ChemXpress
ISSN: 2320-1975

ChemXpress

Short communication | Vol 10 Iss 2

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

Laurent Jaeken*

Department of Applied Engineering, Karel de Grote University College, Antwerpen, Belgium

***Corresponding author** Laurent Jaeken, Department of Applied Engineering, Karel de Grote University College, Antwerpen, Belgium, Tel +3236633031; E-mail: laurent.jaeken@hotmail.com

Received: April 04, 2017; **Accepted:** April 21, 2017; **Published:** April 24, 2017

Abstract

Is a cell a colloid with distribution coefficients and adsorption coefficients as prime physical-chemical parameters allowing a negative-entropy-driven bio-energetic based on coherence, as first proposed by Schrödinger in 1944? Or does a cell possess ordinary water with small solutes including K^+ in solution, and delineated by a membrane in which ion-pumps are located, which continuously have to oppose passive leaks? The latter view, called 'membrane-(pump)-theory' (MPT) underscores all current physiology and cell biology, but is energetically impossible. MPT was disproved by Ling during the 60s and 70s but unfortunately this remained unknown. Ling developed a complete colloid model for the living cell, with a whole set of experimentally approved new equations. All basic tenets of his so-called 'association-induction-hypothesis' (AIH) are experimentally approved. In addition, his AIH is able to explain contemporary new physical data on the coherent behaviour of cells, whereas MPT is incompatible.

Keywords: Colloid; Bio-energetic; Macro-molecules; Solutes; Biochemical energy

Introduction

For a chemist it might come as a surprise that bio-scientists study processes in which the concentration gradients of ions or other small solutes between a cell's interior and its environment are involved, without considering distribution and adsorption coefficients. Indeed, many important physiologic processes are explained without such considerations. But, there is an historic reason for this, although a chemist may be out of touch with this. But more surprisingly also most bio-scientists are out of touch with this.

The historic reason

At the beginning of the 20th century two fundamental points of view with respect to the physical-chemistry of cells circulated:

Citation: 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. ChemXpress. 2017;10(2):122.

(1) Cytoplasm is a water-based solution of macro-molecules and small solutes, which is different and separated from the solution of the environment thanks to the presence of a cell membrane. The latter was supposed to be impermeable for the macromolecules synthesised within the cell and to have unusual semi-permeable properties responsible for the concentration differences of the small solutes. The most remarkable and puzzling aspect is the high intracellular K^+ and low intracellular Na^+ concentration with respect to their concentrations in the environment. Dean [1] proposed that cell membranes must contain a kind of pump, otherwise the observed concentrations could not be explained using the law of Nernst. Later Skou [2] discovered the postulated pump, now generally known as the membrane-located transporter protein Na^+/K^+-ATPase, energised by the well-known biochemical energy-currency adenosine-tri-phosphate (ATP). Dean's proposal was based on the assumptions (a) that cellular water is normal water, so that the distribution coefficient is one, and (b) that intracellular K^+ is in solution, so that K^+ activity equals K^+ concentration. This view was called 'membrane-theory' and later 'membrane-pump-theory' (MPT). Classic physiology and cell biology are based hereupon since about 1930 and so up now.

(2) Cytoplasm, at that time still called protoplasm, is a colloid with unusual properties of water, in which most solutes are much less soluble than in normal water and this explains the differences in concentration of small solutes and ions between the cell's interior and the environment. This was the 'colloid view', which however became almost completely exterminated in 1930.

1930 was indeed crucial. The famous physiologist Hill [3,4] performed a famous experiment. He determined the distribution coefficient of urea between a resting muscle cell and the Ringer solution in which it bathed. He found it to be close to one. So, cell water should be normal water. He also determined the cell's osmotic pressure and, given that cell water is normal water, the most abundant intracellular ion, K^+, must be in solution otherwise the measured osmotic pressure would not be reached. Membrane theory was winning and most followers of colloid views changed their mind. It is of course too simple to reduce history [5-7] to just this experiment, but it was very crucial because it was so simple and convincing. And then 27 years later the proposed pump was found [2] and appeared to work, at least in some experiments, namely in membrane systems, where there was also cytoplasm present [8], but not in other preparations where there was only membrane and no cytoplasm [9,10]. But negative results are always difficult.

Crucial in the steep rise of membrane theory was also a review [11] dealing with 'all what was known' about the Na^+/K^+ pump (Na^+/K^+ ATPase). To be (rather) complete was still possible at that time. Unfortunately, this review was not really complete. A number of experiments which were incompatible with MPT were not mentioned. And what kind of measurements!!

- Experiments demonstrating that the pumps consumed more energy than the cell could deliver [12]. In a later review on the Na^+/K^+ pump Skou [13] admitted that the energetic of the pump was not adequate. He launched an ad hoc hypothesis to deal with it, but his suggestion was experimentally never proved up to now.
- Experiments published in Ann. N. Y. Acad. Sci. by Ling et al. [14] only 2 years before the crucial review of Glynn and Karlish [11] showed that the famous experiment of Hill revealed an exception. Indeed Ling et al. [14] did over the experiment of Hill and confirmed it, and then they tested a large number of other simple solutes with 1 up to 12 carbon atoms in the same experimental setup and found that for most of them the distribution coefficient was much below unity, roughly the lower the larger the molecular size.

The conclusions are straightforward. Cell water cannot be normal water. Cytoplasm must be colloidal with a (high) colloid osmotic pressure almost explaining the measured osmotic pressure on its own, and hence the most abundant intracellular ion, K^+, must be largely adsorbed. Distribution coefficients matter and adsorption coefficients matter. The whole fundament of cell physiology had to be rebuild from these new fundaments, which are not that strange for a (physical) chemist. The polarisation of cell-water into multi-layers [15] and the adsorbed state of K^+ [7,16] during a cell's high-energetic low-entropic resting state are meanwhile demonstrated, but not yet generally known [17,18].

Is there an alternative?

Together with his team, starting from these new fundaments Ling developed an entirely new cell physiology almost completely on his own during a period spanning from the early 50's, when he started to suspect MPT and observed the first serious aberrations, until now [12,19]. His work is monumental, going into dept, theoretically well developed with a large number of new equations, in which of course distribution and adsorption coefficients figure, and with all new equations experimentally corroborated. It deals with solute distribution, permeability, transport, cell potentials, osmosis and cell volume, motility, respiration, trans-epithelial transport, induction, cell regulation, normal cell development and cancer. He experimentally disproved all basic tenets of MPT and developed his own alternative explanation for each of them. But these explanations stay not on their own, but together form an intrinsically simple theory, his so-called 'association-induction-hypothesis'.

Ling's 'association-induction hypothesis'

In a nutshell AIH states that a cell is made of functional agglomerates, which can be inactive (resting state) or active. In the resting state, they consist of a coherent unitarily behaving ensemble ('association') of proteins, many layers of polarised and oriented water, adsorbed K^+ and an adsorbed nucleotide-tri-phosphate (ATP or another). Due to the polarised and oriented water this ensemble of course exhibits very low entropy. It is stable, strictly spoken meta-stable, but Clegg [20] kept cysts from Artemia during 4 years under complete anoxia without measurable metabolism. And early human embryos are kept alive at the temperature of liquid nitrogen, i.e. without metabolism, but also without formation of ice crystals!! External stimuli, often of extremely low intensity, can activate this system, whereby the potential energy of the low-entropy resting state is used to generate useful work (chemical, mechanical, electrical, photon emission). The conformational change of the associated ensemble is brought about by (Lewis) inductive effects going out from the stimulus and not only results in changes of the protein component but also leads to water depolarisation, K^+ desorption and the binding of other ligands (often other macromolecules, eventually other ions or solutes). When the action, for instance muscle contraction or the generation of an action potential, comes at an end, the system is blocked into a lower energy higher entropy state. It can only be recharged into the resting state by the substantial adsorption (not hydrolysis) energy of newly synthesised nucleotide-tri-phosphate. So, the metabolic energy ultimately derived from the sun or from food and leading to this synthesis is only needed after the action, namely to restore rest. Therefore, a cyst or another dormant cell is able to hatch. This description makes clear that rest-to-action and action-to-rest are real phase shifts, interesting stuff for the physical chemist.

The very diverse experimental proofs of AIH

In the same year that Physiologist Ling [12] launched his AIH, a famous Russian physiologist, Nasonov [21] measured that the most diverse kinds of stimuli are able to initiate the most diverse kinds of cellular activities and in all cases this is

associated with the same changes of very diverse physical-chemical parameters, indicative of a phase shift. In 2010 Matveev [22] unified the independent views of Ling and of Nasonov.

Together with his colleagues Ling proved all basic tenets of AIH in a quantitative way by surprisingly strong and many times repeated experiments. One has to make them strong, when one follows aberrant paths. He summerized his work in 4 books [12, 23-25] and numerous reviews [5,6,15,19,26]. Diagnostic medical NMR was developed by his friend Damadian, who followed similar ideas and so found that in cancer cells water is less structured than in normal cells [27]. It means there is less coherence and higher entropy. So, Ling's view already has a most useful application. With respect to all fields of study indicated above, MPT has a completely different explanation, which in my opinion is wrong, though yet widely believed. More precisely MPT has a different explanation for each topic separately, but all these separate explanations do not form a unity. This is due to the fact that they are based on the wrong assumptions: normal water, activity equals concentration, only cell membrane achieves all this, cytoplasm is not involved, energy shortage.

Apart from all the arguments gathered by him in his books, articles and reviews Ling's work more recently got an enormous supplemental boost from a completely independent approach, not from physiology, but from basic physics [17,18,28]. In his book 'What is life?' Schrödinger [29] argued that concentrations of many important cellular components are too low to apply statistical laws such as Fick's law of diffusion in a meaningful way. This is the case for DNA and some regulatory substances, but also for some ions and other solutes in small cells and small sub-cellular compartments. Schrödinger proposed that cellular processes may make use of coherent mechanisms, analogous to those found in physical systems close to absolute zero but applicable at body temperature. His argument was that such mechanisms are much more precise and able to operate below the level of thermal noise, exactly what would be needed to explain life. His proposal was largely neglected, mainly because at that time all data, in particular the findings of Hill were indicating that application of Fick's law for neutral solutes and the law of Nernst for ions without taking distribution and adsorption coefficients into account suffices to formulate fine explanations for cell physiology. Obviously, Schrödinger's idea that '*life feeds on negative entropy*' (1944) could not find its place in MPT because, according to MPT, the media on both sides of the cell membrane do not differ in entropy (ions and water are thought to be free on both sides). MPT has therefore been the greatest obstacle to the spread of physical ideas and methods in cell physiology. As a result, there is a huge gap between cell physiology and both physics and chemistry (especially colloid chemistry). So, investigations into life's coherence remained at the very margins of biological science.

Nevertheless, several independent physical approaches towards the coherent behavior of life emerged, often by famous physicists [30-35] but they did not reach the more biochemically oriented mainstream bio-researchers. Unfortunately, some of these physicists do not refer to the physiology developed by Ling in the discussion of their physical data, although it is the only general physiologic theory which is compatible with their findings [28]. An important finding of the physical study of coherence is that in tumor cells a lowering of the cell's coherence can be observed prior to the onset of genetic damage [36]. So, the field is very promising. Fortunately, research of the coherent behavior of cells is recently becoming a high topic in biophysics, but it should also reach mainstream bio-scientists.

Conclusion

Reaching mainstream bio-scientists is an urgently needed but difficult task, since it necessitates turning upside down numerous interwoven and deeply embedded believes (unproved assumptions) connected to MPT. So, there is a huge educational problem. An alternative physiology of such strength and importance as Ling's AIH should be taken up in general textbooks on general biology, physiology, cell biology and it should figure in basic university courses of the field with a link to the modern physical study of the coherence of life. But all this should still be initiated. It is educationally correct that, when there are two competing theories about such fundamental issues, that scientific education deals with both theories, presents their main arguments and refers to literature for further study. This is the way that future experiments will do the rest. This would give a whole new perspective to bio-scientists of all fields, including medical doctors. Chemists with some basic interest in the chemistry of living organisms and having a look to this article are anyhow already informed by now. Anyhow, no doubt that Ling is one of the greatest but also most ignored biological scientists of the 20th century. Bio-scientists, start reading his work!!

Note: By the way, dear chemists, I encountered an aberrant simple atomic theory algebraically describing all lines of the line spectra of all isotopes [37] without the need to consider orbitals: possibly a huge simplification. Are there some great mistakes in current atomic theory as well?

REFERENCES

1. Dean R. Theories of electrolyte equilibrium in muscle. Biol Symp. 1940;3:331-48.
2. Skou JC. The influence of some actions on an adenosine triphosphatase from peripheral nerves. Biochim Biophys Acta. 1957;23:394-401.
3. Hill AV, The state of water in muscle and blood and the osmotic behaviour of muscle. Proc R Soc London Ser B. 1930;106:477-505.
4. Hill AV, Kupalov PS. The vapour pressure of muscle. Proc R Soc London Ser B. 1930;106:445-76.
5. Ling GN. (a) Nano-protoplasm: The ultimate unit of life. Physiol Chem Phys Med NMR. 2007;(39):111-234.
6. Ling GN. (b) 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 Med Med NMR. 2007;39:1-67.
7. Edelmann L. Doubts about the sodium-potassium pump are not permissible in modern bioscience. Cell Mol Biol. 2005;(51):725-9.
8. Freedman JC. Partial restoration of sodium and potassium gradients by human erythrocyte membranes. Biochim Biophys Acta. 1976;455:989-92.
9. Marchesi VT, Palade GE. The localization of Mg-Na-K-activated adenosine triphosphatase on red cell ghost membranes. J Cell Biol. 1967;35(2):385-404
10. Ling GN, Balter M. Red blood cell ghosts: Hollow membranes or solid bodies? Physiol Chem Phys Med NMR. 1975;7(6):529-31
11. Glynn IM, Karlish SJ. The sodium pump. Annu Rev Physiol. 1975;37:13-55

12. Ling GN. A Physical Theory of the Living State: The association-induction hypothesis; Blaisdell: Waltham, Massachusetts. 1962
13. Skou JC. The energy-coupled exchange of Na^+ for K^+ across the cell membrane: the Na^+, K^+-pump. FEBS 1990;268(2):314-24
14. Ling GN, Miller C, Ochsenfeld MM. The physical state of solutes and water in living cells according to the association-induction hypothesis. Ann NY Acad Sci. 1973:204:6-50
15. Ling GN. 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):91-130
16. 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
17. Jaeken L. The neglected functions of intrinsically disordered proteins and the origin of life. Progr Biophys Mol Biol. 2017;(16):30153-5
18. Jaeken L, Matveev VV. 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;6:139-59
19. Ling GN. Can we see living structure in a cell? Physiol Chem Phys Med NMR. 2014;43:1-71
20. Clegg J. Embryos of *Artemia franciscana* survive four years of continuous anoxia: the case for complete metabolic rate depression. J Exp Biol. 1997;200(3):467-75
21. Nasonov DN. Local reaction of protoplasm and gradual excitation; (English Transl. by Halpern, Y.S.), National Science Foundation, available at Office of Technical Services, US, Washington, D.C., Department of Commerce. 1962
22. Matveev VV. Native aggregation as a cause of origin of temporary cellular structures needed for all forms of cellular activity, signalling and transformations. Theor Biol Med Model. 2010;7:19
23. Ling GN. In search of the physical basis of life; Plenum Press: New York. 1984
24. Ling GN. A revolution in the physiology of the living cell; Krieger Publ. Co: Malabar; Florida.1992
25. Ling GN. Life at the cell and below-cell level. The hidden history of a fundamental revolution in biology; Pacific Press: New York. 2001
26. Ling GN. A historically significant study that at once disproves the membrane (pump) theory and confirms that nano-protoplasm is the ultimate physical basis of life-yet so simple and low-cost that it could easily be repeated in many high school biology classrooms worldwide. Physiol Chem Phys Med NMR. 2008;40:89-113
27. Damadian R. Tumor detection by NMR. Science. 1971;171(3976):1151-3
28. Jaeken L. Linking physiological mechanisms of coherent cellular behavior with more general physical approaches towards the coherence of life. IUBMB Life. 2006;58:642-6
29. Schrödinger E. What is life? The physical aspect of the living cell; Cambridge University Press: Cambridge. Canto edition, Cambridge University Press: Cambridge, 1992. 1944
30. Fröhlich H. Coherent excitations in active biological systems. In Modern Bioelectrochemistry; Gutmann F, Keyzer H, editors. Plenum: New York, 1986; pp. 246-61.
31. Davydov AS. Solitons and energy transfer along protein molecules. J Theor Biol. 1977;(66):379-87.

32. Del Giudice E, Doglia S, Milani M, et al. Collective properties of biological systems: Solitons and coherent electric waves in a quantum field theoretical approach. In Modern Bioelectrochemistry; Gutmann F, Keyzer H, editors. Plenum: New York, 1986;263-287.
33. Del Giudice E, Voeikov V, Tedeshi A, et al. The origin and the special role of coherent water in living systems. In: Fels D, Cifra M, Scholkmann F, editors. Fields of the cell. Research Signpost Fort PO Trivandrum: Kerala; India, 2015;95-111.
34. Popp FA, Chang JJ. The physical background and the informational character of biophoton emission. In Biophotons; Chang JJ, Fisch J, Popp FA, editors. Kluwer Academic Publishers: Dordrecht, 1998. p.238-50.
35. Ho MW. The Rainbow and the Worm. The Physics of Organisms, 3rd edition. World Scientific: Singapore, London. 2008.
36. Plankar M, Jerman I, Krašovec R. On the origin of cancer: Can we ignore coherence? Prog Biophys Mol Biol. 2011;106:380-90.
37. Kanarev PM. The foundations of phys chemistry of microworld, 15th edition, in Russian; English: 10th Ed. 2008.