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THE PERPARATION OF BIOLOGISTS FOR THE APPOACH AND THE INTERDISCIPLINARY FOUNDATION OF THE GENETIC STUDIES

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"*Nothing will be the same anymore in Biology*"
Phillippe Chambon

Molecular Biology and Genetics are disciplines that appeal to Physics, Mathematics and other disciplines with their means of investigation, in order to make clear the code of life and the order and disorder from nature.

Question for physicists : What we call the code of life, does it hide in a dynamic system ?

Erwin Schődinger himself, founder of quantic mechanics, in his book "what is life ?" underlined that the quantiqueand chemical world is based on development and hazard. The order noticed at the superior levels of intergration of the living matter is not possible only because of a multiple development at the inferior levels, that are molecular or because of the number of atoms from genom is very reduced, because the statistics of numbers will lead to reductible behaviours, such as the ones noticed in the living world. From this statement is coming a dogma that had dominated molecular biology for fifty years, the order that was noticed at the level of individuals is generated at the level of genetics through ordonated processes, a fundamental order opposed to dinamics met in Physics.

Biologists begin to belive that the DNA will show its secrets in a dinamic description of its expression.

Conrad Waddington – genetician, along with his compatriot Alan Turing – English mathematician and physicist showed that a cell evolves in time like a ball that rolls down a hill or a mountain. (see Fig. 1)

For physicists, the fact that a stem-cell transforms itself in a basophile ,a macrophage, a red cell or an eozinophile is comparable with the rolling of a ball : more trajectories are possible. They can determine what way the cell will take.

Studies regarding the eggs of frogs made by James Ferrel of the molecular pharmacology from the Department of Stanford University (USA) used a phisic model. The model showed that the *growing-up* of eggs is governed by the second bistabile dynamics the cells possess stabile stages that corespond to two phases of their development (those of *meiosis*) that is the continuous growing within the cell of the progestron concentration, that at a particular concentration it can change the stage.

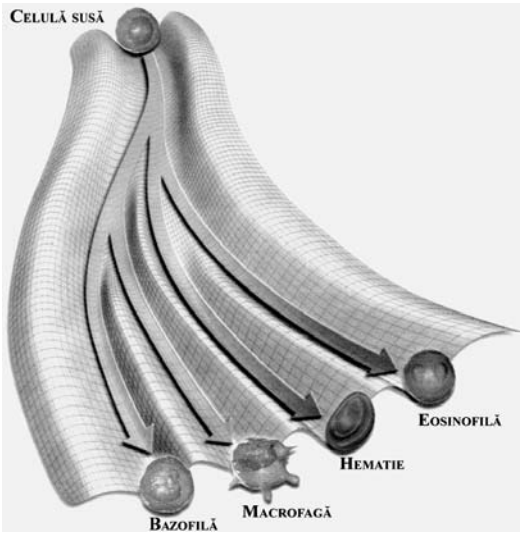

Fig.1

All the time biologists have the tendency to privilege the structure describing the stages in the structural development. In Physics, said Bernard Lofarge, physicists in particular at Pierre an Marie Curie's University, in Paris : we use especially time as principal parameter, that bring us to notice more embrions, in order to detect possible disarguments in their kinetics of maturation. This manner of observing hatching eggs of crocodiles or turtles under different temperatures that give birth to males or females, when the DNA is not changed is specific to Physics.

If we think of thousands of genes and billions molecular *interactions* from te level of cells, about which the rule of big numbers is applied, we arrive at the idea that we can reach a superior order starting from an inferior disorder.

For specialists in Thermodynamics, used to predict the behaviours of a gas, starting from the irregular movement of particles, for specialists in Statistical Networks, Biology offers a new dynamic of *hazard* in order to be studied.

Michael Deen found a method of testing the efficiency of a vaccin against flu.

A specialist in Statistical Mechanic at Rice University (USA), he has recently published his work "*A vaccin against flu*" in which he calls our attention over fluctuations. These fluctuations are in the middle of the war against flu, because these fluctuations show year by year genetical codes of viruses that cause the flu, called mutations, and on the other hand these are the fluctuations of antibodies that form our *immunitary system*. Our immunitary system tries to find out or to produce that antibody that is adopted to that virus in order to make it harmless. Physicians are those who take care of these aspects. They are used to juggle with *aleatory* behaviours of multiple objects.

Thermodynamics specialists have been studying a gas without knowing the trajectory of each and every particle, considering that they are *aleatory*. The laws that govern this hazard, permit them to predict with an accurate precision the temperature of this gas. By coupling the aleatory variations of immunitary answer with the aleatory mutations of the virus, Michael Deen developed "a real thermodynamical of links between proteins proper to the modelling of the answer of immunity system to viruses attacks".

Starting from those antibodies that correspond to this vaccin, the immunitary system explores the period between the forms of possible antibodies searching for a protein (adapted protein). The author, starting from the genetic code and synthesized proteins, on the base of this code, made the correction between virus and antibody. He took into account the fluctuations between the virulent stem and vaccin, on one hand, and between antibodies on the other hand. He determined "the energy" of immunitary system that shows the most adaptable antibodies to the virus. He inferred the medium proportion of a neutralized virus by antibodies at a vaccined and infested person 10 days ago.

Thus, for a given virus he could test the efficiancy of different vaccins whose genetic codes and proteins are more or less closed to the virus (see Fig. 2). The conclusion is that the vaccination is effective if the genetical distance between the vaccin and the stem of the virus is very small. This conclusion emphases an apparent paradoxical phenomenon, often observed to the flu without getting not even an explanation until now : if the distance between the virus and vaccin is intermediate the vaccin worsens even more the sickness and in the end unvaccined persons can defend themselves more effective against the flu.

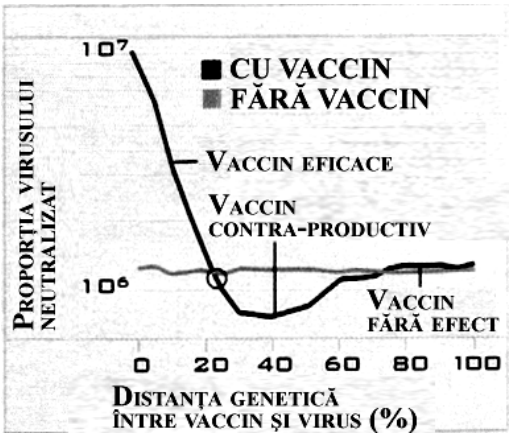

Fig.2

Michael Deen in collaboration with Enrique Muñoz (2004) at the Chemical Department tested the model over the 2003-2004 vaccin. They measured the distance between the used vaccin and the virulent stem focusing over the active parts of bound proteins that pursuit more genetical innovations. Once the distance placed on the curve, the result proved to be in agreement with the results obtained by The American Center of the Control of Diseases, after which the 2003-2004 vaccin against flu proved to be ineffective or had a very small efficiency.

Starting from this thermodynamic model of immunitary system, authorities choose stems that are the closest to the more virulent viruses detected 6 months ago in other hemisphere. Using these parameters and the thermodynamic model, authorities will have a better estimation of the protection that the vaccin has in the pressure of the stems that circulate.

So, by the help of physicists, using a specific method taken from Mechanical Statistics, the biologists and doctors (physicians) have found a solution for public health decisions.

Question for Informatics professors : Can we clarify the data from Genetics by seizing the languages of informatics ?

In 1999, Aviv Regev, student at Weizmann Institute in Isreal, with his professor E. Shapiro started writing about the book of life with "the algebrical processes" (very abstract languages used at informatics). It's about a distributed informatics, already used in mobile phones for web searching machines or for criptographical protocols. Symmetry between computers in communications and biomolecules from cells is fascinating : both are systems created from interactive *entities* without a central coordination. Or, with languages like "stohastic pi-calculus", "membranal calculus" or "ambiental calculus", the informatics professors have today new means capable of implementing these interactions in Biology.

With a new syntactical infrastructure, biologists will be able to simulate, verify and predict or cause models or biological hipothesis.

Informatics professors suggest to the biologists the clarification of notions like function, that is still vague in Biology.

In Informatics these two levels of describing : the implementation that describes how the system is made and specification that describes its logical action. A. Regev shows that "the assignment of a biological function to a biomolecular system may be read as a semantic equivalent between 2 levels : implementation and specification". In the future Distributive Informatics will allow the biologists identical rish languages in order to be expressive but simple in order to be brought up to date. This is the languag used in the books of life. In 2003, Vincent Danos managed to formulate the control of the cycle of life. Vincent Danos and Marc Chiaveri, Nathalie Chabrier, Francois Fages şi Vincent Schater managed during the lab programme : "Tests, programms and systems" from Paris University to produce the genetical adjustment book of cellular cycle into an informatic language from mammals into this genetical adjustments there are implied 150 genes and 700 chemical reactions, governed by 500 *variables*. By accepting the formalisation, biologists can allow the computer to verify the answer to their questions. Examining the biomolecular interactions of a vigourous syntax, using the computer, we know nowadays that CDK-1CYCB protein cannot produce into the cell without the existance before of CDC25C.

As a conclusion, our academic biological education requires :

1. the aptness of analytic programms of Biophysics, Physics, Informatics and Maths for biologists with today's tendencies in practical and theoretical foundation of biological researches.
2. the interdisciplinary approach of study themes during te biology course.
3. the foundation of an adequate didactic approach in order to prepare our students to be able to tackle systemicly and as a whole different problems.
4. the accomplishment of different specified biological competencies in order to integrate easily in our wordly or European biological research.

Question for Mathematicians : Does the representation of the process of expression of genes that a big group of networks permit the development of new concepts and means for their describing ?

Human being have a systemic organisation of a high complexity. How can we represent this complexity ? There are bilions of proteins among which there are certain actions that can be placed at the basis of metabolical processes. Under these circumstances, the genetic code of DNA cannot focus our attention but the points, the directions and the links that take part to a new biology. Beside biologists, sociologists and mathematicians were preocupied by the connections between certain elements of the systems. Starting with Euler, mathematicians have been developing mathods of specific analysis, especially in Paul Erdo's works (1960). Due to the development of networks science by mathematicians, biologists specialised in molecular biology began in the 90's to draw the metabolism network of E-coli and the interaction network between the protein from salt dregs.

The first stage in studying these networks is the collecting of experimental data the second is the topological analysis. By a statistic comparing of biological structures with those well-known networks, we were led to the discovery of their own life specificity.

The dynamic of a human being hides a structure in the network of an incredible complexity statitical analysis of the topology of this interactions network of proteins, shows the existance of some essential proteins from where the majority of connections go (see Fig.3). The red points are essential nodes for surviving but unimportant for the network.

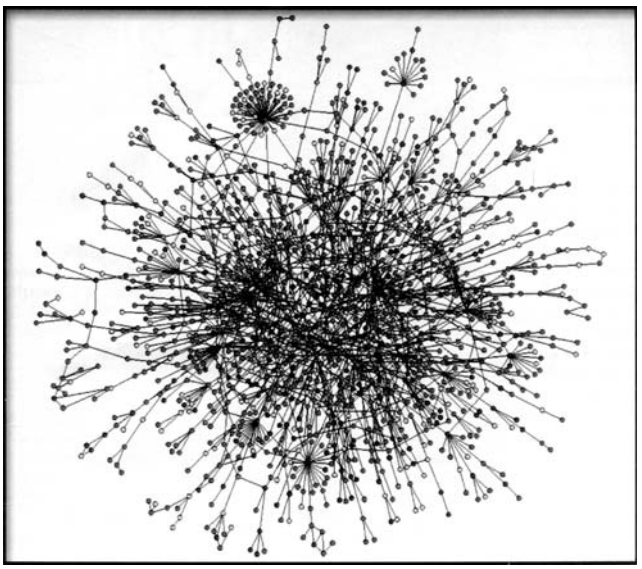

Fig.3

Hiroaki Kitano – a specialist in biological systems in Japan shows that solidity of engineering systems can be obtained by the help of 4 means :

1. a form of control of a system (with feed-back)

2. a redundancy (with more compounds depending on equivalence)
3. a structural stability (with concise mechanisms for the promotion of stability)
4. a modulation (with isolated subsystems)

Without any surprise those 4 means can be met even in biological systems. In other words, the nature uses the same solutions as engineers for the elaboring of cellular machine. Retroactive, stable and modulare, the networks of life have all the qualities of solidity.

Parallel with this activity of analyse of global structures of biological networks, there is another local approach of these structures : the decomposition of these networks or mazes into elementary modules, similar to electronic circuits, Uri Alon, who received this year the ISMB prize (Intelligent Systems for Molecular Biology) discovered "genetic motives", very simple and very frequent that assure the alementary functions. He studied adjustable networks from E-coli bacteria describing how the involved genes intensify from one to another.

In that analysed network he established that some elementary reasons are repeating very often. The elementary analysed structure is composed of 3 genes : X gene that activates Y gene, and those 2 genes, X and Y, activate the third gene Z. The mathematical modelling of this little structure shows that a short intensifing of X gene let the Z gene indifferent. We have to give Y gene enough time under the impulse of X gene for both of them (X and Y) to activate the Z gene. (see Fig. 4)

In electronics it is called *the detection of persistency*, one fact encountered everywhere in electronic circuits, for example on the mobile phone where there is enough to press little the button ON in order to use it, but you have to press more on ON button in order to close it.

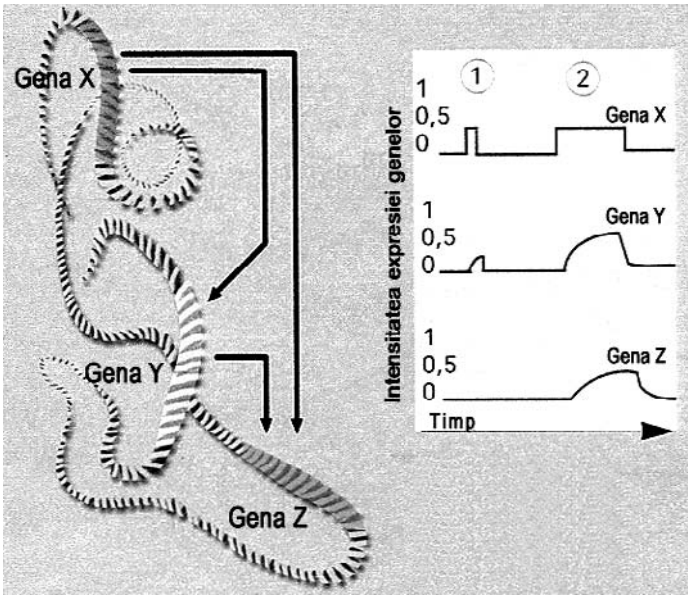

Fig.4

The analogy is striking and this frequent motif could be used inside a human being a type of detector of persistancy in activating the genes. This function will have a great, potential interest: it can make the network insensitive to noises, the fluctuations of genetical intensifying couldn't be taken intoaccount but only starting from one limit. "We need to search for the building bricks of biological networks and for knowing if their global dynamics may be understood in terms of elementary motives of behaviours", shows Uri Alon.

The Spiral of New Genetics

Only by a permanet movement between the real world (in white) and the virtual world (in black), the researchers will be able to advance in the understanding of the cell.(see Fig. 5)

Lining up with Maths, Physics, Informatics and Applied Engineering, Biology is about to invent itself a new destiny. The new Biology will be called *Sistematic Biology* or *Integrative Biology*.

Are we ready for THE NEW BIOLOGY ?

NO!

In this context we consider that for the biologic university education are necessary the following :

1. The harmonization of study programme, for the disciplines of biology, physics, informatics and mathematics for biologists, with the new tendencies in the theoretical and practical fundamentation of biology research ;
2. An interdisciplinary approach of study themes within the framework of biology department, as well as the sciences faculty ;

To substantiate a new proper didactics for the trening of the students in order to be able to interpret systemically, at random and to integrate the problems of biology ;

3. To assign to the students new specific abilityes in biology, but also new connected abilityes in order to facilitate their integration in the european and world-wide biology research.

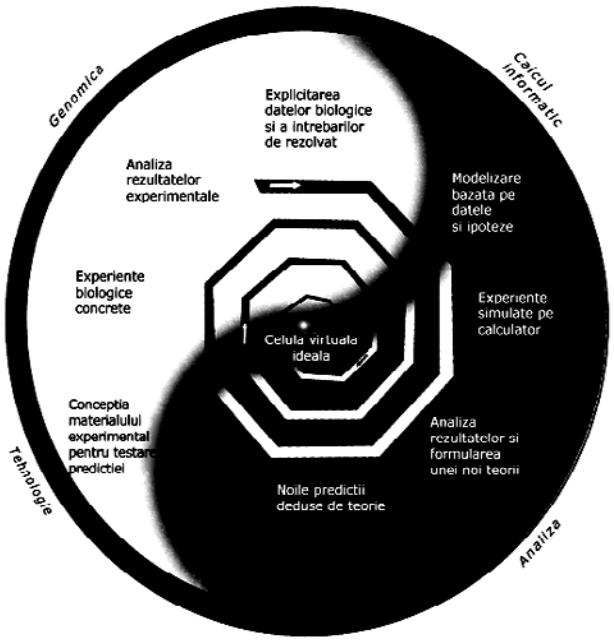

Fig. 5

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