TRENDS IN BIOENERGETICS. AN INTRODUCTION

Erich Gnaiger, Frank N. Gellerich
Department of Transplant Surgery, Clinical and Interdisciplinary Bioenergetics, University Hospital of Innsbruck, Austria

BTK - INTERDISCIPLINARY AND INTERNATIONAL NETWORK IN BIOENERGETICS

BioThermoKinetics (BTK) aims at the advancement in our understanding of biological thermodynamics, kinetics, regulation and control of biological processes from molecular, cellular up to organismic levels. BTK brings together experimentalists and theoreticians with shared interests and affinity for the interdisciplinary field of bioenergetics, bridged by strong personal interactions. Two special developments are remarkable.

First, the interdisciplinary range of BTK is expanding. It draws on the 'classical' topics of bioenergetics with their novel methodological and conceptual developments, penetrates the thermodynamic and biophysical foundations of metabolic dynamics and spreads to physiological, microbiological, medical and biotechnological perspectives. Reflecting the express interests of the editors, special emphasis is placed on new clinical applications, putting theoretical and methodological advancements to the direct practical test.

Second, intensive international collaboration characterizes many contributions on bioenergetics represented in the present volume. In particular, the outstanding input of joint publications by scientists from East and West are a clear-cut positive result of relatively recent political and economical changes. The common efforts of BTK representatives over the past years has strengthened the link between East and West. Through scientific collaboration it was possible to overcome at least a small part of the problems encountered by scientists in economically and politically difficult situations. It seems that this process strikingly increased the force of bioenergetic research. In the future, these efforts should be extended to include the South more explicitly in these scientific developments.

Successful research requires an optimal scientific infrastructure. We should not forget that some years ago parts of western Europe were predominated by unfavourable conditions, as expressed in a letter by Schrödinger written in Innsbruck to Hans Thirring in 1950 (see also his correspondence in the following contribution):

"*Academic Austria gave me the impression that it is irresponsibly suppressed. The diminishingly small amounts of money and foreign exchange, which would be sufficient to allow the free trade of ideas with the rest of the world and thus the free development of Austrian talents, are thick-headedly subdued under common commercial rules. The level of funding is ridiculous, moreover (i.e. even for somebody arbitrarily wealthy) the acquisition of a foreign book or journal is a matter of several months. ... But I, as a foreigner with quite modest resources, can generally acquire anything I need, since I can pay for it from Dublin, whereas my colleague from home has to submit a petition at the National Bank first, if the few Pounds or Francs will be graciously granted. This is an absurdity. UNESCO belongs in a meat grinder, if they don't get on with it. But these asses don't have a clue, feed on caviar and oysters on the respective foreign exchange accounts and belch them ad maiorem dei gloriam. The poor young folks who want to accomplish*

something here can chew on the leftovers of the journals prior to 1938/39. When I told one of them today he should read my paper in Proc Roy Soc 1935, he said: we do not have it."

50 YEARS AFTER ERWIN SCHRÖDINGER'S *WHAT IS LIFE?*

What, apart from the numbers 1944 and 1994, is the link of '*What is* Controlling *Life?*' to Erwin Schrödinger's famous book '*What is Life'*? In the tradition of Ludwig Boltzmann, Schrödinger pioneered biophysics by his unique transdisciplinary approach. He made a distinctive contribution towards a general awareness for the position of thermodynamics in biology, and for the increasing role that biology is to play in the expansion of the foundations of science. '*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* [1].' Linus Pauling who died just at the time when the present book was about to go into print, summarizes Erwin Schrödinger's achievements: "There is no doubt that the Schrödinger equation provides the theoretical basis of chemistry. ... The development of molecular biology has resulted almost entirely from the introduction of the new ideas into chemistry that were stimulated by quantum mechanics. It is accordingly justified, in my opinion, to say that Schrödinger, by formulating his wave equation, is basically responsible for modern biology [2]."

Schrödinger's *What is Life?* is widely celebrated as one of the most stimulating books in biological science of this century. "His book *What is Life?*, which had such a seminal effect on molecular biology, problably had its distant origin in those midnight discussions with Fränzel about the theory of living organisms [3]." On the other hand, differences in scientific opinion may have got entangled with rivalry. "I could not help being sympathetic to Pauling's somewhat egocentric contribtion and in particular his view that Schrödinger's later work on biology, as recounted in *What if Life?*, was confused and misleading [4]". Linus Pauling gave a personal answer to the question "did Schrödinger contribute to modern biology, to our understanding of the nature of life? It is my opinion that he did not make any contribution whatever [2]". Max Perutz ("... the book does not appear to have had much impact on the people already in the field" [5]) cites a controversial note of Francis Crick [5]: "I cannot recall any occasion when James Watson and I discussed the limitations of Schrödinger's book. I think the main reason for this is that we were strongly influenced by Pauling, who had essentially the correct set of ideas. We therefore never wasted any time discussing whether we should think in the way Schrödinger did or the way Pauling did." Quoting James Watson directly, we find quite a different connotation in his recent reflection [6]: "To have success in science, you need some luck. Without it, I would never have become interested in genetics. I was 17, almost 3 years into college, and after a summer in the North Woods, I came back to the University of Chicago and spotted the tiny book *What is Life* by the theoretical physicist Erwin Schrödinger. In that little gem, Schrödinger said the essence of life was the gene. Up until then, I was interested in birds. But then I thought, well, if the gene is the essence of life, I want to know more about it. And that was fateful because, otherwise, I would have spent my life studying birds and no one would have heard of me."

Schrödinger made not only a well established contibution to the developments in modern genetics and molecular biology, he preceded concepts of irreversible thermodynamics for a generalized description of the living organism. Many biologists are fascinated by his clear and penetrating account of irreversibility and entropy balance in open systems. At this early date he marked the transition from classical to irreversible thermodynamics or 'ergodynamics' [7]. Without burdening himself and the reader with the terminological and algebraic jungle that characterizes less popular texts in biological thermodynamics, he described encouragingly the fundamental connection between the entropy principle embraced in the second law of classical thermodynamics. He developed germinating concepts on irreversibility and '*order from disorder*' versus '*order from order*' mechanisms. He drew a picture of evolutionary optimization of dynamical (ordered, organized, organismic) living structures which are selected to keep a balance between the abyss of statistical decay into chaos and the void of static fixation into solid stability.

50 years after the first edition of Erwin Schrödinger's influential book '*What is Life?*', one hot spot of BioThermoKinetics is an issue which remained controversial since that time: '*What is negative entropy?*' Bioenergetics is fundamentally concerned with the irreversible nature of living systems, referring to entropy and the second law of thermodynamics. Biologists who worry about the applicability of the thermodynamic state functions to open irreversible systems, may be highly surprised about the discussions prevalent in physics on the "apparent paradox that natural processes are irreversible, always increasing the entropy of the universe, whereas molecular processes are essentially reversible" [3]. The question of physics "How do we introduce irreversibility into a 'reversible' world?" [8] appears to be opposite to the problem of bioenergetics: How do we apply physical concepts which are based on idealized reversible systems into the irreversible world of life? Hence the title of the present volume of BioThermoKinetics:

WHAT IS CONTROLLING *LIFE?*

Preceding Part 1, some of the translated correspondence with the theoretical physicist and pacifist Hans Thirring reveals the antifascist spirit of Erwin Schrödinger. Not enough appears to be known about his conscientious view of political control and power, as judged from a note that appeared in *Nature*, "Hitler's rise to power drove him, perhaps unnecessarily, from the country [4]". An introductory historical glimpse illustrates the inner necessity for Schrödinger to take deep-cutting consequences against the Nazi regime, primarily at his own free decision.

The interdisciplinary and intellectual spirit of BTK makes its appearance in an extended sense in this book. Part 1 leads from philosophical perspectives and reflections on the scientific method in general towards general topics of bioenergetics.

WHAT IS CONTROL AND REGULATION?

Part 2 contains contributions defining the terms control and regulation in metabolic systems of varying complexity. To obtain further insight into regulation and control of cellular energy metabolism, modern developments of metabolic control theory are discussed. This includes hierarchically organized metabolic systems and offers approaches taking into account the peculiarities of "non-ideal pathways". Some contributions demonstrate the successful application of

metabolic control analysis to metabolic systems. Examples of a quantitative description of pathological alterations of mitochondria in terms of control analysis and its application in drug design are given in Part 6.

WHAT IS THE STATE OF MITOCHONDRIAL RESPIRATORY CONTROL?

Despite intensive research over the past decades, intracellular regulation of oxidative phosphorylation, the stoichiometry of redox pumps and the permeability of the mitochondial inner membrane for protons and cations is still a subject of debate. For example, we find in Part 3 controversial reports on redox slip and leaks linked to mitochondrial electron transfer under non-phosphorylating conditions. In addition, several reports deal with mitochondrial respiratory control by low oxygen, Ca^{2+} and ADP concentrations. Rapid development and accessibility of NMR allows the investigation of intracellular concentrations and fluxes under *in vivo* conditions with increasing spatio-temporal resolution. Problems in quantitative interpretation of these data focus the scientific interest on intracellular compartmentation of metabolites in inhomogeneous spaces. In particular, ADP shuttles and transport across diffusion barriers, and metabolic channeling are discussed in Part 4.

WHAT IS BIOENERGETICS BEYOND MEMBRANES AND MITOCHONDRIA?

The scope of bioenergetics may be interpreted in two ways, either restricted to 'membrane bioenergetics', or in a wider sense including fundamental aspects of physiological energetics. This more general interpretation is represented in Part 5. Contributions focus on cellular and muscle energetics, microbial growth, oscillations of fluxes and metabolites, aerobic and anaerobic metabolism and biotechnological applications.

WHAT IS SPECIFICALLY HUMAN IN CLINICAL BIOENERGETICS?

At present we observe a rapidly increasing number of reports on bioenergetic investigations of human energy metabolism at different levels of integration. What is - other than erring - specifically human in bioenergetics? Both fundamental and applied aims are envisaged. The paradigm that mitochondria are mitochondria are mitochondria is successively replaced by new insights into their differentiation in tissues, and their variation between different species. While the acronyms RLM or RHM hardly need explanation (rat liver and heart mitochondria), the properties of HLM and HHM are insufficiently understood. Ranges of functional properties in human mitochondria, as compared to the rat, have to be quantified for characterizing the healthy state, as a reference for the diagnosis of mitochondrial diseases, effects of aging, and damage under hypoxic or hyperoxic states.

Bioenergetics is not the science for (or of) Dinosaurs: Modern methods of molecular biology and immunology increase the general interest in mitochondrial research. Two examples shold be mentioned: *(1)* Cyclosporin - a drug suppressing immunological rejection of transplanted tissues - has been found to interact with the permeability transition pore of the mitochondrial inner membrane. Its action on the preservation of mitochondrial function during ischemia and reperfusion is now under investigation, complementary to its well established immunological effect. *(2)* Mutations of mitochondrial DNA have been found to be responsible for chronic or inherited diseases. The correlation of these defects on the molecular level with changes on the functional level of organelles, cells, tissues or the whole organism provides a challenge for modern bioenergetics.

WHAT IS VOLUME 3 OF BIOTHERMOKINETICS?

The 6th BTK-meeting takes place in Schröcken (Austria) at Hotel Mohnenfluh. The editors decided not to follow the custom of printing the proceedings and abstracts separately. Volume 3 of BioThermoKinetics, therefore, contains short contributions, abstracts as well *Hot Spots in BioThermoKinetics*. Uncertainties exist as to the numbering of the first two volumes of *Modern Trends in BioThermoKinetics* [9,10], yet with the edition of a third volume in the series, actual numbering appears to be appropriate.

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