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Natural Selection and Thermodynamic Optimality (*).

J.-L. TORRES (**)
Departamento de Física, Universidad Michoacana - Morelia, Michoacán, México (***)
International Centre for Theoretical Physics - P.O.B. 586, 34100 Trieste, Italy

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Summary. — It is assumed that Darwin's principle translates into optimal regimes of operation along metabolical pathways in a biological system. Fitness is then defined in terms of the distance of a given individual's thermodynamic parameters from their optimal values. The method is illustrated testing maximum power as a criterion of merit satisfied in ATP synthesis.

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Darwin's principle of evolution by natural selection has been criticized as being tautological, survival of the fittest meaning little more than «survival of the survivors» [1-3]. Although the central position of darwinism in modern culture cannot be denied, there is some ground for the above accusation of circularity, because he did not define fitness in terms independent of survival.

Darwin's scheme depends on the interaction between individuals and their environment. Random mutations introduce diversity among the former and the latter acts as a filter, selecting the ones best tuned to their surroundings. Although this mechanism of natural selection acts upon individuals, it is *species* that evolve, and through them all higher populational entities, like the set of species in a given ecological system, and the biosphere in final account. The ensuing freedom in the choice of evolutive unit has often led to confusion in the analysis of these phenomena.

Attempts have been made in the past to *prove* evolution by natural selection based on physical laws. This has been accomplished in a few idealized cases, like the hypercycle [4, 5] and related «microscopic» models [6]. One deficiency they

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(***) Permanent address.

all share is their scant physical input, that precludes control over the range of values of many phenomenological parameters involved in their description.

Another approach is based on the assumption that natural selection has led to the optimization of living beings according to various criteria of merit, that one tries to identify based on theoretical and experimental information. Several criteria of optimization have thus been proposed, usually applied to the whole population in a given habitat: maximal «average fitness» [7], maximal efficiency in resource utilization [8], a «maximin» strategy for the one-generation probability of survival [9], minimal metabolized energy per unit of stored biomass [10], etc. The conceptual basis corresponds in each case to the discipline that provided the perceived analogy with an evolving biological ensemble: economics, the theory of games, cybernetics and so forth.

Of greater interest to us will be attempts to characterize fitness in thermodynamic terms. A fundamental tendency of nonequilibrium systems towards stationary states of maximal organization and minimal dissipation constitutes a potentially solid bridge between thermodynamics and Darwin's principle [11]. Such a «thermodynamic arrow» would lead to optimal modes of operation and to biological manifestations like homeostasis, or stability against environmental fluctuations, discernible when complete ecological systems, or even the whole biosphere, become units of evolutive analysis [12, 13]. While the general character of these proposals suggests the form a mature physical theory of evolution might eventually attain, it at the same time hinders experimental verification with contemporary tools.

We are concerned in this article with the following problem: given an individual interacting with its environment, how can one measure its degree of adaptation, *i.e.* its fitness? To solve it we propose that Darwin's principle implies approximate fulfillment of certain optimal conditions along its main metabolical pathways. This provides a criterion of fitness based not on counting survivors, but on verifying how close a given individual comes to satisfying such conditions. Criteria of optimality to be considered are thermodynamic ones: maximal efficiency, maximal power, minimal rate of entropy production, minimal loss of available energy. Relevant processes in metabolical pathways will be those related to energy fixation (photosynthesis), energy transduction (ATP synthesis in glycolysis and respiration, mechanical movement from the actin-myosin system), biomass formation (macromolecule synthesis in variants of the citric acid cycle), etc.

The concept of fitness just outlined is an approximate one, for it depends on optimal conditions separately satisfied along different metabolical pathways, and these are all interconnected. Full characterization of an individual's degree of adaptation would require assigning a weight factor to each of them, and taking an average over the resultant «partial grades». How to determine such weight factors is a problem not to be dealt with here. It belongs to a further stage of development along these lines, one that would justify application of the method to higher populational units. On the other hand, it is precisely its approximate character that should endow this approach with practical value. The manifold interactions of an individual with its environment depend on a large set of parameters, all of which would have to be considered simultaneously in an exact definition of fitness. This would constitute an excessively complex problem in all cases of interest. Our partial, piecemeal characterization would supply the essential elements for a complete picture.

To be sure, important processes along metabolical pathways have been

extensively studied. The problem of photosynthetic efficiency has been treated quantum-mechanically [14], and the question of optimality in biochemical systems has been studied with kinetic models [15-17]. Among other important results, it was proved using the latter that oscillatory regimes of operation are more efficient than stationary states with the same input flux, and that the stability, dissipation rate and control features of a system are all intimately related, and critically dependent upon its nonlinearity. Such a detailed analysis is not possible with the method here advocated. At the same time, kinetic models typically involve about ten free parameters, whose values are not constrained by fundamental concepts and laws. The aim here is to give characterizations of optimality based on as few phenomenological variables as possible. Our approach to the subject is close in spirit to that adopted by Wicken [11].

With the purpose of illustrating the method, maximal power output will be tested as a criterion of merit satisfied in steady-state ATP production. Results will not be definitive, due to insufficient experimental information, but the analysis will furnish useful theoretical insights about the process, and point out indispensable experiments to arrive at a definite conclusion. Furthermore, a parameter will be identified whose value will measure fitness in the sense proposed above.

The tools of «finite time thermodynamics» are ideally suited to this type of enquire. As a discipline it was born recently, with the work of Curzon and Ahlborn [18] on the simplest cycle that maximizes power, when time is introduced assuming finite conductivities at the walls separating the working substance from external heat reservoirs. In the regime of maximum power output they obtained for a 4-branch, Carnot-type cycle the efficiency $\eta_{P_{\max}} = 1 - (T_2/T_1)^{1/2}$, where T_1 and T_2 are the temperatures of the hot and cold reservoirs, respectively. This simple result started a very active period of work on the subject, for it emerged from a condition of optimality, much in the same way that Carnot's expression $\eta_C = 1 - T_2/T_1$ did from the requirement of maximum efficiency. Carnot's discovery eventually led to the concept of entropy and through it to the whole of classical thermodynamics. It was then conceivable that some generalization of Curzon and Ahlborn's ideas might generate another basic quantity, which would play a role in finite-time processes similar to that of entropy in the quasi-static limit. This lofty ideal has not been realized, but work on the subject has already produced some remarkable results. The concept of thermodynamic potentials has been generalized to finite-time events and used to calculate bounds on the work provided by open stationary processes [19]; the most general cycle that delivers maximum power is one with eight branches, none of them adiabatic [20]. Further criteria of merit explored are minimal rate of entropy production [21] and minimal loss of availability [22]. Rather than specific results from finite-time thermodynamics, we will adopt here some of its techniques to study optimality. In particular, we will write down the power for ATP synthesis in terms of its efficiency, much in the spirit of the original work of Curzon and Ahlborn.

1. – ATP synthesis.

ATP production takes place in cells through glycolysis and/or respiration. Glycolysis is an anaerobic process that involves thirteen enzymatic steps and has as its overall effect the break-up of glucose into two lactate molecules, with net yield

of 2ATP:

$$(1) \qquad \{\text{glucose}\} + [2\text{ADP} + 2\text{P}^+] \rightleftharpoons \{2\,\text{lactate}\} + [2\text{ATP}].$$

The *driver* reaction is the one indicated with curly brackets and the *driven* synthesis involves the substances in square ones, where P^+ denotes a phosphate ion. Under normal cell conditions the process occurs from left to right, with (molar) free-energy changes $\Delta G_0 < 0$ for the driver, and $\Delta G_1 > 0$ for the driven reaction. Of course the total free-energy change $\Delta G = \Delta G_0 + \Delta G_1 < 0$. *In vivo* free-energy measurements are not simple, but for glycolysis they have been performed in erythrocytes [23], as respiration is absent in them. The reported efficiency is $\eta = -\Delta G_1/\Delta G_0 = 0.53$.

Respiration is a more complicated process, in which the products from glycolysis are oxidized to CO_2 with net production of 36 ATP molecules:

$$(2) \qquad \{6\text{O}_2 + \text{glucose}\} + [36\text{ADP} + 36\text{P}^+] \rightleftharpoons \{6\text{CO}_2 + 6\text{H}_2\text{O}\} + [36\text{ATP}].$$

Again the driver and driven reactions have been indicated with curly and square brackets, respectively. The corresponding molar free-energy changes are much greater than in glycolysis, and the overall *in vivo* efficiency is [24] around 0.7.

Our first step will be to write the power P in terms of efficiency, the only relevant parameter in our analysis. By definition,

$$(3) \qquad P = \Delta G_1 v,$$

where ΔG_1 is the useful work or free-energy gain in the driven reaction and v is the reaction speed. Now we need a relationship between v and the affinity $A = -(\Delta G_0 + \Delta G_1)$, valid for steady states. This is the kind of information that we only have in very incomplete form. Let us call $v = f(A)$ such a functional relationship between v and A. Using the definition of η,

$$(4) \qquad P = -\Delta G_0 \eta f(-\Delta G_0 (1 - \eta)).$$

Sacktor *et al.* [25, 26] measured *in vivo* concentrations of respiration metabolites in the flying muscle of a certain insect, when it suddenly went from rest to its state of maximum activity, involving a 100 fold increase in ATP flux. They obtained data corresponding to a continuous flying period of one hour, which included transient behaviour and the onset of a new steady state. According to their results, such an enormous increment in reaction velocity was achieved with fractional concentration changes of order 10% between these two steady states. As they did not measure equilibrium concentrations, we cannot calculate ΔG_0 from their data, but we may assume that its fractional change was small too, because it is a smooth function of concentrations. Hence in the following approximate analysis we neglect this change of ΔG_0.

One can then write the power as

$$(5) \qquad P \simeq \eta f_1 (1 - \eta),$$

where the relationship between f and f_1 is clear from eqs. (4) and (5). This functional structure of the power, $P \sim \eta v$, will be very important for the rest of our argument.

We do not know exactly the reaction velocity v in terms of concentrations, and much less so as a function of efficiency, for an enzymatic chain of reactions, and this information is indispensable to proceed along the lines suggested here. This rules out detailed conclusions on ATP synthesis, but, as we will see, much can be learned from an approximate treatment. Our starting point is the reaction velocity for a single reaction in the uncatalyzed case [27]:

$$v = v_{mf}(1 - \exp[-A/RT]), \tag{6}$$

where v_{mf} is the maximum forward reaction velocity and R the gas constant. When v_{mf} and ΔG_0 are fixed, *i.e.* when the resulting power P becomes a function only of η, it turns out to be maximal for an η between 0.5 and 1, whose precise value grows with the magnitude of ΔG_0 (cf. appendix A). This resembles the experimental information mentioned earlier about the efficiency in glycolysis and respiration under physiological conditions. For a single *enzymatic* reaction v is a ratio of polynomials in the individual concentrations involved [28], which sounds rather far from an exponential dependence on the affinity alone, so no similar conclusion to the uncatalyzed case would appear possible. Nevertheless, based on the work of Savageau [29, 30] on biochemical systems, it will be argued (cf. appendix B) that the reaction velocity for an enzymatic chain can be approximately written as

$$v = v_{mf}(1 - \exp[-bA/RT]), \tag{7}$$

where b is a positive parameter that contains the global effect of enzymes. The convenient properties of the resulting power P are not changed by the presence of b (cf. appendix A): it still has its maximum for an η greater than 0.5, whose specific value grows with $|\Delta G_0|$ and b.

As the efficiency $\eta = -\Delta G_1/\Delta G_0$ is a smooth function of concentrations, it follows from the work of Sacktor *et al.* mentioned above that it changes little (say by about 10%, the same as the fractional change in concentrations) within the physiological range of respiration velocities. Hence, using eq. (7) one obtains a v *vs.* η curve like that sketched in fig. 1. From eq. (5) for the power, $P \simeq \eta v$, a graph similar to that in fig. 2 results.

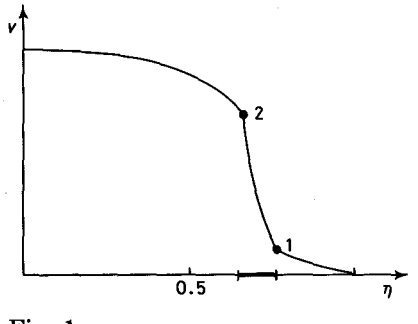

Fig. 1.

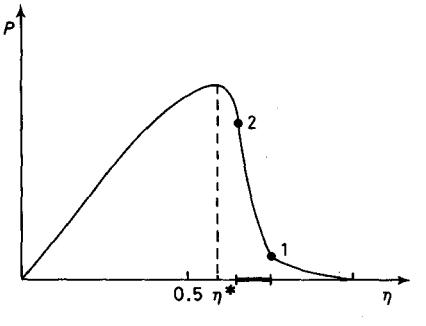

Fig. 2.

Fig. 1. – Sketch of reaction speed v *vs.* efficiency η for respiration, an extrapolation from experimental points 1 and 2 according to eq. (7) in the text. Thick horizontal bar indicates physiological range. From the data of Sacktor *et al.* [25, 26], $v_2 \simeq 100 v_1$.

Fig. 2. – Graph of power *vs.* efficiency. The power $P \sim \eta v$, so it is zero for $\eta = 0$ and $\eta = 1$ and peaks between these two points, in the region $\eta \geqslant 0.5$ (cf. appendix A).

2. – Discussion.

Strictly speaking, it has only been shown (with nontrivial gaps in the argument) that, if concentrations change little within the physiological range, then the power has its maximum for an efficiency greater than 0.5, whose precise value grows with the total free energy fall in the process and with the magnitude of a certain parameter that contains the overall effect of enzymes. Comparison with our experimental information on ATP synthesis, that takes place in glycolysis at $\eta \simeq 0.53$ with $|\Delta G_0| \sim 50$ kcal/mol, and in respiration at $\eta \simeq 0.7$ with $|\Delta G_0| \sim 700$ kcal/mol, led to the proposal that ATP synthesis takes place in both cases close to the regime of maximum power output. The fitness parameter we were looking for in this metabolical pathway would be b: from eq. (7) and the foregoing analysis one can see that, the larger it becomes, the farther the maximal power efficiency η^* moves to the right in fig. 2, and the sharper the curve becomes, so the closer η^* gets to the physiological range of efficiencies. Hence, with respect to ATP synthesis, the fittest individuals according to Darwin's principle would be those characterized by the largest values of b in their population: they would be both the fastest and the most efficient to produce ATP molecules. The accomplishment of such a double feat in performance is the more remarkable, given the opposite roles that efficiency and power play in classical thermodynamics. One of the useful lessons of finite-time thermodynamics is precisely that, although such contrasting behaviour is the one most frequently encountered, it by no means is the only one possible.

Our velocity *vs.* efficiency curve in fig. 1 is an extrapolation based on eq. (7) from just two experimental points, albeit rather important ones, for they correspond to the limits of ATP flux. The shape of the curve that joins them and continues up to $\eta = 1$ (that is, $A = 0$) finds added support from a kinetic model for an autocatalytic chemical system [31]. For respiration, getting points between 1 and 2 in fig. 1 involves no difficulty with matters of principle. But collecting data to the left of point 2 might require an experiment in vitro. In the case of glycolysis the experimental problem increases, because in vivo measurements are usually performed on erythrocytes, whose energetic needs are essentially constant, so their physiological range of ATP fluxes reduces to a point. One could construct a v *vs.* affinity curve of steady states using erythrocytes from different species, as ATP flux varies by about an order of magnitude when certain common animals (mice, goats, men) are considered [32]. A new, perhaps relevant feature in such case is that the enzymes involved would not be identical.

Based on a kinetic model for glycolysis, Rapoport *et al.* [32] obtain a graph of ATP flux *vs.* ATP concentration for erythrocytes from several species, and observe that the *in vivo* point mentioned in the former section is in each case such that ATP (consumption) velocity is maximal at the experimental value of its concentration. From this they conclude that erythrocytes function maximizing *efficiency* in ATP production. Such conclusion is not warranted by their evidence, as the necessary analysis based on *free energy* gains and losses is not carried out. It is interesting to contrast their kinetic approach with our thermodynamic one with respect to the number of phenomenological parameters involved: twelve in their case, compared with just one here.

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APPENDIX A

For $v = v_{mf}(1 - \exp[-A/RT])$, using $A = -(\Delta G_0 + \Delta G_1)$ and $\eta = -(\Delta G_1/\Delta G_0)$, the power can be written as $P = -\Delta G_0 \eta[1 - \exp[(\Delta G_0/RT)(1-\eta)]]$. Hence, for approximately constant ΔG_0, the extrema of P are those of $F(\eta) = \eta[1 - \exp[-\alpha(1 - -\eta)]]$, with $\alpha > 0$. At an extremum η^*, $(dF/d\eta)_{\eta=\eta^*} = 0$ leads to

$$\alpha\eta^* = \exp[\alpha(1-\eta^*)] - 1. \tag{8}$$

It is easily proved that the solution to this equation does correspond to a maximum for $\alpha > 0$. To show that η^* is greater than 0.5 and grows with α, one first verifies that eq. (8) has the solution $\eta^* = 0.5$ when $\alpha \to 0$, then calculates $d\eta^*/d\alpha$ from the same equation and proves this derivative to be positive for $\alpha > 0$.

APPENDIX B

According to Savageau's method for catalyzed chemical systems [29], one assumes a «power law» parametrization for the reaction velocities of its single intermediate reactions (cf. fig. 3):

$$v_I = \vec{v} - \overleftarrow{v} = k_l' \prod_i y_{il}^{g_i'} - k_r' \prod_i y_{jr}^{h_j'}, \tag{9}$$

where $\vec{v}(\overleftarrow{v})$ is the flux from left to right (right to left), $y_l(y_r)$ are concentrations on the left (right) hand side of the reaction (fig. 3*b*), and k_l', k_r', g_i' and h_j' are phenomenological parameters that generalize the kinetic constants and stoichiometric coefficients of the uncatalyzed case. This approximate functional form stems from the well-known speed for individual catalyzed reactions in terms of ratios of polynomials in the concentrations involved [28].

It is possible to divide a system of reactions into subsystems, and write power law expressions for the corresponding velocities [30]. This process of aggregation can be continued until a power law parametrization results for the overall reaction velocity (cf. fig. 3*a*)

$$v = k_l \prod_i x_{il}^{g_i} - k_r \prod_j x_{jr}^{h_j}. \tag{10}$$

We now make a conjecture beyond Savageau's prescription: we know that g_i and h_j reduce to the corresponding stoichiometric coefficients ν_n when enzyme concentrations go to zero (uncatalyzed case); so we assume that, when the enzymes are «turned on», their global effect is to change these coefficients in approximately

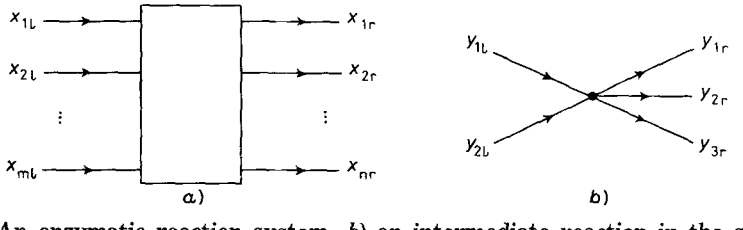

Fig. 3. – *a*) An enzymatic reaction system, *b*) an intermediate reaction in the system.

the same way, *i.e.* we propose

$$g_i \simeq b\nu_i, \qquad h_j \simeq b\nu_j, \tag{11}$$

where b depends on enzyme concentrations and reduces to unity when they are zero. This allows writing v in the desired form:

$$v = v_{\mathrm{mf}}(1 - \exp[-bA/RT]), \tag{12}$$

with $v_{\mathrm{mf}} = k_1 \prod_i x_{\mathrm{il}}^{b\nu_i}$ and A the affinity: $A = RT\left[\ln \prod_i (x_{\mathrm{il}}/x_{\mathrm{il},e})^{\nu_i} - \ln \prod_j (x_{j\mathrm{r}}/x_{j\mathrm{r},e})^{\nu_j}\right]$, where $\{x_{mn,e}\}$ denotes the equilibrium value of the appropriate concentration. The condition $v = 0$ at equilibrium was employed to eliminate $k_{\mathrm{r}}/k_{\mathrm{l}}$.

REFERENCES

[1] C. H. WADDINGTON: *The Evolution of an Evolutionist* (Cornell University Press, Ithaca, N.Y., 1975).
[2] B. C. GOODWIN: *J. Theor. Biol.*, **97**, 43 (1982).
[3] M.-W. HO: in *Beyond neo-Darwinism*, edited by M.-W. HO and P. S. SAUNDERS (Academic Press, London, 1984).
[4] M. EIGEN and P. SCHUSTER: *The Hypercycle* (Springer-Verlag, Berlin, 1979).
[5] J. S. WICKEN: *J. Theor. Biol.*, **117**, 545 (1985).
[6] E. SZALTMÁRY and L. DEMETER: *J. Theor. Biol.*, **128**, 463 (1987).
[7] T. DOBZHANSKY: *Genetics and the Origin of Species* (Columbia University Press, New York, N.Y., 1951).
[8] R. MACARTHUR: *Proc. Natl. Acad. Sci. U.S.A.*, **48**, 1893 (1962).
[9] R. C. LEWONTIN: *J. Theor. Biol.*, **1**, 382 (1961).
[10] B. HANNON: *J. Theor. Biol.*, **80**, 271 (1979).
[11] J. S. WICKEN: *J. Theor. Biol.*, **87**, 9 (1980).
[12] J. E. LOVELOCK and L. MARGULIS: *Tellus*, **26**, 1 (1974).
[13] R. J. CHARLSON, J. E. LOVELOCK, M. O. ANDREAE and S. G. WARREN: *Nature (London)*, **326**, 655 (1987).
[14] GOVINDJEE (Editor): *Photosynthesis: Energy Conversion by Plants and Bacteria* (Academic Press, New York, N.Y., 1982).
[15] E. E. SEL'KOV: *Eur. J. Biochim.*, **4**, 79 (1968).
[16] J. ROSS and M. SCHELL: *Ann. Rev. Biophys. Biophys. Chem.*, **16**, 401 (1987).
[17] G. NICOLIS and I. PRIGOGINE: *Self-Organization in Non-Equilibrium Systems* (Wiley Interscience, New York, N.Y., 1977).
[18] F. L. CURZON and B. AHLBORN: *Am. J. Phys.*, **43**, 22 (1975).
[19] P. SALAMON, B. ANDRESEN and S. BERRY: *Phys. Rev. A.*, **15**, 2094 (1977).
[20] M. H. RUBIN: *Phys. Rev. A*, **22**, 1741 (1980).
[21] P. SALAMON, A. NITZAN, B. ANDRESEN and S. BERRY: *Phys. Rev. A*, **21**, 2115 (1980).
[22] B. ANDRESEN, M. H. RUBIN and R. S. BERRY *J. Phys. Chem.*, **82**, 2704 (1983).
[23] S. MINAKAMI and H. YOSHIKAWA: *Biochem. Biophys. Res. Communs.*, **18**, 345 (1965).
[24] A. L. LEHNINGER: *Principles of Biochemistry* (Worth Publisher, New York, N.Y., 1982), p. 498.
[25] B. SACKTOR and E. WORMSER-SHAVIT: *J. Biol. Chem.*, **241**, 624 (1966).
[26] B. SACKTOR and E. C. HURLBUT: *J. Biol. Chem.*, **241**, 632 (1966).

[27] I. PRIGOGINE: *Thermodynamics of Irreversible Processes* (John Wiley & Sons, New York, N.Y., 1961).
[28] M. A. SAVAGEAU: *J. Theor. Biol.*, **25**, 365 (1969).
[29] M. A. SAVAGEAU: *J. Theor. Biol.*, **25**, 370 (1969).
[30] M. A. SAVAGEAU: *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 5413 (1979).
[31] P. H. RICHTER, P. REHMUS and J. ROSS: *Prog. Theor. Phys.*, **66**, 385 (1980).
[32] T. A. RAPAPORT, R. HEINRICH and S. M. RAPAPORT: *Biochem. J.*, **154**, 449 (1976).