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The non-equilibrium basis of Turing Instability and localised biological work

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ABSTRACT

Turing's theory for biological pattern formation is based on the instability of the homogeneous state, which occurs if certain key criteria are met. The problem of how chemical energy is converted to localised biological work requires one to understand not only the basis of localised power generation, but also the age-old puzzle of how organisms decrease their entropy; these problems can only be solved by the identification of the Turing Instability. At the heart of this is how natural selection, not chemistry, has fashioned the large non-equilibrium overall affinity (ΔG is a large negative quantity) for the oxidation of the fuel molecules.

Natural selection has also resulted in the homeostasis at non-equilibrium values of the hydrolysis of molecules like ATP, GTP, which are the energy links between the overall oxidation of the fuel and biological work. The conditions for such homeostasis are central requirements for the Turing Instability and are the essence of being alive. The Turing-Child (TC) patterns are the spontaneous primary spatial cause not only of localised biological work in multicellular systems (especially those in patterning and development) but also of intracellular patterns including the mitotic spindle and the contractile ring. The Turing picture comprises the nonuniform distribution of the concentrations of the Turing morphogens, cAMP and ATP, and the Child picture is the resulting nonuniform distribution of the metabolic rate and of power. The TC pattern is shaped as the dominant eigenfunction in the combination of eigenfunctions which provides the spatial pattern of the Turing morphogens. The TC patterns and the bifurcation parameter manifest quantisation and symmetry as in music and in applications of quantum mechanics. The notion of correlation diagrams is also introduced.

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1. Non-equilibrium as a source of order

The question of how chemical energy is converted to localised biological work is arguably the most fundamental problem in biology. This is related to another fundamental problem: how do biological organisms decrease their macroscopic spatial entropy. To solve this, we must identify the biological realisation of Alan Turing's "morphogens", first postulated in Turing (1952). These 'Turing morphogens' constitute the biological system that drives the transition from spatial homogeneity to spatial inhomogeneity, and from one form of inhomogeneity to another.

In thermodynamics terms, non-equilibrium is required as the source of order because—in the context of the search for the biological Turing system—if any chemical system is at equilibrium or near equilibrium, a Turing-type instability cannot occur. Instead, stability is universally guaranteed in such a system because of the existence of extremum principles for thermodynamic potentials. Free energy at equilibrium and entropy production near equilibrium in the linear range where Onsager's reciprocity relations hold (Prigogine, 1967, 1969; Kondepudi and Prigogine, 2015). Turing instability does occur when the mechanisms suggested by Turing are subjected to "non-equilibrium constraints": when the overall affinity, or equivalent parameters, such as the chemical parameter B for the chemical mechanism named Brusselator or trimolecular model, gradually increase (Prigogine and Nicolis, 1967; Glansdorff and Prigogine, 1971; Nicolis and Prigogine, 1977; Schiffmann, 1975, 1980; Babloyantz, 1986). We say the thermodynamic branch loses stability at a bifurcation point. The 'affinity' (A) of a chemical reaction is the thermodynamic driving force for the chemical reaction and is equal to the negative of the 'change in the Gibbs free energy per mole of the reaction at constant temperature and pressure' (ΔG). That is $A = -\Delta G$. The absolute value of A or ΔG measures the distance from thermodynamic equilibrium. Large overall affinity can provide a condition for Turing instability and also for large maximum biological work.

Based on this insight it makes sense to search for the Turing morphogens as the bioenergetic intermediates in the overall oxidation reaction (section IV, Schiffmann, 1997a):

$$\text{fuel molecules} + O_2 \rightarrow CO_2 + H_2O.$$

Here, typical 'fuel molecules' are glucose, glycogen—which is a 'condensed glucose'—or lipid. The affinity of this reaction under physiological conditions when glucose is the fuel molecule is substantial, 710 000 cal/mol (Pardee and Ingraham, 1960). To achieve such high overall affinity (a non-equilibrium constraint) in physiological conditions requires that there be a continuous supply of the initial reactants— or that they are present in excess—and that the final ('waste') products can be easily removed from the open biological system upon their production in the reaction space.

Chemically, it is not a trivial matter to obtain far-from-equilibrium overall affinity; however, as already noted, natural selection has taken care of this. The final product, CO_2, is a gas that can bubble away (section IV, Schiffmann, 1997a). Furthermore, as we have noted in earlier work, a fuel molecule often used in biological development is glycogen; and at the onset of key developmental events, glycogen is often present in excess in an embryological system. Gastrulation in amphibians, for example, can provide a canonical example (Schiffmann, 2005). The molecular nature of the other molecules involved in the overall oxidation reaction written above is such that it enhances the non-equilibrium nature of this overall reaction, and guarantees the open-system nature of the biological system. For example, oxygen, the other initial reactant in the overall oxidation, being a small non-polar molecule, manifests high permeability across biological membranes and can enter the system by passive diffusion (Freeman et al., 2014; Alberts et al., 2008); thus, the environment of this thermodynamic embryological system acts as a thermodynamic reservoir for oxygen. The final products, the low-entropy CO_2 and H_2O, are easily removed from the system. CO_2 is a small, uncharged, non-polar molecule, and therefore manifests high permeability across biological membranes, and thus easily removed from the system by passive diffusion (Freeman et al., 2014; Alberts et al., 2008). H_2O, being very small uncharged molecule, can cross biological membranes relatively rapidly, even though it is polar. This permeability is enhanced by facilitated diffusion via the channel protein aquaporin, which is highly selective for water and would not allow other small polar molecules to pass through (Freeman et al., 2014; Alberts et al., 2008). Thus, nature has designed the molecules at both ends of the overall oxidation reaction so as to allow them enter and leave the open non-equilibrium system via mere passive diffusion.

When glucose is the primary energy source and in organisms with placenta, such as humans, the glucose concentration is higher in the mother's blood than in the foetus and it can be transported across the placenta by facilitated diffusion. The placenta can also synthesise and store glycogen and provide glucose via glycogenolysis. The partial pressure of oxygen in maternal blood is higher than in foetal blood, which provides driving force across the placenta. However, carbon dioxide can diffuse in the opposite direction since its partial pressure in the foetal blood is higher than in maternal blood. Thus, all aspects of the overall oxidation reaction are arranged so as to generate and maintain a non-equilibrium system.

In his seminal work, Turing himself was almost explicit that the "Turing morphogens" are intermediates in the general oxidation reaction above (Turing, 1952). The first reaction scheme he suggests is of the form

$$A \rightarrow \{X,Y\} \rightarrow B$$

where the intermediates X and Y are the "Turing morphogens". He wrote: "Four substances A, X, Y, B are involved…The thermodynamics of the problem will not be discussed except to say that it is contemplated that of the substances A, X, Y, B the one with the greatest free energy is A, and that with the least is B. Energy for the