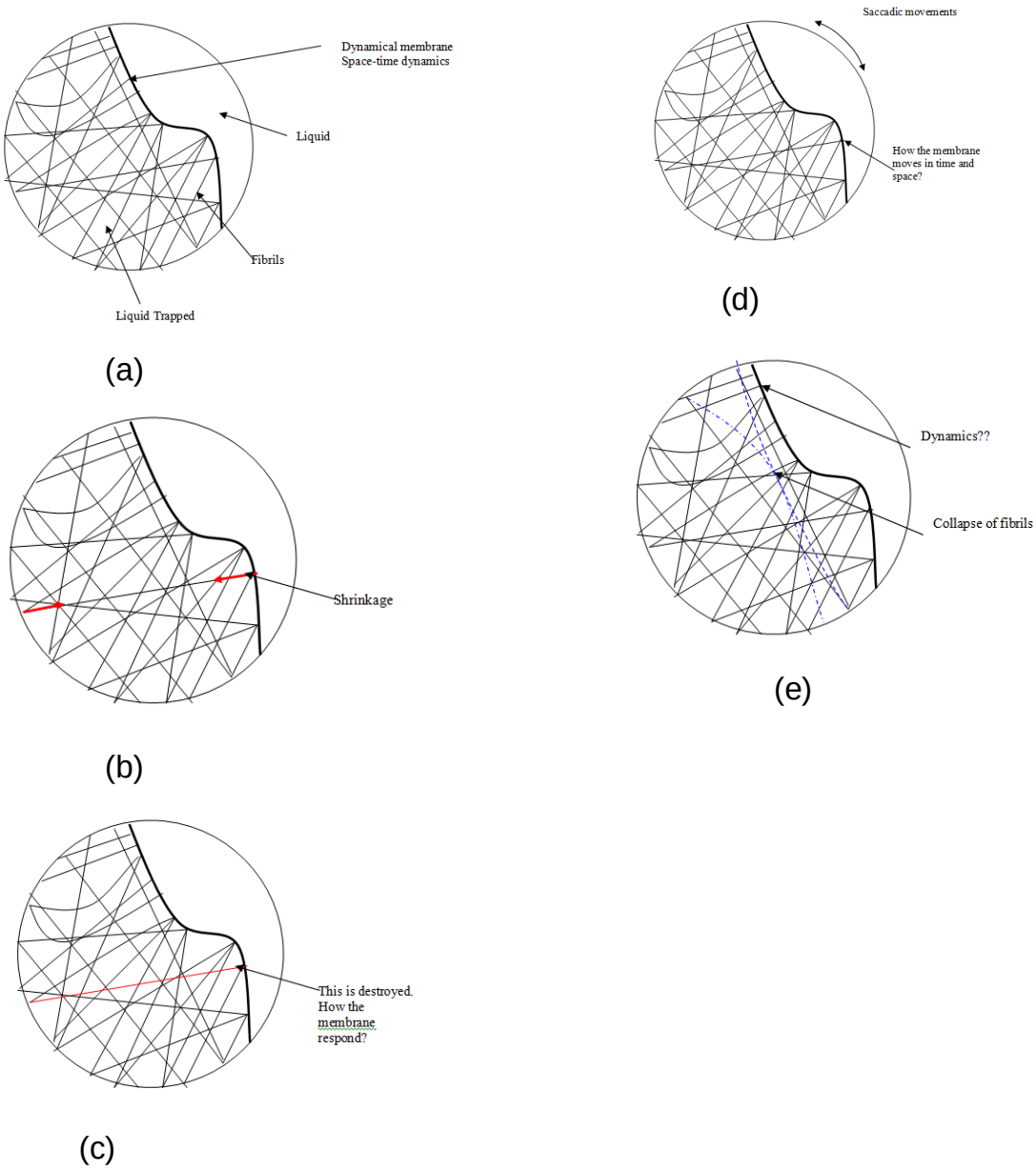

Figure 6. The main phenomena that could generate disturbance in the stability of the vitreous body. a) intends to show the main physical appearance of the vitreous (scheme), the vitreous body is a "set of liquid containers" trapped by networks of collagens; b) The shrinkage of a fiber, this is when for some reason it diminishes its length; c) this is when a fiber is destroyed; d) this the saccadic movements, an external interference; e) This is when liquid escapes from one of "micro-chambers" (traps) generated by the network. (The authors are in great debt with Prof. Tatone (University of L'Aquila, Italy), whose discussions had inspired those pictures). Those scenarios were generated with the hope to model the most important cases only, leaving minor cases untouched.

internal and external factors that could disturb the vitreous state. Note that from Figure 6 presented, the vitreous detachment creates a line that divides the vitreous body into healthy and damaged sections (Le Goff and Bishop, 2008; Sebag 1998). The problem called 'vitreous detachment' starts when it separates from the internal eyeball and go on propagating the damage, but leaving water-like fluid in the place where before was the jelly-like fluid, this is undesirable. In accordance with Halliday et al. (2007), light enters the eye by a transparent membrane, named cornea (Figure 4). Aqueous humor is the name of the liquid behind it. Going futher inside the eye, one has the pupil which is a variable aperture in the eye; it controls light inward the eye. And next is the crystalline, which is a system of lens, one of the most important physical parts of sight. The cornea-lens system focuses light onto the back of

the eye. As highlights Halliday et al. (2007), most of the diffraction of light takes place in the cornea-humor-lens region boundary with the environment; the internal part keeps an almost constant diffraction constant. Rods and cones are sensitive receptors in the back of the eye, named retina. Those receptors are the connection between "optics" and "neural systems". They send the signal to the brain. As pointed out by Bottega and Bishay (2012), retinal detachment is a hazardous affliction which affects many people and may end up in blindness; it is sometimes misleading when this work and the name "neural systems" are said together, here neural systems are mathematical models as it is regression in statistics, not a biological model as it is for neuroscience. Retinal detachment may be a starting point for vitreous detachment, once the boundaries of the vitreous body also include the retina region.

Then, in simple words, given the simplified, but enough, scheme of Figure 4 (the anatomy of the eyes), the knowledge of the most probably states, given Figure 5, and all the potential disturbances in Figure 6, how can we create a quantitative model that takes into account solids physics and genetics?

Given Figure 6, one can simulate each case based upon gene expression. The case (b) in Figure 6, the shrinkage, can be associated to partial degradation of collagens; (c) can be associated to unstable proteins; (e) can be associated to weak force on the fibers, which allows the liquid to escape and the collapse happens. Each of this are proposed model for future studies. Therefore, the challenge is how to have enough information on the genetic level for making a mechanical model with mechanical properties in function of protein expression, degradation, or any third interference. This will lead us to the system schematize in Figure 7: two separated simulators, with different backgrounds, but in the end solving the same problem.

Molecular dynamics: numerical simulations

There are many references on molecular dynamics such as Rapaport (2004), Bulatov and Cai, (2006). In simple terms, molecular dynamics is applicable where there are no significant effects of quantum mechanics and (electro) magnetism. The most attractive from this technology is the simplicity: this is just the integration of the equations of Newton for agglomeration of atoms or molecules, such as in crystals. For macro-systems this is intractable, but for nanosystems this is the state of the art, even classical mechanics being so criticized after relativity and quantum mechanics.

In order to somehow escape from the burden of molecular dynamics and focus on the final structure of molecular systems, some are appealing to meta-heuristics (Benitez et al., 2013). This is advantageous if one needs the final conformation of the molecular systems such as proteins, but it is not advantageous if you need to observe the "dynamics" step by step such as necking in nanowires, see as well that those methods are well-known to "visit" unrealistic solution in the way to the optimized solution.

Finite elements methods: continuous-medium simulations

Loosely stating, one can say that finite element methods is the counterpart of molecular dynamics. Both might be efficient and inefficient. The secret is to know well your problem and make the most suitable choice. Finite element assumes continuity of matter, something clearly not true for crystals (Reddy, 1985). Nonetheless, in some cases, even clearly discrete, one might theoretically assume continuity. However for the case herein, we cannot assume continuity in the case of the healthy vitreous; maybe the damaged area.

RESULTS AND DISCUSSION

Regarding the vitreous detachment problem, collagens – the elementary brick of the bio-network that stabilizes the vitreous body are just proteins, as so, they are under the same set of laws. Proteins are produced constantly in our system. Every protein is produced as result of DNA information. In the same way, it loses its functionality (ies) and disappears. Degradation of protein is a way for our system to use better the limited resources available. Some proteins, such as Transcription Factors, used by cells to create networks of genes, has even seconds of life, others such as the protein in our hair, possibly will never depredate in life. Therefore, collagens need a system for replacing constantly the natural degradation, once it is not considered a "stable" protein. Hence, a model for accounting for that might be quite a useful starting point for inference on the consequence of genetic deficiency on the vitreous detachment and consequences. This is the core of the audacious and incipient proposal of the manuscript. Additionally, there is a subtle consequence of gene expression that is not in general taken into account that is in general the counterpart of protein deficiency: gene sharing (Piatigorsky, 2007). Piatigorsky (2007) had observed that the same protein in the lens of birds was the same taking part in enzymatic processes. Piatigorsky (2007) had ingeniously reported the "hidden-multifunction" existence of proteins: protein expression rate will not just affect its function and non-function, a binary-state universe, but might transform a "function A" into "function B" without changing the protein (primary structure), a N-state universe.

Recollecting Figure 6, one can simulate each case based upon gene expression. The case (b) in Figure 6 in which the "string of collagens" is shrunk, the shrinkage, can be associated to partial degradation; (c) in which the "string"

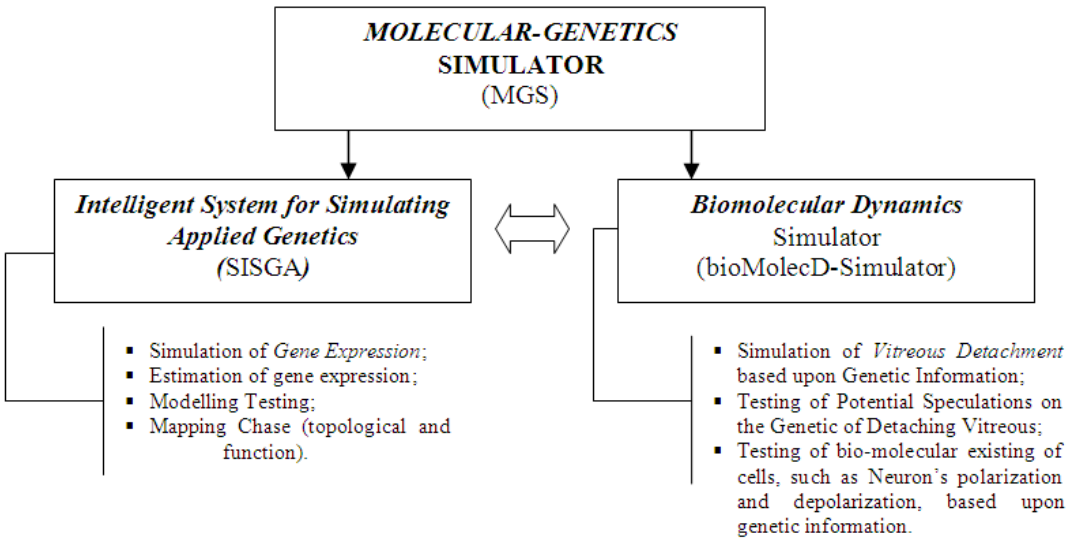

Figure 7. The Molecular-Genetics Simulator (MGS) and its components. (for left leaf, see Pires and Palumbo (2012); for right leaf, see Pires (2012b)). (*Each leaf intends to represent a separated simulator, one is gene expression simulator, while the other is molecular dynamics simulator. They suppose to interact during a real-time simulation for making the MGS*). The final terminations of the tree suppose to represent some potential models for future treatment such as simulation of vitreous detachment based upon genetic information and simulation of gene expression; the former is the right-hand side of the tree, whereas the latter is the left-hand side of the tree.

is disrupted can be associated to unstable proteins; (e) can be associated to weakness on the forces between the connecting parts of the fibers, which allows the liquid to escape and the collapse happens. Each of this are proposed model for future studies.

The importance of those studies is on the possibility of creating a virtual system on the vitreous dynamics. One could attempt to predict time-space movement for diagnoses. This is important if one has information on the genome of someone related to collagen, one could try to simulate possible future anomalies; make quantitative and rich-in-scenario remarks. As it can be encountered on Schoof et al. (2012), some individuals may lose the skin plasticity faster than normal due to genetic natural modifications. Since the plasticity of the skin is associated to collagens, one may extend the idea for the vitreous body, which depends highly on collagens.

This work was born from the efforts of Prof. A. Tatone (University of L'Aquila, Italy) in modeling the vitreous detachment using mechanics of solids and materials and parallels involvements of the authors on molecular dynamics domains. For Prof. A. Tatone (University of L'Aquila, Italy) to succeed, it is necessary to suppose, which is a strong assumption for the case, that the vitreous is continuous. This could hold true to the liquefied part, but not to the healthy section of the vitreous body. The trick of the author, which is skipped over here, is called "network molecular dynamics". The idea is that since the liquid is stabilized by fibers of collagens, something idealized as rods of about 10-20 nm of diameters, one could just take into account the connections (physical contacts) and then considers "fake atoms", from that point on, molecular dynamics will take care.

With the mentioned trick, the computational requirements will be diminished. Furthermore, since they are thin rods, cutoffs and list of neighbors will be something quite applied; if one thinks for a while, for diameters in the orders of 10-20 nm, there is no room for a significant number of neighbors for each "fake atom"; further, since this is a macro-system, this is clearly possible to neglect chemical-originated forces. The "fake" forces in the "fake" atoms will correspond to the 'plasticity-stability' of the network of collagens.

Based upon simulations done by Prof. A. Tatone (University of L'Aquila, Italy), which the authors will not replicate herein, it sounds promising the proposal. However, the simulations referred of Prof. A. Tatone (University of L'Aquila, Italy) are incipient and Prof. A. Tatone (University of L'Aquila, Italy) intends to go on. See that if it is achieved, we will have something quite interesting, a discrete and continuous model for the very same problem. Perhaps, we could use the insights defended by S. Kshevetskii (State University, Russia) and create a continuous-discrete model; this sounds quite promising and profound.

In order to cope with the complexity for correlating the genotype to the phenotype (the undesirable pathophysiology), we propose the intriguing and state of the art computational intelligence. The author intends to study the third generation of neural networks, which

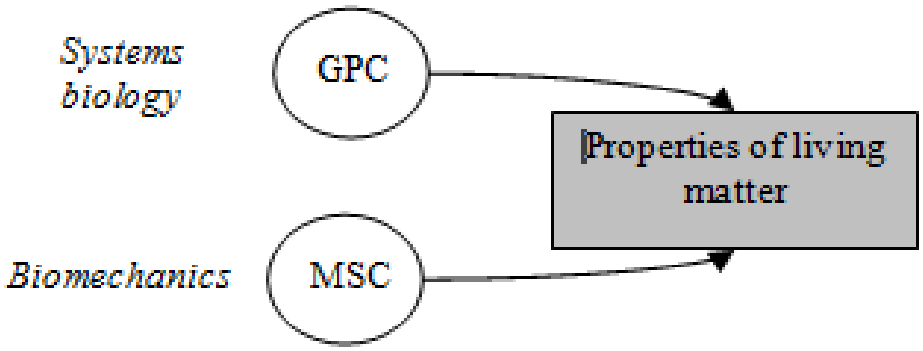

Figure 8. The two antagonistic, but complementary, ways of studying living matter. This is a such of button-up approach (systems biology) and a up-button approach (biomechanics). Perhaps the most interesting is the middle. (The letters means: on systems biology box "G- gene; P – protein; C – Cell"; and on the biomechanics box "M – matter; S – Structure; C – Components"). This picture intends to defend that spite of the fact that both approaches are already being applied in their respective domains, they could be united for further achievement in biomatter modeling in a middle-way approach. Noble (2006) names it the engineering approach.

could create new insights on powerful and fast mathematical-computational models; which surely does not limit the application of models already-known and applied.

In order to simulate the virtual system, which includes mathematical models and simulations, it is propose Java as programming language mainly for its features. The most eminent is the object-oriented programming style.

The technique widely used in medicine is called vitrectomy, as it can be encountered in the internet[5] "A 'vitrectomy' is a surgical procedure in which most of the eye jelly-like material that normally occupies the back two thirds of the eye is removed". This is intended by proposing in this manuscript to avoid removing what nature created with attention and perfection by predicting and taking optimized decisions. Therefore, the proposal is "passive", this is not intended to propose an invasive system, but rather a system to predict and make wise (optimized) decisions. Of course, here is the question of modeling capability rises firmly, this is something that just the serious treatment of the problem could answer, in theory any physical model can be modeled and simulated.

Conclusions

We have disserted on the applicability of biomechanics, molecular dynamics, computational intelligence, and systems biology in the modeling of the vitreous detachment. The motivation is that all the fields discussed are somehow important and could make the difference if united for a final aim, to properly understand the vitreous dynamics that culminate in the vitreous detachment, which can cause blindness. Further, the idea is to prevent instead of "curing"; therefore a noninvasive and predictive-for-action method. Lastly, the work is an ongoing project and has significant challenges to solve before a respectful conclusion could be drawn.

Inspite of the easy-to-point-out hard proposal, the author is highly motivated by the very simple fact that the biggest discoveries in science came out from connecting different fields of science that had achieved remarkable results on their own fields, when no clear and straightforward connection is possible to pinpoint. The use of systems biology for modeling gene information and making them available for simulation in the vitreous detachment is promising. Works on that nature tend in general to be purely mathematical or engineering-based, nonetheless the proposal here might be seen as middle-way where biomedical sciences could gain; by having an exact model for studying the undesirable eye's disorder called the vitreous detachment. Therefore, underpinning the importance of the endeavor is its eminent applicability and challenges.

Mathematics in medicine is quite intriguing movement, but not easy. Endeavors as the one just presented, even with clear initial limitations and difficult steps, might bring to us a novel way of facing medicine.

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[6] See Patient Education Series. Alcon, Inc. by Eyemaginations, Inc.

dynamics and computer simulations of materials and Prof. S. Kshevetskii (State University, Russia) for the inspiring lessons in quantum and classical simulations of particles.

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