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# Microreversible recycled chemical systems. Comment on “A Re-Examination of Reversibility in Reaction Models for the Spontaneous Emergence of Homochirality”

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The question of the onset of the homochirality on prebiotic Earth still remains a fundamental question in the quest for the origin of life.<sup>1</sup> Recent works in this field introduce the concept of recycling,<sup>2–4</sup> rather than the traditional open-flow system described by Frank.<sup>5</sup> This approach has been criticized by Blackmond *et al.*<sup>6</sup> They claimed that such systems are thermodynamically impossible, except in the cases where non-microreversible reactions are introduced, like in photochemical reactions, or under the influence of physical actions (e.g. by crystal crushing<sup>7</sup>). This point of view reveals misunderstandings about this model of a recycled system, overlooks the possibility of energy exchanges that could take place in prebiotic systems, and leads the authors to unawarely remove the activation reaction and energy source from their “non-equilibrium” models. It is especially important to understand what are the concepts behind the notion of recycled systems, and of activation reactions. These points are fundamental to comprehending how chemical systems — and especially prebiotic chemical systems — can be maintained in non-equilibrium steady states, and how free energy can be used and exchanged between systems. The proposed approach aims at the decomposition of the problem, avoiding to embrace the whole system at the same time.

In an open flow system, the difference in chemical potential of the studied compounds is maintained by continuous input and output flows of these compounds (Fig. 1.A). In a recycled system, some low potential compounds are activated back into high potential compounds by an external process (Fig. 1.B). If this recycling results in maintaining the studied compounds in a closed system, it must also be coupled to the consumption of free energy, i.e. the continuous consumption of “fuel” external compounds and disposal of “waste” compounds. Recycled systems are not — and have never claimed to be — strictly closed. In the case of the Activation/Polymerization/Epimerization/Depolymerization system (APED),<sup>3,4</sup> the theoretical model can be mathematically reduced to a closed system of amino acid residues, by impliciting the sources of energy in the kinetic parameters. But when referring to the chemical counterpart of the theoretical reactions, it is clearly stated that this system is linked to the consumption of additional reactants.<sup>8</sup>

The process of recycling aims at maintaining a difference in chemical potentials inside the system. In the case described in Fig. 1.B, the reaction is spontaneous from  $A$  to  $B$  and from  $B$  to  $C$ , and thus from  $A$  to  $C$ . As a consequence, forcing the reaction from low potential compounds ( $C$ ) to high potential compounds ( $A$ ) requires an active process, linked to the consumption of energy. In the case of chemical energy, this means that external compounds of high chemical potential ( $X$ ) are consumed, and low chemical potential compounds ( $Y$ ) are being disposed of. As no  $A$ ,  $B$  or  $C$  are never entering nor leaving the system, these three compounds being only interconverted from one to another, the  $\{A, B, C\}$  system can

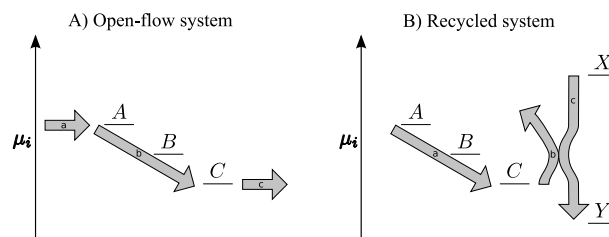


Figure 1: Schematic representation of open-flow and recycled systems. A: a, input flow of compound  $A$ ; b, spontaneous transformation from  $A$  to  $C$  through  $B$ ; c, output flow of compound  $C$ . B: spontaneous transformation from  $A$  to  $C$  through  $B$ ; b, activated transformation of  $C$  into  $A$ ; c, spontaneous transformation of  $X$  into  $Y$ , coupled to the transformation b.

be considered as closed, and the sum of the concentrations  $[A] + [B] + [C]$  is strictly constant. However, it is coupled by a reaction  $A + X \rightleftharpoons B + Y$  to the external system  $\{X, Y\}$ , that is opened so that the difference in chemical potentials is maintained between these two compounds. An activation reaction does not consist in a simple spontaneous reaction, but rather represents a non-spontaneous reaction that is made feasible thanks to the coupling with another reaction, that is spontaneous with a larger difference in chemical potential. It is thus possible to obtain a transfer of free energy, that forces the activated reaction from stable compounds to unstable ones, as in many endergonic biochemical reactions coupled for example to ATP hydrolysis.

In that scope, the assumption that the system is recycled comes from decomposing the whole system into several interconnected subsystems, rather than just stating that the system is globally open, i.e. that some matter is exchanged with the surroundings (Fig. 2.A), or globally closed, i.e. that the system only exchanges energy but not matter (Fig. 2.B). The recycled system is described as closed for some given internal compounds (internal system), but linked to the consumption of compounds from a “reservoir” (external system), matter flow being established as a link between these two systems. The mechanisms that maintains the state of the reservoir are implicit, relying on other processes that are not related to the internal processes of the recycled system (Fig. 2.C). The environment is described as a black-box, that is maintained in a non-equilibrium state by implicit external factors. The recycled system is just “plugged” to this environment acting as a reservoir of free energy. The reservoir system does not need the recycled system to exist, as it is maintained anyway by external sources. But the recycled system relies on the presence of the reservoir, to be maintained in an active state. The reservoir preexists, as an initial requirement to the possibility for a more complex non-equilibrium system to be established.

The recycled system is macroscopically irreversible, even

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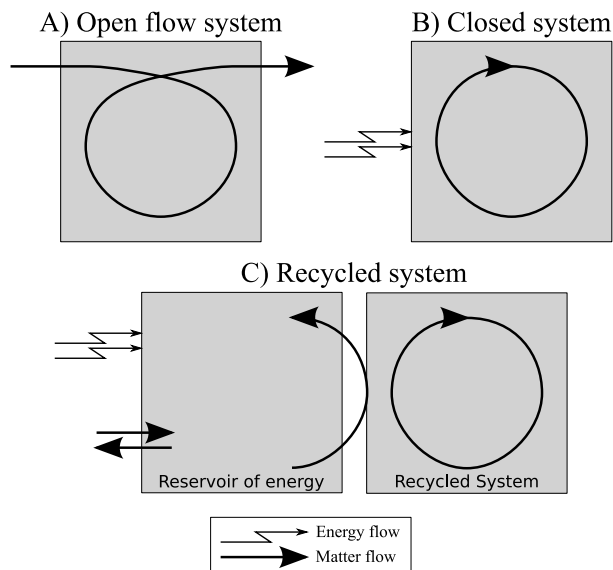


Figure 2: Representation of the decomposition of non-equilibrium systems into subsystems, emphasizing the different exchanges between subsystems and the surrounding.

if composed of microreversible reactions. The origin of this irreversibility is simply the transfer of free energy, and namely chemical free energy, generating unidirectional cycles of reaction. For example, a reaction  $A \xrightleftharpoons[k_{-1}]{k_1} B$  can be activated, linked to the transformation of  $X$  and  $Y$  compounds through the reaction  $A + X \xrightleftharpoons[k_{-a}]{k_a} B + Y$ . The activated reaction is

mathematically equivalent to a  $A \xrightleftharpoons[k'_{-1}]{k'_1} B$  reaction with apparent kinetic rates  $k'_1 = k_a x$  and  $k'_{-1} = k_{-a} y$ ,  $x$  and  $y$  being maintained in non-equilibrium concentration in the reservoir system. The sole intrinsic kinetic constants follow the thermodynamic relationship ( $\frac{k_1}{k_{-1}} = K_1$ ), while the apparent kinetic constants do not ( $\frac{k'_1}{k'_{-1}} = K_a \frac{x}{y}$ ), as they are function of the concentrations of  $X$  and  $Y$ . The condition  $\frac{k'_1}{k'_{-1}} = K_1$  will be only obtained in the case where  $X$  and  $Y$  would be at equilibrium concentrations. It is thus possible to write reactions whose kinetic parameters do not correspond to thermodynamic parameters, as long as it is kept in mind that this is hiding a source of energy and the possible implicit consumption of external compounds. The reaction can of course also be directly activated in one specific direction by a photochemical reaction.<sup>9</sup>

In the case of the APED system,<sup>3</sup> the activation reaction is based on the transformation of non-activated amino acid  $L$  (or  $D$ ) into an activated form noted  $L^*$  (or  $D^*$ ) by a reaction  $L \rightarrow L^*$ . As previously stated, this theoretical activation reaction can represent the transformation of an amino acid into its N-carboxyanhydride form (NCA), which is an activated reaction that relies on the consumption of reactive compounds,<sup>4,10-12</sup> and is in no case a "thermal activation" as stated by Blackmond *et al.*<sup>6</sup> The global formula is  $L + X \xrightleftharpoons[k_{-a}]{k_a} L^* + Y$ . The compound  $X$  corresponds to a high potential compound, and  $Y$  to a low potential compounds,<sup>13</sup> so that the reaction constant  $K_a$  is somewhat larger than one. Moreover, the molecules  $X$  and  $Y$  are maintained constant, so that the reaction comes down

to the first order reaction  $L \rightleftharpoons L^*$  of apparent kinetic rates  $a = k_a[X]$  and  $a_- = k_{-a}[Y]$ . The relationship with the thermodynamic constant is  $\frac{a}{a_-} = K_a \frac{[X]}{[Y]}$ . In order to guarantee  $a \gg a_-$ , it is thus sufficient to guarantee both  $K_a \gg 1$  (i.e.  $X$  is a reactive compound while  $Y$  is a stable compound) and  $[X] \gg [Y]$  (i.e. the system is continuously fed with  $X$  while  $Y$  is dissipated). The spontaneous deactivation is also taken into account, but does not correspond to the microreversible inverse of the activation reaction. This process is the simple hydrolysis of the NCA back to the amino acid, releasing carbon dioxide:  $L^* + H_2O \xrightleftharpoons[k_{-b}]{k_b} L + CO_2$ . The apparent kinetic rate of the reaction  $L^* \rightleftharpoons L$  are  $b = k_b$  and  $b_- = k_{-b}[CO_2]$ . In accordance with the well known reactivity of NCAs,<sup>10</sup> the reaction of deactivation is totally displaced toward the formation of amino acid, i.e.  $k_b \gg k_{-b}$ , so that  $b \gg b_-$ .

The model previously described<sup>3,4</sup> is thus a correct approximation, as both  $a \gg a_-$  and  $b \gg b_-$ . The ratio between  $a$  and  $b$  is also not fixed, depending on  $[X]$ , here again high concentrations of  $X$  favoring the activation reaction. Moreover, the spontaneous hydrolysis of NCA is slow relatively to other reactions in appropriate conditions.<sup>14</sup> In the model described by Blackmond *et al.*,<sup>6</sup> the microreversible reaction of *both* activation and deactivation reactions should have been added, as explained above, but they artificially considering that the activation is the microreversible reverse reaction of the deactivation reaction. They should also have taken into account the fact that energetic compounds are consumed during the activation reaction, but they confused intrinsic kinetic rates with apparent kinetic rates, leading to remove the activating compounds from the system. They thus actually *removed* the activation reaction. There is thus no surprise that the system fails to evolve towards a non-racemic steady state in absence of source of energy. The system does not in any way describe the full APED model.

Maintaining a non-equilibrium chemical system in a non-racemic steady-state relies on maintaining unidirectional cycles of reaction by consuming free energy. The description of such chemical cycles were introduced very early in the origin of life theory by Gánti<sup>15</sup> and Eigen.<sup>16</sup> They are fundamental for the self-organization of matter, as they can induce network autocatalytic properties. The consumption of energy implies that reactions are not detailed balanced: they are proceeding faster in one direction than in the other, even taking into account the microreversibility, driven by the differences in chemical potentials. It is important to distinguish the mechanism of the deracemization process from the energetic source allowing this process to operate. While this distinction is not done in the traditional approach,<sup>5</sup> it appears that the open flow system is the source of energy, and the recycled system is responsible for the network autocatalysis. The purpose of the previous articles<sup>3,4</sup> was to focus on the autocatalytic mechanism itself, and to understand how it works. The fact that energy can flow inside the system was already a known fact, addressed in the study of the potential activation of amino acid into NCAs in prebiotic conditions,<sup>11,12</sup> and was thus let as implicit in the equations (but not in the discussions). The last point is now to understand how the free energy is distributed and used inside the system. This point will be addressed in details in a future publication.

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8. In Ref. 3, page 16736, paragraph “Real Systems”, it is indicated that the system must consume compounds like NO or CO, depending on the conditions. In Ref. 4, page 593, second paragraph, it is indicated that “Practically, chemical energy can be either input directly or indirectly. In the latter case, *a flow of matter still exists*, but uncoupled from the autocatalytic reactions”.
9. A photochemical reaction is of first order in the reactant. The exponential term of the Beer-Lambert law is only accounting for the decrease of the intensity of the incident light while it is penetrating inside the reactor, thus the exponential term proportional to the reactor width  $\ell$ . For systems of low width, for example in the case of a photochemical reaction taking place in a shallow pond with an irradiation coming from the top, the radiation intensity is uniform inside the system, and the Beer-Lambert law reduce to a first order reaction, cancelling the term  $\ell$ .
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13. For example we can have  $X = \text{CO}$  and  $Y = \text{H}_2$ ,<sup>12</sup> or  $X = \text{HNCO} + \text{N}_2\text{O}_3$  and  $Y = \text{N}_2 + \text{HNO}_2 + \text{H}_2\text{O}$ .<sup>11</sup>
14. (a) For example, it could be determined experimentally that the NCA of valine is stable enough towards hydrolysis to survive several hours in water at *pH* 6 and 5 °C, its coupling with amino acids being much faster; (b) Plasson, R.; Biron, J.-P.; Cottet, H.; Commeyras, A.; Taillades, J. *J. Chrom. A* **2002**, *952*, 239–248.
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