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Complex Human Disorders and Molecular System Engineering: Historical Perspective and Potential Impacts

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Abstract—**The challenging nature of complex human disorders has taught us that we can not untangle a disorder unless we understand how the "engine" of molecular systems works. After learning the basic physiology of different organs in the human body, a "molecular revolution" occurred, which has now generated a huge amount of information regarding the function of individual molecules in human cells. The difficult task, however, is to understand how thousands of molecules communicate and work together to deliver a specific function, and more importantly, what goes wrong when the system fails and causes different diseases. The emerging field of systems biology is now opening the door for engineers, to join molecular biologists and enter the era of molecular biomedical engineering.**

I. A Lesson from History

The historical merger of mathematics and physics [1] has taught us that at the interface of two distinct fields, there are possibilities that could have a very high impact. While mathematics found its way into physics a few hundred years ago and their interaction proved to be incredibly fruitful [1], some other areas of science, specially biology, showed to be more resistant to mathematical thinking. This in turn delayed the involvement of engineers, who are indeed applied mathematicians, in biology and specially molecular and cellular biology. Therefore, although in theory biologists feel the absolute need to understand how the engine of molecular systems in human cells works, they are generally skeptical to accept and benefit from the rich field of engineering of complex systems. The field offers a variety of tools and approaches that can be used to study the behavior of complex biological systems in human cells.

II. Simple Biologically-Oriented Models have Historically Proven to be Useful in Biology

A good example that can demonstrate how a simple model in biology can unveil mysteries of biological systems is the well known "double helix" DNA model. This model, which eventually solved a mystery of life, was originally proposed by Watson and Crick [2] based on the instrumental observations of Rosalind Franklin's X-ray diffraction photography [3]. Therefore, the initial experimental observation of Rosalind Franklin was critical to propose the double helix model. However, the model itself, as described in the original 1953 *Nature* paper [2], is a pure model that provides a general picture of DNA structure. This simple yet elegant model, later opened the way to molecular biologists to perform actual experiments, to find out the basic mechanisms involved in DNA replication and transcription. However, the original paper itself does not have any actual experimental data. Similarly, it is feasible in our time to develop simple engineering models, based on the existing experimental observations in published literature, to describe the function of biological systems. Such models may not precisely describe all biological facts that we know. However, they open endless opportunities to biologists to understand the complexity of molecular systems.

III. A Brief History of Fault Diagnosis Engineering

Accurate fault diagnosis of complex computer chips and processors, microelectronics manufacturing processes, pharmaceutical/drug manufacturing facilities, production lines, control systems, power plants, etc., is of high importance, in order to minimize the costs and prevent the risks of system failure [5, 6, 7]. Fault Diagnosis and monitoring are key parts of modern industrial facilities and have gone through considerable development in the past few decades. Now they are inevitable parts of industrial processes and applications. For example, early and precise fault diagnosis in a nuclear power plant is critical for the plant to safely operate, as well as avoiding significant financial loss. Other examples include pharmaceutical, microelectronics, and chemical manufacturing industries.

A fault is defined as an abnormal change of one or several system nodes and variables from their normal operating conditions. Due to the large number of interconnected nodes in a complex system, it is not a trivial task to correctly localize a fault. Mathematical theory of systems has been the starting point of fault diagnosis engineering. For small

systems with well-characterized system equations and models (input-output or state-space differential equations with all the parameters known), it is possible to use the system model for fault diagnosis [7]. For example, using the residuals generated based on the system model [8]. However, even in systems for which precise models and equations are known and available, computational complexity of a fault diagnosis algorithm could be prohibitive. For example, thermal modeling and monitoring of low pressure chemical vapor deposition furnace is of interest in semiconductor manufacturing, to have a tight control on film uniformity [9]. However, fault diagnosis in such a system where its model includes hundreds of partial and ordinary differential equations can take a very long time and computational complexity is enormous.

The situation becomes much more difficult in very complex systems such as a nuclear power plant, where there are so many complex interactions and system variables, with many parameters involved. For such complex systems, methods that work for small systems are not practical. One promising way is to use artificial intelligence type techniques [5]. Such methods rely on less-detailed system models such as logical and Boolean models, in order to make the fault analysis feasible.

In the world of electronics and computers, very large scale integrated (VLSI) circuits were introduced in 80's with hundreds of thousands of transistors [10]. Nowadays VLSI chips with millions of transistors are used in almost every complex electronic device, ranging from computers to cell phones to digital TVs to state of the art medical equipments, etc. Having many millions of transistors and wires with nano-scale dimensions on a single chip makes the chip vulnerable to manufacturing defects.

In the nano-world of a chip, a very small manufacturing flaw can result in a disconnected wire or defective transistor, which can make the chip dysfunctional. In a manufacturing facility, a chip is manufactured based on a particular design and is supposed to provide a specific function. However, during the fabrication process, physical defects such as faulty transistors, open and short wires, …, may happen, which cause the manufactured circuit not to function correctly (according to the design specifications) [4]. Testing of chips and digital circuits is therefore necessary to separate defective manufactured parts from the non-defective ones, to guarantee the delivery of fault-free products to the customers. The test itself is an assessment of the manufactured circuit, according to a set of criteria. During the lifetime operation of electronic systems, the correct operation is a key aspect and is typically referred to as reliability.

IV. Application of Fault Engineering Models in Molecular Systems: An Example

Systems biology envisions that the application of complex system engineering approaches to cell signaling networks will lead to novel understandings and subsequently new treatments for complex disorders. In the area of circuit fault diagnosis engineering, there are a variety of methods to identify the defective or vulnerable components of complex digital electronic circuits. In biological systems, however, our knowledge is very limited regarding the vulnerability of interconnected signaling networks to the dysfunction of each specific molecule.

It has been recently shown that by developing proper biologically-driven digital vulnerability assessment methods, the vulnerability of complex signaling networks to the possible dysfunction of each molecule can be determined [11] [12][13]. To demonstrate the utility of the approach, three well-characterized signaling networks are analyzed: the somatic cellular networks that regulate the activity of caspase-3 or p53 genes, and the neuronal network which leads to the activation or inhibition of CREB (cAMP Responsive Element Binding protein). Interestingly, highly significant differences among the vulnerability values of different molecules are found. Most of the highly vulnerable molecules are closely related and are already known to be the key regulators of these networks [11].

The engineering analysis identified AKT and PKA as the most vulnerable kinases in p53 and CREB networks, respectively, both known as the crucial kinases regulating these transcription factors. Furthermore, experimental data that confirms the ability of this novel approach to correctly predict novel regulators in the CREB network are collected. Overall, biologically relevant vulnerable molecules in complex cellular networks can be identified by developing biologically-oriented fault diagnosis engineering techniques. This cross-disciplinary approach is anticipated to contribute to our understanding of biological systems, due to its capability of discovering the key molecules that may have causative effects in human diseases. Such molecules are promising targets for drug development [14].

V. Medical Research in the Light of Systems Biology

The emerging field of systems biology is going to revolutionize the way we look at medical research. Systems biology concepts and tools have the obvious potential to significantly accelerate us *to answer the most critical health-related questions of the 21st century*. As a matter of fact, most of the human disorders are very complex and result from the failure of a highly sophisticated biological system, rather than the dysfunction of a single molecule or a specific pathway. Systems biology aims at integrating all pieces of information to obtain an idea of how the system works. Within the systems biology framework, different types of biological information such as DNA, RNA, protein, cells,

tissues, and the interactions among them can be pictured together.

To understand and utilize systems biology, a *cross-disciplinary vision*, which ranges from Genomics to Proteomics to Metabolomics, has to emerge. It needs a multidisciplinary group of people, including biologists, engineers, computer scientists, chemists, mathematicians, and physicists, to speak in a common language and develop a global understanding of the system. Needless to say, traditional ways of describing and teaching biology have to be re-examined as well.

Let us conclude with a poetic and historic vision of the reconciliation of complexities, brilliantly pictured in "Elephant in the Dark," a poem by Rumi, the 13th century poet:

…Some Hindus have an elephant to show.

No one here has ever seen an elephant.

They bring it at night to a dark room.

One by one, we go in the dark and come out saying

how we experience the animal:

One of us happens to touch the trunk

"A water-pipe kind of creature."

Another, the ear: "A very strong, always moving back

and forth, fan-animal.

Another, the leg:

"I find it still, like a column on a temple."

Another touches the curved back:

"A leathery throne."

Another, the cleverest, feels the tusk:

"A rounded sword made of porcelain."

This one is proud of his description!

Each of us touches one place and understands the whole in that way.

The palm and the fingers in the dark are how the senses explore the reality of the elephant.

If each of us held a candle there, and

If we went in together,

We could see it

Within our context, the elephant of this amazing piece of poetry resembles the difficult problem we are facing in understanding human complex biology and human diseases. Most probably some of the narrow approaches we have been relying on are not enough to understand the reality as a whole, similar to the individual part of the elephant's body in Rumi's story. And what could be the candle? Maybe systems biology concepts and tools …

The last lesson we can learn from Rumi is the importance of *going together*. Only through collaborative cross-disciplinary efforts we can see the elephant-like multi-facet complex human physiopathology as a whole. An orchestrated teamwork among different disciplines is the key to answer the most critical health-related questions of the 21st century.

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