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Founder of systems chemistry and foundational theoretical biologist: Tibor Gánti (1993–2009)

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HIGHLIGHTS

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~~Tibor Gánti was an extremely deep theoretical biologist and one of the founders of the new field of systems chemistry. He was in many ways ahead of his time and is likely to exert a long-lasting influence on his favourite fields.~~

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ABSTRACT

With his chemoton theory theoretical biologist and chemical engineer Tibor Gánti was one of the most outstanding intellects behind systems chemistry and the at the foundations of theoretical biology. A brief review of his oeuvre is presented. This essay introduces a special issue dedicated to his memory.

1. Introduction

Tibor Gánti, chemical engineer and theoretical biologist, died after long suffering on the 15th of April 2009. His last formal positions were being the editor-in-chief of *Természet Világa* (World of Nature, a Scientific American-like popular science journal) and scientific advisor, paid by the Hungarian Academy of Sciences at the Department of Plant Taxonomy and Ecology at Eötvös University in Budapest. He was an exceptional, pioneering scientist probing into the nature and origins of life. We respect him also as one of the founding fathers of systems chemistry.

His ashes were thrown, in accordance with his will, in the Danube at Zebegény, so much beloved by him. His way through life has been remarkable, devious, and rugged. I am convinced that in a few decades from now his oeuvre (but not his life) will be considered victorious. Here I present a brief overview of this remarkable oeuvre.

Tibor Gánti was a naturalist: ever since childhood he was interested in all aspects of nature, from living beings to caves. Already at elementary school he was deeply concerned with the nature (essence) of life: he figured out that logically the question reaches into chemistry, this is why he decided to study chemistry (chemical engineering at the Budapest University of Technology was a pragmatic choice at the time). Later he realized that chemistry must be the source of life also historically: he has become the number one expert on the origin of life in Hungary.

His microbiological knowledge widened as a leader of the laboratory of Yeast Factory (1958–1965), later he joined the Fine Chemical Factory of REANAL where he became chief engineer (1965–1974) of the biochemical plant. It was in the REANAL period that he worked out and patented several industrial production methods (including one for ATP) that now would be regarded as instances of "artificial metabolism". In 1974 he wrote the summary of this work (*Industrial syntheses by the controlled functioning of enzymatic reaction networks*) and submitted it to the Academy to become a C.Sc. (Candidate for Science,

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a degree higher than Ph.D., mirroring the then Soviet scientific promotion system). In the short breaks of his industrial work he would visit various libraries: this is how he kept himself up-to-date with the unfolding knowledge in molecular biology. His understanding was aided by the fact that he had a period of crystallography in the past. Amazingly for the university community, he wrote the first book on molecular biology (Gánti, 1966) in Hungary (*Forradalom az élet kutatásában*—Revolution life research, 1966). For lack of a substitute this book was used as a textbook at the Medical University for years. The last chapter (Life and death) anticipated the groundbreaking work in theoretical biology that followed. In the same period he was teaching industrial biochemistry to biology students at Eötvös University (1968–1972).

After this he was working on his masterpiece *Az élet princípiuma* (The Principle of Life, 1971) that was published in a popular book disguise—simply, because he saw no alternative then (Gánti, 1971). The first of the part of the book (The new data) is an updated summary of molecular biology (it can be regarded as a revision of his previous book), whereas the second part (The new approach) elaborates on what now we call chemoton theory. With remarkable intellectual bravado he proposes that the minimal organization of life does not include enzymes. This idea – especially in the light of his historic role in communicating molecular biology to the public – is shocking. He realized the basic units of life must be simple but the known enzymes must be the result of a long evolutionary process. Put differently: enzymes speed up and regulate certain chemical processes but one should enquire about the nature of the *regulated* system!

Already in his first book he proposed that life is a combination of two types of process: one drives the system in one direction (such as in the cell cycle or – more generally – development; he called it the main cycle in the first publication: Gánti, 1966), whereas the other is responsible for metabolism and homeostatic regulation. In the first edition of *The Principle* this idea is expressed in the language of abstract chemistry: the main cycle there is template replication and metabolism is provided by cycle transforming raw materials into components of the system. It is crucial that both systems are autocatalytic. This was obvious for everybody in the case of template replication, but most people at the time would not have considered metabolism as autocatalytic. Gánti returned to this issue again and again and pointed out that the Calvin cycle or the reductive citric acid cycle is autocatalytic at the level of the intermediates (while all reactions are catalysed by enzymes). (It has only been recently realized how deep this revelation is.) We have performed biomathematical analyses on those microorganisms whose metabolism is almost completely known. Without exception we have found that all the genes, enzymes and food molecules together are insufficient to kick-start metabolism: a few metabolic intermediates are also necessary as autocatalytic seed: Kun et al., 2008). The self-reproducing "chemical engine" is the cornerstone of chemoton theory.

It is not difficult to realize that the chemoton model thus defined fails to include a boundary system (membrane). Originally Gánti thought that the membrane is of secondary importance, a bit similar to the paper bag that is secondary to the chips it contains. Later he became convinced to modify his position, aided by the publication of the fluid mosaic model of biomembranes in 1972 (Singer and Nicolson, 1972). He then complemented the informational and metabolic susbsystems with a third one: autocatalytic membrane growth. Since 1974 we regard the system triple as the chemoton (Gánti, 1974).

Chemoton theory seeks to establish the fundamental chemical unit of life, its exposition is basically logical. But Gánti emphasized quite early that the theory may offer guidance for research in the origin of life in that we should investigate paths in chemical evolution leading to the spontaneous emergence of chemoton-like systems. He suggested that although nucleic acids had been part of early systems, information stored in specific sequences had been utilised only later in evolution.

This was the status of the theory in the first half of the seventies when Gánti summarized it for the Hungarian publisher Akadémiai Kiadó. The manuscript lay with the various people handling it for half a decade (!) and was finally published in 1979 (Gánti, 1979a). But then, surprisingly, University Park Press in Baltimore volunteered for a parallel publication (Gánti, 1979b).

It is accurate to say that in Hungary Gánti's ideas have been received with complete lack of interest, incomprehension, ridicule and malevolence (out of which perhaps lack of interest was the most tolerable). The case was not only that theoretical biology was not yet a matter for polite society yet (at least in Hungary), but also the neglect of enzymes was regarded as scandalous. On top, hardly anybody agreed to the idea that models need to be characterized in an exact, mathematical manner. In this regard Gánti came up with a genuine novelty: he invented cyclic stoichiometry. The basic idea is very simple: catalysts (including enzymes) normally drop out of overall stoichiometric equations since they are regenerated in the catalytic cycle. This deficiency is usually corrected for by writing the catalyst above the arrow of the reaction; yet this provides only qualitative rather than quantitative information since we are left in the dark as to how much of enzyme converts how much of substrate. But if one mole of catalyst converts one mole of substrate in one turn of the cycle then we are accurate, but for this we do need the number of completed turns. Based on this finding he managed to describe the autocatalytic processes as well.

The theory was not much better off abroad either: Perhaps the most accurate assessment is that people just did not get the idea. Most theoretical biologists then were concerned with evolution and ecology rather than with the question how one can organize chemical reactions into living systems. This situation has recently changed, which makes a difference to the field (but, sadly, not to the originator of these ideas).

Despite the mentioned incomprehension work has not stopped. 1978 saw the second, considerably revised edition of *The Principle* (Gánti, 1978). It was also then that enzymes were assigned a role in the theory, albeit in rather unusual form. Gánti reached back to the original ideas of Woese (1967), Crick (1968) and Orgel (1968) in the late sixties and postulated that replicating templates in the chemotons would evolve into enzymatic RNAs (now called ribozymes). As a matter of fact in his two papers (Gánti, 1979c, 1983) the "RNA world" was in full bloom, despite the fact the most people would know of Gilbert's (1986) essay in this regard.

Gánti influenced and attracted a good number of very talented students (I take the risk of saying that this was a further source of envy), but generally he could not keep them, he was simply too inflexible for that. In a way he was too much a prisoner of his own theory, and he evaluated everything and everybody from this perspective. He did not know how to pack what he wanted to tell for different purposes: "I am good in strategy but bad in tactics", as he would say. This is a key sentence, also for the understanding of his publication difficulties. "He has never learnt how to write papers", a peer once said. It is important to understand what this accurate statement really means. In fact Gánti's papers are very clear, but still they cannot "sell" the idea to suspicious readers.

In the eighties he was working mainly on two things. He wrote his big, two-volume monograph: *Chemoton Theory I–II* (Gánti, 1984, 1989). As an editor-in-chief of Természet Világa he refreshed the journal in many respects (1980–1990). In the early nineties it seemed that the theory was dead, almost nobody was interested in it. It was then that he established the company Cogitator that used to give nature conservation advice to various governmental agencies.

The tide turned in 1995 when John Maynard Smith and I in *The Major Transition in Evolution* attempted to give Gánti the place he deserved (Maynard Smith and Szathmáry, 1995). We did the same

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in a parallel *Nature* review article (Szathmáry and Maynard Smith, 1995). After that the dormant theory began to show signs of life more often. In 2000 a group of experts recommended Oxford University Press to publish Gánti's works, which the publisher accepted in accordance with their internal decision procedures. The new volume (Gánti, 2003a) contains edited versions of two previous books and two essays appreciating the work from the philosophical (James Griesemer, University of California at Davis) and biological (E. Szathmáry) perspectives. Almost at the same time Paul Mezey, the series editor, offered to publish the English translation of the monograph (Kluwer, Mathematical and Computational Chemistry: Gánti, 2003b). Preparatory work for the latter was carried out in the now defunct Collegium Budapest, where Gánti was a Fellow for a year.

In the last five years of his life he was an external member of the astrobiology group (supported by the European Space Agency) at Collegium Budapest. The idea that the so-called dark dune spots on Mars could harbor seasonal, photosynthetic, microbial life (Gánti et al., 2003) has come primarily from him. Time will tell whether he was right or wrong.

As I indicated above, the world has changed considerably. The science of systems chemistry has been firmly established by an essentially European initiative, dealing with the analysis and synthesis of autocatalytic systems of different types. In the relevant publications Gánti's name appears more and more often; see Patel et al. (2015) for an eminent example.

It is pathological in contemporary science that written acknowledgement of Gánti's intellectual influence still does not keep pace with the verbal one. The simple reason is that contemporary granting and publication systems force people to pretend to be original even if they are not (very much) so. This behavior of course undermines the old-fashioned ethics of giving credit where it is due (people tend to cite friends or potentially dangerous referees; the rest does not really count).

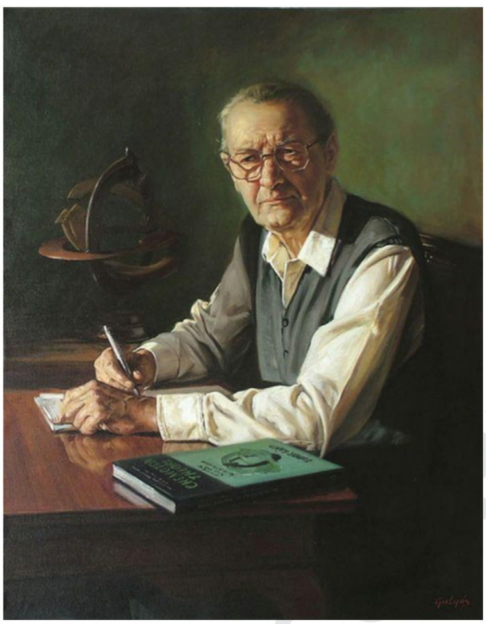

Fig. 1. Tibor Gánti. Painting by László Gulyás.

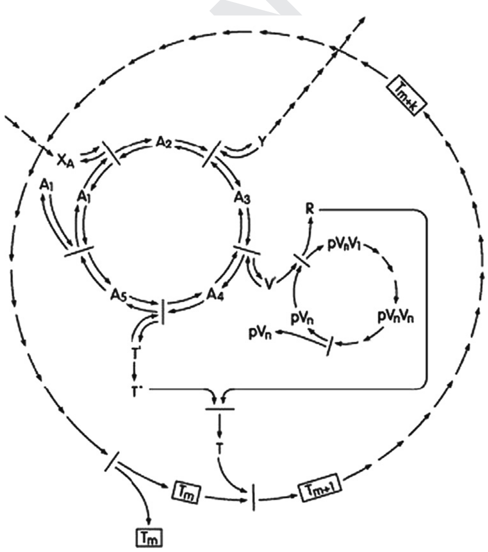

Fig. 2. The standard chemoton model. A_i are the metabolic intermediates, pV_n is a replication template polymer of n subunits V, T_m is a membrane composed of m amphiphilic molecules T. Raw material X and waste Y pass freely through the membrane. All subsystems are autocatalytic. Note that there are several alternative topologies (Gánti, 1984, 1989).

Fig. 3. The chemoton symbol, designed by Tibor Gánti. Taken from his website http://www.chemoton.com/index.php/en/.

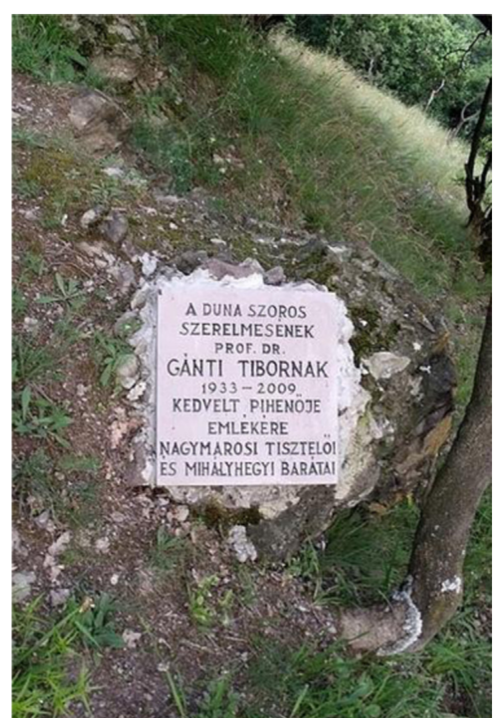

Fig. 4. Memorial site of Gánti on a hill above the Danube Bend.

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In sum I can say that the intellectual seed of Gánti slowly delivers fruit, but the acknowledgement of the farmer is still lagging behind (Szathmáry, 2009). This does not matter for him any longer, but it does matter for the content and moral of science: better late than never. I think that the time will come when his intellectual achievement will be regarded as outstanding. Gánti's interest and work would render him eligible for the (imaginary) title Magister Vitae. As a master of life he has been investigating the foundations of life with unbeliavable endurance and very modest support. He surely was not a Corinthian: he was notoriously unlucky. But Corinthians are soon forgotten, whereas masters of life are remembered with respect ~~(Figs. 1–4)~~.

Acknowledgements

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