PRAMANA
—journal of
physics

Vol. 53, No. 1,
July 1999
pp. 85–91

Biology and the flow of molecular information

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Abstract. The developments during the century in the physical understanding of biological activity are briefly discussed.

Keywords. Biology; molecular information.

PACS Nos 87.5.-v; 87.16.-b

1. Introduction

I propose to discuss in this article the impact of physicists on the evolution of biology during this century. More precisely, I want to describe how statistical mechanics and information theory molded the understanding of the flow of molecular genetic information, and how the relative stability of the genome was finally understood. I will, at the end, describe how this understanding was concomitant with the fast development of automata studies.

The encounter between physics and biology starts with Albert Einstein and his 1905 paper on the motion of small particles suspended in liquids [1]. His article (translated) starts, "*In this paper it will be shown that, according to the molecular-kinetic theory of heat, bodies of a microscopically visible size suspended in liquids must, as a result of thermal molecular motions, perform motions of such magnitude that they can be easily observed with a microscope. It is possible that the motions to be discussed here are identical with the so called Brownian molecular motion*". Einstein referred to Robert Brown's article entitled " *Account of Microscopical Observations Made in the Months of June, July and August* 1827 *on the Particles Contained in the Pollen of Plants; and on the General Existence of Active Molecules in Organic and Inorganic Bodies*" [2]. Those active molecules turn out to be particles bombarded by thermally driven water molecules. For precise experiments on Brownian fluctuations one had to wait for Jean Perrin and his study of colloidal suspensions. He measured the key phenomena predicted by Einstein. Some excerpts read like "*For a given particle the ratio between the square of the displacement and the time is a constant. In a given fluid the size of the particles is important and the smaller the particles the stronger the motion* [3]. This work led Perrin to introduce concepts related to fractals. He was studying the trajectories of the Brownian particles and tried to define a tangent to the trajectories. "*It is an essential character of our particle* (*as it is for the coast of Brittany, if instead of studying it on a map, one could look at it from various distances*) *that, for every scale, one suspects, without seeing them very well,* *details which prevent us absolutely from setting a tangent*." Perrin's work showed that, at the scale of molecular biology, intense agitation of large molecules is a dominant factor. Statistical mechanics rules, and the permanent bombardment by water molecules leads to large positional fluctuations. Recently [4], such molecular fluctuations have even been used to propose models of molecular motors! In such a stochastic world, it is not surprising that life at the molecular scale needs genetic information to perform its precise tasks. This brings us to Niels Bohr.

2. From Bohr to Delbruck and Schrödinger

Niels Bohr was the first modern physicist profoundly aware of the challenges posed by living organisms. He thought that in order to describe them, we must establish a conceptual framework essentially different on the one end from classical physics and chemistry and on the other from quantum mechanics. "*In every experiment on living organisms, there must remain an uncertainty as regards the physical conditions to which they are subjected, and the idea suggests itself that the minimal freedom we must allow the organism in this respect is just large enough to permit it, so to say, to hide its ultimate secrets from us. On this view, the existence of life must be considered as an elementary fact of life that cannot be explained, but must be taken as a starting point in biology, in a similar way as the quantum of action, which appears as an irrational element from the point of view of classical mechanical physics, taken together with the existence of the elementary particles, forms the foundation of atomic physics*". Bohr's point of view on biology was quite philosophical, but his impact on fellow physicists was profound. Already in 1932, he found an enthusiastic disciple in Max Delbruck.

For Delbruck, the problem of genetic mutation and replication presented an enigma. On the one hand, genes were remarkably stable, on the other hand, mutations did occur. He went to Berlin to study with N W Timofeeff and K G Zimmer the effect of soft X rays on mutation and they published in 1935 a very influential paper [5]. "*Uber die natur der genmutation und der genstruktur*". The main results obtained were: mutations increase with the dose of X rays, are independent of the rays energy, from soft to hard, and one mutation is localized on about 10^3 atoms. This is a remarkable ensemble of results, given that at this time the support of genetic information, DNA, was unknown. One had to wait until 1944 for Oswald Avery and colleagues to present strong evidence that DNA was the genetic material. They showed that the DNA extracted from dead members of a pathogenic bacteria strain imparted this pathogenic character to live members of a non-pathogenic strain of the same bacteria [6]. The belief was that the genome was stable, and mutations rare and dependent on high energy excitations. It led many physicists to think, wrongly, that quantum mechanics was involved in the process of genetic information.

Delbruck moved in 1937 to Caltech where he developed the famous phage group and studied the growth of phages, viruses of bacteria [7]. "*Certain large protein molecules (viruses) possess the property of multiplying within living organisms. This process, which is at once so foreign to chemistry and so fundamental to biology, is exemplified in the multiplication of phage in the presence of susceptible bacteria.*" He described in a lovely physicist's way elementary experiments. "*Bacteria first are grown in a test tube of liquid meat broth. Enough viruses of one type are added to the test tube so that at least one virus* *is attached to each bacterium. After a certain period* (*between* 13 *and* 40 *minutes, depending on the virus*), *the bacterium bursts, liberating large numbers of viruses. At the moment when the bacteria are destroyed, the test tube, which was cloudy while the bacteria were growing becomes limpid. Observed under the microscope, the bacteria suddenly fade out*''. Later, in 1946, in a meeting at the Harvey Society, he expressed the physicist's surprise regarding the complexity of biology.

''*Let us suppose that this imaginary physicist was a student of Niels Bohr, a teacher deeply familiar with the fundamental problems of biology, through tradition, he being the son of a distinguished physiologist, Christian Bohr. Suppose now that our imaginary physicist is shown an experiment in which a virus particle enters a bacterial cell and twenty minutes later the bacterial cell lyses and one-hundred particles are liberated. He will say: How come, one particle has become one-hundred particles of the same kind in twenty minutes? That is very interesting. Let us find out how it happens! Does it multiply like a bacterium, growing and dividing, or does it multiply by an entirely different mechanism? This is so simple a phenomenon that the answers cannot be hard to find. In a few months we will know. We will do a few experiments at different temperatures, in different media with different viruses, and we will know.....Perhaps you would like to see this childish young man after eight years, and ask him whether he has solved the riddle of life yet? This is what he may answer: Well, I made a slight mistake. I could not do it in a few months. Perhaps it will take a few decades, and perhaps it will take the help of a few dozen other people. but listen to what I have found, perhaps you will be interested to join me*''.

Finally [8], in 1949 Delbruck gave another address, '' *A Physicist Looks at Biology*'' where he came back to the difference between the two fields. Let us give some excerpts. ''*A mature physicist is puzzled by the circumstance that there are no absolute phenomena in biology. Everything is time bound and space bound. The animal or plant or microorganism he is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity. The organism he is working with is not a particular expression of an ideal organism, but one thread in the infinite web of all living forms. The physicist has been reared in a different atmosphere. The materials and the phenomena he works with are the same here and now as they were at all times and as they are now on the most distant stars. He deals with accurately measured quantities and their casual interrelations and in terms of sophisticated conceptual schemes. The outstanding feature of the history of his science is unification.... Such a situation from the outset diminishes the hope of understanding any one living thing by itself and the hope of discovering universal laws, the pride and ambition of physicists. The curiosity remains, though, to grasp more clearly how the same matter, which in physics and in chemistry displays orderly and reproducible and relatively simple properties, arranges itself in the most astounding fashions as soon as it is drawn into the orbit of the living organism.... If it is true that the essence of life is the accumulation of experience through the generations, then one may perhaps suspect that the key problem of biology, from the physicist's point of view, is how living matter manages to record and perpetuate its experiences*''.

The importance of mutation and at the same time of the stability of the genome was clearly understood at that time. What remained to be discovered was recombination and Delbruck played an important role there too. Let us quote Salvador Luria, a close associate of Delbruck. "*Yet as early as* 1946 *I made a finding that was destined to open up a new insight on how the stability of DNA is achieved. I had long known that bacteriophage, when exposed to ultraviolet light, was killed in a straight forward way, the number of kills being directly related to the amount of light used. But Max Delbruck had noticed certain unexplained irregularities. What I discovered was that when two or more dead phages entered the same bacterial cell, they often became alive again and produced normal live progeny. I interpreted the reactivation, correctly, as a result of genetic recombination. Two or more phages, if they were damaged in different genes, could by genetic exchanges reconstitute an undamaged, completely normal phage. And so I put Jim Watson, my first graduate student in Indiana, repeat the experiments with X rays*". Thus, in 1946, the framework for an information based biology was in place, mutation and recombination starting to be understood. From a different perspective, another physicist, Erwin Schrodinger became interested in the theoretical problems posed by biology.

In "*What is Life*" one of Schrodinger's [9] queries was about the stability of the genome as time went by. Let us quote him, "*In biology a single group of atoms existing in only one copy produces orderly events....One recognizes that we are here obviously faced with events whose regular and lawful unfolding is guided by a mechanism entirely different from the probability mechanism of physics. For it is simply a fact of observation that the guiding principle in every cell is embodied in a single atomic association existing in one, and sometimes two copies, and that it results in producing events that are a paragon of orderliness. Whether we find it astonishing or whether we find it quite plausible, the situation is unprecedented, it is unknown anywhere except in living matter. The case did not arise and so our theory does not cover it – our beautiful statistical theory of which we are so justly proud because it allowed us to look behind the curtain, to watch the magnificent order of exact physical law coming forth from atomic and molecular disorder.... It appears that there are two different mechanisms by which orderly events can be produced: the statistical mechanism which produces order from disorder and the new one which produces order from order....We must therefore not be discouraged by the difficulty of interpreting life by the ordinary laws of physics. We must be prepared to find a new type of physical law prevailing in it*". Schrodinger showed that the genome could not keep its stability as generations went by. He thought that new laws of physics were necessary to explain the relative stability of genomes. He was correct to assert that the evolution of stable forms of life requires considerable precision in the transfer and utilization of genetic information [10]. But new laws of physics are not necessary, the fidelity of the genetic code being maintained during the replication of DNA by editing reactions that remove errors. It is interesting to note that the concept of error correction came from Von Neumann [11] in his beautiful paper on "*Probabilistic Logics and the Synthesis of Reliable Organisms from Unreliable Components*". Without error correction, mutation rates would be unacceptably high. Molecular machines are used for proof reading and error correction, which improve the fidelity of replication by about three orders of magnitude. This precision has been achieved by the co-evolution of a special enzyme mechanism that uses some of the energy of the cell. The concept of molecular motor was out of the possible realm of what Bohr, Schrodinger and Delbruck could think of. As stated by Schrodinger the case did not arise of machines at the molecular level, and so theory did not cover it. Molecular machines are now an active research domain for theoretical physicists [12].

3. The genome era: Molecular recognition and RNA chip

We are today in different times, the genome era [13]. Experimentally determined biological sequences can be obtained with certainty. Genetic information is cast in the form of digital symbol sequences to be downloaded from the computer. Only economic rules limit the standard for the quality of data. Within a few years the main genomes, including the human one, will be available. This amazing increase of information is a challenge and an opportunity; quantitative biology comes of age. At the same time, enzymes that cut, paste, copy, the machinery which allows to copy DNA, transcribe into messenger RNA, translate into proteins are all by now described if not understood [14]. How is genetic information measured? Can one at any time record the expression of genes by measuring all the messenger RNA? Is it possible to develop laboratory evolution of genes? Molecular recognition usually means that a single stranded DNA molecule hybridizes to its complementary strand. This is of practical importance for gene recognition where a short sequence of DNA is used to recognize longer gene sequences by hybridization to the complementary part in the gene [15]. It is usually assumed that, with a precise 20 bases single strand DNA sentence, one can detect the messenger RNA of a gene [16]. In our laboratory we are actively involved in such a study, developing first optimal probes [17], and then arrays [18] of single strand DNA probes to measure gene expression, a so called "RNA chip". The new emerging biology will be quantitative, thus amenable to theoretical modeling, or, in short, an important field for physicists. It is safe to conclude that the era of quantitative biology is starting with the genome projects.

4. The emergence of automata

In parallel with the development of modern biology, information theory and its related field, automata studies, emerged during the Second World War. Princeton was the center of this activity. In 1936, Alan Turing was visiting the logician Alonzo Church. He wrote in Princeton his famous article on computable numbers [19]. "*We may compare a man in the process of computing a real number to a machine which is only capable of a finite number of conditions $q_1, q_2, \ldots, q_r$ which will be called m-configurations. The machine is supplied with a tape running through it and divided into sections* ". The Turing machine was born and some of the molecular machines such as DNA replication and ribosome translation share characteristics of Turing machines.

By the end of the 1940's, Church had published his "*Introduction to Mathematical Logic*" [20] and Von Neumann his "*Theory of Natural and Artificial Automata*" [21], while nearby, at Bell Labs, Claude Shannon was writing his seminal paper on *"A Mathematical Theory of Communication"*[22]. An extraordinary time, captured by these excerpts from Von Neumann: "*Natural Automata*" *are superior to artificial ones, they have power of self diagnosis and self repair... It is to be expected a close relation of self reproduction to self repair... In living organisms malfunctions of components occur. The organism obviously has a way to detect them and render them harmless. The system must contain the necessary arrangements to diagnose errors as they occur, to readjust the organism so as to minimize the effects of the errors, and finally to correct or to block permanently the faulty components. Our modus procedendi with respect to malfunctions* *in our artificial automata is entirely different*". All those explanations were proposed before error correction became an important field in biology.

Another aspect of this effort is well described in Turing's article in the quarterly review, "*Mind*" [23] on computing machines and intelligence where he poses immediately the question, "*Can machines think*?" This is the article on the Turing test played by a man, a machine and an interrogator. The interrogator stays in a room apart from the other two. He asks questions and the answers are typewritten. The object of the game for the interrogator is to determine which of the other two is the man and which is the machine. Turing states his belief, "*It will simplify matters for the reader if I explain first my own beliefs in the matter. I believe that in about fifty years' time it will be possible to programme computers, with a storage capacity of about* 10^9*, to make them play the imitation game so well that an average interrogator will not have more than* 70 *percent chance of making the right identification after five minutes of questioning. The original question*, "*Can machines think*?" *I believe to be too meaningless to deserve discussion. Nevertheless, I believe that at the end of the century the use of words and general educated opinion will have altered so much that one will be able to speak of machines thinking without expecting to be contradicted… We may hope that machines will eventually compete with men in all purely intellectual fields. But which are the best ones to start with? Even this is a difficult decision. Many people think that a very abstract activity, like the playing of chess would be best*". Turing's predictions for our time are to the point! Today, one even proposes that men are on a continuum with the machines they have created [24].

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