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# From prebiotic chemistry to cellular metabolism—The chemical evolution of metabolism before Darwinian natural selection ☆

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## Abstract

It is generally assumed that the complex map of metabolism is a result of natural selection working at the molecular level. However, natural selection can only work on entities that have three basic features: information, metabolism and membrane. Metabolism must include the capability of producing all cellular structures, as well as energy (ATP), from external sources; information must be established on a material that allows its perpetuity, in order to safeguard the goals achieved; and membranes must be able to preserve the internal material, determining a selective exchange with external material in order to ensure that both metabolism and information can be individualized. It is not difficult to understand that protocellular entities that boast these three qualities can evolve through natural selection. The problem is rather to explain the origin of such features under conditions where natural selection could not work. In the present work we propose that these protocells could be built by chemical evolution, starting from the prebiotic primordial soup, by means of *chemical selection*. This consists of selective increases of the rates of certain specific reactions because of the kinetic or thermodynamic features of the process, such as stoichiometric catalysis or autocatalysis, cooperativity and others, thereby promoting their prevalence among the whole set of chemical possibilities. Our results show that all chemical processes necessary for yielding the basic materials that natural selection needs to work may be achieved through chemical selection, thus suggesting a way for life to begin.

*Keywords:* Origin of life; Evolution of metabolism; Chemical evolution; Prebiotic chemistry

## 1. Introduction

Professor Reinhart Heinrich was always keenly interested in biological evolution and natural selection, and especially in the evolution of metabolism. His first works in this field dealt with the optimization of the kinetic parameters of enzymes to produce maximum activity (Heinrich et al., 1987; Heinrich and Hoffmann, 1991), a subject that had been previously explored by Cornish-Bowden (1976). Over the course of time, our mutual scientific interest fomented a close friendship as well as a fruitful scientific collaboration. We had many meetings in Berlin, Tenerife, and Madrid, continually discussing evolution, metabolism, and optimization. Fruit of these discussions was a series of papers on glycolysis optimization (Heinrich et al., 1997a, b, 1999; Meléndez-Hevia et al., 1997; Waddell et al., 1997, 1999) and one which presented his difficult theory on optimization of enzyme parameters in such a way as to make it more accessible to students (Heinrich et al., 2002).

In the last years, as of 2003, we had initiated a very ambitious task: the search for the history of the appearance of all metabolic pathways. In some interesting discussions, Heinrich said that by looking at the structure of a city, it could be possible to know the history of its origin (for example, whether it had been built by radial growth from a small nucleus, like Madrid, or by joining small villages, like Berlin), and that perhaps the historical development of

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☆This paper is dedicated to the memory of Professor Reinhart Heinrich, who was collaborating with us in this subject, and died suddenly when this work was almost finished. His name should be as co-author but it has not been possible, because, with great sadness, we have been told that we had to respect his criterion that he firmly stated of not signing any paper without having seen the last version.

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metabolism could be unveiled in the same way. This observation opened up new modes of inquiry for us and we were soon rewarded with some clear insights. For example, the Calvin cycle uses ribulose 5-P as feeder, so this product had to be available beforehand, and because ribulose 5-P is made only by the pentose-phosphate cycle, we concluded that the emergence of this pathway had to be prior to the Calvin cycle.

Heinrich had another great idea: he though that if we were able to uncover the history of metabolic pathways, it would be possible to calculate the stoichiometric matrix of each stage in its evolution, which would then allow us to have quantitative information about the progression of metabolic complexity. Heinrich designed a computer program to that end and we began our quest.

Heinrich wanted to plot the progress of metabolic complexity over time from its origins, and we needed to explore its history through a logical retrospective reasoning going back to the beginning of metabolism, the end of which would be the origin of life. In sum: the stoichiometric analysis could not be undertaken until its history was accounted for in full. Heinrich started to make calculations with the first results, but they could only be provisional until all metabolic history was completed. We were nearing the end of our task when we learned of the tragic news of Heinrich's untimely death. It is to his memory that we would like to dedicate this paper, both because he participated in this research, and because his ingenious ideas continue to inspire us.

Darwinian natural selection is a powerful mechanism capable of developing many optimized structures and functions, as well as of creating new ones, based on their selective value under competitive conditions This has been specifically studied at the molecular level by Baldwin and Krebs (1981), Cornish-Bowden (1976), Heinrich and Hoffmann (1991), Heinrich et al. (1987, 1991, 1997a, b, 1999), Kacser and Beeby (1984), Meléndez et al. (1997), Meléndez-Hevia and Isidoro (1985), Meléndez-Hevia and Torres (1988), and Meléndez-Hevia et al. (1993, 1994, 1996, 1997).

However, if we try to explain the origin of life by natural selection, a critical problem appears: natural selection can only work if it has three basic materials: information, metabolism and membrane. Therefore, at the origin of life, these had to be achieved previously for natural selection to work, and these qualities could only be done by a prior process of pure chemistry in which any feature of interest for life had no special importance. Therefore, a purely chemical process had to occur prior to natural selection capable of yielding these materials specifically, independent of their value for building life later. In this work we have explored the chemical possibilities of prebiotic chemistry to produce these materials and conclude that prior to natural selection, a previous process only governed by the rules of chemistry must have occurred in order to yield the appropriate materials. Moreover, we show that such a process could be highly favoured, as the chemical reactions involved in it are autocatalytic and/or cooperative.

## 2. Hypotheses and rules

### 2.1. General hypotheses for evolution of metabolism

In a previous work (Meléndez-Hevia et al., 1996) four rules of metabolic evolution were stated as follows:

#### 2.1.1. Bioorganic chemistry

1. Any enzymatic reaction is also chemically possible without the enzyme, although in that case it would occur much more slowly and without a well-defined specificity.
2. All the intermediates of a chain of reactions to be used ultimately in a metabolic sequence must resist rapid decomposition. The strongest reason for this assumption is evolutionary; at the beginning of the pathway design every rudimentary enzymatic reaction occurred very slowly, so unstable intermediates could not have been used.
3. *Material availability* (*Opportunism*): Any material to be used by the new pathway must exist in another metabolic process which was originally developed for a different purpose. Design of this new pathway must preserve the function of the previous one whose material has been used. An inverse chronological application of this rule would eventually lead to the origin of metabolism; on the primordial Earth the first available compounds had to have been made through spontaneous chemical processes.
4. *Kinetic and thermodynamic compatibility*: The new pathway cannot have a reaction involving any thermodynamic or kinetic incompatibility with a previous one that is operating simultaneously in the same space.

### 2.2. Specific hypotheses for the origin of life

The rules mentioned above are the first basic hypotheses of this work. In addition, we shall add others specifically stated for our approach to search for the sequence of events in time that have developed our present metabolism from prebiotic chemistry.

1. *Universality of intermediary metabolism*: The universality of intermediary metabolism has been remarked on by several authors (Morowitz et al., 2000; Smith and Morowitz, 2004), assuming that the basic structure of intermediary metabolism represented by the classical wall chart (see Michal, 1999) is universal. Although there is a general consensus on this point, different parts in the metabolic map must nevertheless be distinguished: on one hand, the central pathway of carbon flux, which is universal, with few exceptions, and on the other hand, the pathways to make ATP, and the pathways to fix carbon and nitrogen, where there is a broad diversity. This distinction is interesting for the purpose of this work.