Life Science Press

Publishing press
Together for Science

Short Communication

Life sciences at an historic turning point

Laurent Jaeken

Antwerp University Association, Karel de Grote-Hogeschool University College, Department of Industrial Sciences and Technology, Laboratory of Biochemistry, Salesianenlaan 30, B-2660, Hoboken, Belgium

***Corresponding author**
Laurent Jaeken
Antwerp University Association
Karel de Grote-Hogeschool University College, Department of Industrial Sciences and Technology
Laboratory of Biochemistry
Salesianenlaan 30
B-2660, Hoboken, Belgium
E-mail: laurent.jaeken@hotmail.com

Received: *December 4th, 2017*
Accepted: *December 19th, 2017*
Published: *December 22nd, 2017*

Citation
Jaeken L. Life sciences at an historic turning point. *Life Sci Press*. 2017; 1(1): 25-30. doi: 10.28964/LifesciPress-1-104

ABSTRACT

The way of thinking about the basics of cell physiology is founded on membrane pump theory. It is deeply embedded in general views on solute gradients, transport processes, cellular rest and action potentials, cell volume control, steady state bio-energetic, etc. This theory is based on the rough statistical behaviour of dilute solutions. If true the precision with which cells would be able to control their life processes would be limited by the roughness of the statistical behaviour of dilute solutions, while it is clear that cellular control must be much more precise. The untenable situation at this moment is that the existence is almost totally ignored of a much more precise paradigm for basic physiology explaining the same above mentioned cellular phenomena in a totally different way. This alternative, Ling's association-induction hypothesis, is based on the cooperative association of some (meta)stable *bound-ATP-unfolded-protein-polarised-water-adsorbed* K^+ coherent low-entropy resting state complexes and their transition into a less-energetic high-entropic action state. This concept brings the level of precision for control down to the atomic level. During the last 70 years indications corroborating this alternative increase at a high rate. There are important implications for understanding cancer and other degenerative diseases. The alternative offers a new background for the interpretation of new data. So, it definitely deserves to become generally known to all involved in life sciences, including those developing and commercialising new applications.

KEY WORDS: Paradigm shift; Membrane pump theory; Association-induction hypothesis; Phase transitions; Coherence; New bio-energetic; Entropy; Structured water.

INTRODUCTION

One of the most fundamental domains of study in life sciences is physiology. The basic unit of life is the cell. Cell physiology investigates how cells and their constitutive parts are functioning. What are the working mechanisms and principles? In order to give answers to these questions cell physiology makes use of chemical and physical principles, uses mathematics to come to a quantitative testable description, and then adds the biological logic.

In life science university curricula basic cell physiology is typically instructed in a rather early year, usually after some basics of chemistry, physics and mathematics are already acquainted. In the further years and during a scientist's further career innumerable details are added, which always without exception are assumed to fit into the basic principles learned in the basic courses including basic cell physiology. And here comes the problem. What when some of the most fundamental ways of thinking about cells appear to be wrong? This would be an immense problem, because it may take sometimes even more than a half century before minds are redirected in a new direction. In general young scientists might have it easier to adapt to a new way of thinking. They know less details to be re-contemplated. Anyhow, university courses will have to be re-written, mentioning both the old and the new view. In doing this students can compare freely, not only during their studies but also during their further career, when they gather new data. Also in the applied industrial and commercial sector it is of prime importance that scientists be informed about general theories, particularly when there is more than one view, because the new view may lead to applications which are unthinkable when only considering the old view.

THE GREAT MISTAKE

In this communication a brief treatise will be given of what clearly is the most important mistake in basic cell physiology of the last 70 years.[1] It took about 50 years for the new view to become known to only a very limited number of life scientists. During this period individual pioneers attacked the problem each of them with their own approach, independent from each other. Each of them developed new theories. There were early data confirming their view and even some applications were already developed. Then, more recently it appeared that these independent approaches are telling the same story, and that the old theory is totally incompatible with the new way of thinking.[2] Clearly the old theory must be abandoned and the new one urgently needs to become known. The number of data confirming the new view starts to boom. Applications are increasing at high speed. But a large majority is still indoctrinated in the old view and tries to understand their own new findings within the old context and ignore the existence of an alternative. They do not see that their ideas are full of internal contradictions. This is particularly so, because during the last decades life scientists are very busy to study ever finer details. They see their protein under study as a very complicated molecular machine and want to unravel its working mechanism. In focusing to the details, the contradictions with the details of other molecular machines, at least when interpreted according to the old paradigm, are not discerned. They do not see that these apparently contradicting data are not at all contradictory when interpreted according to the new paradigm. So, what is needed at this very moment is that the immense amount of new experimental data could be hold against the background of both the old and the new paradigm and be fitted into a more general background. This is impossible as long as only one paradigm is known. Knowledge of the two alternatives is urgent for professors, for students, for present-day scientists in both fundamental life sciences and applied life sciences. About which alternative paradigms it goes?

TWO IMPORTANT ALTERNATIVE PARADIGMS, FROM WHICH ONLY ONE IS KNOWN

During the first half of the 20th century scientists tried to explain one of the most astonishing properties of living cells, namely that the concentration of most low-molecular solutes inside the cells substantially differs from that in the external environment. This holds for almost all solutes present inside and outside the cell. The most remarkable case, however, is that of the alkali ions K^+ and Na^+, which in a chemical sense are quite comparable apart from a minor difference in ionic diameter. Despite this very small difference intracellular Na^+ concentration has about a ten-times lower concentration in cytoplasm than in the environment, a situation called 'exclusion'. In contrast intracellular K^+ has a much higher concentration than that in the environment, a situation called 'accumulation'.

Two schools of thought developed. Some assumed that a cell is delineated by a 'semi-permeable' membrane, which is responsible for the concentration differences. Some suggested that this membrane is provided with some kind of ion-pumps energised by ATP, one of the most common energy currencies in cells. The ions leak through the membrane downhill their concentration gradient and an appropriate pumping mechanism unceasingly compensates this leak by an active transport in the other direction. Insofar these pumps establish a kind of steady state depending on a continuous energy input from metabolism. During cell activity the cell membrane is thought to increase temporarily its permeability so that afterwards these pumps have temporarily to increase their pumping rate. This view became to be known initially as *'membrane theory*' and later as *'membrane pump theory*'.

After Skou[3] discovered a membrane protein which appeared to be responsible for the pumping activity of both Na^+ and K^+, membrane pump theory quickly became the only theory instructed and this situation continues up to now. Part of its success was that at least 'apparently' a large number of physiologic processes appeared to be explainable by assuming the existence of this and some other pumps. They include: solute exclusion and accumulation, transport processes (passive, active and coupled transport), membrane permeability, cellular potentials, control of cell volume, chemiosmosis, motility,…). Let me now guess your reaction: "*It cannot be true that there is something wrong with this"*. My answer: "*Read the appropriate literature, and only then you are in a position to judge. Then, I don't matter what is your judgement. But science should be an open discussion. All alternative views should be known, particularly with respect to such most fundamental processes"*.

Yes, there is an alternative view with roots as far as the beginning of the 20th century. In those early days some scientists had studied colloids. They had observed that when a colloid stays in contact with a solution, solute concentrations in the colloid are often lower than in the surrounding solution. Each solute appeared to have its own concentration ratio or 'distribution coefficient' (partition coefficient). There were also indications that water inside a colloid has very unusual properties suggesting that water in a colloid might be differently structured. The situation in cells appeared somehow comparable. Most solutes are to some extent excluded by cytoplasm and this could be due to a different structure of cytoplasmic water as compared to that of bulk water. Their solubility in structured water might be lower than that in normal bulk water. K^+ is another story: it accumulates. Some first indications appeared that intracellular K^+ might be adsorbed to some cytoplasmic macromolecules. Protein carboxyl-groups are a possibility. Since about 1930 a wrongly interpreted experiment by the famous physiologist A.V. Hill[4,5] lead to a great victory for membrane theory. He had measured the distribution coefficient of urea between resting muscle cells and the Ringer solution in which they bathed. He found it to be close to one. So, it *appeared* that the structure of cell water was similar to that of bulk water outside. Water inside and outside the cell *appeared* as one and the same phase, not as in colloids where there are two phases. If so, intracellular K^+ must be in solution in order to explain the measured osmotic pressure. Clearly membrane theory is the theory to follow.

Nevertheless in the period from 1951 to 1962 Ling[6,7] proved in a very extensive and detailed study that in the experimental setup he used (0 °C, metabolism halted by poisons and by absence of oxygen) the postulated pumps used 15 to 30 times more energy than the cell could deliver. A first disproof of membrane pump theory. In 1973 Ling et al[8] did over the experiment of Hill, found that the measurements were correct, but that his conclusion was based on only a single test substance. Testing many other neutral solutes Ling et al[8] found that for most solutes the distribution coefficient is lower than one, the lower the larger the molecular size. Hence cell water is not normal water, and in that case in order to explain the measured osmotic pressure K^+ must be adsorbed for a quite high percentage. Step by step Ling[7,9-12] developed a quantitative alternative for membrane pump theory called the *association-induction hypothesis (AIH)*. In this really monumental work he disproved all basic tenets of membrane pump theory and proved all basic tenets from his own AIH.[9]

The Alternative: Ling's Association-induction Hypothesis

Some of the most fundamental principles of his AIH are now given (incomplete).

- In the resting state cytoplasm contains cooperative units of associated '*bound-ATP-unfolded-protein-polarised-multilayer-water-adsorbed-K^+(other-solutes)*' acting in a coherent way as a single unit and together constituting a (meta)stable high-energy low-entropy state, which does not consume energy. Clegg[13] was able to keep dormant Artemia cysts alive under complete anoxia without measurable energy expenditure during four years, after which period they were able to hatch. This example makes clear what it means: metastable. It also substantiates that the resting state is indeed a high-energy state. In classic physiology, for instance in muscle cells, the contracted state is assumed to be the high-energy state and the rest-to-action transition is taken as a '*disorder-to-order transition*'.[14] Yet in the absence of ATP muscle cells end up in rigor mortis, so the contracted state should be the low-energy state. In contrast Ling[9,15] states that adsorption of ATP lifts the cooperatively linked *protein-water-ion(solute)* system into its high-energy low-entropy resting state. It is only occasionally that the low-entropy state of structured water is accounted for. In most cases it is not. But, doing this or not doing this is equal to a completely different bio-energetic. The '*new*' bio-energetic and the '*new*' way how ATP functions by adsorption and not by hydrolysis, developed by Ling,[15] is meanwhile confirmed in several ways: by experiments of Ling,[9,11,16] by a theoretical extension of Prigogine's non-linear thermodynamics by Prokhorenko and Matveev,[17] by the finding that many proteins, particularly in Eukaryotes, occur in a physiological unfolded conformation,[18] an assumption made by Ling already in 1962 as a way to explain the long-range cooperative polarisation of water upon the exposed backbone peptide groups.[9,10,19,20] The in vivo presence of polarised multilayers of water in living cells in the resting state and in some model systems is meanwhile well established.[20] and also the adsorption of more than 60% of intracellular K^+ to β- and γ-carboxyl groups of (some) proteins, with some adsorption also to phosphate groups can no longer be doubted.[7,9,10,21-25] The cooperative character of the *protein-water-ion(solute)* complex quantitatively obeys to the Yang and Ling cooperative adsorption isotherm.[9,26]

- External stimulation of a cell function at rest activates the resting *ATP-protein-water-ion(solute)* associative complexes and brings them in their active state. This goes along with ATP hydrolysis, folding of unfolded polypeptide backbones (or binding of the unfolded region to a ligand so that the association with polarised water ends), depolarisation of adsorbed water and desorption of adsorbed K^+ or solutes (eventually combined with association of another ion or a fixed cationic site (for instance in muscle cells actomyosin formation), dissociation of P_i and ADP, after which the system is left in its low-energy high-entropy state. Under the stimulating (local) high free K^+ activity and using the liberated P_i and ADP both as substrate and as allosteric activator glycolysis and respiration are suddenly activated and generate new ATP, which (locally) adsorbs to the ATP-binding proteins and this automatically restores the high-energy low-entropy resting state (in the absence of a new stimulus).[9,11,27] Very recent studies of glycolytic oscillations are consonant with this view.[28]

- The transitions of the system from rest-to-action and from action-to-rest were shown to be cooperative phase transitions obeying to the Yang and Ling cooperative adsorption isotherm.[9,11] Phase transitions by definition imply that more than one phase can exist. From the early days on colloid theories were built upon observations that there are different phases, at least that the cell is another phase than the environment. The famous Russian physiologist Nasonov[29] followed different physicochemical parameters (turbidity, viscosity, hydrophobicity index) in different cell types following very different kind of stimuli and found that in all cases of activation, when the cell's threshold is surpassed, coordinated changes of these physicochemical parameters are observable. This directly indicates that rest-to-action and action-to-rest are real phase shifts. This constitutes a direct disproof of membrane pump theory, which is a one-phase theory, and at the same time it corroborates Ling's view. Under the inhibiting impulse of membrane pump theory for a long period phase transitions have not been studied very much. However, recently phase transitions are becoming again a hot topic, namely in the field of intrinsically disordered proteins[18] and in that of membrane-less organelles. These fields are very much connected with cancer and other degenerative diseases. My prognosis is that the study of these illnesses would benefit a lot by adopting the new paradigm, from which Ling is the main promoter.[18,30,31] After all we thank the development of the medical NMR imaging technique to the finding of Damadian,[32] a friend of Ling, that the water in cancer cells is less structured than in normal cells. According to Ling this means that the order in cancer cells is much less than in normal cells. One should indeed adopt a bio-energetic based on entropy and ATP adsorption[9,11,19,27,33] and suddenly everything becomes

very clear. This means that one also definitely abandons a bio-energetic based on a steady state and on ATP hydrolysis.

- These important changes of so many aspects during action-to-rest and rest-to-action are brought about by what Ling calls *'cardinal adsorbents'*. These are important physiological ligands binding to a *'cardinal adsorption site'* (for instance an allosteric site). ATP is the most important ligand for the action-to-rest transition and Ca^{2+} is one of the ligands for the rest-to-action transition. According to Ling,[9,11,26] the binding of these ligands initiates a Lewis inductive effect, travelling through the protein and reaching the sites of adsorption of water, ions, solutes and other ligands, where as a result binding preferences are changed. Some cardinal adsorbents bring about an electron-donating inductive effect and others an electron-withdrawing one. These are the two possibilities open to a cardinal adsorbent at the moment of its adsorption to an effector (*protein-water-ion complex*). The two effects which are theoretically possible are rest-to-action or action-to-rest.

One comes to see that Ling's AIH is a very complete theory, easy to test, because for major physiological activities complete equations are developed, in which always distribution and activity coefficients figure, and cooperativity among binding places can be quantitatively studied. One can even calculate from experimental data how much (inductive) energy travels from a cardinal binding site to the sites where water, ions, solutes and other ligands are bound.

The greatest rather recent confirmation of Ling's AIH comes from the unification of Ling's AIH with a number of important physical studies of the coherent behaviour of life.[2] Unification could be obtained by interpreting in physiologic terms the different mathematical coherent solutions of a non-linear Schrödinger equation derived by Tuszynski et al.[34] It was shown that Ling's very detailed physiologic theory conforms to the findings of a number of independent renowned physical scientists, who each in their own field studied the possibility of coherence in living organisms. This possibility was first proposed by Schrödinger in 1944 in his book 'What is life?'.[33] Schrödinger argued that concentrations of different molecular species in cells are much too low to apply the statistical equations on which membrane (pump) theory is built. So, he argued that the latter theory cannot be correct. A much finer degree of control could only be obtained in a very ordered system such as in coherent physical systems close to absolute zero temperature. According to him a somehow comparable coherent state should exist in living organisms, but then at body temperature. This proposal is not nothing. He proposed a very low-entropy state, and it is clear that Ling's resting state corresponds to this, but Ling described 'classic coherence', while Schrödinger also considered the possibility of 'quantum coherence'. Details would bring us too far, but the application of non-linear electrodynamics by Fröhlich[35,36], of quantum field theory by Del Giudice et al[37,38], of quantum mechanics by Davydov[39], of non-linear optics by Popp[40] and of polarisation microscopy by Ho[41] all confirmed the view of Schrödinger. This field of study is often executed by physicists and electronic engineers and reported in journals which are not very much read by biochemically oriented reductionist bio-scientists. But it is quickly expanding and gives rise to different kinds of applications, such as new methods for medical diagnosis and therapy based on characteristic frequencies. It is not good to see such techniques as (only) concurrency for biochemically inspired methods. Also in the latter group techniques evolve. And the possibilities will sometimes be concurrently and sometimes complemental. Some techniques will be developed in the sector of electronics and others in the pharmaceutical sector. And sometimes one company will absorb another. It seems good to see this just as an evolution and as an important opportunity.
My advice: for physiologic background read Ling[9] and to get an overview of physical studies on the coherence of life read Ho[41] and Schrödinger.[33]

REFERENCES

1. Jaeken L. How the physical-chemical study of cells took a wrong direction some 50 years ago. The greatest scientific error in biological sciences initiated in 1930. *Chem Xpress*. 2017; 10(2): 122-128.

2. Jaeken L. Linking physiological mechanisms of coherent cellular behavior with more general physical approaches towards the coherence of life. *IUBMB Life*. 2006; 58(11): 642-646. doi: 10.1080/15216540601001699

3. Skou J. The influence of some actions on an adenosine triphosphatase from peripheral nerves. *Biochim Biophys Acta*. 1957; 23: 394-401. doi: 10.1016/0006-3002(57)90343-8

4. Hill A. The state of water in muscle and blood and the osmotic behaviour of muscle. *Proc R Soc London Ser B*. 1930; 106(746): 477-505.

5. Hill A, Kupalov P. The vapour pressure of muscle. *Proc R Soc London Ser B*. 1930; 106(746): 445-476. doi: 10.1098/rspb.1930.0039

6. Ling G. Tentative hypothesis for selective ionic accumulation in muscle cells. *Am J Physiol*. 1951; 167: 806.

7. Ling G. *A physical theory of the living state: The Association-Induction Hypothesis*. Waltham, Massachusetts, USA: Blaisdell; 1962.

8. Ling G, Miller C, Ochsenfeld M. The physical state of solutes and water in living cells according to the association-induction hypothesis. *Ann N Y Acad Sci*. 1973; 204(1): 6-50. doi: 10.1111/j.1749-6632.1973.tb30770.x

9. Ling G. *Life at the Cell and Below-Cell Level. The Hidden History of a Fundamental Revolution in Biology*. New York, USA: Pacific Press; 2001.

10. Ling G. History of the membrane (pump) theory of the living cell from its beginning in the mid-19th century to its disproof 45

years ago – though still thought worldwide today as established truth. *Physiol Chem Phys Med NMR*. 2007; 39(1): 1-67.

11. Ling G. Nano-protoplasm: The ultimate unit of life. *Physiol Chem Phys Med NMR*. 2007; 39(2): 111-234.

12. Ling G. Can we see living structure in a cell? *Physiol Chem Phys Med NMR*. 2014; 43: 1-71.

13. Clegg J. Embryos of *Artemia franciscana* survive four years of continuous anoxia: The case for complete metabolic rate depression. *J Exp Biol*. 1997; 200(Pt.3): 467-475.

14. Volkmann N, Hanein D. Actomyosin: Law and order in motility. *Curr Opin Cell Biol*. 2000; 12(1): 26-34. doi: 10.1016/S0955-0674(99)00053-8

15. Ling G. The physical state of water and ions in living cells and a new theory of the energization of biological work performance by ATP. *Mol Cell Biochem*. 1977; 15: 159-172. doi: 10.1007/BF01734106

16. Ling G. Maintenance of low sodium and high potassium levels in resting muscle cells. *J Physiol*. 1978; 280(1): 105-123. doi: 10.1113/jphysiol.1978.sp012375

17. Prokhorenko D, Matveev V. The significance of non-ergodic property of statistical mechanics systems for understanding resting state of a living cell. *Brit J Math Comp Sci*. 2011; 1(2): 46-86. doi: 10.9734/BJMCS/2011/160

18. Jaeken L. The neglected functions of intrinsically disordered proteins and the origin of life. *Prog Biophys Mol Biol*. 2017; 126: 31-46. doi: 10.1016/j.pbiomolbio.2017.03.002

19. Ling G. The physical state of water in living cells and model systems. *Ann Rev Physiol*. 1965; 125(2): 401-417. doi: 10.1111/j.1749-6632.1965.tb45406.x

20. Ling G. A new theoretical foundation for the polarized-oriented multilayer theory of cell water and for inanimate systems demonstrating long-range dynamic structuring of water molecules. *Physiol Chem Phys Med NMR*. 2003; 35(2): 91-130.

21. Edelmann L. Basic biological research with the striated muscle by using cryotechniques and electron microscopy. *Physiol Chem Phys Med NMR*. 2001; 33(1): 1-21.

22. Edelmann L. Doubts about the sodium-potassium pump are not permissible in modern bioscience. *Cell Mol Biol.* 2005: 51: 725-729.

23. Edelmann L. The physical state of potassium in frog skeletal muscle studied by ion-sensitive microelectrodes and by electron microscopy: Interpretation of seemingly incompatible results. *Physiol Chem Phys Med NMR*. 2014; 43: 75-93.

24. Cope F, Damadian R. Biological ion exchanger resins. IV. Evidence for potassium association with fixed charges in muscle and brain by pulsed nuclear magnetic resonance of ^{39}K. *Physiol Chem Phys*. 1974; 6(1): 17-30.

25. Damadian R, Cope F. Potassium nuclear magnetic resonance relaxations in muscle and brain, and in normal E. coli and a potassium transport mutant. *Physiol Chem Phys*. 1973; 5(6): 511-514.

26. Ling G. The role of inductive effect in cooperative phenomena of proteins. *Biopolym Symp*. 1964; 13: 91-116.

27. Jaeken L, Matveev V. Coherent behavior and the bound state of water and K^+ imply another model of bioenergetics: Negative entropy instead of high energy bonds. *Open Bioch J*. 2012; 6: 139-159. doi: 10.2174/1874091X01206010139

28. Thoke H, Thorsteinsson S, Stock R, Bagatolli L, Olsen L. The dynamics of intracellular water constrains glycolytic oscillations in Saccharomyces cerevisiae. *Sci Reports*. 2017; 7: article 16250. doi: 10.1038/s41598-017-16442-x

29. Nasonov D. *Local Reaction of Protoplasm and Gradual Excitation*. (English Translation by Halpern Y); National Science Foundation, 1962. Available at Office of Technical Services, US: Washington, D.C., USA: Department of Commerce; 1962.

30. Plankar M, Jerman I, Krašovec R. On the origin of cancer: Can we ignore coherence? *Prog Biophys Mol Biol*. 2011; 106(2): 380-390. doi: 10.1016/j.pbiomolbio.2011.04.001

31. Davidson R, Lauritzen A, Seneff S. Biological water dynamics and entropy: A biophysical origin of cancer and other diseases. *Entropy*. 2013; 15(9): 3822-3876. doi: 10.3390/e15093822

32. Damadian R. Tumor detection by NMR. *Science.* 1971; 171(3976): 1151-1153.

33. Schrödinger E. *What is Life? The Physical Aspect of the Living Cell*. Cambridge, UK: Cambridge University Press, Cambridge; 1944. Canto edition, Cambridge, UK: Cambridge University Press; 1992.

34. Tuszynski J, Paul R, Chatterjee R, Sreenivasan S. Relationship between Fröhlich and Davydov models of biological order. *Phys Rev A*. 1984; 30: 2660-2675. doi: 10.1103/PhysRevA.30.2666

35. Fröhlich H. The extraordinary dielectric properties of biological materials and the action of enzymes. *Proc Natl Acad Sci USA*. 1975; 72(11): 4211-4215.

36. Fröhlich H. Coherent excitations in active biological systems. In: Gutmann F, Keyzer H, eds. *Modern Bioelectrochemistry*. New York, USA: Plenum; 1986: 246-261.

37. Del Giudice E, Doglia S, Milani M, Vitiello G. Collective properties of biological systems: solitons and coherent electric

waves in a quantum field theoretical approach. In: Gutmann F, Keyzer H, eds. *Modern Bioelectrochemistry*. New York, USA: Plenum; 1986: 263-287.

38. Del Giudice E, Voeikov V, Tedeshi A, Vitiello G. The origin and the special role of coherent water in living systems. In: Fels D, Cifra M, Scholkmann F, eds. *Fields of the Cell.* Fort P.O., Trivandrum, Kerala, India: Research Signpost; 37/661(2); 2015: 95-111.

39. Davydov A. Solitons and energy transfer along protein molecules. *J Theor Biol*. 1977; 66(2): 379-387. doi: 10.1016/0022-5193(77)90178-3

40. Chang JJ, Fisch J, Popp FA. *Biophotons*. Dordrecht, The Netherlands; Kluwer Acad. Publ; 1998.

41. Ho MW. *The Rainbow and the Worm. The Physics of Organisms*. 3rd ed. Singapore, London: World Scientific; 2008.