

PHYSIOLOGICAL CALORIMETRY: HEAT FLUX, METABOLIC FLUX, ENTROPY AND POWER.

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SUMMARY

Physiological calorimetry is concerned with the measurement of heat flux in living systems where heat flux is associated with the chemical flux of metabolic reactions. Calorimetry can be related to nonequilibrium thermodynamics if information on both the enthalpy of metabolic reactions and the molar Gibbs energy is available. The molar Gibbs energy of reaction (Gibbs force) is the scalar force conjugated to metabolic flux. The force conjugated to heat flux of an irreversible process is the Gibbs energy/enthalpy ratio. Metabolic power and heat flux of irreversible processes are distinguished as the time rate of Gibbs energy and enthalpy changes, respectively. Power is the product of fluxes and forces, related to the internal entropy production by the absolute temperature. In contrast, $T \Delta_r S$ is the "bound energy" change which equals the heat change of a reversible process in a closed system and is not available for work. Heat flux in general is the sum of the dissipated power and the bound energy change per unit of time. This concept can be extended to vectorial heat flux along a temperature gradient. The temperature difference relative to the temperature of the heat source, traditionally viewed as the 'efficiency of a reversible machine', is in fact the thermal force for heat flux between heat source and sink. The thermal force times heat flux is the thermal power which can be maximally converted into work or can be irreversibly dissipated. A clear distinction between heat flux and power is conceptually revealing, despite the fact that both quantities have the same dimension with units [W per volume, or per mass or per defined system] when describing scalar and discontinuous processes.

INTRODUCTION

Calorimetric studies of living cells and organisms are carried out for quantification of total energy expenditure associated with metabolic functions. The metabolic (chemical) fluxes are measured by specific analytical methods and expressed as molar change or extent of reaction per unit of time (per unit of cell volume or biomass). The sum of all metabolic fluxes gives rise to a net heat flux which is measured calorimetrically.

Heat is a form of energy which cannot be converted by the cellular machinery into other forms of useful energy (=work). Nevertheless, physiological calorimetry aims at elucidating cellular functions. At a given temperature, these depend not on heat but on work. The biochemical sources of useful energy in heterotrophic systems are the Gibbs

energy differences of catabolic substrates and products. 'The useful energy which is not converted into work is lost as heat.' This statement can be found in many textbooks on biological energetics. It appears to address the conservation of energy but, of course, the first law of thermodynamics postulates the conservation of internal energy or enthalpy as opposed to useful energy (ref. 1). If not carefully interpreted, the statement under inverted commas is a source of confusion and can lead to an erroneous interpretation of the calorimetrically measured heat flux. The following sections address this source of error in detail.

In a metabolic system which does not perform work in the form of mechanical, electrical, chemical or other useful energy, the Gibbs energy change of the exergonic metabolic reactions is dissipated - as a form of energy. Since a calorimeter measures the heat change, this heat is equivalent to (erroneous conclusion) the irreversible Gibbs energy change. The Gibbs energy change [unit: J per specified system] per time [unit: s] is the power [unit: W per specified system]. According to an Interunion Commission on Biothermodynamics, "the output of many calorimetric experiments is a plot of power (energy evolution per unit of time) as a function of time" (ref. 2). Hence the term "power-time-curve". However, power is the time derivative of work (ref. 3), whereas heat flux is the time derivative of the internal energy or enthalpy change in an irreversible process. Therefore, the terminological distinction between heat flux and power is important, comparable to the significance of a distinction between enthalpy and Gibbs energy.

Comprehension and communication of ideas in thermodynamics relies on a clear terminology. This must be kept in mind particularly when discussing calorimetry, an approach of classical thermodynamics, in the context of nonequilibrium thermodynamics. These concepts are relevant for the regulation of metabolic flux (thermodynamic and kinetic control) and for the method of calorimetry (heat conduction). A discussion of the efficiency of heat engines (e.g. Peltier heat pumps) clarifies the distinction between thermal power (the time rate of useful thermal energy which can potentially be converted into work) and heat flux. Therefore, even the term "thermal-power-time-curve" is not appropriate when, in fact, heat flux as a function of time is reported. The use of thermodynamic terms is an issue not merely terminological (ref. 4).

HEAT FLUX AND METABOLIC FLUX

Chemical reactions are scalar processes characterized by scalar fluxes which are flows of energy or matter per unit volume (or per unit mass). In contrast, vectorial fluxes are flows directed in space and expressed per unit area perpendicular to their

direction. Physiological calorimetry is primarily concerned with the chemical reactions of metabolism.

A simple relation exists between total measured heat flux, tJ_Q [$\text{J}\cdot\text{s}^{-1}\cdot\text{m}^{-3}$], and metabolic flux in aerobically balanced living systems. Then the metabolic flux can be measured as catabolic oxygen flux, kJ_{O_2} [$\text{mol O}_2\cdot\text{s}^{-1}\cdot\text{m}^{-3}$]. The theoretical relation between the enthalpy change and the amount of oxygen consumed is the oxycaloric equivalent or catabolic enthalpy change per amount of oxygen, $4_kH_{O_2}$ [$\text{J}\cdot\text{mol}^{-1} \text{O}_2$] (ref. 5). The simultaneous measurement of calorimetric heat flux and respirometric oxygen flux (calorespirometry) yields the calorimetric-respirometric ratio (CR ratio),

$$\text{CR ratio} = tJ_Q / kJ_{O_2} \quad (1)$$

The CR ratio is the experimental counterpart to the theoretical oxycaloric equivalent when no work is done. Proof for a balanced energy budget is obtained if the CR ratio and oxycaloric equivalent agree in the range of -440 to $-480 \text{ kJ}\cdot\text{mol}^{-1} \text{O}_2$ (ref. 5,6). Taking into account this constant of proportionality, heat flux and oxygen flux are equivalent expressions of the dynamics of aerobically balanced dissipative metabolism.

The unique strength of direct calorimetry is apparent when studying more complex metabolic processes, such as the simultaneous operation of aerobic and anaerobic catabolism. Calorespirometry aids in partitioning the aerobic and anaerobic sources of the total heat flux (ref. 7-9). The stoichiometric conversion of glycolytic fluxes into an equivalent flux of coupled catabolic ATP turnover, kJ [$\text{mol ATP}\cdot\text{s}^{-1}\cdot\text{m}^{-3}$], provides a common and functionally relevant definition of metabolic or "catabolic flux" in either aerobic or anaerobic metabolism (ref. 9,10).

HEAT FLUX AND POWER

Heat flux [$\text{J}\cdot\text{s}^{-1}\cdot\text{m}^{-3}$] and power are dimensionally identical if power, P , is referred to the unit volume [$\text{W}\cdot\text{m}^{-3}$] (alternatively, flux and power are expressed per unit biomass, per individual organism or cell, or generally per defined system). The identity of units has led to the unfortunate suggestion to identify heat flux as power (ref. 2). This contradicts the explicit definition of power as the time derivative of work (ref. 3,11).

Power is the time rate of energy converted into work, $P = dW/dt$ (1 horse power = 745.7 W). A positive sign indicates that work is received by a system (ref. 3) or conserved by a process. Such a process is *reversible* (Fig. 1a). The power of metabolism is the time rate of the Gibbs energy change, $P = dG/dt$. An exergonic Gibbs energy and exergonic power have a negative sign, indicating the spontaneous direction of the reaction and an input into a *coupled process*. A process is *irreversible* if the exergonic Gibbs energy change is not conserved as work, $dG = dD$ (Fig. 1b). If Gibbs

Fig. 1. Process analysis: conservative and dissipative energy and heat changes.

Energy changes in a reversible (a), irreversible (b), and dissipative (c) process (dimension: energy per defined system).

Left row. "Ergodynamic" analysis of work (*ergon*) and Gibbs energy changes. Useful energy is either conserved as work or dissipated,

$$dG = dW + dD$$

dD is the dissipated energy of the process, equivalent to the negative internal entropy production times temperature of the heat sink, $T d_i S$. Importantly, dD is not identical with the total heat exchanged with the heat sink.

Right row. Thermodynamic analysis of heat (*therme*) and enthalpy changes. The first law of thermodynamics,

$$dH = dW + dQ$$

can be expressed by two state functions,

$$dH = dG + dB$$

$dB = T dS$ equals the heat change only if the process is reversible. Generally, the heat exchanged with the heat sink is,

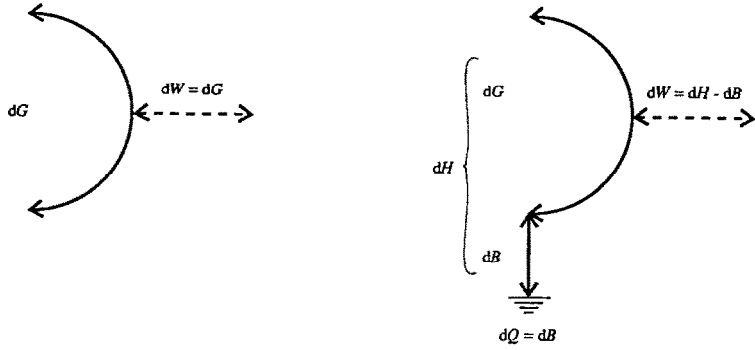
$$dQ = dD + dB$$

Gibbs energy changes, dG , are shown by half cycles, bound energy changes, dB , by straight lines. In contrast to these state functions which are exact differentials, the inexact differentials are indicated by broken lines. dW is the work conserved by the process (arrow to the half cycle, positive), or performed on another process (arrow from the half cycle, negative). In reality, work of one process, k , can only be exchanged by coupling to another process, l , such that for the two coupled processes we have, $d_l W = -d_k W$, and $d_l G = -d_k G$.

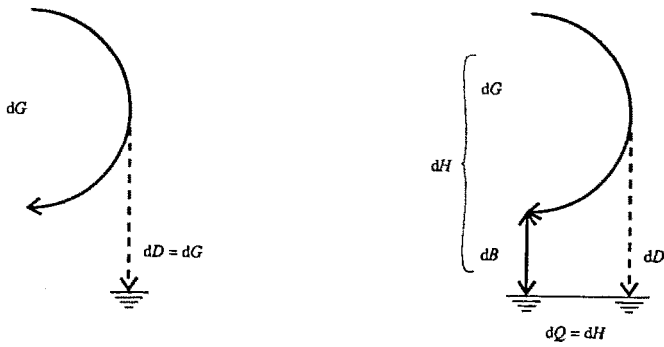
energy is partially transformed into work and partially dissipated the process is called *dissipative* (Fig. 1c): The power input is dG/dt , the power output is dW , and the difference is the dissipated power, dD/dt . Which form of energy is dD ? Its general nature cannot be understood by reference to heat, but the concept of internal entropy production is required for comprehension of the dissipated energy.

In the present analysis of metabolic reactions, the cellular system is considered to be at or near steady state (composition, temperature and pressure are constant) and the energetic parameters refer strictly to the process under consideration. This approach can be viewed as "process analysis" which is required to describe the dynamics of open systems. External transport of matter is usually combined with cellular metabolism. Such transport per se (excluding metabolism coupled to active transport) is not a source of heat but contributes to the change of system parameters. Therefore, dG is not the Gibbs energy change of the system, but the Gibbs energy change in the metabolic reaction catalyzed by the system. For simplicity it is assumed that the only irreversible net process is a chemical reaction, indicated by the left subscript r . The flux of the chemical reaction is quantified as rJ [$\text{mol}\cdot\text{s}^{-1}\cdot\text{m}^{-3}$].

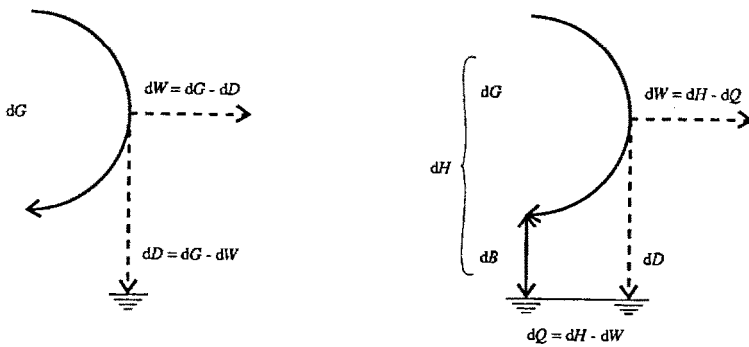
a: reversible process: $dD = 0$



b: irreversible process: $dW = 0$



c: dissipative process



Process analysis of conservative and dissipative energy and heat changes

The total heat flux of a reaction system can be measured directly by calorimetry, rJ_Q . Alternatively, the heat flux associated with the chemical reaction is calculated, rJ_Q , as the product of the chemical flux and the molar enthalpy of reaction, $\Delta_r H$ [J.mol⁻¹], in an irreversible process,

$$\text{heat flux: } rJ_Q = rJ \Delta_r H \quad (2)$$

There is no instrument comparable to a calorimeter for direct measurement of the Gibbs energy or dissipated energy and power of chemical reactions. Analogous to rJ_Q , the power is calculated as the product of the chemical flux and the molar Gibbs energy of reaction, $\Delta_r G$ [J.mol⁻¹],

$$\text{power: } rP = rJ \Delta_r G \quad (3)$$

The power can in general be higher, lower or equal to the heat flux, since the "bound energy change" (eqs. 4 and 5) does not have a sign restriction in chemical reactions. In anaerobic glycolysis, the catabolic Gibbs energy change is up to 60% more negative than the catabolic enthalpy change, hence heat flux underestimates metabolic power by 60% in these cases (ref. 9). In balanced aerobic metabolism, however, the catabolic Gibbs energy and enthalpy changes are nearly identical.

The molar Gibbs energy and enthalpy of reaction are related under isothermal and isobaric conditions at steady state by the equation (Fig. 1),

(Gibbs energy = enthalpy - bound energy) per mol

$$\Delta_r G = \Delta_r H - T \Delta_r S \quad (4)$$

The molar entropy of reaction, $\Delta_r S$, times absolute temperature is the molar "bound energy", $\Delta_r B$. In a reversible reaction, $\Delta_r G = 0$ or $\Delta_r G = \Delta_r W$, there may be a heat flux, yet no useful energy is lost as heat. Therefore, the calorimetrically measured reversible heat change equals the bound energy change (Fig. 1a, right). The bound energy is not free for conversion into work. If the bound energy is zero, or the absolute magnitude is $\Delta_r B \ll \Delta_r G$, then the calorimetrically measured heat change equals the dissipated Gibbs energy. If $\Delta_r B$ is different from zero, however, the dissipated Gibbs energy cannot be measured as heat. Heat is always the sum of the dissipated Gibbs energy *and* the bound energy (Fig. 1).

Multiplication of eq.(4) by the flux of the chemical reaction yields the explicit relation between power (eq. 3) and heat flux (eq. 2) in the absence of work,

power = heat flux - bound energy flux

$$rP = rJ_Q - rJ T \Delta_r S \quad (5)$$

The expression of power in eq.(3) is derived from a fundamental relation in nonequilibrium thermodynamics, where power is defined as the product of a flux and a

conjugated force (ref. 12). Since nonequilibrium thermodynamics does not deal with the thermal changes but rather the Gibbs energy changes of chemical reactions and with the transformation into work (*ergon*), the term "ergodynamics" has been suggested to emphasize this point (ref. 12).

HEAT FLUX AND FORCE IN ISOTHERMAL REACTIONS

The *molar* Gibbs energy of reaction, $\Delta_r G$ [J mol^{-1}] (ref. 3), must be distinguished from the Gibbs energy change, dG or ΔG [J]. This important difference is best explained by analogy with electrical energy [J] which is an *extensive* quantity, clearly distinguished from the corresponding *intensive* 'energy per amount of electrons' that is electrical force [$\text{J.C}^{-1} = \text{V}$]. Correspondingly, $\Delta_r G$ is the 'energy per amount of substance', an *intensive* quantity. It is the force of reaction in nonequilibrium thermodynamics (ergodynamics), and as such $\Delta_r G$ is appropriately described as "Gibbs force" at constant composition, temperature and pressure, $rF_G = \Delta_r G$. Flux times force is power, $P = rJ rF_G$ (eq. 3). Many authors (ref. 14,15) emphasize the need for clarification of the unsatisfactory use of symbols, $\Delta_r G$ versus ΔG which, however, are still retained in the most recent IUPAC recommendations (ref. 3). In addition to a proper symbol, an informative name will help to explain the underlying concept. This should be emphasized further by a consideration of units for Gibbs force of reaction at constant pressure and Helmholtz force, $\Delta_r A$, at constant volume.

mechanical force,	F :	$\text{N} = \text{J.m}^{-1}$
electrical force,	$V, e F$:	$\text{V} = \text{J.C}^{-1}$
chemical force,	$\Delta_r G, rF_G$:	$? = \text{J.mol}^{-1}$
chemical force,	$\Delta_r A, rF_A$:	$? = \text{J.mol}^{-1}$

To motivate discussion along these lines, the unit "Jol" ($1 \text{ Jol} = 1 \text{ J.mol}^{-1}$) was tentatively suggested (ref. 16).

The Gibbs force is conjugated to the chemical flux. Similarly, a force conjugated to the heat flux must be defined such that the product of heat flux and force is power. This conjugated force is obtained by substituting from eq.(2), $rJ = rJ_Q/\Delta_r H$, into eq.(3),

power = heat flux x force

$$rP = rJ_Q \Delta_r G/\Delta_r H \quad (6)$$

Seen in this way, the Gibbs energy/enthalpy ratio of chemical reactions is the driving force, rF_Q , for heat flux, rJ_Q , in an irreversible reaction,

$$rF_Q = \Delta_r G/\Delta_r H \quad (7)$$

HEAT FLUX AND ENTROPY PRODUCTION

Entropy production and power dissipation are related by absolute temperature,

$$d_i S/dt = -P / T = -(dD/dt) / T \quad (8)$$

Internal entropy production and power dissipation (eq. 8) are distinguished by $1/T$ as an integrating factor for entropy. The absolute temperature, T [K], is implicitly included in the thermodynamic "force" symbolized by X (ref. 12),

$$d_i S/dt = J X = J -F/T \quad (9)$$

Here, the generalized (ergodynamic) forces are defined as $F = -X T$. This immediately specifies the Gibbs force as an ergodynamic force, whereas the corresponding X is the chemical affinity/ T (ref. 12), equal to $-\Delta_r G/T$.

In any irreversible *process*, the power is a negative quantity, corresponding to the notion of the second law of thermodynamics that the internal entropy production must always be positive. In contrast, the velocity of transport of organic energy into the cellular system from the outside is a power input into the *system*, with a positive sign. The corresponding external entropy change, $d_e S$, is the entropy received by the *system* (ref. 12), with a negative sign. This is the basis of Erwin Schrödinger's famous sentence (ref. 17): "*What an organism feeds upon is negative entropy.*"

The internal entropy change, $d_i S$, is quantitatively related to the dissipation of Gibbs energy (eq. 8), and is thus an expression of the extent of *irreversibility* of a process irrespective of heat changes. In the steady state, the system parameters are unchanged and the positive internal entropy production is compensated by a negative external entropy change, $d_e S$, involving the transport of heat and matter (ref. 11). In contrast, the molar reaction entropy, $\Delta_r S$ (eqs. 4 and 5) is the molar heat change of a *reversible* isothermal reaction. This multiple meaning of "entropy" contributes to the puzzlement propagated by thermodynamic terminology. There appears to be a constructive solution. The integrating factor for entropy in isothermal systems, $1/T$, is a constant, hence redundant. Most commonly, the reaction entropy term is in turn multiplied by absolute temperature, $T \Delta_r S$ (eqs. 4 and 5). This suggests that the molar "bound energy change" should be reported as such, $\Delta_r B$ [$\text{J}\cdot\text{mol}^{-1}$], without going through the futile cycle of division and subsequent multiplication by temperature. This would remedy substantially some confusion persisting in the literature.

HEAT FLUX AND THERMOPILES

The form of eq.(3), applied for isothermal processes, is generally applicable,

$$P = J F \quad (10)$$

For vectorial heat flux along a temperature gradient, the dissipated thermal power is,

$$P = J_Q (dT/T) dz^{-1} \quad (11)$$

Vectorial heat flux, J_Q [$J.s^{-1}.m^{-2}$], is the flow of heat across the area (ref. 3) perpendicular to the temperature gradient (for simplicity considered to be oriented in the z direction only). The conjugated force is the relative temperature gradient in the z direction [m^{-1}]. The thermal power or time rate of "thermal free energy" change is expressed per unit area times distance (= volume) across which the heat flows. The thermal free energy change is the theoretical maximum amount of work which can be conserved (or dissipated) in the process. Note that in the description of a continuous process the dimensions of heat flux [$W.m^{-2}$] and thermal power [$W.m^{-3}$] are different.

Heat flux across the thermopiles of a heat conduction calorimeter is conveniently described as a discontinuous process. At steady state heat flux, a constant temperature *difference* is maintained across the thermopiles from the experimental vessel to the constant temperature heat sink. Ideally, the total heat flow across the wall of the vessel is identical to the heat flow to the thermopiles. Discontinuous heat flux is expressed per unit volume of the calorimeter vessel [$J.s^{-1}.m^{-3}$]. In the discontinuous description, the dimensions of heat flux, J_Q , and thermal power per unit volume, P , are identical [$W.m^{-3}$]. Therefore, the conjugated force, F_Q , is not an absolute temperature difference but the dimensionless relative temperature difference (compare eq. 11),

$$P = J_Q (T_h - T_l)/T_h \quad (12)$$

The driving force for heat flux in conductive heat transfer is,

$$F_Q = (T_h - T_l)/T_h = P / J_Q \quad (13)$$

If heat flux is spontaneous, h and l indicate the high and low temperature, respectively, and J_Q has a negative sign such that the dissipated power (eq. 12) is negative. Consider an electrical calibration when electrical energy is dissipated and received by the calorimeter vessel as a positive enthalpy change at temperature T_h . At steady state, the same enthalpy change is lost from the vessel at temperature T_h as heat, ΔH . In an irreversible heat flux, the total heat conducted from T_h to T_l at the heat sink is, $\Delta_t Q = \Delta H$ (negative sign). The internal entropy change due to this irreversible process is (ref. 12),

$$\Delta_i S = (1/T_h - 1/T_l) \Delta H \quad (14)$$

Multiplication of eq.(14) by the experimental reference temperature of the heat sink yields,

$$T_l \Delta_i S = -(T_h - T_l)/T_h \Delta H \quad (15)$$

Thereby, the integrating factor $1/T_j$ (j for either high or low) is replaced by the dimensionless integrating factor T_l/T_j . For the limit of an isothermal system this yields automatically an integrating factor of unity. The term on the left side of eq.(15) is the negative thermal free energy, $\Delta G = -T_l \Delta_j S$. The potentially useful (free) thermal energy which can be converted into work is the heat input minus the "bound energy" (compare eq. 4). Under reversible conditions, the bound energy is the heat flux from the heat engine to the low-temperature heat sink. Substituting the definition of thermal free energy and eq.(13) into eq.(15) and solving for the thermal force, we obtain,

$$F_Q = \Delta G/\Delta H \quad (16)$$

With the use of eqs.(16) and (13), substituted into eq.(12), the relation between thermal power and conductive heat flux is expressed in the form of a flux-force product,

$$P = J_Q \Delta G/\Delta H \quad (17)$$

Comparison of the thermal power (eq. 17) and the chemical power of isothermal reactions (eq. 6) illustrates the generality of the distinction between heat flux and power.

It is instructive to note that the relative temperature difference, $(T_h - T_l)/T_h$ (eq. 12), is viewed in classical thermodynamics of heat engines as the 'efficiency of a reversible machine' (ref. 18). This thermodynamic "efficiency" (eq. 13) is not an (ergodynamic) power efficiency, but is now recognized as a driving force: With increasing force, there is a proportional increase of the power associated with a given heat flux. This concept is familiar from various analogous fluxes and conjugated forces: With increasing voltage (force) the electrical power increases at constant current (flux). At thermal equilibrium, the temperature difference and thus the force is vanishingly small whence vectorial heat flux is zero. The thermal power can be fully converted into work at a maximum ergodynamic efficiency of unity (for a discussion of energy coupling in thermopiles see ref. 19). In heat conduction calorimeters (ref. 20), the thermal power across the thermopiles is not fully dissipated but is partly transformed into the electric signal. This signal is proportional to the temperature difference and hence to the total heat flux. Even under reversible conditions, however, the heat flux from the high-temperature heat source into a heat engine is not fully converted into work, except under the impossible condition of $T_l = 0$ K.

The thermal force in heat conduction calorimeters is always very small, hence a near-equilibrium condition is maintained and the heat flux increases linearly with the thermal force within the limits of detection. This is different far from equilibrium with large magnitudes of the force (ref. 21). The thermal conductivity depends on the heat

capacity which is a function of temperature. Therefore, the conductivity is not only variable but is a function of the force which restricts the application of Onsager nonequilibrium thermodynamics (ref. 12,22). It appears to be advantageous to combine the two interdependent terms - the heat content as related to the heat capacity (= 'concentration of heat') times thermal force - for the analysis of the dynamics of vectorial heat flux far from equilibrium.

FLUX-PRESSURE RELATIONS

In chemical reactions, the near-equilibrium condition appears to be much more restrictive for application of linear flux-force relations (ref. 22). The theoretical dependence of the phenomenological conductivity on the concentration of substrates and products is well recognized (ref. 22). The relevant concentration or activity term and the Gibbs force are interdependent (ref. 23). Again, the combination of the two interdependent terms - a concentration term times Gibbs force - is suggested for the analysis of the dynamics of metabolic reactions (ref. 23). Such a combination is well established in the thermodynamic and kinetic theory of diffusion (ref. 24): The product of local concentration times chemical potential (driving force) yields the osmotic pressure gradient [$\text{J.m}^{-3} = \text{Pa}$], and pressure is linearly related to flux. From this perspective, the dynamics of chemical diffusion is analyzed in terms of a flux-pressure relation which is linear in a region far beyond the near-equilibrium domain of linear flux-force relations (ref. 23). The combination of biochemical, respirometric and calorimetric methods is required to test the phenomenological concept of generalized flux-pressure relations in complex metabolic systems.

The distinction between power and heat flux draws on a theoretical framework with wide ramifications. Cellular heat flux and metabolic power are basically distinguished properties, an understanding of which is required for further investigations into the energetics and control of dissipative metabolic processes.

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