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OPTIMUM EFFICIENCIES OF ENERGY TRANSFORMATION IN ANOXIC METABOLISM
THE STRATEGIES OF POWER AND ECONOMY

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INTRODUCTION

Anoxic Muscle and Mussel

We are all fascinated by high-power phenomena in nature, be they the flash-like jet-propulsion of an escaping squid, the outburst of energy in a hunting cheetah, or the explosive sprint of a racing athlete. The underlying physiological processes have evolved under the selective pressure of optimizing effective power strategy (P-strategy), just as the potential for rapid growth and reckless resource exploitation is rooted in r-selection of species (MacArthur & Wilson, 1967; Gnaiger, 1983a).

A different kind of attraction stems from the vigilant economy prevailing in the living world. Economy-strategy (E-strategy) favours traits that not only use resources effectively, but efficiently. At the maximum input-output efficiency of energy transformation, however, the rate becomes infinitely slow (Prigogine, 1967). Therefore, maximum power output and maximum efficiency are mutually exclusive and consequently P-and E-strategy propagate divergent traits.

My aim is to explain some of the diversity of energy metabolism in terms of the power-economy concept of optimum action (P/E-concept). I will discuss high-power, anoxic muscular exercise, and high-economy, endurance of invertebrates in anoxic environments as characteristic examples. Anoxic metabolism provides the catabolic power at the extremes of low and high metabolic energy flow in animals. Anoxic metabolism is not only phylogenetically the most primitive process of biological energy transformation (Broda, 1975; Livingstone et al., 1983), it is functionally the most versatile mechanism to power maintenance, growth or locomotion in bacteria (Fenchel & Blackburn, 1979; Stouthamer, 1977), plants (Crawford, 1978), and animals including man (Hochachka & Somero, 1984). The physiological functions

addressed here, namely locomotion and maintenance, contribute significantly to survival and dispersal, and hence to evolutionary fitness. Somatic and reproductive growth are, like locomotion, energy expenditures above or competing with maintenance requirements. It is therefore reasonable to assume that the energetics of growth follow the patterns of the power-efficiency trade-off, as captured by the model of muscular energetics and environmental anoxibiosis (Gnaiger, 1983a).

First I will outline the distinctive characteristics of the power-economy concept of optimum action by explaining the properties of a simple (one-compartmental) linear energy converter (Kedem & Caplan, 1965). For a functional interpretation of biochemical energy metabolism, we have to take into account the two-compartmental structure of the catabolic-anabolic machinery of cells. A formal derivation of the theory is given in the Appendix (where equations are labelled A1 etc.).

In putting the P/E-concept to the empirical test, I will draw mainly on experimental data gained on vertebrate muscle (di Prampero, 1981; Kushmerick, 1985) and anoxic mussel (Wijsman, 1976; de Zwaan, 1983). By rationalizing the optimum efficiencies of anoxic ATP-production (Gnaiger, 1983a), improved insight is gained into the general patterns of biochemical and physiological adaptation. Some evidence is available suggesting that the P/E-concept can explain the differential constraints on growth rate and growth efficiency (Westerhof et al., 1983; Koch, 1985). Therefore, the distinction between density-dependent selection for maximum epidemic growth (r-strategy) and maximum sustaining capacity (K-strategy) (Boyce, 1984) can be understood as a special case within the framework of the P/E-concept of optimum action.

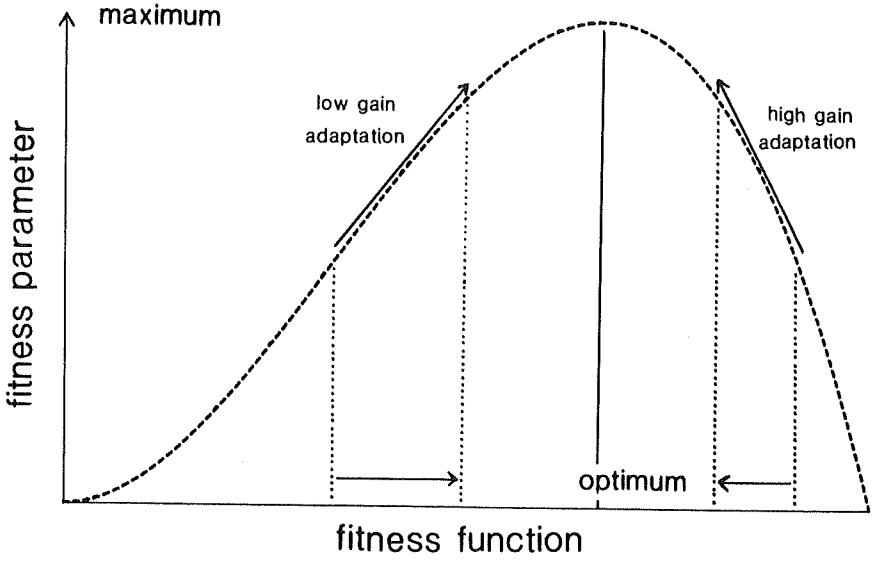
OPTIMUM VERSUS MAXIMUM EFFICIENCY

Classical thermodynamics defines the maximum amount of work which can, under defined conditions, be extracted from the conversion of a unit amount of substrate. Complete (100%) extraction of Gibbs energy or maximization of efficiency to 100% implies complete reversibility with infinitely slow net rates, that is equilibrium of a stable system. This maximum cannot be optimum for life. On the contrary, the dynamics of life and work depend on efficiency and irreversibility in proportioned balance. A limited reduction and therefore optimization of efficiency is required. Seen from this perspective, irreversibility is not a mere waste of energy but is necessary for optimum system performance in time. P-strategy maximizes the work per unit

time which is power ($J\ s^{-1}$ = W). Think of a 100-m race: maximum power output is equivalent to the minimum time required for a given amount of work; the inevitable cost of minimizing time is rapid exhaustion, i.e. a high dissipation of energy at a low (optimum) efficiency. E-strategy, however, increases the time of sustained submaximum power output by simultaneously increasing the power output per unit power input (i.e. efficiency). The increase in (optimum) efficiency is limited according to the relative selective values of energy and time.

Mathematically, optimum principles are not clearly distinguished from extremum (minimum or maximum) principles (Hildebrandt & Tromba, 1985). For physiological functions and evolutionary success, however, a strict distinction applies: independent variables (fitness functions) are optimized in order to maximize fitness (Fig. 1). Every modification of a fitness function towards the optimum is an adaptation or acclimation. The assignment of

Fig. 1. Adaptation is optimization of a fitness function (horizontal arrows) to maximize a fitness parameter (sloping arrows) under a defined set of constraints.



a specific optimum value to the fitness function depends on (1) our hypothesis about the functional significance and resource limitations of the process under study, and (2) on the physicochemical relationship between fitness parameter and fitness function which dictates the need for a "best compromise" (Fig. 1). The distinction between maximization and optimization of a particular variable has important practical and theoretical consequences. However, there is a tendency to consider maximization of a simple and intuitively appealing function as adaptive. The scientific view in an energy-rich culture is likely to be dominated by the paradigm of optimum efficiency for maximum power (Odum & Pinkerton, 1955). Accepting that scientific paradigms follow the trends in society (Kuhn, 1970), we are not surprised that - after the oil crisis - the maximum efficiency of an energy converter (Kedem & Caplan, 1965) has been misleadingly renamed as "optimum efficiency" (Stucki, 1980). Efficiency is a fitness function with an optimum that is different from the maximum in most cases (Fig. 1). By this argument, the calculation of degrees of decoupling which maximize power efficiency at various force efficiencies in mitochondria (Stucki, 1980) is explained as a physiologically irrelevant exercise (for more detailed explanation of terms see below). To retain the physiological significance of optimum efficiency as a fitness function, we must define the environmental conditions and physiological processes which stipulate P- or E-strategy (Gnaiger, 1983a).

Today many biochemists believe exclusively in an enzyme kinetic regulation of metabolic rate. While the necessarily irreversible character of biochemical pathways is generally recognized, they deny explicitly the possibility to rationalize entirely the thermodynamic terms, and hence to define exact optimum efficiencies, in relation to the control of metabolic fluxes (Atkinson, 1977; Newsholme & Start, 1973). However, with the aid of optimization techniques (Maynard Smith, 1978; Calow & Townsend, 1981; Krebs & McCleery, 1984), the concept of P- and E-strategy allows biochemical free-energy changes to be rationalized in relation to the control of flows through biochemical pathways. This aspect of ecological physiology is fundamental to the growing theory of evolutionary energetics. A principle hypothesis of evolutionary energetics, then, is the prediction that power output and input-output efficiencies of biochemical energy conversion follow the strict optimum patterns of P- and E-strategy.

Energy transformation at optimum efficiency is the product of the evolution of energy-coupled systems. The dynamics of such systems is described by an important theory of the "thermodynamics of irreversible

processes" (Prigogine, 1967). By definition, conservation of work in the output reaction is a fully reversible process. Functionally, this conservation of energy is the most significant task in cellular energy transformation. Moreover, cells operate as isothermal energy converters, so thermal changes are merely accompanying features in the transformation of chemical energy. In this context, it is logical to replace the terms irreversible and non-equilibrium thermo-dynamics by ergodynamics, defined as the theory of coupled dissipative (irreversible) and conservative (reversible) energy flow. Ergo-(work-) dynamics is that branch of energetics which is concerned with the transformation and performance of work in time, the "motion of energy" (from Greek ergon = work). The coupling of an input force to an output force of equal magnitude but reversed in sign yields 100% efficiency. The net force in such a system is zero: it is in ergodynamic equilibrium. In contrast, physicochemical or thermodynamic equilibrium is defined as a state of minimum energy content. The Gibbs energy of a system in ergodynamic equilibrium is high, since each half reaction of the coupled reaction is maintained away from its partial physicochemical equilibrium by the compensation of input and output forces. A system in ergodynamic equilibrium is fully coupled; the antagonistic input and output forces cannot dissipate via leaks, that is by decoupling. Only fully coupled systems will be discussed here for reasons explained below.

POWER, ECONOMY, AND FITNESS

The power-economy concept (P/E-concept) of optimum action is based on a dynamic interpretation of Gibbs energy changes characteristic for living cells. In the steady state, chemical potential differences between the substrates and products provide the driving force for the metabolic machinery. Without the pressure or drive of a chemical force, the reaction rate is zero even in the presence of enzymes. In a range of low forces and in many enzyme-catalyzed reactions there exists a near-linear relationship between the driving force and metabolic flow (Caplan & Essig, 1983). Therefore a direct relationship exists between chemical force and metabolic power: power is the product of force and flow.

Oxygen, like the fuels carbohydrate, lipid and protein, is a catabolic substrate. Hence, oxygen deprivation implies a state of "starvation" whereby limitation is in terms of chemical energy per mole instead of available amount of organic substrate. The chemical driving force is the molar Gibbs energy of reaction (kJ mol^{-1}) at constant temperature and

stable concentrations of substrates and products. Chemical force can be set free either to give rise to chemical, mechanical and other forms of work, or to be dissipated irreversibly as entropy. The proportion of the two antagonistic aspects of the input force, conservation and dissipation, is the efficiency. It characterizes the instantaneous power potential of the system when the kinetic parameters are constant.

The general flow-force relationship applies equally to power input and output of an energy converter, but the input-output net force determines the rate of the coupled reaction. The input force drives the coupled reaction at a maximum rate if it is not compensated by output force, that is at an output force of zero. Then the power input is maximum, yet the power output (output flow x output force) and efficiency are zero (Fig. 2a; f = 0). Low power output despite a high rate of the coupled process is due to inefficient energy conversion. This is functionally advantageous only if the actual fitness parameter is the reaction rate instead of power output (Kedem & Caplan, 1965). The reaction rate, and consequently power input as well as output, are zero at the limit of ergodynamic equilibrium at maximum efficiency (Fig. 2a; f = 1.0). Between these limits, maximum power output is achieved (Fig. 2a). P-strategy involves a compromise between maximum rate and maximum efficiency.

Power strategy produces instantaneously maximum power output of a system. Power-optimum efficiency is 50% in a one-compartmental linear energy converter; that is the input-output efficiency at which power output is maximum, at constant input force (Fig. 2a). P-strategy evolves under circumstances when resource availability is unlimited but resource utilization is constrained by the input mechanism (e.g. aerobic hypoxia), or when instantaneous benefits from power output outweigh the necessary cost of relatively inefficient resource dissipation.

Power input is utilized more economically at higher efficiencies. With increasing output force and force efficiency (Eq. 2.1) the input-output net force is reduced. Efficiency induces an ergodynamic inhibition of the coupled flow. This is why the power input is progressively depressed with increasing efficiency. At high efficiency, the reduction of the rate of the coupled reaction reduces the power output (Fig. 2b; "ergodynamic inhibition"). E-strategy involves a compromise between maximum power and maximum efficiency.

E-strategy optimizes power output at an economical level. The resulting economical power is the product of power output times the value of

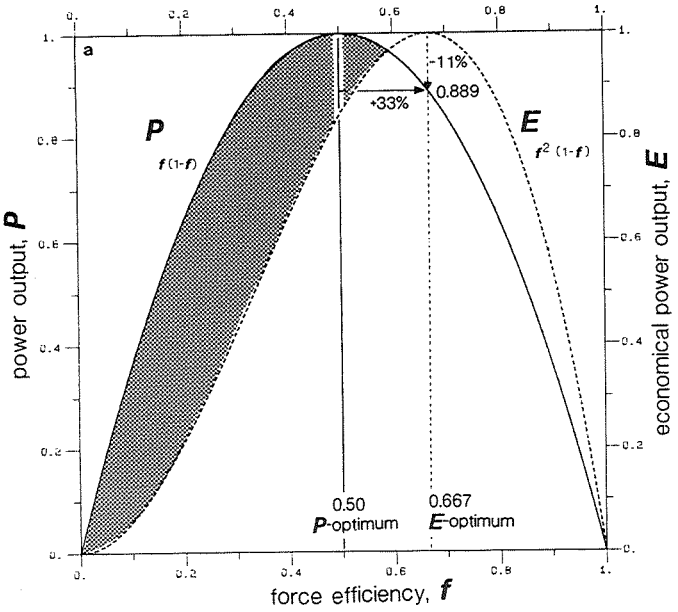


Fig. 2a. Optimization of force efficiency (normalized force ratio, f) to maximize two divergent fitness parameters, power output (P) and economical power output (E = fP), in a one-compartmental, fully-coupled linear energy converter. Plots are normalized relative to the maximum of each fitness parameter at constant input force (Eq. A4.2 and A5). In a fully-coupled system, the force efficiency equals the input-output energy or power efficiency, that is total output divided by total input. Power output is maximum at the P-optimum efficiency, whereas the product of efficiency and power output is maximum at the E-optimum. E-optimum efficiency is increased by 33% while power output is decreased by only 11% in E- relative to P-strategy (arrows).

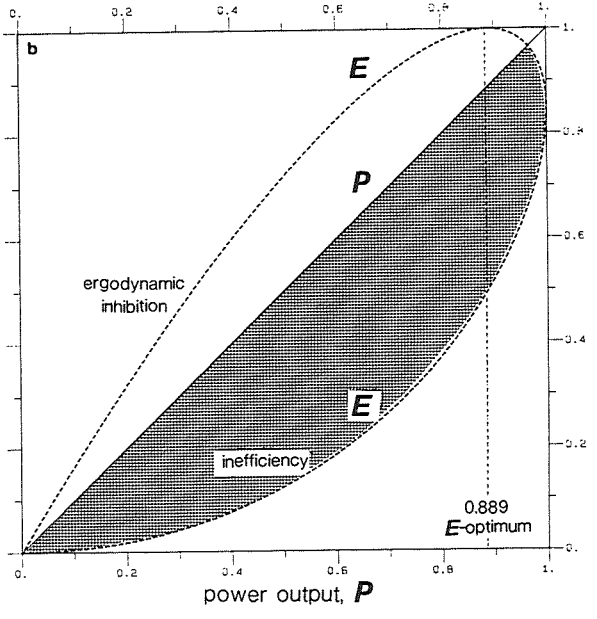


Fig. 2b. Optimization of power output (P) to maximize economical power output (E; projection of E on P from Fig. 2a). At low efficiencies, the low power output and high rate of energy loss yield very low values of economical power (lower broken line, "inefficiency"). E reaches only 50% at a pseudo-optimum power at f=0.33. E is still 16% below maximum due to low efficiency at the maximum power output. At supra-optimum efficiencies, the low power output and low rate of energy loss yield a slow decrease of economical power with decreasing power output and increasing efficiency (upper broken line, "ergodynamic inhibition" of the reaction rate due to a depression of net force).

efficiency (Fig. 2a). In E-strategy, economical power is the fitness parameter that is maximized (Fig. 1) in which case efficiency (Fig. 2a) and power output (Fig. 2b) are optimized fitness functions. E-strategy evolves under limited resource capacity when the long-term benefits from economical resource utilization, and hence enduring potential, outweigh the disadvantages of relatively low power output tuned at a reduced level.

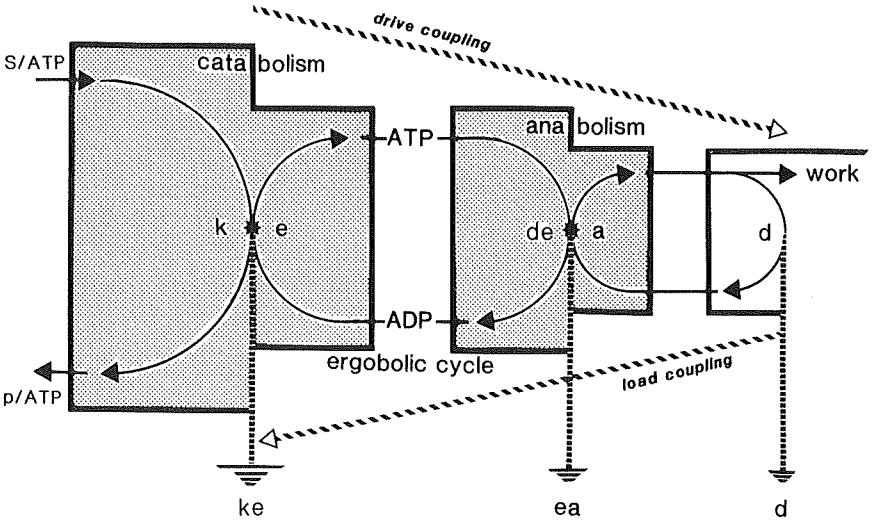
Economical optimum efficiency is a continuous function of the relative selective values of minimizing energy dissipation and minimizing time. A characteristic example of E-strategy is obtained if power is multiplied with the numerical value of efficiency (Stucki, 1980). Then economical optimum efficiency is 66.7% in a simple linear energy converter (Fig. 2a). Whereas the power input falls off by 33%, the power output drops only by 11% as the efficiency is increased from the power-optimum (0.50) to the economy-optimum (0.67; Fig. 2a). This assumes that the input force and the internal conductance (the kinetic properties) of the system are maintained constant.

Mismatched strategies of resource utilization and diminished resource capacity are reasons for the tragic death of starving people. Moreover, it is general ecological and physiological knowledge that rates of growth and locomotion of organisms are frequently constrained by limited environmental or internal resource capacities. Resource capacity differs from instantaneous resource availability, in that the term resource (buffering) capacity incorporates the potential for resource regeneration as well as the potential for recycling or effective waste disposal. Power input draws on the resource capacity. A decrease in power input leads to a proportional decrease in power output at constant input-output efficiency. Increased efficiency, however, yields a decrease of resource dissipation (power input) per unit power output, and therefore increases the endurance time. Since resources are limited, the efficiencies of metabolic energy conversion must be optimized according to the selective advantages of P- or E-strategy under the prevailing environmental and physiological conditions. For systems with sufficient adaptive flexibility, therefore, the P/E-concept predicts different optimum efficiencies of energy conversion according to the selective value of a specific mode of performance. Power strategy leads to an equal balance of dissipation (net-drive) and conservation (compensative output). Higher economical efficiencies are possible, but are only optimum in the long run when energy saving is more successful than a more powerful, fast, and less efficient performance.

COUPLING OF FLOWS AND FORCES, AND ERGOBOLIC POWER

Cells are ergodynamic structures (Fig. 3) in which total energy flow is functionally related to the coupling of input to output flows and input forces to compensative forces. Besides photosynthesis, the most important process of biological energy transformation is that occuring in catabolism. In the overall process, two coupled half reactions are distinguished, one characterized by a high driving force, that is a strongly exergonic (negative),

Fig. 3. Two-compartmental energy transformation in the catabolic-anabolic energy chain. Metabolic flows (half-cycles) are normalized on the basis of ATP-coupling stoichiometries; S/ATP and p/ATP are substrate consumption and product formation, respectively, per molar ATP-cycle. In the metabolic steady state, the ergobolic cycle of ATP-formation (e) and ATP-utilization (de) is balanced. In the dissipative steady state, the energy sinks (ke, ea, and d) balance the catabolic input. d is the dissipative half-cycle, e.g. in protein-turnover or crossbridge cycling. Mismatched drive-coupling may induce compensation by futile (ad) cycles. Excessive load-coupling induces non-steady state depletion of ATP-equivalent energy stores.



molar Gibbs energy of reaction, and the other by energy conservation (endergonic). Let us define the driving reaction, where reduced fuel substrates (carbohydrate, lipid, protein) are oxidized, as the catabolic half reaction, and the energy-conserving half reaction, where ADP is phosphorylated to ATP and phosphocreatine or phosphoarginine stores are replenished, as the ergobolic reaction.

The term "ergobolic reaction" (Gnaiger, 1983a; compare ergodynamics), indicates that changes in cellular ATP/ADP ratios or phosphagen stores take place by ergodynamic coupling to catabolic or anabolic half reactions (Fig. 3). These ergobolic net changes are endergonic or exergonic, respectively, and have a specific function in regulating the efficiency of metabolic energy transformation. No net changes of adenylates and phosphagens occur in the ergobolic steady state when ATP-turnover mediates the biochemical "energy unit" of ATP from catabolism to anabolism. The ergobolic flow is expressed as the rate of ATP production, $\dot{N}_e$ (µmol ATP/h) ($\dot{N}$ denotes dN/dt). The conjugate ergobolic force is the Gibbs energy of phosphorylation of one mole ADP to ATP, that is the phosphorylation potential, $\Delta_e G$:

$$ADP + P_i \rightarrow ATP$$

$$\Delta_e G = \Delta_e G^{o'} + RT \ln \left(\frac{[ATP]}{[ADP] \times [P_i]} \right) \qquad (1)$$

$\Delta_e G^{o'}$ varies as a function of cellular pH, divalent cation (especially magnesium) activity, ionic strength and temperature. At cellular pH of 7 and pMg of 2.7, $\Delta_e G^{o'}$ is 30 kJ/mol ATP, decreasing at more acid pH (Alberty, 1969). The only value relevant for the cellular reactions is $\Delta_e G$, the actual ergobolic potential: +51 kJ/mol ATP or mJ/µmol ATP is a typical in vivo value for aerobic cells, but it may decrease to +44 kJ/mol ATP under anoxia due to a decrease in pH and ATP/ADP-ratio and an accumulation of inorganic phosphate, P_i (Dawson et al., 1978; Gnaiger, 1983a). In resting vertebrate muscles, the creatine kinase buffers ATP at essentially constant levels of some 7mmol/dm^3 and ADP levels at µmolar concentrations, and the phosphate levels are very low (di Prampero, 1981; Kushmerick, 1985). Under these conditions, $\Delta_e G$ exceeds +60 kJ/mol ATP (Eq. 1). This wide range of Gibbs energy changes of phosphorylation is in remarkable contrast to the many textbook statements referring to some constant or cellular standard value.

Catabolic flow, $\dot{N}_{k_i}$, is measured in various ways; as catabolic substrate consumption, $\dot{N}_{k_s}$; as the rate of oxygen consumption, $\dot{N}_{k_{O2}}$; or as

the rate of accumulation and excretion of endproducts, $_{k}\dot{N}_{p}$. Accordingly, the catabolic input force is expressed as the Gibbs energy change per mol substrate ($\Delta_{k}G_{s}$ = -2879 or -2873 kJ/mol glycogen, at a glycogen concentration of 1.0 and 0.09 mol/dm^3, respectively, and otherwise typically aerobic cellular conditions; see Gnaiger, 1983a; here glycogen is always used for glycosyl-units). Since 6 mol O_2/mol glycogen are consumed in aerobic catabolism, the catabolic force of oxygen is $\Delta_{k}G_{O2}$ = -2873/6 = -479 kJ/mol O_2 . This value is nearly identical with the oxycaloric equivalent, $\Delta_{k}H_{O2}$, for the substrate glycogen (Gnaiger, 1983b). Therefore, the calorimetric measurement of aerobic heat dissipation yields the catabolic power directly (Gnaiger, 1983c). This is not true, however, for anaerobic catabolism.

Based on catabolic pathways or biochemical maps, a specific stoichiometry is calculated between catabolic and ergobolic rates. According to this "mechanistic stoichiometry", we expect 37 (or 38) mol ATP generated per mol glycogen oxidized, which converts to a stoichiometric coefficient for oxygen of 37/6 = 6.17 ATP/O_2. For anoxic catabolism, the mechanistic stoichiometry is 1.5 ATP/lactate and 3 ATP/glycogen, or 2.75 ATP/succinate and 4.71 ATP/glycogen (Gnaiger, 1977; Tab. 1).

The mechanistic molar stoichiometry, $\nu_{ATP/i}$ (i = catabolic reactant), provides the important link between ergobolic and catabolic flows and forces. The catabolic force efficiency, $_{k}f$, and flow efficiency, $_{k}j$, are defined here as the ergobolic/catabolic flow and force ratio, respectively, normalized for the ATP-stoichiometry.

$$_{k}f = \frac{-\Delta_{e}G}{(\Delta_{k}G_{i} / \nu_{ATP/i})} \qquad (2.1)$$

$$_{k}j = \frac{_{e}\dot{N}}{(_{k}\dot{N}_{i} \times \nu_{ATP/i})} \qquad (2.2)$$

In Eq. (2), the two expressions in brackets can be understood as the catabolic coupling force and flow, respectively, normalized for the mechanistic ATP-coupling stoichiometry. We define (Gnaiger, 1983a)

$$\Delta_{k}G = \Delta_{k}G_{i} / \nu_{ATP/i} \qquad (3.1)$$

$$_{k}\dot{N} = _{k}\dot{N}_{i} \times \nu_{ATP/i} \qquad (3.2)$$

From Eq. (2.2) and (3.2) we see that for the fully coupled process ($_{k}j$ = 1), the ergobolic rate of ATP production, $_{e}\dot{N}$ (μmol ATP/h) is numerically

identical to ${}_k\dot{N}$, which then is the rate of ATP-turnover (μmol∞ATP/h). In most cases, Eq. (3.2) is the only means for calculating the rate of ATP-turnover, with the assumption that ${}_kj = 1$.

Using Eq. (2) the force and flow efficiencies are calculated (Tab. 1)

$$ {}_kf = \frac{-\Delta_e G}{\Delta_k G} \qquad (4.1) $$

$$ {}_kj = \frac{\dot{e}N}{\dot{k}N} \qquad (4.2) $$

For the above example of glycogen respiration, the aerobic catabolic force efficiency is obtained from Eq. (2.1) or (4.1),

$$ {}_kf = \frac{51}{479/6.17} = \frac{51}{78} = 0.66 $$

The product of flow efficiency and force efficiency is the input-output power efficiency or ergodynamic efficiency, η, which equals the force efficiency at ${}_kj = 1$;

$$ {}_k\eta = {}_kj \times {}_kf = \frac{-{}_eP}{{}_kP} \qquad (5) $$

The ergoblic power output, ${}_eP$ (mJ/h; = mJ/s = mW), is the product of the rate of ATP-formation and ergobolic potential (Eq. A3.2). This composite function of catabolic energy conversion is clearly recognized in biochemical studies where the ATP-equivalent catabolic flux and the ATP/ADP-ratio, pH, etc. are taken into consideration. At low efficiencies, catabolic power input, ${}_kP$, is mainly dissipated, rendering the ergobolic power output low (Fig. 2; inefficiency). At high efficiency, the net catabolic-ergobolic potential or "ATP-coupling potential" (Eq. A1) is low; therefore the rate of energy conversion and hence power output is low again (Fig. 2; ergodynamic inhibition). The P- and E-optimum functions based on linear ergodynamic equations are derived in the Appendix (Eqs. A4.2 and A5).

LOWEST ATP GAIN - HIGHEST ATP PRODUCTION

During burst activity over periods of some 40 seconds, strenuous muscular exercise is powered by the lactate pathway in vertebrates (di Prampero, 1981). This is also true for invertebrates, where the lactate and the opine pathways (Livingstone et al., 1983) have two features in common,

typifying the state of physiological anoxia: (1) these pathways are employed when ATP demand is highest, and (2) they are the pathways with the least gain in ATP per unit substrate, that is 3 ATP/glycogen (Tab. 1). This interconnexion may at first sight appear to be paradoxical: Could an athlete runner win the race by extracting more ATP from the glycogen stores of his muscles? The ergodynamic analysis yields a definitive answer: The high ATP/glycogen coefficients of the succinate-propionate-acetate pathways are unsuitable for fostering high rates and provide relatively low power output, due to ergodynamic inhibition (Fig. 2). Efficiencies exceeding 0.7 are certainly incompatible with P-strategy. This explains why even invertebrates capable of utilizing high-efficiency pathways at low rates, switch to the less efficient lactate pathway to power muscular exercise in the presence and absence of environmental oxygen (Zebe et al., 1981, Putzer, 1985).

Under environmental anoxia, most euryoxic invertebrates produce succinate as the major glycolytic end product initially (I), whereas the propionate-acetate pathway predominates after a transient period (II). The

Table 1. ATP-stoichiometry and ergodynamic characteristics of fully coupled catabolism of glycogen in aerobic muscle (ox) and in anoxic pathways with the formation of different end products (anox). f_{opt} is the theoretical optimum compartmental force efficiency corresponding to the respective strategy in a two-compartmental energy chain. For further explanation see text and Gnaiger (1983a).

Pathway	ATP/glycogen-units		$\Delta_k G$	$\Delta_e G$	k^f	function	strategy
	$\nu_{ATP/S}$	%	(kJ/mol ATP)				(f_{opt})
ox	37	100	-78	62	0.80	muscle, rest	E_{II} (0.80)
ox			-78	50	0.64	muscle, high ox exercise	P (0.67)
lactate	3.0	8.1	-81	51	0.63	muscle, onset of anox exercise	P (0.67)
succinate	4.71	12.7	-70	51	0.74	environ. anox, initial	E_I (0.75)
prop.-acetate	6.33	17.1	-56	44	0.79	environ. anox, long-term	E_{II} (0.80)
propionate	6.43	17.4	-55	44	0.81	environ. anox, long-term	E_{II} (0.80)

stoichiometric ATP coupling coefficient, $\nu_{ATP/S}$ (the "biochemical efficiency"), of these pathways is high relative to lactate-glycolysis (Tab. 1), and coincides with a decreased proton generation per mol ATP-turnover (Gnaiger, 1980a; Pörtner et al., 1984). These traits are generally recognized as the most significant biochemical adaptations to anoxic tolerance. However, the biochemical-stoichiometric perspective does not reveal any advantage of initial succinate accumulation over propionate-acetate production. During aerobic recovery, propionate is resynthesized to glycogen as readily as is succinate. Yet, the great majority of euryoxic invertebrates accumulate and excrete propionate only after an initial lag-time which may last up to 18 hours (Kluytmans et al., 1978). Is it lack of enzyme-kinetic flexibility, that prevents an immediate metabolic switch to the propionate pathway with a yield of 6.4 mol ATP/mol glycogen instead of only 4.7 mol ATP/mol glycogen in the succinate pathway?

An ergodynamic analysis is required to understand the adaptive significance of initial succinate accumulation and secondary propionate-acetate production, and to fully appreciate the kinetic fine-tuning of the metabolic machinery. An economical energy converter must not only transform free energy at a characteristic optimum efficiency but must, first of all, extract effectively free energy from the available substrate ($\Delta_k G \times \nu_{ATP/S}$ must be high; Tab. 1). A more detailed analysis of the complex compromise in optimization of catabolic energy conversion helps to explain why and when the succinate or the propionate-acetate pathway are most advantageous (Gnaiger, 1983a).

However, three questions have yet to be solved: (1) How can we rationalize the high force efficiencies observed in aerobic and anaerobic catabolism? If economical power output in terms of ATP were the definitive fitness parameter in E-strategy, then the force efficiency is expected to be 0.67, instead of 0.74 and 0.80 for succinate (I) and propionate (II) respectively. Moreover, the lactate pathway - the most typical example for P-strategy - should operate at a force efficiency of 0.5 instead of >0.6, if the system were selected for maximum ergobolic power output. (2) What is the rate of anoxic ATP-turnover? A discrepancy between anoxic heat dissipation and enthalpy changes of biochemical reactions suggests that ATP-turnover, calculated from biochemical measurements, presently underestimates total catabolic rates under anoxia (Gnaiger, 1980b; 1983a; Shick et al., 1983). (3) What is the functional significance of ATP production? Metabolism is not simply designed to produce ATP. ATP is an intermediate

for transmission of energy to various ATP-utilizing processes. ATP-turnover is the energetic coupling of catabolism and anabolism; hence the term "ergobolic cycle" (Fig. 3). Energy metabolism can be understood only as the integrated process of anabolic ATP utilization and catabolic ATP formation. This argument is simple but important, yet it is frequently ignored.

The catabolic-ergobolic optimum efficiencies in P- and E-strategy in one compartment do not retain their characteristic values when seen in the context of whole-system function. Analysis of the metabolic system as a two-compartmental energy chain (Fig. 3) explains the high catabolic efficiency as optimization of energy-chain efficiency.

THE TWO-COMPARTMENTAL CATABOLIC-ANABOLIC ENERGY CHAIN

Metabolism is structured into catabolic and anabolic reaction sequences (Fig. 3). This partitioning is a prerequisite for the flexibility and regulatory capacity of cellular metabolism to utilize various fuel substrates for the entire variety of "anabolic" functions such as biosynthesis, active transport, electrical signal transmission and mechanical work, via ATP (Atkinson, 1977). For metabolic control, the conductance of catabolism must be matched with that of anabolism, and this in turn must be adjusted to the external load conductance (Appendix A.2). Instead of catabolic efficiency and ergobolic power output, now the overall efficiency of the energy chain and the anabolic power output are recognized as the proper criteria for optimum cellular functions.

The anabolic power output is here defined as the power of any process that is driven by coupling with the utilization of ATP-equivalent energy. The anabolic coupling force, $\Delta_a G$, is the output force normalized in relation to the ergobolic driving force, $-\Delta_e G$ (compare Eq. 2 to 4). For instance, $\Delta_a G$ is the force generated in an actin-myosin crossbridge that is formed in one ATP hydrolysis cycle. Analogous to the efficiency of the catabolic compartment, the anabolic force efficiency is defined as

$$ {}_a f = \frac{\Delta_a G}{\Delta_e G} \qquad (6) $$

The overall- (ka-) efficiency of the two-compartmental energy chain, ${}_{ka}f$, is the product of the catabolic and anabolic force efficiencies (Wilkie, 1974),

$$ {}_{ka}f = {}_k f \; {}_a f \qquad (7) $$

If any one of these efficiencies is near zero, then the anabolic power output is near zero. Conversely, if one efficiency is unity, then the flow through the respective compartment is regulated entirely by the other energy converter; the two compartments merge effectively into one.

This ergodynamic definition of compartmentalization is amply reflected by local separation of catabolic and anabolic functions in cell organelles and tissues. Differentiation of cytosolic and mitochondrial potentials of ATP, yields information on different control sites of metabolic flux (Klingenberg & Heldt, 1982), as does the distinction of reversible and irreversible enzyme steps within a metabolic reaction sequence (Newsholme & Start, 1973). The following consideration is restricted to ergodynamically defined compartments of energy transformation and to bulk estimations of chemical potentials (Tab. 1).

Enzymes and membrane transport systems exert "active" control over the conductance coefficients of catabolism and anabolism ($_kL$ and $_aL$, the kinetic constants; see Appendix). Like the ATP-stoichiometry, the conductance coefficients are evolved features of the metabolic mechanisms maintaining living systems in a functional state. One strong argument is that, for reasons of regulatory capacity, both energy transforming compartments are optimized according to P- or E-strategy. In the steady state of such systems, the catabolic and anabolic conductance coefficients, $_kL$ and $_aL$, must be tuned such that the internal conductance ratio (Eq. A8), $_{ka}m = {}_kL/{}_aL$, equals the compartmental (catabolic or anabolic) force efficiency. This specific stability criterion is derived in Appendix A.3 (for $_kf = {}_af$). In order to increase the ergobolic potential (Eq. 1) for obtaining a high economical catabolic efficiency, the anabolic load or conductance for ATP-utilization, $_aL$, must decrease ($_{ka}m$ increases; E-strategy). Then a state of "drive-coupling" is maintained (Fig. 3). Conversely, the ergobolic potential drops in response to a lowering of anabolic force efficiency and increased anabolic load, $_aL$ ($_{ka}m$ decreases), whence the catabolic force efficiency decreases (P-strategy) and the rate of ATP-regeneration speeds up (Eq. A2). This mechanism maintains then a new steady-state in response to a step-increase of the external load ("load-coupling"; Fig. 3). This ergodynamic model incorporates active kinetic control of catabolic and anabolic conductance coefficients. It is consistent with the view (Thauer et al., 1977) that fast aerobic growth is controlled by anabolism (load-coupling in P-strategy), whereas catabolism appears to be rate limiting in many anaerobes (drive-coupling in E-strategy; Fig. 3).

Consideration of P- or E-strategy with respect to compartmental

energy chains suggests a serious problem in traditional interpretations of optimum efficiencies. If one compartment of a two-compartmental system is singled out (oxidative phosphorylation; Stucki, 1980), then a catabolic efficiency of 0.67 would be interpreted as indicating E-strategy on the basis of one-compartmental analysis of a fully coupled process (Fig. 2a). However, the ka-efficiency of the entire energy chain would then amount to 0.44, taking hypothetically equal compartmental efficiencies as an example (Fig. 4.1; $_{k}f = {}_{a}f$). Certainly, a system displaying an input-output force efficiency of <0.5 can no longer be interpreted as E-strategy. On the other hand, the catabolic-anabolic energy chain of bacterial growth has been subjected to a black-box analysis (Westerhof et al., 1983). Consequently, these authors interpreted a total force efficiency of $\sqrt{0.67}$ as E-strategy. However, the compartmental force efficiency would then have to be 0.67 = 0.82 (Eq. A13), far beyond previous expectations for simple E-strategy.

With the concept of the ergodynamic structure of the catabolic-anabolic energy chain, it is possible to explain the high compartmental force efficiencies of anoxic catabolism. The optimum efficiency for maximum anabolic power output turns out to be $_{k}f = {}_{a}f = 0.67$ with a ka-force efficiency of 0.44 (Fig. 4, P). While 0.67 is the E-optimum in one-compartmental systems (Fig. 2), the same characteristic value is now recognized as the P-optimum for a two-compartmental system. This prediction is consistent with the expectation that the lactate pathway evolved under the selective pressure favouring P- rather than E-strategy to power hypoxic activity (Sidell & Beland, 1979; Tab. 1). Muscular power output provides a means of measuring external transmission of anabolic power directly. The maximum efficiency of the anabolic compartment is 0.66 in DNFB-poisoned muscle (dinitrofluorobenzene inhibits phosphocreatine splitting; Kushmerick & Davies, 1969; Wilkie, 1974). This supports the assumption that catabolic and anabolic efficiencies are tuned at the same level according to P-strategy (Fig. 4, P). Moreover, in high aerobic exercise the maximum overall ka-efficiency in large vertebrates is 0.41 (Heglund & Cavagna, 1985; compare $_{ka}f_{opt}$ = 0.44; Tab. 2). Reference to experimental maximum efficiencies of mechanical power output is warranted when these external ergodynamic efficiencies are taken as indications of internal force efficiencies (see Eq. 5). At the extreme of zero external efficiency at isometric contraction, external transduction of anabolic force is prevented. This apparent decoupling effect is minimized at maximum external efficiencies.

E-strategy of a two-compartmental system predicts an optimum

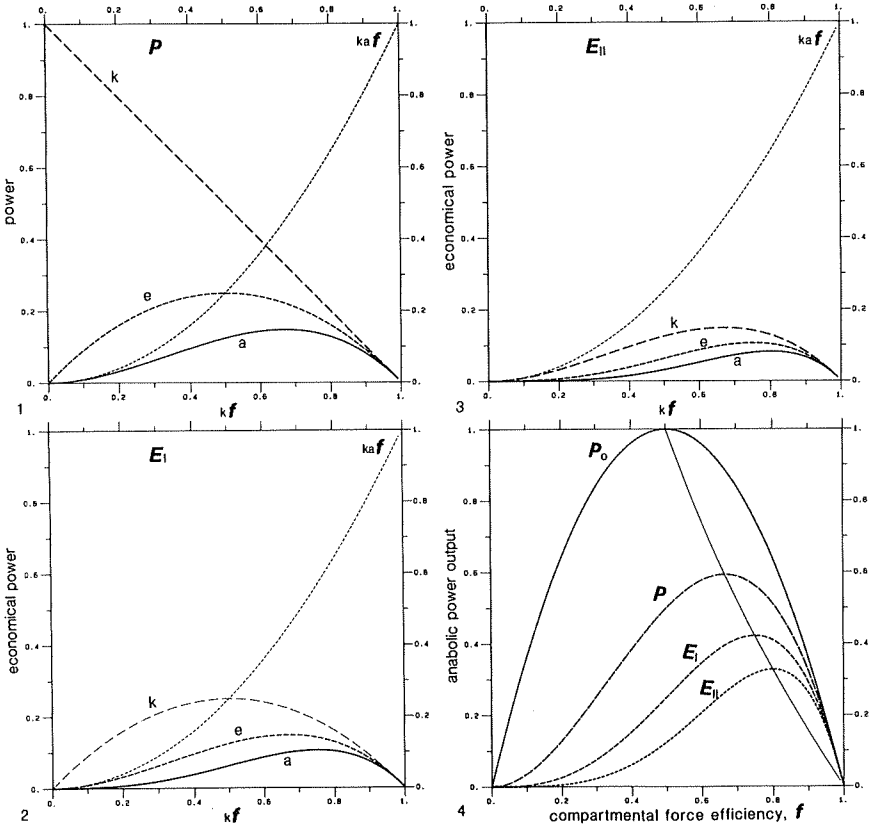
Fig. 4. Optimization of catabolic force efficiency in catabolic-anabolic coupled metabolism at constant catabolic input force. Two linear systems (Fig. 2a) are connected in series. $_{ka}f$ is the catabolic-anabolic force efficiency of the system under the assumption that both compartments operate at identical efficiencies. k, e, and a are catabolic power input, ergobolic and anabolic power output, respectively, normalized relative to maximum power input in P-strategy (4.1-4.3).

4.1 P-strategy: The optimum catabolic force efficiency for $_{e}P$ is 0.50 (Fig. 2a) but 0.67 for maximum anabolic power output (Eq. A14, m=2).

4.2 E_I-strategy: The optimum force efficiency for phase-I economical $_{e}P$ is 0.67 (Fig. 2a) but 0.75 for maximum economical $_{a}P$ (Eq. A14, m=3).

4.3 E_{II}-strategy: The product of efficiencies in both compartments defines the degree of phase-II economy. Optimum efficiencies for $_{e}P$ and $_{a}P$ are 0.75 and 0.80 respectively (Eq. A14, m=4).

4.4 Comparison of the optimum functions of two-compartmental steady-state anabolic power output (from 4.1-4.3, normalized at unit $_{k}L$) and one-compartmental transient-state anabolic power output (P -strategy, normalised relative to maximum power output at unit $_{a}L$; Eq. A14, m=1). The continuous line intersecting the power maxima is a plot of Eq. A14 with m substituted from Eq. A10. This plot can be interpreted as the optimized power output of a non-linear system with f^{m-2} as feedback parameter (and hence omitted from the left side of Eq. A14). In the physiological range of force efficiencies from 0.5 to 0.8, an apparent linear relationship is then observed between power output and force efficiency.



compartmental efficiency of 0.75 (Tab. 2; Fig. 4, E_I). The force efficiency for the succinate pathway of 0.74 appears no longer to be unreasonably high (Tab. 1).

In a two-compartmental system, an additional degree of freedom is gained in the development of E-strategy: A second stage of economy can be expected when the efficiency of both compartments counts as a weighting factor in the fitness parameter (Appendix A.3). Consequently, for E_{II}-strategy an optimum compartmental force efficiency of 0.80 is predicted (Fig. 4, E_{II}). Actually, this agrees with the catabolic force efficiency of the propionate and propionate-acetate pathway in the secondary phase of long-term anoxia (Tab. 1).

The theoretical definition of distinctive strategies does not necessarily imply discontinuous jumps between P- and E-optimum states. While the switching on and off of a biochemical pathway actually represents a step change in the normalized catabolic input force, the distinct strategies overlap due to gradual changes of ergobolic potentials. Accordingly, a continuous ergodynamic optimum function (Eq. A14) describes the intermittent optimum efficiencies of a fine-tuned energy chain in the steady state (Fig. 4.4). In the next section this analysis is extended to highlight the ergodynamic significance of a prominent non-steady state process in muscular physiology.

Table 2.

P- and E_I-optimum force efficiencies in a two-compartmental energy chain. The optimum efficiencies for one compartment, $_k{}^f$, are higher, and the optima for the whole energy chain, $_{ka}{}^f$, are lower than the optimum efficiencies in a one-compartmental system (underlined numbers). P and E_I are given in per cent of their maximum values at the respective optimum efficiencies of the energy chain.

k^f	ka^f	P	k^f	ka^f	E_I
<u>0.50</u>	0.25	84.4	<u>0.667</u>	0.444	93.6
0.667	0.444	100	0.75	0.563	100
0.707	<u>0.50</u>	98.9	0.816	<u>0.667</u>	94.7

THE DUAL ROLE OF PHOSPHOCREATINE IN P- AND E-STRATEGY

The predominant role of phosphocreatine or phosphoarginine in powering maximum activity during short periods of time is widely documented ("all-out efforts"; di Prampero, 1981) and is recognized as a non-steady-state process. The creatine kinase reaction is in equilibrium with the ATP-system, so ergobolic depletion by maximum ATP-demand conforms to a one-compartmental energy transformation. In this state of load-coupling (Fig. 3), the anabolic conductance for ATP-utilization far exceeds the limiting condition of steady-state conductance matching (Eq. A8). This is the kinetic advantage of a one-compartmental strategy for maximizing instantaneous anabolic power output (P_0-strategy, Fig. 4.4).

P_0-strategy for one completely coupled compartment determines the optimum force efficiency at 0.50. This is also the experimentally observed efficiency of mechanical transduction of phosphocreatine splitting (Curtin et al., 1974). The internal efficiency loss of a series of energy converters is avoided in one-compartmental transformation. If two energy converters are connected in series and each operates at 50% efficiency, then the overall efficiency of the system reduces to 25% (Eq. 7). In that mode of operation, however, anabolic power output would be 16% below the two-compartmental maximum (Tab. 2). Clearly, a price must be paid for the advantage of regulatory capacity obtained in compartmental, catabolic-anabolic energy conversion. The one-compartmental, transient-state mechanism of phosphocreatine or phosphoarginine depletion provides the more powerful strategy in explosive all-out efforts. Due to its simplicity, it may well be the most primitive mechanism of biological energy coupling (Koch, 1986), originally evolved without constraints set by energy resources and clearly in a situation favouring r-strategy.

In addition to this anoxic involvement of creatine kinase, its integration in aerobic ATP transport, and in buffering ATP and ADP concentrations is well recognized (Hochachka & Somero, 1984; Stucki, 1980). A regulatory function of the creatine kinase reaction in aerobic muscle exercise has only recently been suggested (Kushmerick, 1985). The ergodynamic interpretation of these data indicates a transition from E-strategy to P-strategy as the muscle switches from a resting state to high aerobic exercise.

Application of the concept of a fully coupled energy chain to interpret aerobic metabolism requires a comment at first. One-compartmental

black-box analysis and emphasis on phenomenological coupling coefficients (Caplan & Essig, 1983) may mask some functional relationships of catabolic rate and force efficiency. On a whole-organism or cellular level, the significance of the standard metabolic rate is readily accepted in terms of maintenance requirements (Bayne, 1986) or spinning of futile cycles (Hue, 1982). Why should any maintenance requirements be absent on the subcellular level? Since mitochondrial state-4 respiration and coupling coefficients <1.0 may, to a large extent, be related to mitochondrial "anabolic" ATP-requirements for maintenance, phenomenological decoupling cannot be interpreted as functional decoupling. Instead of invoking the hypothesis of maximization of efficiency by decoupling (Stucki, 1980), force efficiencies of oxidative phosphorylation can be interpreted within the framework of a fully coupled (Harris et al., 1980), two-compartmental energy chain (this does not, however, exclude a completion of the dissipative cycle, as illustrated in Fig. 3). A specific bypass mechanism (site I in yeast; Erecinska et al., 1978) as opposed to decoupling influences the force efficiency via stoichiometry; a bypass may optimize the force efficiency comparable to the switching between different anoxic pathways. The involvement of phosphocreatine breakdown in the transition towards increasing aerobic work loads can be interpreted as an important ergodynamic control mechanism in the energy chain (a more detailed explanation: Gnaiger, in prep).

From NMR- (nuclear magnetic resonance) studies on vertebrate muscle operating at different aerobic steady-state levels (Kushmerick, 1985), it can be calculated that the efficiency of aerobic catabolism decreases from a resting level of 0.80, to 0.64 at high aerobic exercise (Tab. 1; ox). This change of catabolic force efficiency is induced by a decrease of phosphocreatine content and an increase in inorganic phosphate and ADP concentrations with increasing aerobic work load (Kushmerick, 1985). Therefore, oxidative phosphorylation operates at the E_{II}-optimum at rest (compare $_{k}f = 0.79$ for oxidative phosphorylation in liver in a "resting state"; Stucki, 1980), passes through the E_{I}-optimum at low activity levels, and operates according to P-strategy at high steady-state exercise (Fig. 4). Appropriate tuning of anabolic force efficiencies is possible by adjusting the sliding distance of the actin filaments per mol ATP-turnover (Yanagida et al., 1985).

GENERAL CONCLUSIONS

Interactive tuning of catabolic and anabolic conductance

coefficients is required to stabilize compartmental force efficiencies at optimum levels (Fig. 4). In the life time of organisms, adjustments of conductance coefficients are possible within genetically fixed limits. Random sets of enzymes and other variables of rate control will eventually lead to steady states (Kacser & Burns, 1973), but these would not produce predictable optimum patterns. Ergodynamic optimum functions provide a baseline by which the vast diversity of potentially adaptive enzyme-kinetic traits can be rationalized. Linear or non-linear ergodynamic concepts of metabolic energy chains offer an a priori approach (in the sense of Calow & Townsend, 1981) to the study of biochemical adaptation. This approach may lend more credibility to the expanding theory on metabolic strategies, by removing circular arguments and limiting otherwise virtually endless parades of ad-hoc constructions on adaptation.

In evolutionary time, selection of ATP-coupling stoichiometries and of basic enzyme-kinetic properties have produced economically regulated systems. These are characterized by a synergistic relation between active enzyme kinetic control of metabolic conductance and ergodynamic control via driving forces and compensative coupling. Ergodynamic optimum functions emphasize the complementary nature of active and passive regulation. The theory of two-compartmental optimum functions postulates the matching of catabolic and anabolic conductance coefficients in relation to the load. Over-proportional activity of enzymes in an anabolic pathway yields a lower fitness than intermediate improvements of enzymes in catabolic and anabolic pathways. Evolutionary biologists generally find intermediate enzyme kinetic properties associated with protein heterozygosity, and recognize that "a chain of intermediate fitnesses can result in superior fitness" (Mitton & Grant, 1984). These theoretical predictions are consistent with empirical correlations of heterozygosity, growth efficiency and growth rate (Bayne, 1986). Finally, for translating physiological fitness into evolutionary fitness, the possible advantages of optimization and scope for regulation over maximization of rates must be considered in relation to environmental perturbations (Calow, 1984; Stebbing & Heath, 1984; Wieser, 1985), ecosystem stability (Ott, 1981) and cultural developments (Talsma, 1980).

Without incorporation of evolutionary mechanisms of optimization or adaptation, previous physicochemical attempts to describe biological systems or biological evolution failed to provide an adequate thermodynamic definition of life. The classical approach based on the Second Law or on states of "negentropy" (Schrödinger, 1944) does not address specifically

biological features, since local decreases of entropy or increases in "order" are commonplace in inhomogeneous abiotic systems. The theory on "dissipative structures" includes, on the other hand, explicitly the time-evolution and statistical properties of macroscopic systems (Prigogine, 1980). While this theory is important for understanding the spontaneous formation of sometimes rather spectacular structures far from equilibrium, the time-evolution of the dissipative structures relates to an ontogenetic development of non-linear systems but not to biological evolution which requires a sequence of generations of quasi-repetitive systems. Indeed, it would be surprising if biological evolution could be modelled without incorporating the recognized basis of evolutionary theory. Ergodynamic optimum functions provide a link between physicochemical concepts and the biological theory of evolution. As a consequence of restrictions on the variety of possible steady-states by selection, optimized systems survive, and propagate genetically the traits of matched catabolic and anabolic conductance coefficients as well as the scope for fine-tuning of these coefficients. By developing and genetically propagating properties of ergodynamic optimum structures, living systems are invariably distinguished from the non-living world.

APPENDIX

A.1. LINEAR P- AND E-OPTIMUM FUNCTIONS

Based on the theory of linear energy converters (Kedem & Caplan, 1965), the fully coupled rate of ATP production is related to the net catabolic-ergobolic potential or "ATP-coupling potential", $\Delta_{ke}G$,

$$\dot{N}_e = -{}_kL\,(\Delta_kG + \Delta_eG) = -{}_kL\,\Delta_{ke}G \qquad (A1)$$

where ${}_kL \geq 0$ is the phenomenological conductance for the catabolic process. The condition of complete coupling implies $\dot{N}_e = \dot{N}_k$ (Eq. 4.2). Substituting for Δ_eG from Eq. (4.1) yields the relationship between ergobolic flow and force efficiency,

$$\dot{N}_e = -{}_kL\;\Delta_kG\;(1 - {}_kf) \qquad (A2)$$

Power is the product of a flow times the conjugate force,

$$\text{input:}\quad {}_kP = \dot{N}_k\,\Delta_kG \qquad (A3.1)$$

output: $${}_{e}P = {}_{e}\dot{N}\ \Delta_{e}G \qquad (A3.2)$$

The catabolic power input, ${}_{k}P$, and ergobolic power output, ${}_{e}P$, are a quadratic function of the catabolic coupling force. Combining Eqs. (4.1), (A2) and (A3) (under the condition of Onsager symmetry, see Caplan & Essig, 1983),

$${}_{k}P = -{}_{k}L\ \Delta_{k}G^{2}\ (1 - {}_{k}f) \qquad (A4.1)$$

$${}_{e}P = {}_{k}L\ \Delta_{k}G^{2}\ {}_{k}f\ (1 - {}_{k}f) \qquad (A4.2)$$

${}_{e}P$ is maximum for any fixed catabolic coupling force in Eq. (A4.2) if ${}_{k}f = 0.50$ (P-strategy; Fig. 2). One characteristic degree of economical power output (Stucki, 1980),

$${}_{e}P\ {}_{k}f = {}_{k}L\ \Delta_{k}G^{2}\ {}_{k}f^{2}\ (1 - {}_{k}f) \qquad (A5)$$

is maximum for any fixed catabolic force, $\Delta_{k}G$ in Eq. (A5), if ${}_{k}f = 0.667$ (E-strategy, Fig. 2).

A.2. CATABOLIC-ANABOLIC COUPLING. THE STEADY STATE

To maintain metabolic control, the catabolic and anabolic compartment must operate at a steady-state, i.e. input and output flows for the energy converters must be equal. Analogous to catabolic input (Eq. A2), in a fully coupled system anabolic ATP input, ${}_{de}\dot{N}$, is controlled by the anabolic force efficiency and conductance coefficient, ${}_{a}L \geq 0$.

$${}_{de}\dot{N} = {}_{a}L\ \Delta_{e}G\ (1 - {}_{a}f) \qquad (A6)$$

Substituting for $\Delta_{e}G$ from Eq. (4.1) yields

$${}_{de}\dot{N} = -{}_{a}L\ \Delta_{k}G\ {}_{k}f\ (1 - {}_{a}f) \qquad (A7)$$

At steady state, catabolic output rate (Eq. A2) equals anabolic input (Eq. A7). This equality yields the internal steady-state conductance ratio, ${}_{ka}m$,

$${}_{ka}m = \frac{{}_{k}L}{{}_{a}L} = {}_{k}f\ \frac{1 - {}_{a}f}{1 - {}_{k}f} \qquad (A8)$$

The normalized external flow of the anabolic product, expressed as ATP-equivalents (compare Eq. 3.2), is a linear function of the anabolic output force and the external (load) conductance, ${}_{ex}L$,

$$ {}_{ex}\dot{N} = {}_{ex}L \, \Delta_e G \, {}_a f \qquad (A9) $$

Again, expression (A9) must equal the anabolic flow (Eq. A6) to ensure steady-state conditions. This requires that the external steady-state conductance ratio, m, is tuned at

$$ m = \frac{{}_a L}{{}_{ex} L} = \frac{{}_a f}{1 - {}_a f} \qquad (A10) $$

By multiplying the anabolic input flow (Eq. A6) times the anabolic input force, $-\Delta_e G$, we obtain the anabolic power input (Eq. A11.1); the anabolic power input times the force efficiency yields in turn the anabolic power output in the case of complete coupling (Eq. A11.2),

$$ {}_{de}P = -{}_a L \, \Delta_e G^2 \, (1 - {}_a f) \qquad (A11.1) $$

$$ {}_a P = {}_a L \, \Delta_e G^2 \, {}_a f \, (1 - {}_a f) \qquad (A11.2) $$

Finally, after substituting in Eq. (A11.2) for ${}_aL$ and $\Delta_e G$ from Eq. (A8) and (4.1) respectively, the anabolic power output is

$$ {}_a P = {}_k L \, \Delta_k G^2 \, {}_k f \, {}_a f \, (1 - {}_k f) \qquad (A12) $$

A.3. THE TWO-COMPARTMENTAL OPTIMUM EFFICIENCY FUNCTION

If catabolic and anabolic force efficiency are equal, then the ka-efficiency is a quadratic function of the compartmental efficiency, f (Fig. 4; Eq. 7),

$$ {}_{ka}f = f^2 \qquad (A13) $$

For such a system, the anabolic power output (Eq. A12) can be rewritten as

$$ {}_a P \, f^{m-2} = {}_k L \, \Delta_k G^2 \, f^m (1 - f) \qquad (A14) $$

In Eq. (A14) an efficiency parameter with the exponent m was introduced which is related to P- and E-strategy. m = 2 is obtained in the straightforward derivation of Eq. (A14) from (A12), which indicates power-strategy (Fig. 4; P). m = 3 is derived from Eq. (A5) for economical power output in one compartment (Fig. 4; E_I). A second economy stage can be distinguished at m=4 (Fig. 4; E_{II}). For a two-compartmental energy chain this function can be rationalized as indicating economy strategy for both energy transforming compartments; then the more pronounced E_{II}-strategy prevails.

Insertion of the characteristic values of m for P-, E_I- or E_{II}-strategy into Eq. (A10) yields the optimum compartmental efficiencies, f_{opt}, at which any chosen fitness parameter attains its maximum value (Fig. 4.4),

$$f_{opt} = \frac{m}{1 + m} \qquad \text{(A15)}$$

Comparison of Eq. (A12) and (A14) shows that for the maintenance of a steady-state the external conductance ratio is restricted to $m \geq 2.0$. This lower boundary condition for the steady state yields the P-optimum force efficiency of 0.67 for one compartment in the energy chain (P-strategy). Note that a catabolic efficiency of 0.67 would be mistakenly interpreted as indicating E-strategy, if the implications of the two-compartmental energy chain are ignored (Tab. 2).

The physical interpretation of Eq. (A15) is surprising: The external steady state conductance ratio, m (Eq. A10), is the exponent in Eq. (A14). In physical terms, m is the relative endurance time during which f units of energy input provide a constant power, whereas 1+m is the relative time required for the provision of f units of energy output at constant power. This leads to a definition of efficiency as a ratio of time. The present analysis is restricted to fully coupled systems where the efficiency can be equivalently calculated on the basis of force, energy and power ratios. Now efficiency can also be expressed as a time ratio.

$$f_{opt} = \frac{{}_{in}t^*}{{}_{out}t^*} \qquad \text{(A16)}$$

${}_{in}t^* = (1+m)\ t^o$ is the absolute endurance time in units of t^o during which one unit of energy input drives the coupled process at a constant rate. ${}_{out}t^*$ is the time required to obtain one unit of energy output at a constant rate. P-strategy minimizes the time ${}_{out}t^*$. ${}_{in}t^*$ sets the value of endurance time in relation to power output, and is the quantity required to find the optimum

in the compromize between maximum time and maximum power output in E-strategy. This is a non-mechanistic, ergodynamic view of optimum efficiency.

The two-compartmental ergodynamic model as introduced here is applied to rationalize physiological fitness in cellular energy metabolism.

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