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Question 1: Commentary Referring to the Statement "The Origin of Life can be Traced Back to the Origin of Kinetic Control" and the Question "Do You Agree with this Statement; and How Would You Envisage the Prebiotic Evolutionary Bridge Between Thermodynamic and Kinetic Control?" Stated in Section 1.1.

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Abstract The paper summarizes thoughts induced by some of the programmatic questions Pier Luigi Luisi posed for discussion at the Erice workshop.

Keywords Thermodynamic versus kinetic reaction control · Metabolic versus genetic autocatalytic cycles in prebiotic chemistry

The terms 'thermodynamic-' and 'kinetic control' of product formation in a system of chemical reactions are meaningful only if referring to specified chemical steps, specified conditions, and specified products. The criterion for stating that a chemical reaction proceeds under *thermodynamic* control is NOT whether under given conditions the more (or most) stable of the possible products is formed, but rather whether the chemical equilibrium between product(s) and starting material(s) remains *established* under the conditions of product formation such that alternative products are in (established) equilibrium with each other. We may also speak of (partial) thermodynamic control when at least the latter is the case, without the equilibrium between products and starting material being established. *Thermodynamic* reaction control *must* lead to the more stable product; *kinetic* reaction control *may* lead to it. Observing the formation of the more stable product leaves the question of control undecided, while observation of a less stable product positively

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means that the reaction proceeds under *kinetic* control (with reference to products that would be more stable).

To take the prototypical example of prebiotic chemistry: the highly exothermic formation of adenine from HCN under most of the conditions applied proceeds under kinetic control since under these conditions the product adenine will not be in *established equilibrium* with either its starting material, or with alternative products. Furthermore, if water were part of the environment (what would be a reasonable assumption for 'prebiotic conditions'), adenine is obviously not the 'most stable product', since its enforced (acid/base-catalyzed) hydrolysis leads to formic acid, CO_2, glycine, and ammonia.

While it has become a truism that life requires an overall chemical environment that is far from equilibrium, kinetic control of life processes is a requirement for the overall process, but parts of it can proceed under (partial) thermodynamic control. Biochemistry must be rich in examples that demonstrate co-operation of kinetic and thermodynamic control: any enzymically catalyzed biochemical reaction in principle can operate under both regimes, depending on factors such as the degree of exergonicity of the reaction, the catalytic efficiency of the enzyme, the concentration of reaction partners, or the reaction temperature.

What has been paramount to the origin of life with respect to the dichotomy of thermodynamic versus kinetic control is the central role of catalysis in imposing kinetic control on structural changes of a chemical environment held far from equilibrium by kinetic barriers.

Introductory Remarks to the Addendum "On Metabolic and Genetic Cycles"

The abstract volume of the Erice workshop featured an addendum entitled "About Primordial Genetic and Metabolic Cycles" to the author's comments (see above) to the first of Luigi Luisi's "Basic Questions". While the content of this addendum did not really refer to that question (the meaning of which the author disagreed with, see above), the writing of the addendum was inspired by the question's second part which said: "...and how would you envisage the evolutionary bridge between thermodynamic and kinetic control?" The addendum turned out to be a response to a modified version of the question, namely, to one that could read: "How would you envisage the bridge between potentially primordial geochemistry that had been disordered and one that gradually became self-organizing?" In retrospect, the addendum may also amount to a comment to Luisi's "Basic Question No. 8" referring to "Theoretical Models of the Origin of Life". The writing of the addendum had also been influenced by what the author, as well as others, see as the three-pronged approach of origin-of-life science to its central problem, three-pronged in the sense that there are three distinct schools of thoughts, "geneticists, metabolists and compartmentalists", pursuing research in distinctly different directions and, when communicating among each other, tend to take stands sometimes bordering on a kind of scientific iconoclasm. The thoughts discussed in the addendum should be seen as an attempt to bring the three camps nearer together. The addendum reproduced below is a modified version of what appeared in the ERICE abstract volume. Originally meant as just a contribution to discussions expected to arise at the workshop, the addendum given in the abstract booklet did not give any reference to the thinking of others. Here, in the published version of the addendum (see below), this omission is corrected. Many of the views expressed in the addendum in an "organic chemist's language", and especially the point that primordial autocatalytic cycles could store 'genetic' information irrespective of whether they involve

informational oligomers or not, have long been implicit or explicit part of the thinking of representatives of the 'metabolists' school featuring names such as Dyson (1982, 1985), Kauffman (1986, 1993), Waechtershaeuser (1988, 1990), Morowitz (Morowitz et al. 2000; Smith and Morowitz 2004), Szathmary (2000), Lancet (Segre et al. 2000) among others. The author thinks that his deliberations might be of interest to both geneticists and metabolists in their own search for *their* autocatalytic cycles, once we could come nearer to each other with respect to what we should mean by the term 'genetic' in the context of primordial replicating systems, and whether in such a context we should differentiate between 'metabolic' and 'genetic' autocatalytic cycles.

On Primordial 'Metabolic' and 'Genetic' Cycles

When a chemical environment undergoes spontaneous exergonic structure changes ('starting materials' to 'final products') accompanied by production of heat, the environment is, so to say, 'wasting' its structural and energetic potential for the contingent generation of a potentially large diversity of intermediate products lying energetically as well as structurally between starting materials and final products. Catalysts can *explore* such a structure- and reactivity-space in the sense that they can provide access to alternative reaction pathways that will generate parts of that diversity of possible chemicals between starting materials and final products. In such explorations, catalysts accelerate the overall rate by which the environment reaches (partial) equilibrium, since they can make final products be formed under conditions under which no product formation may take place in their absence. Given such catalysts, the environment has no choice but to follow the chemical paths they stipulate. Such a catalytically explored chemical environment may make first steps towards acquiring attributes of 'minimal chemical life' when catalysts not only accelerate the environment's equilibration, but when they become capable of *exploiting* the environment's structural and energetic potential quasi 'for the sake of their own existence'. Such can be the case, when out of the library of alternative reaction pathways, opened by catalysts, emerges a loop that amounts to a *catalyst's* autocatalytic replication. In an etiological context, such a loop may be said to represent the most elementary form of a *potentially* genetic cycle.

Another type of reaction loop that can emerge as a consequence of the exploration of a chemical environment's structure and reactivity space is one that, driven by the free energy of starting materials, connects intermediate products (substrates as opposed to catalysts) in a cyclic pathway: such a cycle is referred to as autocatalytic *metabolic cycle*. This type of cycles differs from the kind of cycles referred to above in that none of the constituents of the cycle acts as a catalyst of reaction steps, yet each constituents acts, by virtue of its very affiliation with the cycle, as a catalyst (*circuit-catalyst* as opposed to *reaction-catalyst*) of the formation of itself and of all other constituents of the cycle (Smith and Morowitz 2004). In such a classification, the type of cycle that would have the potential of acting as a genetic cycle is a 'not-only-circuit' catalysts containing autocatalytic cycle. In this context, 'reaction' catalysts are catalysts that act through physical intervention on reaction paths inside and/or outside the cycle.

There are reaction catalysts that can become, and such that cannot become members of an autocatalytic cycle. Representatives of the first group (e.g. low molecular weight compounds; 'organo-catalysts') can either be components of the original chemical environment, or can emerge as contingent components of the component libraries that are produced through the exploration process. The latter can be induced and also sustained by another group of catalysts, molecules or materials that are part of the chemical environment,

but do not become members of a cycle. Prime examples would be inorganic catalysts and catalytically active external or internal mineral surfaces.

Why it may make sense to differentiate between two types of *autocatalytic cycles* on the basis of the criterion of whether the constituents are products/substrates only, or whether among the constituents there are reaction catalysts, requires justification. Let us assume an environment with such autocatalytic cycles containing reaction catalysts as constituents and compare status and function of these (replicating) catalysts to the status and function of (replicating) RNA-sequences that act as ribozymes in a hypothetical RNA world: In their *own* world, status and function of those organo-catalysts can be analogous to status and function of ribozymes in the RNA world: what their individual *chemical constitution* is to those organo-catalysts corresponds to what the individual *chemical constitution –the individual base-sequence* – is to the ribozymes. Crucial among the differences between the two worlds is not the difference in chemical structure of the two types of catalysts, or how they exert their function, but the catalyst's degree of potential structural *diversity* and functional *efficiency.* Apart from these differences, the chemical structures of organo-catalysts contained in an evolving system of primordial autocatalytic cycles can be said to embody genetic information in a conceptually analogous way as base-sequences of ribozymes are supposed to embody such information in an RNA-world. The function that a pattern of self-replicating reaction catalysts in a cooperating system of autocatalytic cycles could fulfill for that system can be analogous to the function of what, in an functioning RNA-world, we would refer to as the system's 'genome'.

Any attempt to classify the functional status of reaction cycles in models of biogenesis must radically simplify potential reality. In order to provide a glimpse of the conceivable chemical complexity that is bound to erode such classifications, let us consider the following scenario: If, in a specific chemical environment, a constituent of a metabolic cycle were capable of (spontaneously or catalytically) forming a reaction product that turned out to be a catalyst for any of that cycle's reaction steps without becoming itself a constituent of the cycle (or any other cycle), then this catalyst would also be a self-replicating catalyst, since it would catalyze its own formation via the circuit-catalytic metabolic cycle. Hence, in the specific environment in which such a transformation would occur, the formation of that catalyst would be 'heritable' without any of the constituents of the cycle being a reaction catalyst. To be sure, the environmental dependence of the formation of such an external catalyst may render its replication less robust than if the catalyst were a constituent of the cycle. A benefit of the excursion to a simple scenario such as this might be the insight that transformations of 'circuit' catalysts into reaction catalysts could constitute, in principle, one of the ways how metabolic cycles could respond to a changing environment.

Another aspect that complicates classifications relates to the following. Even though in presumably most cases a pragmatic differentiation between a circuit catalyst and a reaction catalyst based on chemical considerations seems clear enough, this is not so at a more basic level. Take the reductive citric acid cycle (Morowitz et al. 2000; Smith and Morowitz 2004) as a prototypical representative of a metabolic cycle in which all constituents clearly appear to be products or intermediates and not (reaction) catalysts: Since there is no limit to be set with respect to how many covalent intermediates derived from reactants and catalyst a conventional catalytic cycle can involve, we could – in principle – declare the constituent oxaloacetate as being a (reaction) catalyst for the synthesis of acetate from the starting materials carbon dioxide and reductants. It is just the additional connection between (the 'product') acetate and (the 'catalyst') oxaloacetate via (the additional intermediate) pyruvate that converts the catalytic cycle into an autocatalytic cycle; on the level of classifications,

closing that ring segment converts what in the catalytic cycle is a (reaction) catalyst to what in the autocatalytic cycle is a circuit catalyst. The difference between what is supposed to be a circuit and what a reaction catalyst in autocatalytic cycles is basically a difference referring to the 'valency' of the catalytic potential of a catalyst. Not-only-circuit-catalysts in autocatalytic cycles are catalysts with a multivalent catalytic potential.

If what in self-organizing primordial systems may have been equivalent to 'genetic information' had not necessarily to be stored in, and retrieved from, a specific sequence of recognition elements bound to a covalently constituted self-replicating polymer, then the debate between geneticists and metabolists can move beyond structural aspects and focus on the critical question of evolvability of genomes residing in sets of self-replicating (reaction) catalysts of the type delineated above. The literature contains instructive examples of this debate (Orgel 2000). From an organic chemist's point of view, the question cannot be profitably discussed without recourse to a specific environment, to its chemistry, and its energetic and structural potential for becoming 'explored' by catalysts. On a formal level, however, the answer seems clear enough: the larger the diversity of catalytically accessible alternative pathways and products between starting materials and final products, the greater the opportunities for contingent growth and complexification of chemical changes as consequence of the opening of pathways by catalysts, and the higher the chances for a system of autocatalytic cycles to become able of adapting to changes in the environment. But, however large the diversity of structures and reaction pathways that can be explored by catalysts between starting materials and final products, the structural playground for systems of cooperating autocatalytic reaction cycles to evolve by growth and complexification is bound to be small in comparison to the immense potential diversity of structures that is, in principle, accessible through mutational replication of functioning informational polymers. Replication cycles of such polymers are prototypical genetic cycles, since all of the members of the cycles are not-only-circuit-catalysts for their own formation (replication of sequences) with the potential of members to emerge as catalysts for reaction steps of either their own cycles, or of cooperating cycles. The evolutionary potential of catalytic informational polymers is essentially unlimited, it is so incomparably greater than the potential of systems that explore structure space by autocatalytic cycles operating with low molecular weight organo-catalysts, that the difference has become the essential reason for the basic supposition of the 'geneticists', namely, that life's beginning coincided with the emergence of replicating informational oligomer systems. It is, therefore, important to ask, conceptually as well as experimentally, as to whether informational oligomer systems of a, to be sure, structurally and functionally elementary form, could emerge as a result of catalytic explorations of structure space in chemical environments of the type referred to above, whether such oligomers could be formed in concert with metabolic and (elementary forms of) genetic cycles? Again, there is no way to answer this question, except on the basis of a realistically conceived geochemical scenario, and by studying its hypothetical chemistry. The question reminds us, how little we actually know.

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