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Chapter 7

EFFICIENCY AND POWER STRATEGIES UNDER HYPOXIA. IS LOW EFFICIENCY AT HIGH GLYCOLYTIC ATP PRODUCTION A PARADOX?

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I. INTRODUCTION

A. HIGH EFFICIENCY IS ADAPTIVE

"Efficiency and speed characterize the time value of the modern age".[11] Processes should be efficient, fast, and powerful. The term *efficiency* is used in common and scientific language with different meanings, and correspondingly vague definitions may lead to confusion. In bioenergetics, efficiency is strictly defined as the output/input power ratio, that is the fraction of useful energy (exergy) converted into work. By increasing efficiency, the invested exergy can be reduced at constant gain. As such, efficiency is an eminent resource which remains poorly exploited in present technology and society. Today, high efficiency is valued as an achievement and goal. In physiology and ecology high efficiency is considered to be adaptive.[2] Why, then, are efficiencies of technologically designed and biologically evolved processes limited?

B. HIGH POWER-LOW EFFICIENCY: AN EVOLUTIONARY PARADOX?

Phosphorylation of adenosinediphosphate (ADP) to adenosinetriphosphate (ATP) ranks among the most important energy transformations in the biosphere. In aerobic and anaerobic heterotrophic systems, ATP production is energetically driven by exergonic catabolic reactions at the expense of reduced organic substrates. Glycolysis to lactate yields 3 mol ATP per mol glycosyl-unit,[3] which is merely 8.1% of the aerobic coupling stoichiometry of 37 mol ATP per unit glycogen. At an efficiency of Gibbs energy conversion of c. 65%, lactate production represents a low efficiency pathway.[4]

The Gibbs-energy efficiencies in the high power mode are nearly identical in respiratory and glycolytic ATP production in skeletal muscle,[5] despite the more than tenfold difference of the ATP/glycogen stoichiometries. The low efficiency in these two contrasting high power pathways of aerobic and anoxic ATP production indicate the functional importance of optimizing (in contrast to maximizing) efficiency.

When the succinate-propionate-acetate pathways were discovered in euryoxic invertebrates,[2,6] the interpretation in terms of biochemical adaptation was readily at hand: the stoichiometric ATP/glycogen ratios are up to 2.1-fold higher compared to the lactate pathway. Efficiencies increase to >80%.[4] Obviously, high ATP stoichiometry and efficiency are of selective advantage under anoxia when power is low and energy is limited. This familiar explanation of increased efficiency is important, but it addresses only half of the problem: why are efficiencies of ATP production different in various pathways? Is there a functional role for low efficiency? Or is low efficiency at high glycolytic ATP and lactate production a paradox?

The notion of "increased" efficiency reflects the historical fact that the lactate pathway was discovered first. Decades later, the more efficient succinate-acetate-propionate pathways were investigated — hence "higher" efficiencies. Consider a reversed time course in scientific discovery: if Meyerhof would have worked on anoxic mussels (*Mytilus*) instead of frog muscles, he might have discovered succinate production. Then the stoichiometry of 4.73 mol ATP per mol glycosyl-unit in the succinate pathway[4,7] would serve now as the anoxic reference stoichiometry, observed in many invertebrates under environmentally induced *passive* anoxia. Subsequently in our imaginary history of comparative biochemistry, lactate production would be discovered with a "lower" ATP stoichiometry, leading to the question: what is the advantage of the "decreased" anoxic ATP gain at high power output? If high efficiency is adaptive, is therefore low efficiency maladaptive?

The high efficiency pathways are widespread in passive invertebrates and may well represent a phylogenetically early character. Diminution of efficiency appears to be an

evolutionary paradox, considering the low efficiency of ATP production in the high power lactate pathway operating in specialized skeletal muscle under extreme work loads. Why are the biochemically efficient pathways with the highest ATP yield not exploited under active anoxia, when ATP demand is highest?

This apparent evolutionary paradox can be resolved on the basis of nonequilibrium thermodynamics (*ergodynamics*). Classical thermodynamics defines maximum efficiency but is insufficient for explaining optimization strategies of energy transformation. An introduction to the relevant physicochemical parameters will (1) clarify the controversial notion of efficiency in the context of metabolic energy conversion. The biochemical ATP-stoichiometry and flux ratios are an important component of efficiency of catabolic ATP production. In addition, efficiency depends on the chemical potentials and forces calculated as the molar Gibbs energy changes under typical cellular conditions. (2) This leads to a discussion of the control of flux from the perspective of efficiency and coupling. ATP stoichiometries per se are insufficient for solving the paradox of the low efficiency lactate pathway. (3) The discussion of optimum efficiencies of energy transformation will provide the framework for a quantitative solution of the apparent paradox on the evolution of inefficient pathways for meeting high output demands. Maximization of power and efficiency of ATP production are mutually exclusive. An outline of ergodynamic principles in metabolic energy conversion in the catabolic-anabolic energy chain yields a quantitative concept for assessing the economical nature of metabolic design and the balance of ATP demand and ATP supply. This opens new insights into the network of biochemical adaptation, particularly relevant for hypoxia and anoxia under which conditions the extremes of high and low metabolic power are observed.

II. METABOLIC EFFICIENCY AND POWER IN BIOENERGETICS

The relation between efficiency and physiological adaptation is addressed in many contexts. Even the "lactate paradox" described in high altitude physiology may be fundamentally connected to (aerobic) efficiency.[8] Energy transformation between coupled input and output processes requires efficiency. Ergodynamic efficiency is the fraction of exergy obtained in the output (driven) process relative to the exergy invested in the input (driving) process. Efficiency is a function of the relation between input and output *forces* and of the tightness of coupling between the input and output *fluxes*. Power (Gibbs energy change per unit of time) is the product of flux and force. Complementary to the fluxes, the ergodynamic forces are quantified as a basis for calculating the power and efficiency of metabolic energy transformations.

In bioenergetics the fluxes are the rates of chemical reactions, ion fluxes across membranes, electric current densities, or velocities of mechanical movement in actin-myocin interactions. The corresponding forces are the molar Gibbs energies of reaction determined at cellular conditions, the chemical and electric potential differences across membranes, and the mechanical forces of movement. For instance, consider catabolic oxygen flux or the rate of oxygen consumption as the input flux, and the flux of ATP production as the output flux. The output/input flux ratio is the experimental ATP/O_2 ratio which is an important component of metabolic efficiency. In the biochemical literature the flux ratio is frequently even considered to be *the* expression of efficiency. However, it must be recognized that bioenergetic efficiencies are not merely molar ratios but express Gibbs energy ratios or power ratios. The catabolic power input is the product of oxygen flux and input force. The power output of ATP production is the ATP flux times the output force. The corresponding input and

output forces are the molar Gibbs energy of catabolic oxygen consumption and the molar Gibbs energy of phosphorylation. The efficiency can be regulated by changes in the flux ratio (e.g., uncoupling) and by changes in the force ratio (e.g., changes of the phosphorylation potential). Catabolic efficiency is functionally important in terms of the output flux of ATP production and in terms of the output force for maintaining a high phosphorylation potential as required for biochemical and physiological purposes.

A. AN UPPER LIMIT OF EFFICIENCY AND TIME AS A RESOURCE

Darwin's theory of evolution establishes a historical perspective in the natural sciences by its focus on selection as a "driving force" of biological change in time. Similarly, an emphasis on time is introduced into "finite time thermodynamics" by analysis of the causal relation between ergodynamic forces and fluxes in irreversible processes.[9] The time-exergy framework interrelates a variety of theories on dynamic systems, such as evolutionary theory, economics, technological engineering, ergodynamics, information theory, cybernetics, and chaos theory. In an interdisciplinary field with rapid transitions from conventional to mundane terminology, it is particularly important to evaluate traditional concepts and definitions, to be able to link them with specific contemporary developments.

The second law of thermodynamics, which may be called the *dissipation or entropy law*, sets the absolute theoretical limit on the maximum efficiency at 1.0. The second law provides a rigorous definition of efficiency in terms of "high grade energy" (exergy, useful work free energy, or Gibbs energy). Emphasis is placed on the distinction between energy (first law of thermodynamics) and exergy introduced by the second law. This implies a consideration of entropy (bound energy)[10] associated with the energy. Exergy is exclusively that quality of energy which can theoretically be converted into mechanical work. Exergy can be dissipated and is then irreversibly lost, whereas energy is always conserved in the transformation between various forms and qualities of energy and in the flow of energy between a system and its surroundings. In chemical thermodynamics, the difference between enthalpy, ΔH, and Gibbs energy, ΔG, reflects the distinction between energy and exergy. In turn, thermodynamic or thermal efficiency, η, is based on energy, whereas *erg*odynamic or power efficiency, ϵ, is always related to ex*ergy* (erg = work). Ergodynamic efficiency is the fraction of exergy converted into work, with a maximum value of one when no exergy (Gibbs energy) is dissipated.[11]

Actual ergodynamic efficiencies in biological Gibbs energy transformation are commonly well below unity. Classical thermodynamics defines the maximum theoretical limit of efficiency, but cannot rationalize the extent by which a process falls short of maximum efficiency.[12] Concepts of nonequilibrium thermodynamics (ergodynamics) address this important question in an evolutionary context, by contrasting *exergy and time* as limiting resources. High efficiency saves exergy, at the cost of time. High power output (= work per unit of time) saves time, at the expense and dissipation of exergy, leading to low efficiency. As a practical example consider the *economy speed limit* when driving a car. Different environmental conditions and functional demands exert specific selective pressures with divergent emphasis on *efficient* utilization of exergy in economy strategy or *effective* utilization of time in power strategy.[5]

The exclusion of high power and maximum efficiency is at its limit related to the concept of reversibility of classical thermodynamics. As the efficiency approaches 100%, the coupled process becomes fully reversible. Simultaneously, the net flux approaches zero, since only at zero net flux (velocity) all frictional, dissipative effects are annihilated. 100% efficiency causes coupled processes to stop. This can be visualized on a balance in *equilibrium* ("*equal measures of weight*") when the opposing gravitational forces counterbalance each other: there is no falling or lifting of balanced weights.

Optimum efficiency depends basically on two aspects:

1. on the relation between efficiency and power output. Maximum values of both cannot be achieved simultaneously. The relation between power and efficiency is a complex function of system design (morphology, physiology and biochemistry).
2. on the relative fitness values of the resources, exergy and time. Increased power output saves time but costs exergy. The exergy and time values are set by the interactions with the environment (behavior, ecology). In commerce, exergy and time are embodied in a common currency: money. A common currency is the essence of optimization theory and tradeoff models in evolutionary physiology and ecology.[13] Fitness is the obvious evolutionary criterion of merit. But fitness, as a currency of evolution, is difficult to measure. It is the result of optimization of survival, fecundity, and generation time. Fitness depends fundamentally on the balanced investment of exergy and time, on optimized metabolic efficiency and power.[14]

Maximum metabolic power output[15] is an oversimplification as a general criterion of "thermodynamic optimality" which would apply only under conditions of sustained effluence. Owing to overexploitation of resources and diminution of carrying capacity, maximum power strategy (*r*-selection) converts into poor fitness measured as the propagation of this strategy through subsequent generations in a densely populated environment.[5] *K*-selection under resource limitation does not produce phenotypes with maximum metabolic power, else the biosphere would consist of ever faster biological racing machines.[14] An understanding of the physicochemical basis and the physiological trade-offs of metabolic efficiency is essential for a firm scientific establishment of the concept of metabolic adaptation.

B. FUNDAMENTAL COMPONENTS OF METABOLIC EFFICIENCY

1. Gibbs Energy and Power

The "definition of efficiency given by classical equilibrium thermodynamics is inadequate to furnish a result of practical interest for mitochondria" since it is "confined to the forces involved in the process of oxidative phosphorylation and neglects the flows".[16] The nonequilibrium thermodynamic formalism defining efficiency as a power ratio[17] is invoked for the imperative consideration of both forces and fluxes. The postulated limitation of classical thermodynamics to furnish an unequivocal definition of efficiency, however, is in remarkable contrast to the fundamental relation between efficiency and the second law (of classical thermodynamics). Consider the definition of efficiency, ϵ, as the output/input ratio of Gibbs energy (exergy) changes measured over a common time interval,

$$\epsilon = -\frac{d_{tr}G_{out}}{d_{tr}G_{in}} = -\frac{P_{out}}{P_{in}} \qquad (1)$$

Exergy transformation (tr), $d_{tr}G$, per unit of time, dt, is power (Equation 2). Therefore, exergy efficiency and power efficiency are identical. A conflict does not exist between the exergy efficiency of classical thermodynamics and power efficiency of nonequilibrium thermodynamics. Caution is required not to be misguided by inappropriate terminology.

Efficiency is a dimensionless quantity [$J \cdot J^{-1}$ or $W \cdot W^{-1}$], with a maximum of 1. In a completely uncoupled respiratory chain no ATP is produced (zero mitochondrial output flux) and the output Gibbs *energy* change, $d_{tr}G_{out}$, is zero. In this case, the efficiency of mitochondrial exergy conversion (Equation 1) is zero, independent of the output *force* measured by the phosphorylation potential.

Power [W = J · s^{-1}] is exergy [J] per unit of time [s],*

$$P = \frac{d_{tr}G}{dt} = J\,F \tag{2}$$

The definition of power commonly used in ergodynamics is the product of flux, J, and force, F (right-hand side of Equation 2). Importantly, metabolic power is not identical to metabolic flux. Catabolic oxygen flux is converted to catabolic power by multiplication by a force, the Gibbs energy change per mol O_2 consumed, approximately -480 kJ · mol^{-1} O_2. Correspondingly, mechanical power is not identical to speed. The forces are equally important. Metabolic power can be measured by direct calorimetry as heat dissipation per unit of time (heat flux) when catabolism is fully aerobic, but heat flux underestimates the catabolic power of anoxic pathways.[4] Again, the corresponding force must be considered to convert thermodynamic heat flux into ergodynamic power.[10] Muscle physiology apart, most studies on physiological and biochemical adaptations are confined to the fluxes.

2. Gibbs Energy and Force

Confinement to the forces and neglect of the fluxes is implied in a definition of efficiency if chemical forces rather than Gibbs energies are used in Equation 1. Then the critique of the definition of efficiency[16] appears to be correct. However, this neglects the distinction between Gibbs energy change, $d_{tr}G$, and force, F (Equation 2). The contrast is obscured in most textbooks by reference to the chemical *force* as molar Gibbs *energy*. The *molar* reaction Gibbs energy is the driving force of a reaction. Importantly, Equation 1 is *not* based on *molar* Gibbs energies. The Gibbs energy efficiency derived from classical thermodynamics does implicitly account for the fluxes. This view warrants careful explanation.

Force and Gibbs energy are contrasted as intensive and extensive properties, respectively (see footnote in Section II.B.1). The fundamental distinction between exergy and force is underscored at the level of *SI* units for mechanical force [J · m^{-1} = N] and electric force or voltage [J · C^{-1} = V]. Corresponding to the lack of clarity in the distinction between Gibbs energy and force, a separate unit for chemical force[10] is unfortunately not yet incorporated into the system of *SI* units.[18] Electric energy (exergy [J]) is force [J · C^{-1}] times the amount of electrons or charge [C] (electrical advancement). Gibbs energy (exergy [J]) is chemical force [J · mol^{-1}] times the amount of reacting substance [mol] (reaction advancement). Let the advancement of (electro)chemical reactions be $d_r\xi$ (mol per unit system size), such that any flux, J, is[11]

$$J = \frac{d_r\xi}{dt} \tag{3}$$

Then exergy transformation is the product of advancement, $d_r\xi$, and the corresponding force, F (Equation 4). The power of transformation, P_r, is flux times force (compare Equations 2 and 5),

$$d_rG = d_r\xi\,F \tag{4}$$

* *Extensive quantities*, such as power, P [W], Gibbs energy of reaction, d_rG [J] or the amount of substance B in a reaction, d_rn_B [mol], may be expressed *per unit of system size* (volume or biomass) throughout the text, without introducing a different name or symbol. Strictly, power per volume should be indicated as P_V. The size of biological systems is frequently quantified in terms of dry biomass. Then the units of the size-specific quantities P, d_rG, and d_rn_B are [W · g^{-1}], [J · g^{-1}], and [mol · g^{-1}].

$$P_r = \frac{d_r\xi}{dt} F \tag{5}$$

In catabolic energy transformation, the Gibbs energy output in the phosphorylation reaction, d_pG (Equation 1; see footnote in Section II.B.1), is calculated by multiplication of (1) the *amount* of ATP produced in substrate level phosphorylation and electron transport, $d_r\xi = d_pn_{ATP}$, and (2) the output *Gibbs force* of phosphorylation, $F = \Delta_pG_{ATP}$ [kJ · mol^{-1} ATP] (Equation 4),

$$d_pG = d_pn_{ATP}\,\Delta_pG_{ATP} \tag{6}$$

To avoid confusion between Gibbs energy change, d_pG, and force, Δ_pG_{ATP}, the latter should be termed *Gibbs force*.[10,11] This is more appropriate than the conventional term *molar reaction Gibbs energy*. The output force is the exergy per mol ATP produced. The Gibbs force is the partial derivative of Gibbs energy ($F = \partial G/\partial_r\xi$; Equation 4), at constant temperature and pressure,

$$\Delta_pG_{ATP} = \left(\frac{\partial G}{\partial_p n_{ATP}}\right)_{T,p} \tag{7}$$

In practice, the Gibbs force for cellular conditions is calculated from the standard Gibbs force (equilibrium constant) and the phosphorylation potential (mass action ratio),

$$\Delta_pG_{ATP} = \Delta_pG'^{o}_{ATP} + RT \ln\left(\frac{[ATP]\,c^o}{[ADP][P_i]}\right) \tag{8}$$

[ATP], [ADP], and [P_i] are the sum concentrations of adenosine triphosphate, adenosine diphosphate, and inorganic phosphate (including protonized and Mg-complexed species). c^o is the standard concentration (1 mol · dm^{-3}), $\Delta_pG'^{o}_{ATP}$, is the standard Gibbs force at specified pH, magnesium activity, temperature, and unit activity of ATP, ADP, and P_i (Figure 1). The Gibbs force of phosphorylation is routinely used in ^{31}P-NMR studies for calculating free ADP concentrations from Equation 8, assuming equilibrium between the creatine kinase reaction and phosphorylation of ADP.

Depending on the equilibrium constants reported in the literature since 1969, the calculated standard Gibbs force varies by more than ±2 kJ · mol^{-1}. $\Delta_pG'^{o}_{ATP}$ increases with pH above pH 6.5 and increases with decreasing Mg^{2+} activity in the range of 10 to 0.001 mmol · dm^{-3} (pMg of 2 to 6; Figure 1). The temperature dependence is comparatively small, at an increase of 1 kJ · mol^{-1} when the temperature is changed from 15 to 37°C. At 2 mmol · dm^{-3} Mg^{2+} activity (pMg = 2.7), $\Delta_pG'^{o}_{ATP}$, changes only slightly between pH 6.5 and 7.0, from 32.8 to 33.6 kJ · mol^{-1} ATP (Figure 1; square and circle, referring to cellular states I and II, see below).

Changes of the cellular ATP/ADP ratio and inorganic phosphate exert a strong effect on the actual output force. The concentration dependent term (the additive term in Equation 8 on the right) increases from 21 to 28.5 kJ · mol^{-1} with an ATP/ADP ratio increasing from 5 to 100 at 1 mmol · dm^{-3} P_i. This yields Gibbs forces of phosphorylation in the range of 55 (state I) to 62 kJ · mol^{-1} at pH 7. Under anoxia, ATP/ADP ratios and pH values tend to drop simultaneously, and anoxic Gibbs forces of phosphorylation decline (state II: 48 kJ · mol^{-1} at an ATP/ADP ratio of 1.5, 3 mmol · dm^{-1} P_i and pH 6.5).

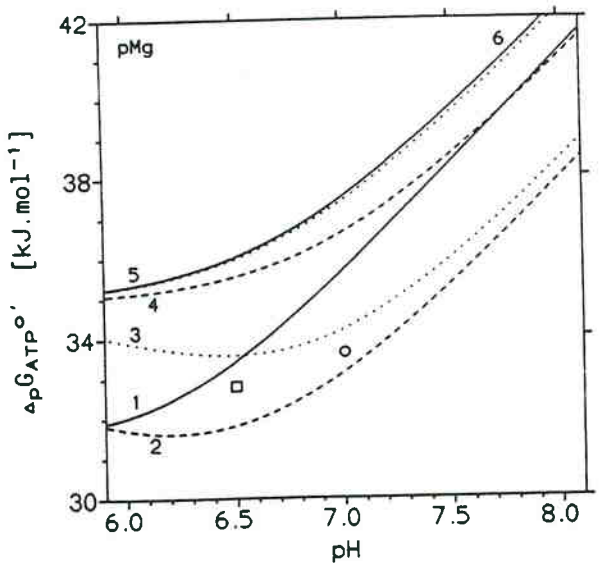

FIGURE 1. Standard Gibbs force of phosphorylation of ADP to ATP, $\Delta_pG'^{o}_{ATP}$ [kJ · mol^{-1}], at sum concentration of ATP, ADP, and P_i of 1 mol · dm^{-3}, as a function of pH and pMg (pMg = $-\log[Mg^{2+}]$). pMg values (numbers) correspond to free Mg^{2+} activities of 0.1 mmol · dm^{-3} (pMg = 1) to 1 μmol · dm^{-3} (pMg = 6). For the reaction

$$ADP^{3-} + HPO_4^{2-} + H^+ = ATP^{4-} + H_2O$$

the standard Gibbs force at 25°C (RT = 2.479 kJ · mol^{-1}) is[41]

$$\Delta_pG^o_{ATP} = -RT \ln K = -3.4 \text{ kJ} \cdot \text{mol}^{-1}$$

The equilibrium constants for the binding of H^+, Mg^{2+}, and Ca^{2+} are from References 41 and 42. Calculations are for pCa = 6 and ionic strength of 1 to 2 mmol · dm^{-3}. The circle and square are the values at pMg = 2.7 corresponding to states I and II (see text).

3. Force, Advancement of Reaction, and Flux

The input flux of aerobic metabolism is routinely measured as catabolic oxygen flux. The corresponding Gibbs force, $\Delta_kG_{O_2}$, is the partial derivative of Gibbs energy per unit oxygen consumed in the catabolic reaction k. Consider catabolism of glycogen (k) and phosphorylation of ADP (p) as the input and output reactions,

$$\text{p, } \nu_{ATP} = 1: \qquad 0 = -\text{ADP} - P_i + \text{ATP} + H_2O \tag{9.p}$$

$$\text{k, } \nu_{O_2} = -1: \qquad 0 = -1/6 \text{ Glyc} - O_2 + CO_2 + 5/6\ H_2O \tag{9.k}$$

The Gibbs force per glycosyl unit, Δ_kG_{Glyc}, is -2800 to -2900 kJ · mol^{-1} Glyc in aerobic respiration. Division by 6 yields $\Delta_kG_{O_2}$ (Equation 9.k) of -470 to -480 kJ · mol^{-1} O_2. For quantification of fluxes and forces not only the *type* of reaction but the stoichiometric *form* must be defined in terms of stoichiometric numbers, ν_i. These are the numbers preceding the symbols for each substance in Equation 9, 1 and -1 in most cases. ν_i is positive for products and negative for substrates.

A general definition of Gibbs force requires reference to the stoichiometry and particularly to the advancement of reaction, $d_r\xi$.[18] The Gibbs force of a defined reaction r, Δ_rG_B [kJ · mol^{-1} B], is the partial derivative of Gibbs energy per advancement, at constant temperature and pressure (compare Equation 4),

$$\Delta_rG_B = \frac{\partial G}{\partial_r\xi_B} = \nu_i \frac{\partial G}{\partial_r n_i}; \qquad |\nu_B| = 1 \tag{10}$$

The substance with unit stoichiometric number is explicitly given by subscript B, such that $d_r\xi_B = -d_r n_B$ for substrates, and $d_r\xi_B = d_r n_B$ for products.

$$d_r\xi_B = \frac{1}{\nu_i} d_r n_i ; \qquad |\nu_B| = 1 \tag{11}$$

For example, $d_k\xi_{Glyc}$ refers to the stoichiometric form $0 = -Glyc - 6\ O_2 + 6\ CO_2 + 5\ H_2O$, where $\nu_{Glyc} = -1$. $d_k\xi_{O_2}$ refers to the same type of reaction k in the form of Equation 9.k.

Equations 9.p and 9.k define the stoichiometries for ATP flux, J_{ATP}, and catabolic oxygen flux, J_{O_2}. Chemical flux is the time derivative of the advancement (Equation 3; mol $\cdot$ s^{-1} per unit system size),*

$$J_{ATP} = \frac{d_p\xi_{ATP}}{dt} = \frac{1}{\nu_i}\frac{d_p n_i}{dt} ; \qquad \nu_{ATP} = 1 \tag{12.p}$$

$$J_{O_2} = \frac{d_k\xi_{O_2}}{dt} = -\frac{d_k n_{O_2}}{dt} ; \qquad \nu_{O_2} = -1 \tag{12.k}$$

In respiration, $d_k n_{O_2}$ is a negative quantity since oxygen is removed. In contrast, respiratory oxygen flux and the advancement of the catabolic reaction are positive if oxygen is consumed. The negative sign in Equation 12.k takes account of the stoichiometric number of oxygen (Equation 9.k). The subscript k indicates the chemical transformation of oxygen in the reaction, in contrast to the change of oxygen in the system, dn_{O_2}. The need for this distinction stems from the higher complexity of open compared to closed systems. Open flow respirometers[19] offer the advantage of steady state measurement of oxygen flux at constant oxygen concentration. At steady state the concentration change is zero ($dn_{O_2} = 0$), irrespective of the magnitude of the chemical fluxes ($d_k n_{O_2} < 0$). No information on flux is obtained from measurement of cellular ADP and ATP concentrations at steady state of the adenylate levels. Therefore, accurate experimental evaluation of the ATP flux presents a problem in living systems.

The distinction between $d_r n_i$ (Equation 11) and dn_i (equivalent to dc_i if all extensive quantities are expressed per unit volume) is particularly important when developing a form of Equation 10 which is practical for actual calculations of the Gibbs force of catabolic reactions under cellular conditions. At constant temperature, pressure, and defined concentrations (activities), a metabolite i has a defined chemical potential, μ_i, which is the partial molar derivative of Gibbs energy [kJ $\cdot$ mol^{-1} i],

$$\mu_i = \left(\frac{\partial G}{\partial n_i}\right)_{T,p,n_j \neq n_i} \tag{13}$$

The concentrations of all other substances j do not change for calculating the chemical potential (partial molar Gibbs energy). In Equation 10, however, the partial derivative of Gibbs energy per advancement indicates an infinitesimally small change not only of a particular metabolite i. Simultaneously and in stoichiometric proportion, substrates are removed and products are generated in the chemical transformation r. Therefore, Equation 10

* Without implicit reference to the unit system size (volume, V), the time derivative of the advancement is the flow of reaction, $I_B = J_B V$ [mol $\cdot$ s^{-1}]. See also footnote in Section II.B.1.

TABLE 1
Standard Chemical Potentials, μ_i° (Equation 15), Expressed as Molar Gibbs Energies of Formation, $\Delta_f G_i^\circ$ [kJ · mol^{-1}], for Calculating Gibbs Forces of Reaction at Standard State and 25°C (298.15°K)[a]

Substance, *i*	Formula	State	$\mu_i^\circ = \Delta_f G_i^\circ$	Comment
Oxygen	O_2	g; 100 kPa	0.0	Definition
		aq; 1 mol · dm^{-3}	16.56	See note b
Hydrogen ion	H^+	aq; pH 0	0.0	Definition
		aq; pH 7	−39.954	$-RT$ ln(10) pH
Water	H_2O	l	−237.178	Ref. 37
Carbon dioxide	CO_2	g; 100 kPa	−394.40	Ref. 39[c]
		aq	−386.00	Ref. 39
Carbonic acid	H_2CO_3	aq	−623.18	See note d
Bicarbonate ion	HCO_3^-	aq	−586.94	Ref. 39
α,β-D-Glucose	$C_6H_{12}O_6$	aq	−917.0	Ref. 37
Glycosyl-unit	$C_6H_{10}O_5$	aq	−661.8	Ref. 40[e]
L-Lactate ion	$C_3H_5O_3^-$	aq	−516.7	Ref. 37
Ethanol	C_2H_6O	aq	−181.0	Ref. 37
Succinate ion	$C_4H_4O_4^{2-}$	aq	−690.4	Ref. 37
Propionate ion	$C_3H_5O_2^-$	aq	−361.1	Ref. 38
Acetate ion	$C_2H_3O_2^-$	aq	−376.9	Ref. 37

Note: aq — aqueous dilute state (1 mol · dm^{-3}); l — liquid; g — gaseous (100 kPa = 750.06 mmHg); 4.184 J/cal. For extended compilations see References 37 and 38.

[a] The standard Gibbs force of a reaction is related to the equilibrium constant, K (compare Equation 14),

$$\Delta_r G_B^\circ = \Sigma \nu_i \mu_i^\circ = -RT \ln K$$

[b] The solubility of oxygen in pure water at a standard pressure of $p_{O_2}^\circ$ = 100 kPa is 1.256 mmol · dm^{-3} at 25°C. At the standard concentration of 1 mol · dm^{-3}, therefore, the standard molar Gibbs energy of formation of aqueous oxygen is

$$\Delta_f G_{O_2}^\circ = -RT \ln(0.001256)$$

[c] For converting the value reported at a standard pressure of 1 atm (101.325 kPa) to the new IUPAC standard pressure of 100 kPa, a correction of −0.03 kJ · mol^{-1} is required.

[d] CO_2(aq) and H_2CO_3(aq) refer to the partially hydrated system $CO_2 + H_2CO_3$.

[e] Calculated from the standard Gibbs force of hydrolysis of glycogen of −18.0 kJ · mol^{-1} (Reference 3) and the values of glucose and H_2O in this table.

can be written as the sum of stoichiometrically proportioned chemical potentials of all substrates and products,

$$\Delta_r G_B = \sum_i \nu_i \mu_i \tag{14}$$

Analogous to Equation 8, the chemical potential is composed of a standard term μ_i°, and a concentration dependent term:

$$\mu_i = \mu_i^\circ + RT \ln(a_i/a_i^\circ) \tag{15}$$

where a_i is the activity of i and a_i° is the standard activity (1 mol · dm^{-3}; concentrations can be used in dilute solutions; 100 kPa for gases; see Tables 1 and 2). The concentration

TABLE 2
Chemical Potentials, μ_i [kJ · mol^{-1}], at Two Different Cellular States (I and II), Characterized by Various Values of p_{O_2}, pH, p_{CO_2}, and Activities, a_i [mmol · dm^{-3}] (Concentrations), of Dissociated Organic Acids

Substance, i	State I	State II	μ_i(I)	μ_i(II)	Comment
Oxygen	20 kPa	0.01 kPa	−4.0	−22.8	$\mu_{O_2} = RT \ln(p_{O_2}/100)$
Hydrogen ion	pH 7	pH 6.5	−39.95	−37.10	$\mu_{H^+} = -RT \ln(10)$ pH
Carbon dioxide	3 kPa	5 kPa	−403.1	−401.8	$\Delta_f G^\circ_{CO_2} + RT \ln(p_{CO_2}/100)$
L-Lactate ion	0.5	5.0	−535.5	−522.0	$\mu_i = \Delta_f G^\circ_i + RT \ln(a_i)$
Succinate ion	0.01	5.0	−718.9	−703.5	
Propionate ion	0.5	2.0	−379.9	−376.5	
Acetate ion	0.1	2.0	−399.7	−392.3	

Note: When inserted into Equation 15 (see comments; $\Delta_f G^\circ_i$ from Table 1), then a_i must be expressed in the same units as the standard concentration [mol · dm^{-3}] for standard pressure (100 kPa). Water is at unit activity. The chemical potential of glycogen equals the standard molar Gibbs energy of formation (Table 1), since the activity of the polymer does not change at various concentrations. The Gibbs force of catabolic reactions is calculated as the sum of stoichiometric numbers times μ_i (Equation 14).

TABLE 3
Balanced Stoichiometries in Aerobic and Anoxic Catabolism of Glycogen

Product, P	$-\nu_{Glyc}$			$\rightarrow$	ν_P	$+\nu_{H^+}$	$\nu_{\infty ATP}$
CO_2	1 Glyc + 6 O_2			$\rightarrow$	6 CO_2 + 5 H_2O		37
Lactate	1 Glyc	+ H_2O		$\rightarrow$	2 Lac^-	+2 H^+	3
Succinate	7 Glyc + 6 CO_2	+ H_2O		$\rightarrow$	12 Suc^{2-}	+24 H^+	33
Propionate	7 Glyc	+ H_2O		$\rightarrow$	12 Prp^- + 6 CO_2	+12 H^+	45
Propionate + acetate	3 Glyc	+ H_2O		$\rightarrow$	4 Prp^- + 2 CO_2 + 2 Act^-	+6 H^+	19

Note: The catabolic pathways are specified by the end products, P. In addition to the stoichiometric numbers, the ATP coupling stoichiometry, $\nu_{\infty ATP}$, is shown. Note that additional protons are produced when bicarbonate accumulates (except in the succinate pathway where CO_2 is removed). The stoichiometric form is chosen to yield integer stoichiometric numbers. From these, the relevant stoichiometric ratios are calculated (Table 4).

After Gnaiger.[4,7]

independent standard chemical potentials of several reactants and products in aerobic and anoxic catabolism of glycogen are listed in Table 1. The relation between the equilibrium constant and the standard Gibbs force of reaction is also shown in Table 1. Chemical potentials are calculated according to Equation 15 for two specified cellular states in Table 2. In combination with balanced stoichiometries of catabolic reactions (Equation 9.k; see also Table 3), these chemical potentials are used to calculate the Gibbs forces of reaction with the aid of Equation 14. The resulting Gibbs forces of various catabolic pathways at two cellular states are summarized in Table 4 ($\Delta_k G_{Glyc}$).

Fluxes and forces are defined in strict correspondence such that their product yields power (Equation 2), e.g., for aerobic respiration of glycogen,

$$P_p = J_{ATP} \Delta_p G_{ATP} \qquad (16.p)$$

$$P_k = J_{Glyc} \Delta_k G_{Glyc} = J_{O_2} \Delta_k G_{O_2} \qquad (16.k)$$

TABLE 4
Stoichiometric Ratios, Gibbs Forces, and Catabolic Force Efficiency, f_k, in Aerobic and Anoxic Catabolism of Glycogen, at the Two Cellular States Characterized in Table 2

Product, P	P:Glyc	ATP:Glyc	ATP:P	∞ATP:H^+	Δ_kG_{Glyc}	$\Delta_kG_{\infty ATP}$	f_k	P/E
CO_2	6	37	6.17		−2919	−78.9	0.79[a]	*E*
						−78.9	0.70	*P*
					−2798	−75.6	0.63	*P*
Lactate	2	3	1.5	1.5	−252	−84.0	0.66	*P*
					−219	−73.1	0.66	*P*
Succinate	1.714	4.7	2.75	1.38	−328	−69.6	0.79	*E*
					−293	−62.2	0.77	*E*
Propionate	1.714	6.4	3.75	3.75	−370	−57.5	0.96	*E*
					−358	−55.7	0.86	*E*
Propionate + acetate	1.333	6.3	3.75	3.17	−381	−60.1	0.91	*E*
	0.667		2		−365	−57.6	0.83	*E*

Note: The stoichiometric ratios are calculated from Table 3. P:Glyc = $\nu_P/-\nu_{Glyc}$, mol end product per glycosyl-unit; ATP:Glyc = $\nu_{\infty ATP}/-\nu_{Glyc}$, ATP cycles per unit glycogen; ATP:P = $\nu_{\infty ATP}/\nu_p$, ATP cycles per unit end product; ∞ATP:H^+ = $\nu_{\infty ATP}/\nu_{H^+}$, ATP cycles per unit proton produced by accumulation of organic acids. If changes in bicarbonate are significant, the additional proton stoichiometry must be taken into account (Ref. 4). Δ_kG_{Glyc} [kJ · mol^{-1} Glyc] and $\Delta_kG_{\infty ATP}$ [kJ · mol^{-1} ∞ATP] are calculated from Tables 2 and 3, inserting Glyc and ∞ATP for substance B. Upper and lower values are for states I and II. The catabolic force efficiency, f_k, is calculated at Δ_pG_{ATP} of 55 and 48 kJ · mol^{-1} ATP for states I and II.

[a] Force efficiency in the resting state at an ATP/ADP ratio of 100 and Δ_pG_{ATP} = 62 kJ · mol^{-1}.

Since power is flux times force (Equation 16.p; 16.k), the power ratio or ergodynamic efficiency is the flux ratio times the force ratio.

4. Internal Efficiency is Flux Ratio Times Force Ratio

Substituting Equations 16.p and 16.k into Equation 1, we obtain the efficiency as the product of the flux ratio, $Y_{ATP/O_2} = J_{ATP}/J_{O_2}$, and force ratio, $-\Delta_pG_{ATP}/\Delta_kG_{O_2}$,

$$\epsilon = -\frac{P_p}{P_k} = \frac{J_{ATP}}{J_{O_2}}\frac{\Delta_pG_{ATP}}{-\Delta_kG_{O_2}} \tag{17}$$

The catabolic input force is exergonic (negative; Table 4) and the reaction proceeds spontaneously in the forward direction. Either it dissipates the exergy irreversibly in the uncoupled catabolic process, k, or it transduces part of the input to drive the output reaction, p. Such coupling leads to efficiency (Equation 17).

The output force of phosphorylation is endergonic (positive). The corresponding flux would spontaneously proceed backwards, rendering J_{ATP} negative (ATP is removed; Equation 12.p). The resulting exergonic power dissipation would indicate internal entropy production, that is loss of exergy owing to ATP hydrolysis as opposed to exergy conservation in phosphorylation. Spontaneous power generation, equivalent to a negative internal entropy change, is not possible. Power with a positive sign requires input, either external or internal:

1. External power input into the system (positive) is a transfer from the environment across the system boundaries. This is what Schrödinger referred to as negative entropy.[11]

2. Internal power input originates from an exergonic (negative) transformation within the system. Catabolism is the most important internal input process in heterotrophic cells coupled to drive the positive ATP flux against its intrinsic, endergonic force.

As pointed out above, the efficiency of classical thermodynamics is not restricted to the forces. However, classical efficiency considers exclusively *external* work or power performed by the system on its surroundings. The notion of efficiency of ATP production was criticized from this traditional point of view.[12] Clearly, delimiting the cell as a biological system, the exergy of catabolic ATP production is not work performed on the surroundings. Moreover, ATP concentrations do not even change with time at metabolic steady state, whence the exergy content of the cell in terms of ATP remains constant. It appears, therefore, that an expression of the efficiency of ATP production is meaningless.

This apparent conflict is resolved by recognizing that the concept of ergodynamic efficiency is not restricted to classical analysis of system output/input efficiency. Ergodynamics incorporates *internal efficiency* of exergy transformations within the system, based upon information about coupled processes within the system boundaries (Equation 17). In contrast, external efficiency is quantified in a black box approach. For instance, the external efficiency of protein turnover is zero. Black box analysis reflects neither the efficiency of catabolic ATP production nor the anabolic efficiency of making a peptide bond.

The stoichiometries of reactions k and p (Equation 9) do not contain any information on the ATP:O_2 coupling. It is highly informative, however, to relate the experimental flux ratio to the limiting, "mechanistic" ATP:O_2 coupling stoichiometry.

5. Normalized Flux Ratio and Force Ratio in Relation to Coupling Stoichiometry

The coupled process of glycogen respiration is

$$\text{kp:}\quad 0 = -1/6\ \text{Glyc} - O_2 - 6.17\ \text{ADP} - 6.17\ P_i + CO_2 + 7\ H_2O + 6.17\ \text{ATP} \tag{18}$$

Here a coupling stoichiometry is assumed of 37 mol ATP per mol glycosyl-unit (ATP:Glyc = 37; or 39 depending on the transport mechanism for cytosolic NADH into mitochondria). This yields a coupling stoichiometry based on oxygen, ATP:O_2, of 6.17. The normalized flux ratio, j,

$$j = \frac{J_{ATP}}{J_{O_2}\,(\text{ATP:O}_2)} = \frac{Y_{ATP/O_2}}{\text{ATP:O}_2} \tag{19}$$

relates the actually measured flux ratio, Y_{ATP/O_2}, to the theoretical ATP:O_2 coupling stoichiometry. j of unity defines a fully coupled process. This does, of course, not imply 100% efficiency. The normalized force ratio, f (force efficiency; Table 4),

$$f = -\frac{\Delta_p G_{ATP}}{\Delta_k G_{O_2}/(\text{ATP:O}_2)} \tag{20}$$

would equally have to be unity to yield 100% efficiency (compare Equation 17),

$$\epsilon = jf \tag{21}$$

In fully coupled processes, ergodynamic efficiency and force efficiency are equal, $\epsilon = f$. Normalized flux ratios <1 are due to uncoupling. In the case of fully coupled output and

input fluxes, the Gibbs energy ratio can be replaced by the normalized force ratio or force efficiency, f.

The stoichiometry for the normalized flux and force ratio is obtained directly when dividing the catabolic reaction (Equation 9.k) by the ATP:O_2 ratio of 6.17,

$$\text{p, } \nu_{ATP} = 1: \quad 0 = -\text{ ADP} - \text{P}_\text{i} + \text{ ATP} + \text{H}_2\text{O} \tag{22.p}$$

$$\text{k, } \nu_{\infty ATP} = 1: \quad 0 = -\text{ 1/37 Glyc} - \text{ 6/37 O}_2 + \text{ 6/37 CO}_2 + \text{ 5/37 H}_2\text{O} \tag{22.k}$$

None of the stoichiometric numbers are unity in Equation 22.k. However, for the unit advancement of reaction (22.k), there is the potential for a unit cycle of ATP (1 mol ATP formed and hydrolyzed simultaneously). Although ATP does not appear in reaction (22.k), it is related to a unit stoichiometric number for the ATP cycle, $\nu_{\infty ATP} = 1$. The symbol for the ATP cycle, ∞ATP, indicates that no net ATP is formed in the turnover of the cycle. The catabolic flux referring to the stoichiometric form of Equation 22.k, $J_{\infty ATP}$, in units of potential ATP cycles, is the flux *of* oxygen *multiplied* by the ATP:O_2 stoichiometry,

$$J_{\infty ATP} = J_{O_2}(ATP{:}O_2) \tag{23}$$

$J_{\infty ATP}$ is the potential ATP turnover per unit time calculated for fully coupled catabolism. The corresponding catabolic force per unit ∞ATP is the force *per* oxygen *divided* by the ATP:O_2 stoichiometry,

$$\Delta_k G_{\infty ATP} = \Delta_k G_{O_2}/(ATP{:}O_2) \tag{24}$$

Substituting these definitions into Equations 19 and 20, the normalized flux ratio and force efficiency are obtained,

$$j = \frac{J_{ATP}}{J_{\infty ATP}} \tag{25}$$

$$f = -\frac{\Delta_p G_{ATP}}{\Delta_k G_{\infty ATP}} \tag{26}$$

The normalized catabolic force, $\Delta_k G_{\infty ATP}$ (Table 4; Equation 24), is based on the stoichiometric ATP cycle [kJ · mol^{-1} ∞ATP], as opposed to $\Delta_p G_{ATP}$, the Gibbs force based on total ATP production [kJ · mol^{-1} ATP]. Importantly, the power of a chemical reaction is independent of the selected stoichiometric form of the reaction (see Equation 16.k). This is also true when calculating catabolic power by multiplication of Equations 23 and 24.

The efficiency and flux ratio are reduced to zero by uncoupling the respiratory chain which yields maximum oxygen flux at minimum efficiency. Therefore, it is logical to ask how ergodynamic efficiency and the control of metabolic flux are interrelated.

III. METABOLIC EFFICIENCY AND THE CONTROL OF FLUX

The relation between chemical fluxes, J, and effective forces, $F = \Delta_r G_B$, depends on (1) the catalytic properties of the system, expressed by the reaction coefficient b, and (2) the activity of molecules, α, which freely interact with the force and are transformed in the

reaction advancement. On a volume basis, the latter term is a concentration or activity, α, calculated from the activities of all reactants and products. Then the ergodynamic relation describing the dependence of the flux on the force is[20]

$$J = -b\,\alpha\,F \tag{27}$$

Linear nonequilibrium thermodynamics is concerned with reaction conditions where the conductivity is constant. The conductivity, L, is the reaction coefficient times α,

$$L = b\,\alpha \tag{28}$$

A constant conductivity implies a constant linear slope, L, between flux and force. More generally, linear and nonlinear flux/force relations are described by Equation 27 which thus links linear nonequilibrium thermodynamics with an emphasis on the forces, and kinetics with an emphasis on concentrations or activities as flux control variables.[20]

A. THE DEGREE OF COUPLING: IS UNCOUPLING ADAPTIVE?

In coupled reactions, the effective force, F (Equation 27), is a function of both input and output forces and of the degree of coupling. Depending on the degree of coupling,[17] a fraction d of the normalized input force, $d\,\Delta_k G_{\infty ATP}$, is available to push the phosphorylation of ADP against the endergonic phosphorylation force (Equation 29.p). Conversely, a fraction d of the (positive) output force, $d\Delta_p G_{ATP}$, offsets the driving (negative) input force, rendering the effective net force less exergonic (Equation 29.k). Under conditions of Onsager reciprocity,[17]

$$J_{ATP} = -b\,\alpha\,(d\,\Delta_k G_{\infty ATP} + \Delta_p G_{ATP}) \tag{29.p}$$

$$J_{\infty ATP} = -b\,\alpha\,(\Delta_k G_{\infty ATP} + d\,\Delta_p G_{ATP}) \tag{29.k}$$

Inserting Equation 26 into the above expressions, the fluxes are expressed as a function of the normalized input force, force efficiency, and degree of coupling,

$$J_{ATP} = -L\,\Delta_k G_{\infty ATP}\,(d - f) \tag{30.p}$$

$$J_{\infty ATP} = -L\,\Delta_k G_{\infty ATP}\,(1 - df) \tag{30.k}$$

The degree of coupling, d, is zero in a completely uncoupled process, and the input flux proceeds at its unrestricted maximum (Equation 30.k). When $f = d$, then the output flux is zero (Equation 30.p). This situation is called "static head",[17] corresponding to State 4 in mitochondrial respiration. d reaches a maximum of 1 in the fully coupled process.

Uncoupling is an important mechanism for the generation and dissipation of heat, e.g., in brown fat, increasing oxygen flux (expressed as J_{O_2} or $J_{\infty ATP}$) and decreasing J_{ATP}. Apart from this function, it was postulated that a degree of coupling below the maximum of 1.0 is adaptive for economical ATP production and rapid growth. Characteristic degrees of coupling, $d < 1$, were described as a mechanism of optimization of efficiency in mitochondrial respiration[16] and bacterial growth.[21] Can a reduction of the degree of coupling be adaptive? If so, could then a low degree of coupling — hence low efficiency — explain the paradox of the low efficiency of ATP production in the lactate pathway?

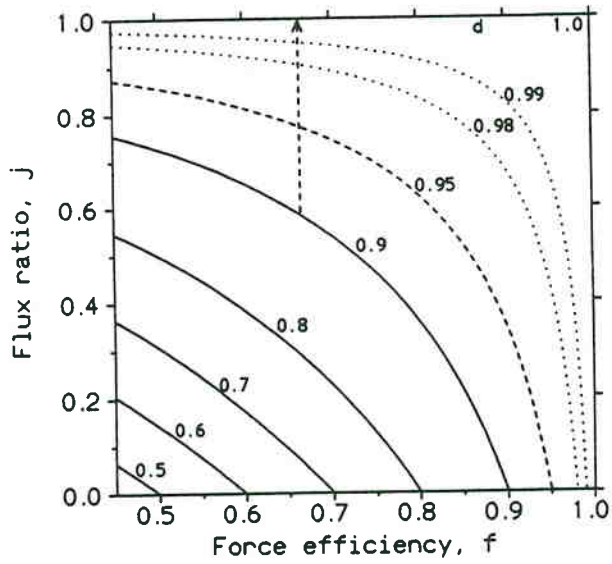

FIGURE 2. Output/input flux ratio, j, as a function of force efficiency, f, and degree of coupling, d (Equation 31). The range of force efficiencies >0.5 is shown as relevant in catabolic ATP formation. d is indicated by numbers (0.5 to 1.0). Arrow: At constant $f = 0.67$, the flux ratio increases with increasing d. Therefore, maximization of the degree of coupling is adaptive in terms of a high ATP/O_2 or ATP/Glyc flux ratio.

Evidently, an increase of the degree of coupling improves the flux ratio. The normalized flux ratio (Equation 25) is obtained when dividing Equation 30.p by 30.k,

$$j = \frac{d - f}{1 - df} \tag{31}$$

The flux ratio declines at constant d with an increase of f (Figure 2). At constant force efficiency, the flux ratio increases with the degree of coupling with a steeper gain at higher f (Figure 2; arrow).

Multiplication of the fluxes (Equation 30.p and k) by the corresponding force (from Equation 26) yields the relation of power to the degree of coupling and force efficiency,

$$P_p = L\,\Delta_k G^2_{\infty ATP} f\,(d - f) \tag{32.p}$$

$$P_k = -L\,\Delta_k G^2_{\infty ATP}\,(1 - df) \tag{32.k}$$

Power dissipation in the completely uncoupled process (Equation 32.k; $d = 0$) is maximum independent of f. In aerobic catabolism, power and heat dissipation are nearly equal which explains the strong calorigenic effect of uncoupling. In contrast, the plots of power output (Equation 32.p) show that at any force efficiency, an increase of the degree of coupling increases the normalized power output (Figure 3; arrow).

Finally, power efficiency (substituting Equation 32.p and k into Equation 1) is obtained as a function of d and f:

$$\epsilon = \frac{d - f}{1/f - d} \tag{33}$$

Power efficiency is enhanced by increasing the degree of coupling at any given force efficiency (Figure 4)! The ergodynamic efficiency is highly sensitive to small changes of

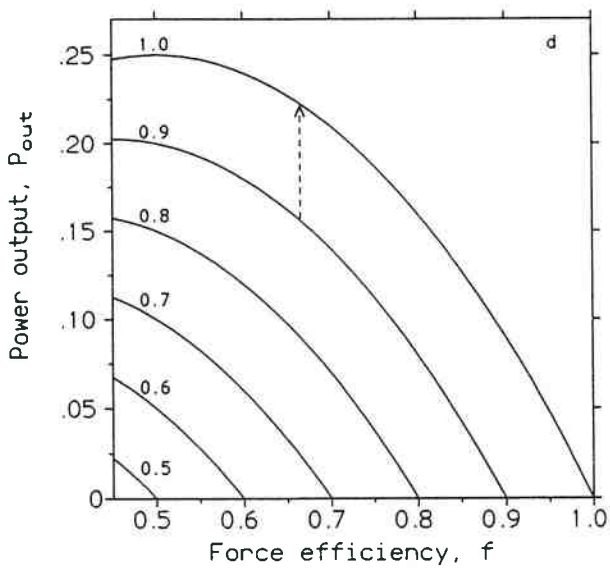

FIGURE 3. Power output, P_{out}, as a function of force efficiency, f, and degree of coupling, d (Equation 32.p). The conductivity and the input force are constant and normalized at unity. Arrow: At constant $f = 0.67$, the power output increases with increasing d (shown by numbers). Therefore, maximization of the degree of coupling is adaptive in terms of high power output.

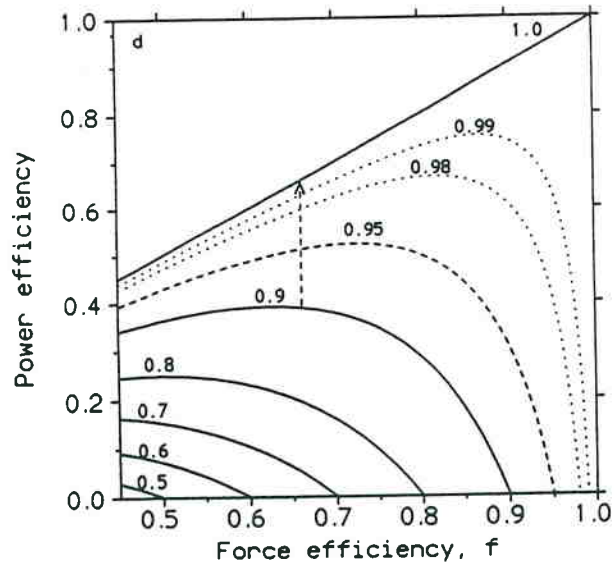

FIGURE 4. Power efficiency, ϵ, as a function of force efficiency, f, and degree of coupling, d (Equation 33). Arrow: At constant f = 0.67, the power efficiency increases with increasing d (shown by numbers). Therefore, maximization of the degree of coupling is adaptive in terms of high power efficiency.

the degree of coupling.[17] Apart from increased heat loss, there is no functional advantage of low degrees of coupling in comparison with fully coupled energy transformations ($d = 1$). Contrary to optimization, submaximum degrees of coupling are a constraint (except for thermal regulation) and are pathological, e.g., induced by toxicological agents.

Output flux (Figure 2), power output (Figure 3), and power efficiency (Figure 4) decline to zero as the force efficiency approaches the value of the degree of coupling, $f = d$. This restricts the force efficiency to $f < d$. Therefore, an increase of the degree of coupling

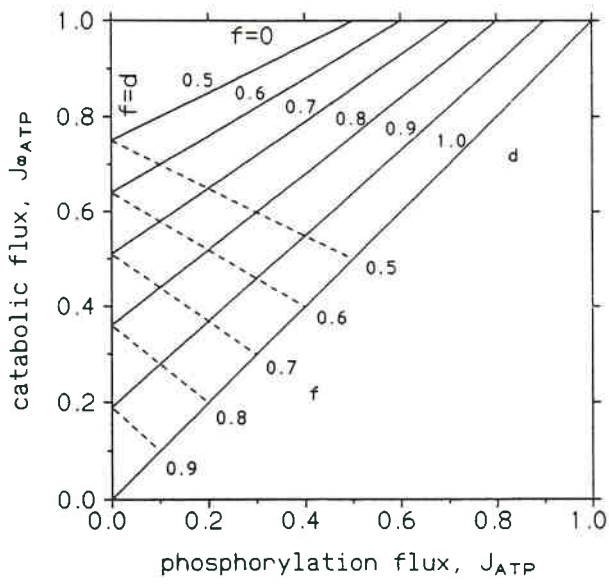

FIGURE 5. Theoretical relation between normalized input flux, $J_{\infty ATP}$, and output flux, J_{ATP}, as a function of force efficiency, f (numbers 0.5 to 0.9, stippled lines), and degree of coupling (numbers 0.5 to 1.0, full lines). At any constant f, the output flux increases and the input flux decreases with increasing d (compare Figure 2). At constant output flux, the demand for input flux decreases with increasing d, and the force efficiency increases simultaneously. Therefore, maximization of the degree of coupling is adaptive in terms of both high output flux and low input flux, and in terms of the maintenance of a high phosphorylation potential (high force efficiency at constant input force). The relations between input and output fluxes at constant f and d are, respectively,

$$J_{\infty ATP} = (1 - f^2) + d\,J_{ATP}$$
$$J_{\infty ATP} = (1 - d^2) - f\,J_{ATP}$$

Along the Y-axis at zero phosphorylaton flux, the static head (State 4) situations are described by the equality $f = d$. Along the X-axis at unit normalized catabolic flux, the level flow situations are described by a zero output force and zero force efficiency, $f = 0$.

increases the phosphorylation potential which can be maintained by a constant input force. The relations between input and output fluxes are shown in Figure 5 as a function of degree of coupling and force efficiency. At any load imposing a constant ATP demand, this demand must be met by a constant ATP supply to maintain the adenylate levels at an adjusted steady state. Increasing the degree of coupling at constant phosphorylation flux lowers the catabolic flux and thus the demand for substrate supply (Figure 5). Viewed horizontally at constant catabolic flux, the output flux increases with d (Figure 5). Maximization of the degree of coupling expands the scope for matching ATP supply with ATP demand.

At steady state, functional optimization demands full coupling, which is an adaptive feature of glycolytic substrate level phosphorylation.[4] Efficiencies of mitochondrial ATP production and growth can be optimized, but not by submaximum degrees of coupling.[5] The low efficiency paradox of the lactate pathway requires a different explanation.

B. THE TRADE-OFF BETWEEN EFFICIENCY AND POWER

1. Covariation of Efficiency and Power

As the degree of coupling increases, power output and power efficiency increase simultaneously (Figures 3 and 4). Consequently, there is scope for covariation of power output and efficiency in poorly coupled processes. In growth, for example, only part of the input

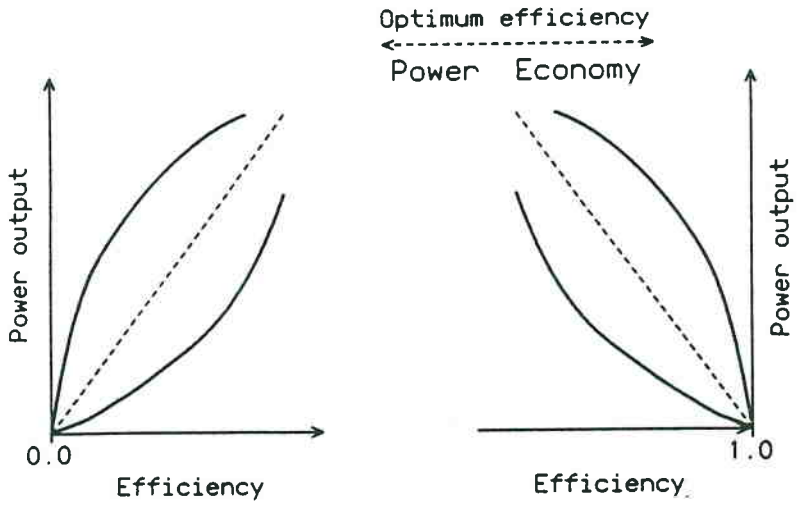

FIGURE 6. The relation between power and efficiency depends (1) on the range of efficiencies characteristic for the system (left or right part), and (2) on the shape of the power/efficiency function (indicated by the different full and dashed lines). Optimum efficiency values depend on the strategy of maximizing either power or economy. Economy is evaluated as a combination of power output and efficiency. Left: At low efficiencies, an increase of efficiency is adaptive due to the coupled increase of both power and efficiency. Right: In the range of high efficiencies, efficiency is optimized either to increase the economy at the cost of time, owing to decreased power output (shift to the right). Or efficiency is optimized to increase power output at the cost of energy (shift to the left). The conflict between maximizing power *or* efficiency is general at high efficiency, independent of flux/force linearity. It is the exact position of the optimum value which varies with nonlinear or linear behavior.

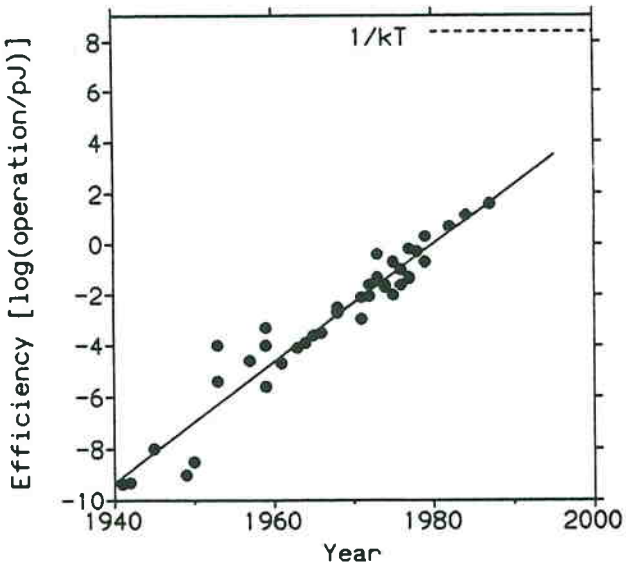

FIGURE 7. Increase of efficiency during the evolution of computers. The exponential increase of the number of logical operations performed per unit exergy invested indicates a simultaneous increase of efficiency and power. A possible theoretical limit to the efficiency is obtained when the exergy invested into the unit logical operation reduces to the Boltzmann constant times absolute temperature, kT (after Landauer[43]).

is geared to the specific output of anabolic ATP utilization, whereas maintenance and locomotion constitute parallel branches of energy demand. Power output increases with increasing efficiency even when the system is fully coupled ($d = 1$) in the range of very low efficiencies (Figure 6, left part).

A recent example of such desired coevolution of power and efficiency is the increase of both efficiency and speed of computers (Figure 7). The coupled increase of power and

efficiency (Figure 6, left part) is expected in early evolution of functionally deficient energy converters in biology and technology.* This directs us again to the low efficiency paradox: is the lactate pathway functionally deficient in comparison with the more efficient alternative pathways of glycolysis?

2. Economy Contra Power

The trend shown in Figure 6 (left) at very low efficiencies changes as efficiency is increased to intermediate levels and towards its maximum value (Figure 6, right). This trend holds true even if the assumption underlying the pattern in Figure 3 does not apply. This is indicated in Figure 6 by the various shapes of the power/efficiency relation. The exact value of the optimum efficiency for maximum power output depends on the actual behavior of the flux/force relation (Equation 27).

In a linear energy converter, power input decreases continuously with increasing force efficiency (Equation 32.k), and power output increases at very low efficiency as long as the effect of the increasing f dominates over the effect of the decreasing expression, $d - f$ (Equation 32.p). At the theoretical limit of maximum efficiency, power output declines gradually to zero (Figures 3 and 6). Maximum efficiency and power strategy are mutually exclusive. This "ergodynamic inhibition"[5] at high efficiency provides a basis for rationalizing the adaptive advantage of comparatively low but optimum efficiency in power strategy (Figure 6; right part, arrow pointing left in the high efficiency region). The pathways activated in economy strategy operate at higher optimum efficiency and at reduced power (Figure 6; arrow pointing right). This saves energy owing to the combined effects of (1) higher output per unit input and (2) metabolic depression, in part presumably due to ergodynamic inhibition (Figure 6; horizontal arrow pointing right). For both energy saving effects, economy strategy requires maximization of the degree of coupling.

Power strategy in a fully coupled linear energy converter would imply an optimum efficiency of 0.5 (Figure 3; power output is maximum at $f = 0.5$).[22] Partial uncoupling would shift the optimum force efficiency for maximum power output further to the left (Figure 3). Optimization for maximum power output is not achieved by uncoupling (do not keep pressing the clutch on the highway!), but optimization of efficiency requires selection of the proper coupling stoichiometry (the gear ratio) in relation to the input and output forces. The efficiency of ATP production in the lactate pathway is typically 0.66 (Table 4). This appears even higher than expected on the basis of the optimization model shown in Figure 3. Specific nonlinear flux/force relations (Equation 27) may shift the optimum to the right.[15] At this stage, however, systemic features of metabolic design have to be considered to provide estimates on the adaptive significance of efficiencies observed under the divergent economy and power strategies.

IV. OPTIMUM EFFICIENCIES IN POWER AND ECONOMY STRATEGY

A. ATP SUPPLY AND ATP DEMAND: SERIAL ENERGY TRANSFORMATION

Only few investigations on the control of metabolic flux pay sufficient attention to both the coupled process of catabolic ATP supply and the complementary coupled process of

* Many computers can be switched from "turbo" speed to a lower "economy" speed, saving electric (battery) power at the cost of time. Optimization in the mode of operation of a particular design under different constraints of time and energy (acclimation) must be distinguished from optimization in the improvement of design (adaptation). The best cars designed for high power and speed are less efficient than the best cars designed for high efficiency. Every design, in turn, operates at its highest efficiency at an optimum (submaximum) speed and power.

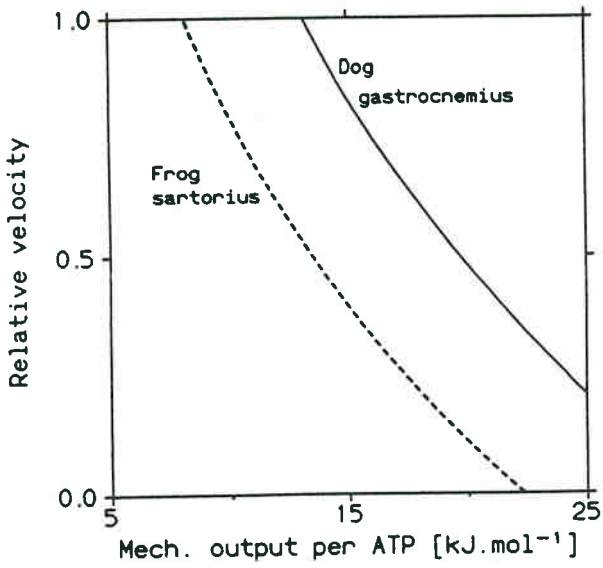

FIGURE 8. Empirical decrease of the relative velocity of contraction with increasing mechanical output exergy per mol ATP hydrolyzed [kJ · mol^{-1}]. (After di Prampero[24]).

ATP utilization catalyzed by various ATPases.[23] Neglect of serial energy transformation is particularly true in studies on optimum efficiency of oxidative phosphorylation in isolated mitochondria. However, catabolic mechanisms of ATP supply did not evolve in isolation. The trade-off between power and efficiency is also observed for ATP utilization and muscular performance (Figure 8).[24] Ultimately, optimization in response to selective pressures must be interpreted in the systemic context of cellular functions, matching ATP supply and demand.[5] Therefore, metabolic efficiencies cannot be assessed solely by catabolic efficiencies of ATP production, ϵ_k, nor by a black box analysis irrespective of the structured nature of the cell. The serial energy transformation of ATP production *and* ATP utilization must be considered. Upon formation of ATP, splitting of ATP is a secondary input process and biochemical or mechanical work is the output with efficiency ϵ_a in anabolic or other ATPase catalyzed reactions (such as actomyosin ATPase, ion pumps, etc.). Here the term "anabolic" is used in a very general sense of physicochemical output with ATP-equivalent exergy as the input. One of the most important implications on optimum efficiency stems from the *multiplication law of serial efficiencies*, for calculating the overall efficiency, ϵ_{ka},[5,25]

$$\epsilon_{ka} = \epsilon_k \epsilon_a \tag{34}$$

The structured design of the metabolic machinery provides flexibility for channeling various fuel and storage reserves into catabolic ATP production, which then branches off to specific sites of ATP demand. As a trade-off, the mathematical product of serial efficiencies is smaller than either individual component (Equation 34), concomitantly compromizing the final power output, P_a (compare Equation 1),

$$P_a = -\epsilon_{ka} P_k \tag{35}$$

As an adaptive compensation, increased compartmental efficiencies, ϵ_k and ϵ_a, counteract the serial multiplication effect. This explains why catabolic efficiencies of ATP production in power strategy are higher than the predicted value of 0.5 which is optimum merely for one-compartmental energy transformation (Figure 9; one-compartmental power output, P_o-strategy, vs. two-compartmental power output, P-strategy).

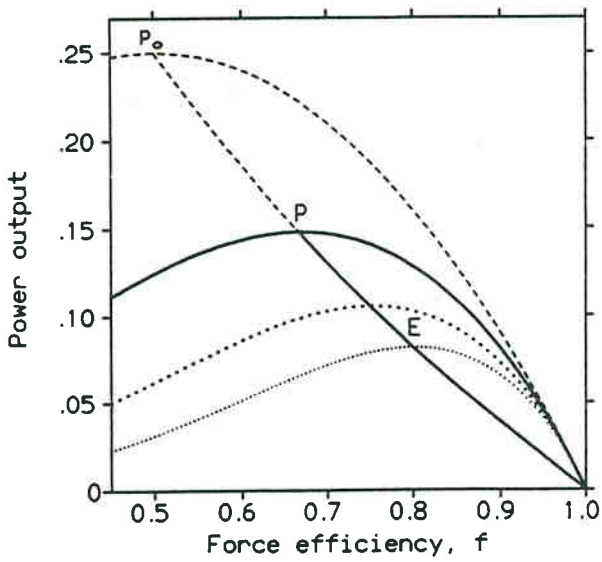

FIGURE 9. Power output, P_a, as a function of the component force efficiency in the two-compartmental energy chain at various power and economy strategies. Each serial force efficiency, f, is assumed to be optimized according to identical criteria, $f = f_k = f_a$. The conductivity, L_k, and input force, $\Delta_k G_{\approx ATP}$, are normalized at unity (Equation 39). P (full line) — power strategy in fully coupled, serial energy conversion, $m = 2$. E (dotted lines) — economy strategies with increasing emphasis on efficiency as the optimum efficiency shifts to the right and the maximum declines; $m = 3$ and 4. An increase of m is due to repression of the external load (Equation 37). The continuously decreasing line intersects the power maxima at optimum efficiencies (Equation 40 substituted into Equation 39). This line is dashed in the low efficiency region ($f < 0.67$; $m < 2$ indicating unbalanced overload) beyond the range where catabolic and anabolic conductivities are matched. An overload leads from balanced two-compartmental power strategy, P, successively to exhaustive one-compartmental power strategy, P_o (dashed line, with ATP hydrolysis as the input and muscular or biochemical, anabolic work as the output, $m = 1$). After Reference 5.

"To understand the performance of the machine it is of the greatest importance to discover the efficiencies of its different parts. If one element is appreciably less efficient than the others this bottleneck will limit the performance of the whole system."[25] The efficiencies of ATP utilization and ATP production are related in two contrasting ways:

1. *Antagonistic or compensatory* increase of anabolic efficiency at a decrease of catabolic efficiency, and vice versa, maintains overall efficiency constant. This compensatory or homeostatic response is expected under perturbing conditions when one of the component efficiencies fluctuates away from the optimum range, particularly under nonsteady state conditions.
2. *Synergistic* increase of anabolic efficiency at an increase of catabolic efficiency, and vice versa, augments the adaptive shift of efficiency of the individual component. If selection leads to adaptation of cellular systems by way of optimization of each component in the sequence of energy transformations, then the synergistic pattern forms a general trend in transitions between power to economy strategy.[5]

B. UNCOUPLING vs. FUNCTIONAL BRANCHING: PARALLEL ENERGY TRANSFORMATION

For carrying out various cellular functions simultaneously, the energy chain is branched, thus channeling fractions of the catabolic ATP flux towards different sites of parallel ATP utilization. From the perspective of a single function such as locomotion or growth, functional branching diminishes the efficiency and appears to partially uncouple the ATP demand from the total ATP supply. However, functional branching requires coupled catabolism and coupled energy transformation in each parallel branch of ATP utilization. Branched energy

allocation for maintenance, osmoregulation, sensory functions, locomotion, and growth must be analyzed in terms of functional trade-offs.[13] The underlying optimization models incorporate phenotypic expressions of Darwinian fitness with the complexity of balancing statistical long-term and short-term success. In contrast, uncoupling is due to molecular constraints (except for dissipative thermoregulation). These constraints are pathological, or tell us that while evolution leads to optimization, perfection has not been and may never be attained.

A conflict emerges when several life support functions operate synchronously at different rates. How can synergistic optimization of serial efficiencies be accomplished concurrently according to different strategies? Such complex optimization is aided by three mechanisms:

1. *Time separation* of functions requires repression of ATP-utilizing pathways while one particular pathway is turned on. This is the principle of energy allocation by compensation.[26] Consideration of optimum efficiencies in the sequence of energy transformations adds a new perspective to the adaptive significance of performing specific needs sequentially rather than by increasing total metabolic power.
2. *Cellular and tissue differentiation* separates different functions spatially. For muscular power output, such separation goes as far as the recruitment of different fiber types for different velocities, thus optimizing mechanical power output and efficiency.[27] It is interesting to note that differentiation occurred much more pronounced at the level of "anabolic" energy transformation. No centralized "catabolic power tissue" evolved for the transmission of energy to various target tissues for subsequent power utilization. The strategy of separating spatially not only the parallel branches of energy utilization but the sequence of power generation and consumption is the domain of centralized electric power plants in our society, yet environmental concern and modern insights into improved efficiency may successfully initiate a trend towards decentralization.
3. *Metabolic channeling* of ATP by functional coupling of the creatine kinase carrier effectively separates different functional branches into parallel metabolic compartments with limited bulk phase equilibration of common metabolites.[28]

Since ATP utilization is partitioned into various physiological components including maintenance, the efficiency of any specific function (such as anabolism in animal growth) is low when normalized against total power input. Growth efficiency (in physiological energetics based on external enthalpy fluxes,[11] not estimated by internal Gibbs forces) increases with increasing metabolic power.[29] At efficiencies below the power-optimum, an increase of efficiency leads to an increase of power output (Figure 6). Such covariation of power and efficiency, however, does not characterize the evolution of catabolic pathways which are optimized in the high efficiency region (Figure 6). Energetically, the dominating purpose of catabolism is the generation of ATP. Therefore, catabolic ATP production is "monofunctional", in contrast to multifunctional anabolic ATP utilization.

C. EXTERNAL LOAD AND STEADY STATE: MATCHING OF CATABOLIC AND ANABOLIC CONDUCTIVITIES

Evolutionary optimization of metabolic design follows trajectories of power strategy and various degrees of economy strategy. Such trajectories for synergistic serial efficiencies (Equation 34) are described by the normalized power output as a function of catabolic and anabolic efficiencies (Figure 9; P and E). For maintaining the metabolic chain at steady state, catabolic ATP production, $J_{ATP,p}$, must equalize anabolic ATP utilization, $J_{ATP,p}$ (dp indicating dephosphorylation of ATP, the reversal of reaction Equation 22.p). Metabolic steady state depends upon the matching of catabolic and anabolic conductivities, L_k and L_a:[5]

$$\frac{L_k}{L_a} = f_k \frac{1 - f_a}{1 - f_k} \tag{36}$$

Steady state depends further on a matching of the conductivity for the external load L_{ex} (ion leaks, mechanical stress, cellular growth and division) to the "anabolic" conductivity,[5]

$$m = \frac{L_a}{L_{ex}} = \frac{f_a}{1 - f_a} \tag{37}$$

Based on steady state conductivity matching and full coupling, anabolic power output, P_a, is in the linear range,[5]

$$P_a = L_k \, \Delta_k G^2_{\infty ATP} f_k f_a \, (1 - f_k) \tag{38}$$

In synergistic optimization, each serial force efficiency, f, is tuned according to identical selective pressures, $f = f_k = f_a$. With this equality and the parameter m (Equation 37) injected into Equation 38, power output is (Figure 9)

$$P_a = L_k \, \Delta_k G^2_{\infty ATP} f^m \, (1 - f) \tag{39}$$

For a two-compartmental energy chain, $m = 2$ indicates power strategy (see Equation 38). The maximum of power output is obtained at an optimum compartmental force efficiency of $f_{opt} = 0.67$ (Figure 9, *P*):

$$f_{opt} = \frac{m}{1 + m} \tag{40}$$

This optimum efficiency for power strategy agrees with the efficiency calculated for ATP production in the lactate pathway (Table 4). Thereby, the apparent paradox is resolved; whereas high efficiency is adaptive in economy strategy, efficiency of ATP production in the lactate pathway is comparatively low and optimum for power strategy. Moreover, consideration of serial energy transformation resolves the apparent discrepancy between the optimum efficiency of 0.5 for maximum power output and the observed efficiency of 0.67 in the lactate pathway. Rather than being a compromise between power and economy,[4] the increase from 0.5 to 0.67 is a necessary payoff in power strategy based on serial energy conversion.

In economy strategy, efficiencies >0.67 are selected since the maximized function is not power output but a combination of power and efficiency.[16] The maximized economy function is quantified as the product of power and efficiency, $P_a f^{m-2}$, with the exponent $m - 2$ indicating the degree of economy strategy ($m - 2$ equals zero in power strategy). This economy function requires implicit consideration of non-linear flux/force relations.[5,20] A continuum of optimum functions exists for various extents of economy, with increasing emphasis on efficiency and exergy contra power and time (Figure 9; *E*). For instance, at $m = 4$ the optimum compartmental efficiency is 0.80 (Equation 40; compare f_k in Table 4). Catabolic efficiencies of ATP production are expected to follow these trajectories even if the energy chain is branched and various life support functions are lumped into a combined "anabolic" conductivity, L_a (Equation 36), and a composite power output, P_a (Equation 38).

D. OVERLOAD, MISMATCH OF ATP DEMAND vs. CATABOLIC SUPPLY, AND MAXIMUM POWER

As the external load on a cell increases, a limit is reached beyond which catabolic ATP supply cannot cope with the accelerated ATP demand. In such bursts of activity, ATP levels would be depleted immediately to exhaustion. Particularly skeletal muscle cells are adapted to explosive all-out efforts by escaping into a one-compartmental maximum power mode, by drawing on stores of phosphocreatine, phosphoarginine or other phosphagens. The creatine kinase reaction is near equilibrium with the ATP and the corresponding Gibbs force of phosphorylation. Thereby, high levels and high Gibbs forces of phosphorylation are maintained until a significant fraction of the phosphocreatine pool is consumed.[24] This implies effectively a one-compartmental transformation, cutting the energy chain short of the dissipative step of catabolic ATP production and avoiding the multiplication effect of serial efficiencies. The slower catabolic regeneration of the phosphagen pool is delayed until post-exercise anaerobic and aerobic recovery. This is another example of time separation (see above) for optimization of efficiency in maximum power strategy.[5]

In one-compartmental power strategy, efficiencies <0.67 lead to a further increase of normalized power output (Figure 9, P_O). The theoretical optimum efficiency of 0.5 for maximum power output in fully coupled energy transformation (Figure 3, $d = 1$) agrees with experimentally observed efficiencies of mechanical power output based on phosphocreatine splitting.[30]

Towards depletion of ATP levels and diminishing relative velocity of contraction, the mechanical exergy output per mol ATP increases (Figure 8). Although this pattern is based upon observations in one-compartmental energy transformation,[24] it is suggestive of synergistic regulation of catabolic and anabolic efficiencies if also applicable to situations of ATP supply/demand balance (Figure 9).

E. ADAPTATION: CATABOLIC PATHWAYS AND OPTIMUM EFFICIENCIES UNDER ANOXIA

Comparison of optimum and observed efficiencies explains the low efficiency in the high power lactate pathway compared to the high efficiencies of the low power anoxic pathways (Table 4). Moreover, aerobic efficiencies of ATP production span nearly the same range of efficiencies observed in the distinct anoxic pathways, despite the large difference in aerobic and anoxic ATP:Glyc coupling stoichiometries. Such conservation of efficiency at variation of stoichiometry indicates the adaptive significance of the normalized force ratio or force efficiency in addition to the importance of the ATP:Glyc coupling stoichiometry.[4,14]

For calculation of force efficiencies of catabolic ATP production, we need accurate redox and atomic balances of the catabolic reaction equations, including the corresponding ATP:Glyc coupling stoichiometries (Table 3). The ATP:lactate coupling stoichiometry may range from 1 to 1.5, depending on the fractions of glucose and glycogen utilized simultaneously. A typical value for skeletal muscle is 1.3.[24] For comparison of different pathways, 100% glycogen utilization is assumed. The involvement of amino acids such as transamination of aspartate to alanine has to be considered separately. In the present context, the emphasis is on the fundamental pattern rather than exploration of the entire range of energetic and biochemical adaptations to anoxia and hypoxia. In contrast to the lactate pathway, the succinate-propionate-acetate pathways do not reveal the familiar 2:1 ratio of end product formed per glycosyl unit. The P:Glyc stoichiometries (Table 4) account for anoxic CO_2 fixation or CO_2 production in these pathways (Table 3). ATP:Glyc is twice the ATP:Lac coupling stoichiometry, since 2 mol lactic acid are produced per glycosyl-unit without any changes in CO_2 (Table 1). Use of the same multiplication factor of 2 for calculating the ATP:Glyc ratio in the propionate pathway would immediately lead to a violation of the

Second Law of thermodynamics, owing to a force efficiency of ATP production calculated at >1. However, in the balanced propionate pathway only 1.7 mol propionic acid are produced per glycosyl-unit, whence the ATP coupling stoichiometry increases from 3.5 per mol propionate to 6.4 per mol glycosyl-unit (Table 4).

Calculation of chemical potentials under cellular conditions usually relates to bulk phase concentrations (Table 2). This would be inappropriate for metabolites partitioned into cellular microcompartments.[31] Microcompartmentation and metabolic channeling effectively increase the reaction coefficient and hence the conductivity (Equation 28), yet it does not affect the Gibbs force calculated for an entire catabolic pathway. The chemical potential of glycogen is independent of glycogen concentration (Table 1). Moreover, bulk phase properties are appropriate for excreted or accumulating end products. Cellular activities (concentrations) must be known for any particular situation. Two typical states under aerobic (I) and long-term anoxic or microxic conditions (II) are summarized in Table 2 (see Reference 4). Some differences in the resulting catabolic forces (Table 4) relative to data published earlier[4] are due to a new evaluation of the standard chemical potentials (Table 1). The catabolic force efficiencies tend to be slightly higher for the same cellular conditions, particularly owing to the standard Gibbs force of phosphorylation estimated at a higher value in comparison with earlier calculations for the same conditions of pH and pMg (Figure 1). The calculated force efficiencies (Table 4) must not be treated as constants but as typical values characteristic for a specified range of cellular conditions.

Table 4 reveals two distinct adaptive ergodynamic mechanisms for increasing anoxic ATP gains relative to the lactate pathway:

1. Increase of the catabolic Gibbs force, $\Delta_k G_{Glyc}$, in pathways leading to end products of lower chemical potential than lactate; this provides scope for increasing the ATP:Glyc ratio at constant efficiency.
2. Coupling a higher fraction of the catabolic input force to the output force of ATP production; this increases the catabolic force efficiency, f_k, and leads to amplification of the first mechanism for improving the ATP:Glyc ratio.

Optimization of coupling stoichiometries in various catabolic pathways is a result of long-term selection and genetic adaptation. Short-term kinetic mechanisms of biochemical acclimation must be responsible for the flexibility to adjust metabolic efficiencies quickly according to the appropriate power or economy strategy. Having established a close agreement between the theoretically predicted and observed ranges of catabolic efficiencies of ATP production on the basis of coupling stoichiometries and cellular chemical potentials, the question remains if cells and organisms show the flexibility to operate at optimum efficiencies even during transitions between power and economy strategy. With respect to the evolution of catabolic pathways, the *P/E*-concept provides a quantitative approach for the assessment of adaptation on the level of ATP:Glyc stoichiometries in relation to *in vivo* Gibbs forces. The kinetic switching between power and economy strategies supports the *P/E*-concept on the level of short-term acclimation in terms of minutes or seconds.

F. ACCLIMATION: TRANSITIONS BETWEEN POWER AND ECONOMY STRATEGY

A distinction must be made between the short-term mechanisms of switching on and off metabolic pathways, and evolutionary criteria of pathway selection. The switching mechanism must be kinetic, since ergodynamics provides the rather rigid frame (like gears) of metabolic organization!

The transition from power to economy strategy shifts the emphasis from high power to a compromise between high efficiency and low power. For metabolic shutdown, however, this compromise in *E*-strategy turns out as a coupled adaptation of reducing metabolic power *by* high efficiency. Upon transitions from work to rest in aerobic skeletal muscle, the increase of force efficiency of ATP production is remarkably similar in comparison to the gain in efficiency upon a switch from the anoxic lactate to the succinate-propionate-acetate pathways (Table 4).

In aerobic skeletal or insect muscle the switching from economy to power strategy is effected by varying the output force (phosphorylation potential; 50 to >60 kJ · mol^{-1} economy strategies of anoxic pathways are primarily determined by their different ATP/glycogen stoichiometries, with a simultaneous change of the catabolic input force and the ATP output force (Table 4).

1. Aërobic Conditions

There is ample evidence for the large scope of both catabolic and anabolic efficiencies in the energy chain. Catabolic efficiencies vary under aerobic conditions particularly due to changes in the output force. At rest, the Gibbs force of phosphorylation increases up to 72 kJ · mol^{-1} ATP (cat biceps),[32] implying a force efficiency of $f_k = 0.91$ and high level economy strategy (Figure 9; compare Table 4). This makes the muscle ready for instantaneous bursts of power, momentarily cutting the energy chain short of the compromising serial element of catabolic ATP regeneration. Maximum contraction velocity (which is proportional to mechanical power output at constant load), therefore, is only possible at the cost of draining the phosphocreatine store, with high speed but low mechanical exergy output per unit ATP hydrolyzed (Figure 8). Before the phosphocreatine store is fully depleted, ATP levels start to fall, concentrations of free ADP and inorganic phosphate increase, and glycolytic flux is fully turned on. The catbolic efficiency of ATP production in the lactate pathway remains nearly constant at 0.66 even if pH levels decline to 6.5, owing to the simultaneous decrease of the exergonic input force and the endergonic output force (Table 4).

With a continuing increase of ADP levels towards exhaustion,[33] the compensatory increase of mechnical output exergy per ATP concurs with a decline of the contraction velocity (Figure 8). The flexibility of efficiency of ATP utilization under non-steady state conditions in skeletal muscle[24] illustrates the importance of the compensatory relation between the serial efficiencies in the energy chain. At steady state work loads when ATP supply and ATP demand are matched, an increase of mechanical exergy output per ATP cycle with decreasing velocity (Figure 8) would indicate synergistic regulation of component (k and a) efficiencies, such that $\epsilon_k \approx \epsilon_a$ (Figure 9).

2. Anoxic Conditions

Many invertebrates which tolerate anoxia excrete mainly propionate and acetate during long periods of anoxic exposure. Under these conditions, the propionate/acetate flux ratio is >2, as required by the redox balance when glycogen is the sole substrate (Table 3).[4,7] Such a pattern is observed under long-term anoxia favoring economy strategy, for example, in the aquatic oligochaete *Lumbriculus variegatus*[34] and in the medical leech *Hirudo medicinalis*.[35] In the latter, succinate accumulates during the intial 1-h period of anoxia, at the expense of malate. The lactate pathway is activated only under physiologically induced hypoxia and power strategy when the leeches are stimulated to high locomotory activity. Under active hypoxia, the high-efficiency succinate-propionate-acetate pathways are not employed. This pattern reflects the power/economy concept according to which the high efficiency of the succinate-propionate-acetate pathways is unsuitable to foster high power

output, and a low efficiency of the lactate pathway is an adaptive prerequisite for maximizing power.

Application of the ergodynamic power/efficiency exclusion principle for explaining bioenergetic adaptations under hypoxia received support and contradiction, the latter in defense of the opposite hypothesis on *co*evolution of power and efficiency.[36] Such coevolution is intuitively appealing and renders the low-efficiency paradox in lactic glycolysis unexplained. Rather than providing a general principle of evolution, covariation of power and efficiency is restricted to the low-efficiency region (Figure 6), whereas the power/efficiency trade-off is empirically well documented for ATP production and is theoretically expected in the physiologically relevant high-efficiency domain (Figures 8 and 9). Optimization in contrast to a unidirectional selection for ever-increasing efficiency is a consequence of the ergodynamic exclusion principle (Figure 6). As an alternative to the power/efficiency trade-off, it was postulated that the high-efficiency pathways cannot support high power under hypoxia owing to their inability to run in parallel with high aerobic respiration.[36] The theoretical limitations of this view were discussed elsewhere in detail.[14] A crucial experimental support for the ergodynamic concept on optimum efficiency stems from a test of the transition from resting economy to active power strategy under both aerobic and anoxic conditions.

Like the leech and many other euryoxic invertebrates, *Lumbriculus variegatus* does not produce lactate under passive environmental anoxia (Figure 10.1; anoxic, 0 min stimultion, *E*-strategy). Succinate accumulates to 6 μmol per gram wet weight after 2 h of passive anoxia (Figure 10.2; anoxic, 0 min stimulation, *E*-strategy) and increases up to 10 μmol per gram wet weight when passive anoxia is prolonged for another 2 hours (not shown).[34] Neither under these anoxic conditions nor under aerobic exposure does succinate accumulation contribute to the high-power mode of ATP production induced by electrical stimulation (Figure 10.2; *P*-strategy). It is the low-efficiency, high-power lactate pathway which is switched on to support high energy flux in locomotion (Figure 10.1; *P*-strategy). Even when a slow flux through the succinate pathway has already been induced by 2 h of passive anoxia, and despite the fact that succinate levels can increase almost twice as much during prolonged anoxia, the high-efficiency pathway is not able to generate a high ATP flux as required during stimulation. *E*-strategy and maximum power are mutually exclusive irrespective of aerobic or anoxic conditions (Figure 10).

V. CONCLUSIONS

Adaptation to hypoxia and anoxia leads to the expression of high-efficiency pathways with accumulation of succinate, propionate, and acetate. The Gibbs force efficiency of ATP production is 80 to 90% in these pathways. Under passive anoxia, invertebrates such as intertidal mollusks or benthic oligochaetes do not utilize the less efficient glycolytic pathway to lactate where ATP is produced at an efficiency of only 66%. High efficiency saves exergy and hence increases fitness due to prolonged survival. Increased efficiency of stoichiometrically coupled ATP production in the lactate pathway would imply higher power output per unit of power input. High power output is the primary goal during heavy glycolytically sustained exercise. Did evolution paradoxically fail to exert selective pressures on the efficiency of anoxic ATP production in active vertebrate muscle, where efficiencies are so much lower than in the sluggish anaerobic intertidal mussel?

The explanation for the apparent paradox that maximum power is not achieved at maximum efficiency is derived from a basic ergodynamic exclusion principle. All forces are simultaneously zero in a system at physicochemical equilibrium, then the net fluxes are

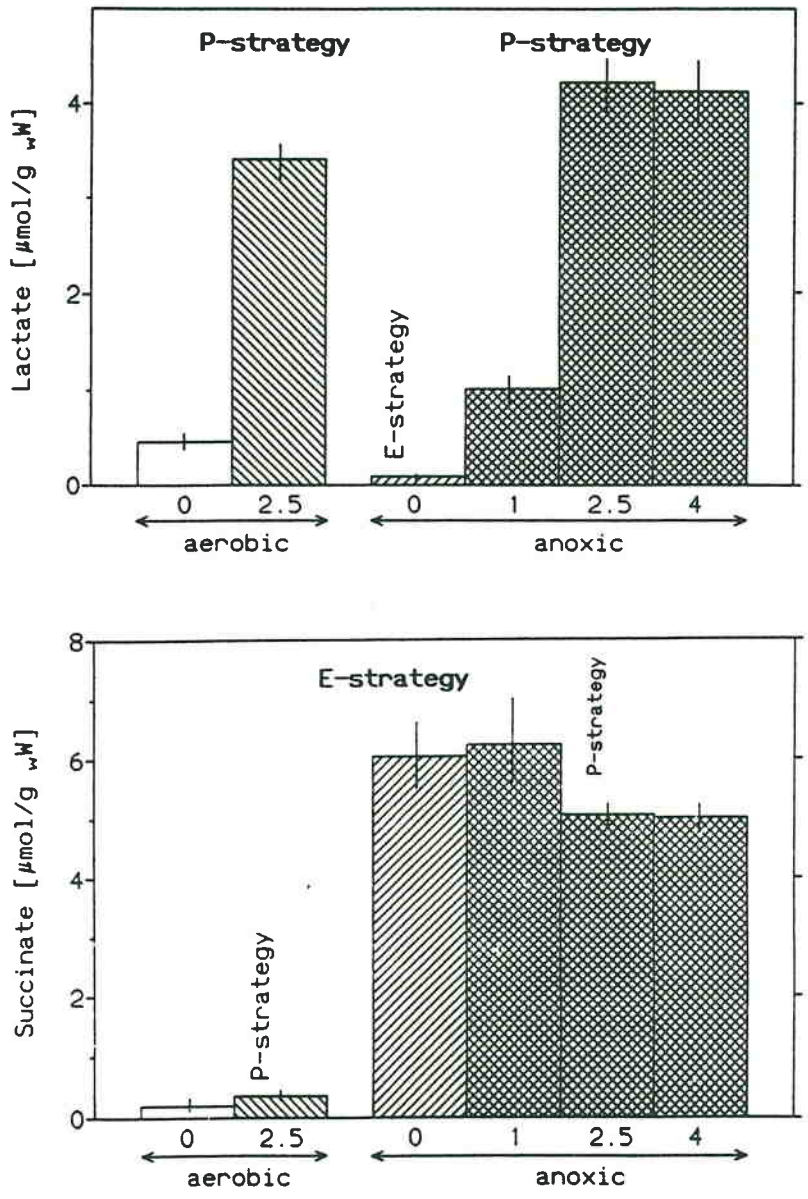

FIGURE 10. Power strategy in active hypoxia and anoxia (*P-strategy*) and economy strategy in passive anoxia (*E-strategy*) in the aquatic oligochaete *Lumbriculus variegatus*. Experiments at 20°C, groups of worms with wet weight of c. 100 g/individual, 17% dry weight (from Putzer; Reference 34). *P-strategy* involves maximum power output at low efficiency during accumulation of lactate [µmol · g^{-1} wet weight] at 1, 2.5, or 4 min of electrical stimulation (25 V, 100 Hz, 5 ms pulses) under both aerobic and anoxic environmental conditions. Without stimulation, lactate levels are low in the *aerobic* control (left; 0 min) and after 2 h of passive anoxia (right; 0 min). *E-strategy* involves low power output at high efficiency during accumulation of succinate [µmol · g^{-1} wet weight] after 2 h of passive anoxia (right, 0 min stimulation). Succinate remains at control levels after 2.5 min of aerobic stimulation (left) and does not increase further upon 1, 2.5, and 4 min stimulation under anoxia (right).

zero. When an arbitrarily high force of the driving reaction is completely offset by the force of a coupled output process, then the system is in ergodynamic equilibrium. The efficiency is maximum and equals 1.0, and the net flux is zero like in physicochemical equilibrium but for a different reason. In the high efficiency domain, the power output decreases with an increase of efficiency towards ergodynamic equilibrium. In this region the indirect proportionality between power and efficiency is independent of linear or non-linear flux/force relationships. The antagonistic energetic constraints of passive anoxia (environmentally induced) or active anoxia (physiologically induced) provide striking examples for transitions between *economy strategy* with low power and high efficiency, and *power strategy* with high power and low but optimum efficiency.

The dichotomy between power and economy strategy in metabolic exergy conversion is empirically related to divergent physiological demands. In different ecological contexts the limiting resource is either exergy, which then promotes economy strategy (*E*-strategy); or the limiting resource is time, and effective utilization of time is achieved in power strategy (*P*-strategy). The *P*/*E* distinction is reminiscent of the differences in *r* and *K* selection in habitats which are characterized by low and high population densities in relation to the resources.

Catabolic stoichiometries and efficiencies of aerobic and anoxic ATP production have evolved in the frame of serial energy conversion: energy transformations providing the ATP supply are connected in series to the energy transformations generating the ATP demand. Catabolic and anabolic efficiencies are multipled to obtain the overall efficiency. This multiplication of serial efficiencies must be accounted for in any concept on optimum compartmental or overall efficiencies.

Except for heat dissipation and thermal regulation, fully coupled ATP production is functionally superior to partially uncoupled energy transformations. Functional branching towards different modes of ATP utilization in maintenance and various physiological performances is different from uncoupling. Such branching and parallel energy utilization may obscure the overall pattern of optimum efficiency.

The principle of local, decentralized cellular energy production is maintained under aerobic and anoxic conditions. In contrast, specific anabolic, ion transport and mechanical output performances are centralized in highly specialized tissues and organs. Specialized output performances such as mechanical power output in skeletal muscle are most suitable for studying optimum efficiencies of ATP utilization, whereas all tissues under maintenance and activated states are suitable of studying optimum efficiencies of ATP production. Catabolic and anabolic efficiencies may be antagonistic and compensatory, thus maintaining overall efficiency constant. Alternatively, a synergistic simultaneous change of anabolic and catabolic efficiencies augments the adaptive shift of the efficiency of the individual component.

Matching of kinetic (enzymatic) conductivities in catabolic and anabolic compartments is essential for the metabolic economy. Ergodynamic inhibition by high efficiency of ATP production can be compensated by an increase of specific enzyme activity and enzyme concentration and by maintaining high metabolite activities, thus accelerating flux at constant force. The superiority of this strategy of high conductivity is constrained by the high indirect costs of maintaining elevated concentrations and turnover of enzymes. Nevertheless, this strategy is both efficient and effective in stable eutrophic environments, and in tissues with comparatively constant high power output, such as the heart. Tissues geared towards high burst activity for a short time, however, encounter low efficiency and high direct costs during explosive performances of the power of life.

ACKNOWLEDGMENT

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APPENDIX: LIST OF SYMBOLS

All extensive quantities are here implicitly divided by system size (volume; wet or dry biomass or amount of protein are other common expressions indicating the size of biological

systems). Thereby size-specific quantities are obtained. For instance, power, P, is implicitly divided by volume, avoiding the more complex symbol for power per volume, P_V [W · m^{-3}]. A conventional unit for the volume is the liter [1 liter = 1 dm^3 = 10^{-3} m^3].

Name	Symbol	Relation	SI Unit	Notes (Equation[s])
Reaction coefficient	b	$b = L\,\alpha^{-1}$	$mol \cdot J^{-1} \cdot s^{-1}$	27–29
Degree of coupling	d			29–33
Normalized force ratio	f	$f = -F_{out}/F_{in}\lvert\nu\rvert$		20,26[a]
Ergodynamic force	F	$F = \partial G/\partial_r\xi$	$J \cdot x^{-1}$	4
Gibbs energy (exergy)	G	$G = H - TS$	$J \cdot m^{-3}$	4
Reaction Gibbs energy	d_rG	$d_rG = d_r\xi_B\Delta_rG_B$ $= d_r\xi F$	$J \cdot m^{-3}$	5
Gibbs force of reaction	Δ_rG_B, F_B	$\Delta_rG_B = \Sigma_i\,\nu_i\,\mu_i$ $= (\partial G/\partial_r\xi_B)_{T,p}$	$J \cdot mol^{-1}$	14[b] 4, 7, 10
Normalized flux ratio	j	$j = Y_{out/in}\,\lvert\nu\rvert^{-1}$		19, 25[a]
Flux of chemical reaction	J_B	$J_B = d_r\xi_B/dt$	$mol \cdot s^{-1} \cdot m^{-3}$	3, 12[c]
Conductivity	L	$L = -JF^{-1} = b\alpha$	$mol^2 \cdot J^{-1} \cdot s^{-1} \cdot m^{-3}$	28, 30
Change of reacting substance	d_rn_i	$d_rn_i = d_r\xi_B\nu_i$	$mol \cdot m^{-3}$	11
Power	P	$P = d_{tr}G/dt = JF$	$W \cdot m^{-3} = J \cdot s^{-1} \cdot m^{-3}$	2, 5
Power of reaction r	P_r	$P_r = d_rG/dt$ $J_B\,\Delta_rG_B$	$W \cdot m^{-3}$	16, 32
Flux ratio	Y_{ATP/O_2}	$Y_{ATP/O_2} = J_{ATP}/J_{O_2}$		19
Power efficiency, ergodynamic efficiency	ϵ	$\epsilon = -P_{out}/P_{in} = jf$ $= d_{tr}G_{out}/d_{tr}G_{in}$		1, 17, 21
Chemical potential	μ_i	$\mu_i = (\partial G/\partial n_i)_{T,p,J\neq i}$	$J \cdot mol^{-1}$	13, 15[d]
Stoichiometric number	ν_i			
Advancement of reaction	$d_r\xi$	$d_r\xi_B = d_rn_i\,\nu_i^{-1}$ $\Delta_r\xi = \int J\,dt$	$mol \cdot m^{-3}$	11, 12[e] 3

[a] ν is the coupling stoichiometry with reference to which the experimentally observed flux and force ratios are normalized, e.g., the ATP:Glyc stoichiometric ratio, $\nu_{ATP/Glyc}$ (Equation 18). The subscripts out and in indicate the entity chosen to measure output and input fluxes (Equations 9.p and 9.k; see subscript B in footnote b).

[b] The subscript B indicates that any reaction stoichiometry is transformed such that $\lvert\nu_B\rvert = 1$.

[c] The extensive quantity corresponding to the size specific (scalar) flux is the (scalar) flow, I. For example, $J_{O_2} = I_{O_2}\,V^{-1}$ (catabolic oxygen consumption by the organism divided by the volume of the organism).

[d] Since the extensive quantities are divided by volume, then $dn_i = dc_i$ if volume is constant.

[e] The symbol for the extensive advancement, $d_r\xi$, is here used for the size-specific quantity. If these should be distinguished, $d_rY = d_r\xi\,V^{-1}$.

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