Encounters at a boundary: a (very) brief history of the interactions between Physics and Biology

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Interest in the Physics of living systems, or Living Matter, probably goes back to the first time an enquiring set an eye on an organism. However, any attempt to frame the understanding of its structure and workings in terms of the physical principles known at the time has, more often than not, gone wayward. Up to recently the reason has been a lack of understanding of the fabric of biological systems. For several centuries, every time a mechanistic understanding of the world emerged, it tried to encompass biological systems but did not go very far in this endeavour because of limited knowledge about the composition and basic material structure of living systems (Jacob, 1976).

At the moment, a number of circumstances are coming together to make us think that it is time for a new onslaught on the question of the Physics of Living Matter. Part of the optimism is derived from the fact that over the last fifty years we have acquired a sound understanding of the elements that make up living systems and of some of the ways they interact to achieve functionality (Alberts et al.2002; Lodish et al. 2002; Martinez Arias and Stewart, 2002; Pollard and Earnshaw, 2002; Wolpert, 2006). This process has built on a blend of Biochemistry, Genetics and Molecular Biology and produced a first approximation list of components and their organization thus opeining a door to answer old questions and has generated new ones. As a result Biology is in the midst of a transition from descriptive and qualitative to analytical and quantitative, generating new types of questions and developing and implementing new approaches many of which come from the physical sciences and engineering.

In this impasse one could have a sense of ‘deja vu’ and feel that this will be another futile onslaught at the old chestnut of a physical explanation of biological processes and systems. Or maybe not. For this reason, it might be worth our while to summarize earlier attempts to bridge the gap between the physical and biological sciences. This could be an interesting exercise for two reasons. First, because History always teaches us something about the questions and the methods to solve a particular problem. Also because the efforts of the past have (sometimes hidden in their succeses and failures) the seeds for the future. In this spirit, here are some notes, brief but hopefully telling, about the attempts that have been made over the last 100 years, to look at Biology from the perspective of the Physical Sciences.

The questions

Biology is, principally, about answering four interrelated questions:

- The nature of Heredity

- The Laws and Mechanisms of embryonic development and shape forming (morphogenesis)
- The Physical and Molecular Basis of Behaviour
- The Evolution of Living Systems.

These are intriguing issues that lie at the heart not only of basic curiosity but which ultimately impinge on the well being of humans. Natural philosophers and scientists have always had a go at them but the answer, for a long time, was more speculative than anything of substance. One exception to this were questions associated with the senses, as they were not only close to human fascination but open to experimental probing. Thus, for example, the physiology and physics of perception, particularly visual perception, has always provided a natural playing ground for individuals with an enquiring mind. I. Newton, R. Descartes, J.W. Goethe and J.C. Maxwell, dabbled with experiments and theories to explain issues of visual phenomena. Another important exception is the work of W. Harvey which relied on precise measurements of the blood flow and the circulatory system within the realm of mechanics and Physics. Life itself has never strayed very far from purely physical explanations, as clearly revealed in the discussions of A.Volta and L. Galvani on the relationship of electric currents to biological specimens which, in the long run, lead inevitably to neurophysiology.

However, much of the mystery underlying the structure and working of living systems had to wait for a material understanding of Heredity and its molecular underpinning (Jacob, 1976; Judson, 1979). Interestingly the way to the complete answer was laid bare by the work of G. Mendel with a heavy influence of physical sciences and an appreciation of the value of quantitative approaches. One of the lessons to be derived from an analysis of Mendel's work is that a problem has to be ripe for a given approach and this sometimes, frustrates human curiosity which, unable to wait, attempts explanations and visions of particular issues e.g origin of species, laws and causes of embryonic development, physical basis of perception, earlier than a solution is possible. In the absence of a sound basis, these explanations become speculations.

It is now clear that we have a sound answer to the first of the four questions and that great strides are being made towards the answer of the other three. So, there is still much to be done and it is clear that the complete answer to those questions will have to seek help beyond classical Biology. The last twenty years, with the knowledge extracted from the structural and functional analysis of genomes and the deluge of technology to deal with the large amount of information derived from this analysis, are a prelude to a challenging but interesting period in which it is certain that a new Biology will be born. It is our belief that much of this will come from a renewed attempt to bridge the gap between Physical and Biological Sciences.

Mathematical and theoretical Biology

There have been many attempts to find theoretical frameworks to understand biological systems. This is particularly true of the last 100 years when the advances and successes of Physics, Chemistry and Mathematics have invited similar approaches to biological questions (summarized and reviewed in Fox Keller, 2002). One intriguing effort was launched by CH Waddington who , towards the end of a remarkable career as an experimental embryologist, brought together in Edinburgh a group of disparate people to discuss theoretical possibilities for Biology in a series of meetings (Waddington ed. 1968-1972). This was an interesting exercise as at the time Genetics and Biochemistry were beginning to yield the first glimpses into the working of living systems thus providing an apparently sound basis for a theoretical approach.

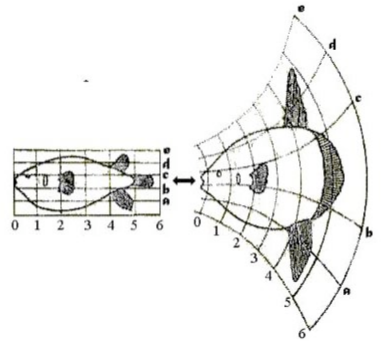


Illustration from the work of D'Arcy Thomson, showing how forms can evolve from one another through geometrical

This effort focused very much on aspects of generation of form (morphogenesis), the working of the nervous system and Evolution. The Edinburgh discussions were very theoretical and in most instances premature, as there was no information upon which to build models or theories. From our present perspective they read like medieval disquisitions on the planetary system. Interesting but misguided. The search for theoretical and mathematical foundations of Biology has interesting forerunners, as in the classic work of D'Arcy Thomson (1917) on the geometrical basis of biological shape and the possibility that there are principles underlying this important property of organisms. In this line of thought it is important to mention the attempts of N. Rashevsky to establish a School of Mathematical Biology at the University of Chicago (see Fox Keller, 2002). However, with few exceptions, these attempts to find mathematical representations of biological processes became futile exercises into interesting mathematics. One such example is the application of catastrophe theory to Biology (Thom, 1976) which is conceptually interesting but difficult and of little practical value. A conclusion from these exercises is that there is always a possibility to find an equation or a formulation to describe a biological process but in the absence of data to fit the relevant parameters, it is only a representation of that phenomenon rather than an explanation for it.

Amongst the exceptions to this rule, two stand out. One is the work of N. Wiener (1948) on control theory and its implications for biological systems which allowed a sound conceptual ground for a view of living systems as self regulating machines. The other one is a paper by A. Turing (1952) on spatial and temporal patterns of chemical reactions which has served as an inspiration for many generations of theoretical biologists and has had some influence on modern approaches to problems of pattern formation (Meinhardt, 1982).

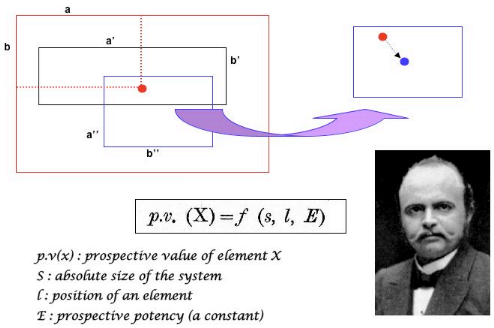
Despite easy criticism of many of these attempts it is important to remember that some areas of Biology, particularly Genetics and Ecology, did benefit from the application of Mathematics and the development of theory. This is likely because here there was an obvious need to do so and also because the elements for such an analysis (data) were there. Thus, the development of population genetics took place hand in hand with the development of statistical methods and R. Fischer and S. Wright stand out as dabblers in both areas (Provine, 1971).

The Physics connection

While during the XX century mathematical approaches and purely theoretical constructs were of little help to solve most of the important questions of Biology, biologists profited from the incursions of physicists and chemists in their territory. Perhaps this is because Biology is about experiments; rather than abstractions, what was needed at the time was the data to quantify and on which to build theories. This in turn demanded the development of methods that would allow the identification of the building blocks of Living Matter, their organization and their activity. Since Living Matter is organic matter, nobody better equipped for this task than physicists and chemists who are fit to develop sophisticated tools in tune with the problems they want to solve (Dyson, 1999).

One branch of Biology has never been too far from the physical sciences: Neurobiology. From the moment A. Volta and L. Galvani could see that there was a relationship between electric currents and some of the activities of Living Matter, the analysis of neural activity and its underlying mechanisms have never bee too far from the physical sciences. This culminates in the work of A Hodgkin and A. Huxley (1952) on the physico-chemical principles of neural transmission which lays down the foundation for the analysis of neural activity.

In addition to the biology of the nervous systems, of which much remains to be discovered, there is the whole organism, its emergence from the egg and its progressive organization into functional units of which the nervous system is but one. Perhaps the first person to make a serious attempt to deal with this problem from the experimental and theoretical points of view was Hans Driesch. In a series of lectures (1907) summarizing his work as an experimental scientist, he tried to find Principles underlying the emergence of living organisms. Physics is very much at the roots of his thinking and he uses concepts such as fields, potentials and related formulations with strong resonance to the physical Sciences. At all times he seeks a mechanistic explanation with a theoretical grounding. The questions that he poses and his formulations are very advanced for his time. He understands well what he is wants to know:



$$p.v.\ (X) = f\ (s,\ l,\ E)$$

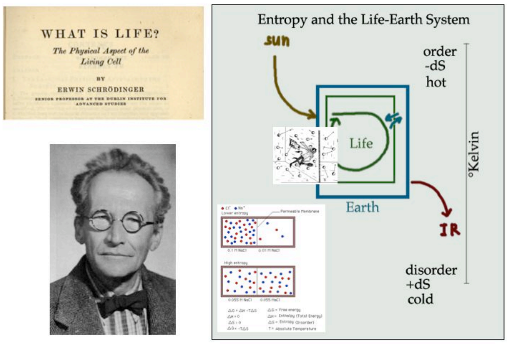
p.v(x) : prospective value of element X
S : absolute size of the system
l : position of an element
E : prospective potency (a constant)

H. Driesch, (1907) The science and philosophy of the organism

In the Science and Philosophy of the organism (1908) Hans Driesch explored the existence of physical principles underlying the development of organisms. He even proposed an expression for the prospective value (p.v) of a cell during development. However, he could not transform his ideas into concrete biological expressions

"If we are going to explain what happens in our system by the aid of causality based upon a constellation of single physical or chemical factors and events, there must be such a thing as a machine"

He then works out what kind of a machine could account for what he observes as essential properties of living systems and the deeper he thinks, the more he wonders whether what he thinks is needed is possible. When probing into the properties that such a machine must have, particularly on issues like reproduction, self organization and regeneration, though he is right as to what kind of a machine can perform these tasks and gets close to formulating an 'ideal cell', he reckons that such a machine is impossible and drifts into philosophical speculations that lead him into vitalism. He was very close to a very modern formulation of the problem of embryonic development in terms of concepts and language which would fit very well in today's framework but his inability to move forward was derived from the lack of proper knowledge of Genetics, Cell and Molecular Biology. Laying these would occupy most of the XX century and questions such as the ones posed by Driesch would have to wait.



In his book Schrödinger explored the structural and functional principles underlying the physics of Living Matter.

A second most significant attempt to look at Biology from the point of view of Physics came from the physicist's side: E. Schrödinger's book What is Life (1944). This small book, often hailed by physicists as their road map for the way into Biology, served as an inspiration and a guide for several generations of physicists. Though close study has led to the view that "what was true in this book was not original and what was original was known not to be true" (Perutz, 1987). This might be a harsh assessment of a piece of thinking which, at the very least, formulated Biology in a manner that was (and is) attractive to physicists, and although it is easy to argue that Perutz is right as he was so close to Biology, it might reflect two different ways of looking at the world and two different intuitions. The book deals with two questions. The first one, central at the time, concerns the nature of the structure of the hereditary material. The second, more abstract, emphasizes the need to explore the thermodynamic basis of Living systems. One of the most compelling themes of the book is the believe that there might be new laws of Physics lurking in biological systems:

Living matter, while not eluding the 'laws of physics' as established up to date, is likely to involve 'other laws of physics' hitherto unknown……. from all we have learnt about the structure of living matter, we must be prepared to find it working in a manner that cannot be reduced to the ordinary laws of physics. And that not on the ground that there is any 'new force' or what not, directing the behaviour of the single atoms within a living organism, but because the construction is different from a anything we have yet tested in the physical laboratory.

We must therefore not be discouraged by the difficulty of interpreting life by the ordinary laws of physics. For that is just what is to be expected from the knowledge we have gained of the structure of living matter. We must be prepared to find a new type of physical law prevailing in it.

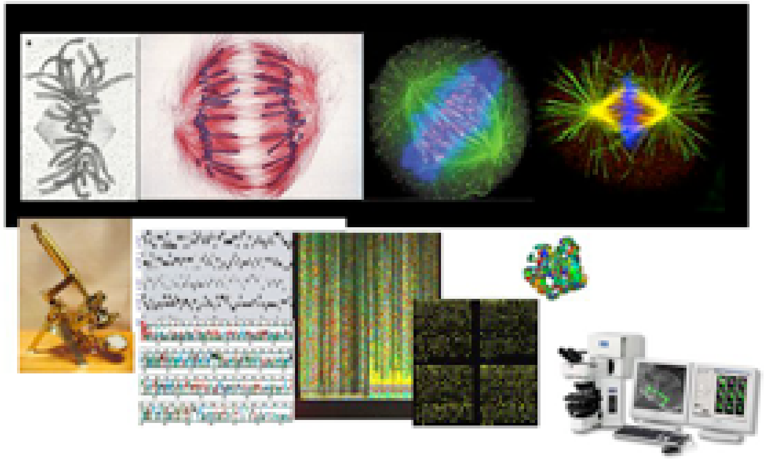
He may be vague in this, but he also may be right and today we are in a good position to test it as we move, increasingly into organizational aspects of living systems. In this regard, the issue of structure-function and its relationship to order, found an important theoretical grounding in the paper of Turing (1952) on the chemical basis of morphogenesis and, very significantly, in the work of I. Prigogine, who established the notion of biological systems as non-linear dissipative structures (Prigogine and Nicolis, 1977) which is just beginning to explored in full (Karsenti, et al. 2006).

However, if one is to highlight real practical, tangible successes at the interface of Physics and Biology, one has to look at hypothesis driven instrumentation and the focus this has provided on biological objects. As Feynman said in his famous lecture that raises the curtain for nanotechnology (Feynman, 1960).

"*We have friends in other fields--in biology, for instance. We physicists often look at them and say, "You know the reason you fellows are making so little progress?" (Actually I don't know any field where they are making more rapid progress than they are in biology today.) "You should use more mathematics, like we do." They could answer us--but they're so polite, so I'll answer for them: "What you should do in order for us to make more rapid progress is to make the electron microscope 100 times better."*

The development of microscopy has allowed increasing resolution and insight into the composition, structure and activity of Living Matter.

The top shows a number of images of mitotic cells in metaphase from early optical devices until modern confocal microscope images.,



The development of optical devices in particular has been a constant in the progress of the biological Sciences (Harris, 1999). From Hooke and Leeuwenhoek to the development of the electron and now the confocal microscope, this has been, probably, the most important string of influence from the physical to the biological sciences. And it is likely to continue. One important branch of this interest to look ever deeper and more precisely, was the development of structural Biology pioneered by JD Bernal, M. Perutz, J. Kendrew work on X ray diffraction for determining the structure of proteins (1938-

1959). At the moment the attempts to extend this work to bridge the gap between the molecular and the cellular interfaces are high in the local agendas.

The contributions of physicists to Biology have not just been technical, for physics is, above all, a way of looking at the world and asking questions. In the 30s and 40s a number of physicists turned their attention to issues of heredity and reproduction and in doing so led a dramatic turn in the way of looking at problems, in the manner of setting and doing experiments. Reductionism took hold of Biology and bacteria and bacterial phages, bacteriophages, took center stage for a new kind of biologist. The outcome of all this toiling is known as the 'phage school' . Here physicists like M. Delbrück, L. Szilard, G. Stent and S. Benzer, working with biologists like A. Novick and S. Luria amongst others, with a keen eye for simple, quantitative and elegant experiments made great strides towards the understanding of the hereditary principles and materials (Cairns et al. 1992). Slowly but surely, this road meets the stream of the structutal biologists and leads to the elucidation of the structure of DNA by J. Watson and F. Crick with the assistance of R. Franklin and M. Wilkins in the most iconic and well known example of the power of the collaboration of Physics and Biology.

Biologists and Principles.

The interactions between physicists and biologists created a conceptual and experimental framework, Molecular Biology, which in the 60s and 70s led to significant discoveries in the structure and organization of living systems. The crucial element of this work is the collaboration between the two disciplines and the fact that physicists, here, were not just providing instruments but a way of thinking, a way of looking, a way of finding things out which combined with the questions and the insight of biologists generated a large number of discoveries and tools.. The combination has always proven powerful. The interactions of F. Crick with J. Watson first and then with S. Brenner, the developments of S. Benzer or the contributions of L. Wolpert, an engineer turned into a biologist (Wolpert, 1969, 2005) are excellent examples of these achievements.

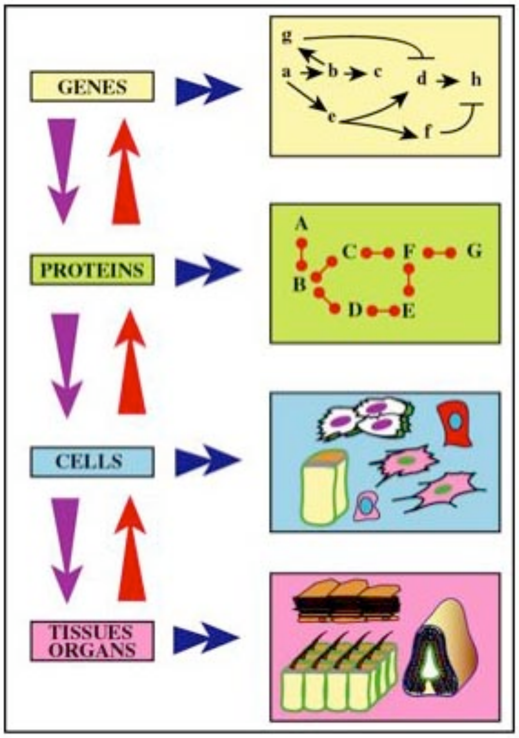
Any account of the history of the Physics of Living Matter cannot forget to mention some contributions from solo biologists which, have looked for universal principles under the rules of reductionism and sometimes have found a guide towards them. Thus, the concept of homeostasis, introduced by W. Cannon (1932) plays a very important role in our current frameworks to understand the workings of Living matter. And in the same vein one should not forget the seminal contributions of J. Monod and F. Jacob on enzyme kinetics (Monod et al, 1973) and gene regulation (Jacob and Monod, 1962) as well as of M. Ptashne (1986) on the principles of gene expression and choice at the molecular level. These works have exerted a tremendous influence in the way we see and perceive biological processes and it is not surprising that they are still used as references in the transition in which we find ourselves.

Systems biology: looking for the forest in the trees

The last ten years have seen the emergence of the field of "Systems Biology" which is being hailed as a synthesis of much that has been summarized above. There are many definitions and arguments of Systems Biology, but the truth of the matter is that approaches to biological questions as "systems" is what Biology has always been and is currently about (Hartwell et al. 1999; Kirschner, 2005). It is difficult to find a biologist, now or fifty years ago, whose interest is not to understand the workings of the system they work with. Having said this, it is also true that there is something new and important in the formulation of questions in the framework of Systems Biology. An crucial element of the approach is the development of computational methods to retrieve and deal with the amount of necessary information which lies in waiting in genomes and proteomes. This leads to models which, much in an engineering fashion, try to put the system back together. Systems Biology is as much about reverse engineering as it is about data mining and organization. The exercise is full of traps and while going through it, it is worth baering in mind the admonitions of A. Garcia Bellido (1989) when musing over current issues of developmental biology and pattern formation:

> *"the analytical approach, aimed at elucidating the molecular elements and the biophysical mechanisms of the transformation of morphogenetic information between levels of organization in development, uncovered a new world that transcends the comfortable and naïve one of historical contingency in morphogenesis. We found that there is more for developmental biologists to do than merely to describe: there is, at least, a morphogenetic syntax to be ascertained . After taking apart our four dimensional toy from the top down, we are now left with the task of finding out, from the bottom up, the logical rules by which it was put together. This may prove to be a difficult task, specially if, working at the bottom level, we forget that it was at the top that we wanted to explain".*

It is always in this toing and froing between levels of description and complexity that the catch lies. This issue of the relationship between levels is an integral part of biological systems and the one where, if we can understand it, might lie some of the new principles that Schrödinger was talking about. ,



Biological systems are composed of structures and activities at interrelated length scales and an important challenge of current research is to probe for the existence of Principles within this structure.

Systems Biology draws many ideas and tools from Mathematical Biology and much more from modern developments of Computational Biology. And it is clear that this will usher a new era in all of these areas of research (Coen, 2004). But the most important substrate of this discipline, and what singles it out from earlier theoretical approaches, is that it uses real data. No more of the speculations and curiosities that abound in the older formulations.

The physics of Living Matter: back to the future

In the same way that Systems Biology has a continuity with other branches of both experimental and theoretical Biology, the Physics of Living Matter also follows from earlier efforts of cross interactions between disciplines. It is tempting to look at the Physics of Living Matter as some form of a XXI century Biophysics, but this would be to miss important nuances that highlight dynamic aspects of Living Matter which have not been prevalent in Biophysics. As it is the case for Systems Biology there is an unprecedented amount of information derived from the structural and dynamic activities of molecules and cells that has to be processed and much that has to be gathered anew. Also, new developments in imaging and sensing are opening new dimensions in the way we look at Living Matter. An important characteristic of biological systems is their dependence on different interrelated lengthscales all of them functional. One of the great challenges lies not only in understanding the organization of each of these lengthscales but in seeing how the properties of the higher order ones emerge from the lower order ones.

The Physics of Living Mattter is about obtaining the dimensions of living sytems, about developing the methods to obtain the numbers which might lead to the laws the Schrödinger and others craved for, it is about developing a chance to probe for those laws. It looks for Principles in accurate and precise observations. Diffusion in the sticky milieu that is the extracellular space, or the activities of the polymers that configure the cytoskeleton will obey known physical laws, but they might do so under conditions and with constraints that might reveal new dimensions to those laws. We shall also have to deal with the issues of how reactions with small numbers of molecules (and we are just beginning to get a feeling for these numbers) which might be stochastic, have deterministic consequences at the cellular level.

The Physics of Living Mattter could be construed as an integral part of Systems Biology but, while an important element of Systems Biology is to develop methods and models to deal with large data sets, an emphasis of Physics of Living Matter is in the input of the Physical Sciences on Biological questions, on the precise measurement of the components and their dynamics at the different length scales. Both have to face the inconvenient aspects of modeling complex systems with a limited amount of information.

Living Matter is the business of Physics as it is the business of Systems Biology. The bridge between the two is ushering a new era in Biology. There is every reason to believe that the development of a Physics of Living Matter will result not only in further and intriguing insights into Biology but also in the development of new ways and tools to look at biological systems. This will have an impact in areas of research that are not very far from Biology, particularly Medicine and thus will pave the way for the development of a Physics of Medicine (Varmus, 1999).

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