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ENERGY AND ENTROPY FLOWS IN LIVING SYSTEMS

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Energy and entropy flows in living systems

by

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DEDICATION

This work is dedicated to my family; to my parents, Gunars and Antonija Briedis, and to my brother, Robert.

I. INTRODUCTION

Life is a costly, energy consuming process which develops and sustains gradients in temperature, pressure, concentration, and chemical affinity. Living systems fuel this process through the capability of transforming energy from one form to another through intricate chains of biochemical and physiochemical events. In this sense, they have been compared to a complex chemical factory in which the primary purpose is the creation and maintenance of life.

This analogy suggests that the principles of thermodynamics and transport phenomena used for analyzing physical systems may be applied to the study of energy flows in the development, growth, and regulation of living organisms. The application of the principles of conservation of material and of energy to biological systems has appeared frequently in thermodynamics research since the mid-nineteenth century. Calorimetric studies of the heat production of animals were performed in the late 1700s by Lavoisier and Laplace and subsequently served as a basis for more rigorous thermodynamic analyses. In the late 1800s, the link between food as a fuel, the heats of combustion of the nutrients in the food, and the resulting heat production by the system was demonstrated. These later studies warranted assumptions about the applicability of the laws of conservation of matter and energy, although the data were not analyzed to represent the proper thermodynamic quantities.

The first law of thermodynamics and the concepts and quantities used therein often imply a restriction to measurements done on systems at

equilibrium since some of the quantities used in the first law expression are defined rigorously only at equilibrium. Classical thermodynamics is a study of static situations constrained largely to spatially homogeneous, time-invariant entities. Biological systems are inherently complex and heterogeneous, open, transient, and not at equilibrium. This indicates the need for additional studies using irreversible or nonequilibrium thermodynamics in which the concept of local equilibrium permits the use of equilibrium thermodynamic variables.

The first law, however, does serve as an adequate and useful tool in the macroscopic analysis of biological systems over relatively short time spans. Classical thermodynamic theory can be used in dealing with overall features, constraints, and consequences to obtain limiting statements about the system and its operation. It is a bookkeeping device and has no predictive capabilities.

The concepts of irreversible thermodynamics allow further insights into the thermodynamic description of biological systems through the use of ideas such as local equilibrium, entropy flow, entropy production, and stationary states. Many biological processes may be modelled by the phenomenological relations between forces and fluxes developed by Onsager in 1931. The investigation is somewhat simplified in living organisms which operate within a limited temperature range and at nearly constant pressure and which are composed of solutions that may be considered ideal.

The second law of thermodynamics implies that the entropy of an isolated system in which irreversible processes take place must increase.

Since most of the processes in living systems are irreversible, Prigogine (80) has hypothesized that the specific internal entropy production rate of living systems must be positive but that it continually decreases as a system develops, matures, and ages. These two ideas suggest that life may be placed into a global framework in which living things contribute to the overall entropy increase of the universe.

Once the first law analysis has provided a thorough understanding of the energy flows of a system, irreversible thermodynamics, subject to overall energy balance constraints, serves as a predictive tool to characterize and quantify the dissipatory mechanisms and efficiencies of energy conversion in living systems.

This study will in part deal with the human body during work and exercise. The physiology of the human at work provides basic information about the effects of stress on the nature, range, and efficiency of the resultant energy flows. Energetics and mechanics of athletic events and of single muscle activity are well-documented by many researchers in the field of work physiology providing an excellent data bank, although some of the data are misrepresented and incomplete.

The thermodynamics of growth and development will be examined in systems such as the avian egg and microbial cultures. Newly developed applications of material and energy balances in studies of microbial energetics will be extended to include applications of the second law of thermodynamics and a qualitative evaluation of entropy production for these systems.

In summary, the primary goals of this work are to perform a comprehensive thermodynamic analysis of the flows of material, energy, and entropy which occur in living systems, to use the resulting generalized energy and entropy balances to evaluate and reinterpret existing data on these quantities, to gain an understanding of the energy and entropy relationships in development, growth, and regulation processes, and to suggest experiments to further the understanding of these processes.

II. LITERATURE OVERVIEW

The following is a summary of the important literature in areas pertinent to this study. Contributions originate from several independent disciplines, so the related literature is potentially vast.

This section is intended to briefly describe these main areas and present a concise account of the work done in each. The nature of this work is such that a literature review is more coherent if more specific and analytical comments are presented when the individual topics are discussed in the body of the thesis.

A. Energy and Biology

The study of the thermodynamics of living systems is by no means new. Calorimetric studies were being performed on guinea pigs and other species as early as the 1700s. However, not until the twentieth century were such studies performed on specific subsystems of living organisms, such as muscle.

1. Muscle contraction energetics

Huxley (60) made great contributions regarding the microscopic muscle contraction mechanism with the sliding filament theory. Through the use of electron-microscopic observation, he was one of the first to recognize the cross-bridge linking of muscle filaments as the force-generating mechanism in muscle. This area is still an active area of research since many details remain to be investigated.

Hill (54, 55) and Wilkie (117) were some of the first to begin studies on the measurement of work performed by muscles. Hill's force-velocity relationships for isolated muscle demonstrated that the maximal force developed when a muscle is contracting is a function of the velocity of contraction. This work formed the foundation for the mechanical study of muscle.

The study of the energetics of muscle contraction was a logical consequence of the mechanical studies. Major contributions describing heat production during working conditions, the changes in chemical substrates in working muscle, and muscle efficiencies were made by Fenn (43, 44), Hill (56, 57, 58), Hill and Howarth (59), Wilkie (120), Curtin et al. (32), and Edwards et al. (36). In situ research was done by Stainsby (105, 106). Almost every study showed that performance of muscular work by contraction resulted in an increased heat production by the muscle, called the Fenn effect, and an increased energy consumption rate. The work done by Hill (54), Kushmerick and Paul (67), and Stainsby (105, 106) demonstrated the direct proportionality between muscle energy consumption and muscle oxygen uptake. Recently, the effect of muscle length and the degree of muscle filament overlap on muscle energy consumption has been determined by Matsumoto and McPhedran (73) and Aubert and Gilbert (7). A good review of muscle energetics studies has been presented by Kushmerick (66).

2. Exercise physiology and energetics

Advancing from the isolated muscle to the human body as the system under analysis, the field of exercise physiology developed as a link

between mechanical and energetics studies during the early 1900s.

The energetics of sprinting and running were studied as early as 1923 by Sargent (95) and in 1930 by Fenn (45, 46). Knuttgen (63) studied the effects of stride length on energy consumption. Later research included "work platform" analyses which allowed the calculation of kinetic and potential energy changes on a per stride basis. Such work was done by Cavagna et al. (25, 26, 27) and Margaria (70) for sprinting, walking and running.

The drag effects associated with running into a wind as compared to still air were investigated by Pugh (84) and Davies (33).

A complete study of the work performed by a man-bicycle system was done by Diprampero et al. (35) in 1979 and on the effect of various cycling frequencies by Seabury et al. (98).

As the popularity of long-distance running increased, so did the research done on its effects on the human body. These studies are exemplified by work done by Saltin et al. (94), Costill (30), and Maron and Howarth (72) on marathon running.

A typical outcome of work-energy studies was the analysis of working efficiency. These types of calculations were found throughout the literature previously cited and were specifically considered in the work done by Whipp and Wasserman (115) on phosphorylative- and contraction-coupling efficiencies, by Suzuki (110) on the efficiency of fast and slow twitch muscle fibers, and by Stainsby et al. (107) in a review of commonly used efficiencies and baselines.

Because some of the efficiencies found in running, jumping, and sprinting were much larger than what was usually given in the literature for muscular work, the idea of reusable elastic energy storage in muscles became a popular research topic. Abbot et al. (2) and Abbot and Bigland (1) were some of the first to quantitatively study the effects of negative work, or work done on the muscle system, during bicycle pedalling. Cavagna et al. (28) performed experiments on isolated muscle and found an increased capacity to perform work immediately after stretching. The capacity diminished as the time between the stretch and subsequent contraction increased. Assmusen and Bonde-Petersen (4, 5) and Margaria (71) did studies on the elastic energy storage during jumping, running, and cycling. Each group concluded that it was definitely possible to reuse stored elastic energy as a direct source of energy for contraction, thereby lowering the muscle's subsequent demand for chemical energy. These storage effects were quantified for single muscles and other living tissue by Alexander and Bennet-Clark (3) and Minns et al. (74). Currey (31) found that tendons served as the best living tissue for elastic energy storage. He attributed this to the viscoelastic behavior of this tissue caused by the internal rearrangement of the molecules of tendon tissue to minimize strain.

Åstrand and Rodahl (6) have published a complete and concise text that is presently the definitive work in the field of exercise physiology.

These studies have proved to be excellent sources of data for performing energy balances on the human body during stressed conditions.

3. Development and growth

The study of development and growth has been an interesting topic of energetics research. The energy transformations accomplished by an organism during growth are the direct cause of the notable macroscopic changes observed during this period of the organism's lifetime.

The chicken egg has served as an excellent system for study. Romijn and Lokhorst (90, 91, 92) have measured the fetal heat production and fetal respiration in eggs as an assessment of the metabolism of the embryo. They have calculated both convective and evaporative heat loss from the egg and have attempted to perform an energy balance. Their success is questionable and will be discussed later in this work.

Romanoff (89) has compiled a comprehensive, quantitative analysis of the prenatal development of various avian embryos. He has dealt with all pertinent components of the developing eggs and has discussed both chemical and energy transformations. His book has been useful in this study and will be referred to again.

The study of microbial growth is a second area of research that has been important in this research. The energy transformations and energy content of bacteria have been investigated by Battley (10), Senez (101), Hadjipetrou et al. (52), Forrest and Walker (47), De Hollander et al. (34) and others. Through elemental balances and a thorough investigation of growth yields and substrate uptake, these investigators have been able to write explicit expressions for the growth of microbial organisms. The biochemical pathways of biosynthesis have been well-defined. Although the results of their work have not been used specifically in this research,

they have served as a basis for understanding the useful techniques described in the paragraph to follow.

The methods of material and energy balances have seen recent success in applications to the study of microbial cultures by Erickson (37, 38), Roels (88), Erickson and Patel (40, 41), Erickson and Hess (39), and Erickson et al. (42). These investigators' use of electron balances has made the microbial culture a highly analyzable system, particularly helpful for the purposes of this study.

The text written by Bailey and Ollis (8) on the fundamentals of biochemical engineering has served as an excellent source of background information in this area.

B. Entropy and Biology

The question of whether entropy is a quantity of significance for living systems has been debated by many scientists by various approaches. Brillouin (18), Schrödinger (97), and Von Bertalanffy (114) all recognized that living organisms were able in some way to control entropy production because they were open systems and were capable of exchanging material and energy with their surroundings. Their writings, cited by many of their successors, were an instigation of and inspiration for further research in this particular field.

The tendency to consider entropy as a measure of disorder has been the cause of much confusion. Living things seemed to avoid decaying to a state of disorder and, therefore, have been perceived by many to be in violation of the second law of thermodynamics. The work of Brillouin (18),

Schrödinger (97), and Morowitz (76) soon discouraged such comparisons between entropy and disorder as a reason for denying the relevance of entropy in biology. They attempted to justify the apparent trends in entropy production by considering the entropy flows as compensation for the entropy changes due to the establishment of order. Living systems were described as feeding on negative entropy, or "negentropy," which permitted the apparent decrease in entropy due to the ordering process of biosynthesis.

Brillouin (18) also discussed the fact that since living things were open systems, they were not bound by the second law of thermodynamics for closed systems. He was among the first to consider the use of information theory as a means of quantifying the entropy changes resulting from organization. Several other authors (76, 97) have discussed the concept of relating entropy and information. This idea will be considered in the discussion of entropy and organization.

1. Irreversible thermodynamics

With the development of the concepts of irreversible thermodynamics by Onsager in 1931, their use in describing living systems became an active area of research within two decades' time (61). Prigogine and Wiame (83) were the first to suggest the applicability of irreversible thermodynamics in biology. They argued that, because living organisms reach a final equilibrium only at death at which the internal entropy production is zero, the rate of specific internal entropy production must be decreasing, but possibly fluctuating, in the approach to that state.

2. Development and growth

The development and growth of organisms became an area of intense academic debate in the mid-1960s. Trincher (112, 113) questioned the use of Prigogine's hypothesis in biology and used the heat emission data from developing eggs to demonstrate his objection. He used experimental data on heat loss from fertilized eggs (90, 92) and incorrectly equated the specific internal entropy production to the heat loss from the egg. Since the experimental data showed that during embryonic development the rate of specific heat production increased, he concluded that the entropy production rate increased and that Prigogine's hypothesis was incorrect or inapplicable.

Zotin (122) argued that Trincher's calculation had not considered the increasing weight of the active embryo and therefore the calculations of specific entropy production were wrong. Zotin recalculated these values and found that as the embryo grew, the specific internal entropy production decreased.

In further studies, Zotin and Zotina (124) discussed the concept of steady states in developing organisms and related entropy production to growth rates of animals. They examined experimental data of heat production and respiration of many developing organisms and found that Prigogine's hypothesis seemed to apply. The same was shown for man. In so doing, Zotin compiled a very complete collection of heat production data for a variety of developing animals and a concise explanation of the possible role of entropy production in development, ageing, and growth (123).

Brief periods of increased rates of entropy production were found in situations where organisms deviated from steady state, such as in the early stages of oogenesis and during the regeneration and healing of wounds. Zotin and Zotina (124) also showed that malignant growths caused a sudden deviation from steady state as the metabolic rate of cancerous cells was much higher than that of normal cells. By having done this, they were one of the first to suggest that entropy production rates could serve as a means of describing the state of an organism, its health and development.

Zotin (123) refined his theory of homeostatic and developmental steady states in a thorough analysis of the entropy production during development. He again reaffirmed the validity of Prigogine's hypothesis in the development, growth, and ageing of living organisms.

Several other researchers have considered entropy production changes in relation to changes in steady state operation to model the oscillatory phenomena which occur in biology, such as the regulatory mechanisms of homoiothermic animals, "biological clocks," and the overall behavior of biological systems (11, 49).

Entropy production was considered to be a direct cause for the ageing of organisms, as discussed in studies by Sacher (93), Calloway (22), and Balmer (9).

The question of evaluating entropy production during embryogenesis has persisted. Schaarschmidt et al. (96) considered the evaluation of the internal dissipation function, ψ, of a yeast cell colony in two portions, that which is dissipated externally, ψ_d, and the part that remains

bound in the system, ψ_u. They assumed that respirative and glycolytic metabolisms determine all dissipation processes occurring in organisms. By measuring the difference between metabolism, $\dot{q}_M$, and the specific rate of heat production, $\dot{q} = \psi_d$, the bound dissipation could be directly measured.

They used calorimetric measurements on a growing yeast culture to determine that ψ decreased monotonically with the age of the organisms and became zero for systems at equilibrium.

Hiernaux and Babloyantz (53) considered the use of nonlinear irreversible thermodynamics to evaluate dissipation during embryogenesis. They showed that nonlinear thermodynamic models properly predicted the increase in entropy production during the early stages of development.

Three years later, Lurie and Wagensberg (69) argued that nonlinear thermodynamics need not be invoked to explain heat dissipation during embryogenesis. They attempted to include the effects of the entropy change due to reaction and did not assume that internal entropy production could be approximated simply by heat production calculations. As a result, the total rate of specific entropy production was written as the sum of entropy addition due to growth and the changes resulting from biomass organization and differentiation. In initial growth phases, the growth term was expected to make a large positive addition to the entropy production. Beyond these initial periods of growth, the organization term, assumed by the authors to be negative, became the dominant term.

Although the entropy production had been rewritten in a concise form, it had not simplified the calculation or eliminated the difficulty of measuring internal entropy production.

3. Entropy and evolution

Early embryonic development has often been considered to be a miniaturized display of evolutionary processes. It was inevitable that irreversible thermodynamics was to become an instrument with which to study aspects of evolution. Prigogine et al. (81, 82) and Nicolis and Prigogine (78) stated that fluctuations and dissipation on the molecular level can eventually drive an entire system to some new, stable regime. An example of this effect is seen in fluid mechanics where small instabilities in laminar flow near the critical Reynolds number eventually cause the flow to become turbulent. In biological systems, such a sudden transition is seen in the sudden depolarization of excitable membranes. The authors hypothesized that under far-from-equilibrium conditions, new structures could appear as a consequence of fluctuations. If the new structure were more stable, evolution and Darwin's "survival of the fittest" could be viewed as having occurred through such mechanisms. A major argument in opposition to this idea is that the apparent probability of such an occurrence is prohibitively low (16).

4. Irreversible thermodynamics and muscle contraction

An entirely different area in which irreversible thermodynamics has been applied in biology is energy conversion in muscles. Caplan (23) was the first to model muscle contraction as a linearly-coupled energy con-

verter using thermodynamic forces and fluxes. Wilkie and Woledge (121) showed that his model did not adequately agree with data and concluded that it was therefore incorrect. Bornhorst and Minardi (13, 14, 15) defended Caplan and showed good agreement with integrated data. They further modified Caplan's model using Huxley's sliding filament theory of muscle contraction. Their approach included the effects of muscle length variation (15). The site of the linear energy converted was then assigned to be at the cross-bridge coupling of the myosin and actin fibers of muscle and not the entire muscle. The force generated was postulated to be a function of the number of activated cross-bridges.

Caplan (24) has offered a good summary of the nonequilibrium approach to biochemistry and to muscle contraction. Other applications are discussed by Katchalsky and Curran (61).

From these highlighted works, it is apparent that there is at present no coherence between these separate but related fields. In order that communication be improved between physiologists and thermodynamicists, vocabularies should be unified and standardized so that the data being measured can actually be represented by the intended thermodynamic quantities and that phenomenological coefficients have practical physiological meaning.

In the techniques, analyses, and applications described in the pages to follow, it is hoped that some progress will be made toward this end.

III. TECHNIQUES AND ANALYSIS

A. The Mass Balance

The first step in interpreting relationships between mass and energy flows is the development of generalized material balances. Balances are performed first on the overall mass and then on specific species of interest.

$$\frac{dM}{dt} = \frac{d}{dt} \sum_i m_i = \sum_j \dot{W}_j \delta_j = \sum_j \sum_i \dot{\omega}_{ij} \delta_j + \sum_k \sum_i \dot{r}_{ik} \qquad (1)$$

M = total mass within system boundaries

m_i = mass of chemical species i

$\dot{W}_j$ = mass flowrate of stream j crossing the system boundaries

$\dot{\omega}_{ij}$ = mass flowrate of the ith species in the jth stream, such that $\dot{W}_j = \sum_i \dot{\omega}_{ij}$

$\dot{r}_{ik}$ = rate at which species i is produced in the kth chemical reaction ($\sum_i \sum_k \dot{r}_{ik} = 0$ if the reaction rate is on a mass basis)

δ_j = quantity indicating direction of flow, + 1 in, - 1 out.

A system gains mass from or loses mass to the streams crossing its boundaries. Each of these streams may be composed of several species i. The composition of the streams is affected by the k chemical reactions occurring within the system.

For a particular species i,

$$\frac{dm_i}{dt} = \sum_j \dot{\omega}_{ij}\delta_j + \sum_k \dot{r}_{ik} \tag{2}$$

$$\dot{r}_{ik} = \tilde{M}_i \nu_{ik} \frac{d\xi_k}{dt} \tag{2a}$$

where ν_{ik} is the stoichiometric coefficient of i in the kth reaction (positive for products, negative for reactants), $\tilde{M}_i$ is the molecular weight of i, and ξ_k is the molar extent of reaction k. The molar extent is a normalized extensive property related to the number of moles reacted by the following relationship:

$$d\xi_k = \frac{dn_i}{\nu_i} \tag{2b}$$

where dn_i is the number of moles of i consumed or produced in the kth reaction. If species i is a product, ν_i and dn_i are both positive and the extent increases. If the species being observed is a reactant, ν_i is negative and dn_i decreases which also indicates the progression of the reaction by an increase in extent. The time rate of change of extent, $d\xi_k/dt$, is often written as the velocity of reaction, v_k. Extent changes may also occur without reaction when a species i is added to or withdrawn from the system.

The species mass balance can then be written

$$\frac{dm_i}{dt} = \sum_j \dot{\omega}_{ij}\delta_j + \sum_k \tilde{M}_i \nu_{ik} v_k \tag{3}$$

Several species are of particular physiological interest as measures of the metabolic activity in a system operating in resting or in stressed states. The first quantity is the measure of oxygen consumption rate.

$$\sum_j \dot{\omega}_{O_2 j} \delta_{O_2 j} = \frac{dm_{O_2}}{dt} - \sum_k \tilde{M}_{O_2} \nu_{O_2 k} \frac{d\xi_k}{dt} .$$

Oxygen consumption is usually measured in volumetric units, ml O_2/min, so that the quantity $\dot{V}_{O_2}$, the oxygen uptake rate, may be related to the mass uptake rate by

$$\dot{V}_{O_2} = \frac{\sum_j (\dot{\omega}_{O_2 j} \delta_{O_2 j}) RT_o}{\tilde{M}_{O_2} P_o} \tag{4}$$

where T_o and P_o are the chosen reference temperature and pressure. If the time rate of oxygen storage is negligible ($dm_{O_2}/dt = 0$), then

$$\dot{V}_{O_2} = \frac{-RT_o}{P_o} \sum_k \nu_{O_2 k} v_k \tag{4a}$$

The main function of oxygen is to serve as an oxidant in physiological reactions, making $\nu_{O_2 k}$ a negative quantity.

Carbon dioxide is an eventual product for virtually all oxidizing reactions in living systems. The production of CO_2 is given by

$$\sum_j \dot{\omega}_{CO_2 j} \delta_{CO_2 j} = \frac{dm_{CO_2}}{dt} - \sum_k \tilde{M}_{CO_2} \nu_{CO_2 k} v_k$$

The storage of carbon dioxide in living tissue may not always be negligible. In hypercapnic conditions, this amount may be more than an order of magnitude higher than oxygen accumulation because of the HCO_3^-/H_2CO_3 buffer system of the cellular fluid (48). However, for normal cell function, a steady state assumption leads to the following equations:

$$\dot{V}_{CO_2} = \frac{\Sigma(\dot{\omega}_{CO_2 j}\delta_{CO_2 j})RT_o}{\tilde{M}_{CO_2}P_o}$$

$$- \dot{V}_{CO_2} = \frac{RT_o}{P_o} \sum_k \nu_{CO_2 k} v_k \tag{4b}$$

Since CO_2 is a reaction product, the $\nu_{CO_2 k}$'s are positive numbers.

The ratio of carbon dioxide production ($- \dot{V}_{CO_2}$) to oxygen consumption ($\dot{V}_{O_2}$) is called the respiratory quotient. This ratio serves as an indicator of the types of substrates or fuels (carbohydrates, fats, proteins) being oxidized by the system.

$$R \equiv \frac{- \dot{V}_{CO_2}}{\dot{V}_{O_2}} = \frac{\sum_k \nu_{CO_2 k} v_k}{\sum_k \nu_{O_2 k} v_k} \tag{5}$$

The oxidation of biological fuel to high-energy compounds utilized for cellular function involves various complex biochemical pathways and cycles. The combustion of these organic fuels is usually simplified to consider only the oxidation of carbohydrates (C), fats (F), and proteins (P) as the three major chemical reactions. Then the reaction terms of

Equation 5 may be rewritten as

$$R = \frac{\nu^{C}_{CO_2} v_C + \nu^{F}_{CO_2} v_F + \nu^{P}_{CO_2} v_P}{-(\nu^{C}_{O_2} v_C + \nu^{F}_{O_2} v_F + \nu^{P}_{O_2} v_P)}$$

If each chemical reaction is rewritten so that the stoichiometric coefficient of oxygen is equal to one, as shown for the combustion of glucose below,

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

rewritten to

$$\frac{1}{6} C_6H_{12}O_6 + O_2 \rightarrow CO_2 + H_2O$$

and $v_C + v_F + v_P = v_{TOT}$, the total reaction velocity, then

$$R = \frac{\nu^{C}_{CO_2} v_C + \nu^{F}_{CO_2} v_F + \nu^{P}_{CO_2} v_P}{(+1) v_{TOT}} \tag{5a}$$

$$R = \frac{\nu^{C}_{CO_2} v_C}{v_{TOT}} + \frac{\nu^{F}_{CO_2} v_F}{v_{TOT}} + \frac{\nu^{P}_{CO_2} v_P}{v_{TOT}} \tag{5b}$$

The ratios $\nu^{k}_{CO_2}/\nu^{k}_{O_2}$ are relatively constant for each specific class of organic compound (C, P, or F) regardless of the particular molecule being combusted. Typical values from Lehninger (68) are

$$\left[\frac{\nu_{CO_2}}{-\nu_{O_2}}\right]_C = 1 \qquad \left[\frac{\nu_{CO_2}}{-\nu_{O_2}}\right]_P = 0.80 \qquad \left[\frac{\nu_{CO_2}}{-\nu_{O_2}}\right]_F = 0.71$$

Replacing v_k/v_{TOT} with x_k, a simple expression for the respiratory quotient results

$$R = 1.0x_C + 0.80x_P + 0.71x_F \tag{6}$$

which is valid for interpretation of measured values if the following limitations are observed:

1. The accumulation of oxygen and carbon dioxide is negligible.
2. The combustion reactions are normalized with respect to oxygen.
3. The total number of chemical reactions occurring may be grouped into three major compound groups, carbohydrates, fats, and proteins.
4. The ratio of stoichiometric coefficients $\nu_{CO_2}/-\nu_{O_2}$ is approximately constant in a particular compound group independent of the specific molecule type.

Material balances are important in primary analysis because they characterize the reactant consumption and the product type and removal rate, important quantities in the subsequent step, the energy balance analysis.

B. The Energy Balance

The open system first law expression may be written in general in a form modified from Seagrave (99):

$$\frac{d}{dt}[U + \phi + K] = \sum_{j}^{N} (\hat{H}_j + \hat{\phi}_j + \hat{K}_j)\dot{W}_j\delta_j + \dot{Q} - \dot{W} \qquad (7)$$

The terms on the right represent flows across the boundaries of the system. The left represents the time rate of change of energy within the system. All three quantities on the left must be related to a chosen reference state. Potential energy is referenced to a convenient position in a potential field. For the kinetic energy, K, the reference state is zero velocity relative to a stationary coordinate system. These two terms are usually negligible in biological systems although situations do exist where their contributions are important. These are addressed further in the discussion. The reference state for the internal energy, U, depends largely upon the system being considered.

1. Development

Internal energy may be written as

$$U = m\hat{U} \qquad (8)$$

where m is the mass of the system and $\hat{U}$ is its mean specific internal energy. Specific internal energy changes reflect changes at the molecular level within the system. The energy of molecules of a given species may be altered in several ways, by changes in thermal energy, in specific volume or pressure, in strain, and in the electrical charge of the system particles.

Then

$$d\hat{U} = d\hat{U}_T + d\hat{U}_V + d\hat{U}_D + d\hat{U}_E \tag{9}$$

where $d\hat{U}_T$ represents the thermal contribution, $d\hat{U}_V$, the volume changes, $d\hat{U}_D$, the deformational specific internal energy, and $d\hat{U}_E$, the electrical specific internal energy. These dependences are written more generally as

$$\hat{U} = \hat{U}(T, \hat{V}, \varepsilon_s, z_p) \tag{10}$$

which expresses internal energy as a function of the intensive parameters temperature, T, specific volume, $\hat{V}$, strain, ε_s, and charge, z_p. These are internal parameters of the system.

The differential of $\hat{U}$ is written as a function of the four intensive variables,

$$d\hat{U} = \left(\frac{\partial \hat{U}}{\partial T}\right)_{\hat{V},\varepsilon_s,z_p} dT + \left(\frac{\partial U}{\partial \hat{V}}\right)_{T,\varepsilon_s,z_p} d\hat{V} + \sum_s \left(\frac{\partial \hat{U}}{\partial \varepsilon_s}\right)_{T,\hat{V},z_p} d\varepsilon_s + \sum \left(\frac{\partial \hat{U}}{\partial z_p}\right)_{T,\hat{V},\varepsilon_s} dz_p \tag{11}$$

The third term on the right represents a summation of s deformations and the fourth term is a summation over p charged particles.

The term $\left(\frac{\partial \hat{U}}{\partial T}\right)_{\hat{V},\varepsilon_s,z_p}$ is the specific heat at constant volume, $\hat{C}_V$, and $\left(\frac{\partial \hat{U}}{\partial \hat{V}}\right)$ is h_V, the isothermal specific energy of compression.

In addition to the changes in total internal energy, U, which occur due to changes in intensive properties, changes in extensive properties

and concentration can also affect U; i.e.

$$dU = dU_{\text{intensive}} + dU_{\text{extensive + composition}}$$

The changes in intensive properties have been described in Equations 10 and 11. Changes in extensive internal energy are due to changes in the system mass and composition which may occur by changes in the mass of any or all species i of the system, so that

$$dU_{\substack{\text{extensive} \\ \text{+ composition}}} = \sum_i \left(\frac{\partial U}{\partial m_i}\right)_{T,\hat{V},\epsilon_s z_p} dm_i \tag{12}$$

Equation 11 is rewritten as

$$dU = m d\hat{U} + \sum_i \left(\frac{\partial U}{\partial m_i}\right) dm_i \tag{13}$$

and the rate expression obtained by taking the time derivative of Equation 13 is

$$\frac{dU}{dt} = m \frac{d\hat{U}}{dt} + \sum_i \left(\frac{\partial U}{\partial m_i}\right)_{T,\hat{V},\epsilon_s,z_p} \frac{dm_i}{dt} \tag{14a}$$

The partial derivative, $\left(\frac{\partial U}{\partial m_i}\right)_{T,\hat{V},\epsilon_s,z_p}$ is equivalent to $\underline{\hat{U}}_i$, the partial molal internal energy of species i, so that

$$\frac{dU}{dt} = m \frac{d\hat{U}}{dt} + \sum_i \underline{\hat{U}}_i \frac{dm_i}{dt} \tag{14b}$$

The second term is expanded by replacing dm_i/dt with the mass balance Equations 2 and 2a, which leads to

$$\frac{dU}{dt} = \frac{m d\hat{U}}{dt} + \sum_i \underline{\hat{U}}_i \left[\sum_j \dot{\omega}_{ij}\delta_j + \sum_k \tilde{M}_i \nu_{ik} v_k\right]$$

$$\frac{dU}{dt} = \frac{m d\hat{U}}{dt} + \sum_i \sum_j \underline{\hat{U}}_i \dot{\omega}_{ij}\delta_j + \sum_i \sum_k \underline{\hat{U}}_i \tilde{M}_i \nu_{ik} v_k \qquad (15)$$

The second term, $\sum_i \sum_j \underline{\hat{U}}_i \dot{\omega}_{ij}\delta_j$ is equal to $\hat{U}dm/dt$ and represents the change in system internal energy due to the net addition of mass. This system growth is caused by integrated flow differences as is demonstrated when Equations 2 and 2a are summed over all i species

$$\sum_i \frac{dm_i}{dt} = \sum_i \sum_j \dot{\omega}_{ij}\delta_j + \sum_i \sum_k \tilde{M}_i \nu_{ik} v_k$$

and $$\sum_i \frac{dm_i}{dt} = \frac{dm}{dt} = \sum_i \sum_j \dot{\omega}_{ij}\delta_j$$

since $\sum_i \sum_k \tilde{M}_i \nu_{ik} v_k = 0$ when the reaction term is written on a mass basis. The summation of $\underline{\hat{U}}_i$ over all species of the system is equivalent to the mean internal energy of the system, $\hat{U}$. Equation 15 is now written as

$$\frac{dU}{dt} = \frac{m d\hat{U}}{dt} + \frac{\hat{U} dm}{dt} + \sum_i \sum_k \underline{\hat{U}}_i \tilde{M}_i \nu_{ik} v_k \qquad (16)$$

Combination of Equations 11 and 16 results in an expanded expression for the rate of internal energy change in the system;

$$\frac{dU}{dt} = \hat{U}\frac{dm}{dt} + m\hat{c}_V\frac{dT}{dt} + mh_V\frac{d\hat{V}}{dt} + \sum_s\left(\frac{\partial U}{\partial \epsilon_s}\right)\frac{d\epsilon_s}{dt} + \sum_p\left(\frac{\partial U}{\partial z_p}\right)\frac{dz_p}{dt}$$

$$+ \sum_i\sum_k \hat{\underline{U}}_i\tilde{M}_i\nu_{ik}v_k \qquad (17)$$

The last three terms on the right side of Equation 17 may be further simplified.

The term $\sum_i\sum_k \hat{\underline{U}}_i\tilde{M}_i\nu_{ik}v_k$ is considered for isochoric, isobaric systems so that the partial molal internal energy and enthalpy are equal. For ideal solutions, a good approximation in most living organisms,

$$\tilde{M}_i\hat{\underline{U}}_i = \tilde{M}_i\left(\frac{\partial U}{\partial m_i}\right) = \tilde{M}_i\left(\frac{\partial H}{\partial m_i}\right) \qquad (18)$$

$$\tilde{M}_i\left(\frac{\partial H}{\partial m_i}\right) = \frac{\partial H}{\partial n_i} = \tilde{H}_i \cong \hat{H}_i \qquad (19)$$

where $\tilde{H}_i$ is the partial molar enthalpy which is approximately equal to $\hat{H}_i$, the specific enthalpy.

Substitution of the results of Equations 18 and 19 into the term $\sum_i\sum_k \hat{\underline{U}}_i\tilde{M}_i\nu_{ik}v_k$ yields

$$\sum_i\sum_k \hat{\underline{U}}_i\tilde{M}_i\nu_{ik}v_k \cong \sum_i\sum_k \hat{H}_i\nu_{ik}\frac{d\xi_k}{dt} = \sum_k\sum_i \hat{H}_i\nu_{ki}\frac{d\xi_k}{dt} \qquad (20)$$

As shown by Strunk (109), $\sum_i \nu_{ik}\hat{H}_i = \Delta\hat{H}_{Rk}$, the molal heat of reaction for the kth reaction.

Therefore, with the assumptions implied in Equation 19,

$$\sum_k \sum_i \hat{U}_i \tilde{M}_i \nu_{ik} v_k \cong \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} . \qquad (21)$$

The term $\sum_s (\partial U/\partial \varepsilon_s) d\varepsilon_s/dt$ represents the dependence of system internal energy on the state of strain in the system, a geometric dependence. Elastically deformable bodies are capable of storing elastic energy as an elastic potential that is released when the system is allowed to return to its original unstrained geometric configuration.

For the one-dimensional case, the strain, $\varepsilon_s = \delta_s/\ell_o$, where δ_s is the increment of deformed length in the sth strain and ℓ_o is the original system length.

Because some elastic systems are capable of storing energy upon compression while others do so upon tension, a generalized length term ℓ' is defined as

$\ell' = \ell - \ell_o$ when energy is stored under tensile forces

$\ell' = \ell_o - \ell$ when energy is stored under compressive forces,

where ℓ_o serves as the reference.

In each case, the character of the system must be known to make the proper choice of the generalized length term. The forces are assigned a positive value whether they are compressive or tensile. The direction

of the change in internal energy is determined by the length changes, $d\ell'$.

The strain, ε_s, is now rewritten with the new length term, $\varepsilon_s = \ell_s'/\ell_o$. Then,

$$\sum_s \left(\frac{\partial U}{\partial \varepsilon_s}\right) \frac{d\varepsilon_s}{dt} = \sum_s \left(\frac{\partial U}{\partial \ell_s'}\right) \frac{d\ell_s'}{dt} .$$

The term $(\partial U/\partial \ell_s')$ is symbolized by f_s, the applied force, tensile or compressive, which is the product of tensile or compressive stress and the area through which it acts (62).

$$\sum_s \left(\frac{\partial U}{\partial \varepsilon_s}\right) \frac{d\varepsilon_s}{dt} = \sum_s \left(\frac{\partial U}{\partial \ell_s'}\right) \frac{d\ell_s'}{dt} = \sum_s A\, \ell_o \sigma_s \frac{d\varepsilon_s}{dt} = \sum_s f_s \frac{d\ell_s'}{dt} \qquad (22)$$

where A is the area and σ_s is the stress acting through area A.

The system internal energy change due to electrical charge is simplified by making use of the fact that total charge, dq, is related to the particle charge, z_p, by the expression from Kestin (62)

$$dq = \sum_p z_p F dn_p$$

where F is Faraday's constant and dn_p is the number of charged particles with charge z_p.

Then

$$\sum_p \left(\frac{\partial U}{\partial z_p}\right) dz_p = \sum_p \frac{\partial U}{\partial (z_p F n_p)} d(z_p F n_p) = \left(\frac{\partial U}{\partial q}\right) dq$$

When $(\partial U/\partial q)$ is expressed as the electrical potential difference across which the charge is maintained, $\nabla\psi_p$, the expression for system energy changes due to changes of electrical charge is

$$\left(\frac{\partial U}{\partial q}\right) dq = \nabla\psi_p \, dq$$

The equivalent expression for the time rate of change of the internal energy of an isochoric, isobaric system is given below as Equation 23.

$$\frac{dU}{dt} = m\hat{C}_V \frac{dT}{dt} + \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} + \sum_s f_s \frac{d\ell_s'}{dt} + \nabla\psi \frac{dq}{dt} + \hat{U} \frac{dm}{dt} \qquad (23)$$

The kinetic and potential energies of the flows, the elastic energy storage, and the electrical charge energy are required in the energy balance in only a relatively few cases in living systems. When these effects are temporarily neglected, the most frequently useful expression for the energy changes of an open, transient system containing ideal solutions is

$$m\hat{C}_V \frac{dT}{dt} + \hat{U} \frac{dm}{dt} + \sum_k \tilde{H}_{Rk} \frac{d\xi_k}{dt} + \frac{d\phi}{dt} + \frac{dK}{dt} = \sum_j \sum_i (\hat{H}_{ij}\dot{\omega}_{ij}\delta_j) + \dot{Q} - \dot{W} \qquad (24)$$

2. Discussion of terms

Terms and dimensions are defined and discussed below, using the following symbols to represent dimensions:

M = mass, F = force, T = temperature, t = time, n = moles,

L = distance

$\sum_j \sum_i (\hat{H}_{ij}\dot{\omega}_{ij}\delta_j)$:

$\hat{H}_{ij}$ = specific enthalpy (FL/M) of species i in stream j entering or leaving the system referenced to T_o, P_o and pure elements

$\dot{\omega}_{ij}$ = the mass flowrate of species i in stream j (M/t)

δ_j = +1 for input stream, -1 for output streams.

The energy content of flow streams is described by this term. The enthalpies are evaluated at their interface conditions. This term is important in evaluating the flows of products and reactants of reactions occurring in the system and often serves as an indirect measure of the reaction term on the left of the equation. In this instance, the term is divided into two portions, $\sum_j \sum_i [(\hat{H}_{ij}\ \dot{\omega}_{ij})_R\delta_j + (\hat{H}_{ij}\dot{\omega}_{ij})_P\delta_j]$. The former term represents those flows which are directly related to reactions (R) within the system, such as the flow of oxygen and carbon dioxide. The latter term is used to describe flows of passive (P) streams of species such as nitrogen which do not directly participate in reactions.

$\dot{Q}$: $\dot{Q}$ = rate of heat gain by the system from the surroundings (FL/t).

$\dot{Q}$ denotes the heat appearing at the system boundaries. It is an indirect measure of the inefficiencies of biological processes since $\dot{Q}$ is usually negative for living systems and heat is lost by the systems.

$\dot{W}$: $\dot{W}$ = rate at which work is performed on the surroundings by the system (FL/t).

The evaluation of this term is a major portion of this study. The evaluation of the performance of physical work and the rate of doing work will be discussed in Section IV.

$m\hat{C}_P \frac{dT}{dt}$:

m = the mass of the system contents (M)

$\hat{C}_P$ = the specific heat (FL/MT) of the system contents

T = the average temperature (T) of the system contents.

This term represents the thermal portion of the internal energy of the system.

$\hat{U} \frac{dm}{dt}$:

$\hat{U}$ = specific internal energy (FL/M) of the system contents referenced to T_o, P_o, and pure elements. It is an average internal energy if a system is heterogeneous.

$\hat{U}$ dm/dt allows for internal energy changes due to variation in the mass of the system. These changes may be due to loss or gain of mass caused by flows, as in mass gain by consumption of substrates or mass lost in respiration or sweating, or they may also be a result of growth of a developing system.

$\frac{d\phi}{dt}$:

ϕ = the potential energy of the system referenced to a convenient position in a potential field.

The potential energy change corresponds to a change in the position of the system in the potential field which causes a change in the potential experienced by the system. The potential of interest is usually gravitation, so that $d\phi = mg\ dz$. The gravitational acceleration is symbolized by g, m is the system mass, and dz is the height displacement in the gravitational field.

$\frac{dK}{dt}$:

K = the kinetic energy of the system referenced to a state in which the system has zero velocity relative to a stationary coordinate system.

The total kinetic energy may be written as $K = \sum_n \frac{m_n v_n^2}{2}$, summed over n particles of the system. For a rigid body, the velocity of a particle is $v_n = \dot{\rho} + \underset{\sim}{\omega} \times \underset{\sim}{r}_n$, where $\dot{\rho}$ is the velocity of the system origin relative to stationary coordinates, $\underset{\sim}{\omega}$ is the angular velocity of the moving axis, and $\underset{\sim}{r}_n$ is the distance from the origin to the particle n. Then the total kinetic energy is

$$K = K_{trans} + \frac{1}{2}\ \underset{\sim}{\omega} \cdot \underset{\approx}{I} \cdot \underset{\sim}{\omega}$$

where K_{trans} is the translational kinetic energy and $\underset{\approx}{I}$ is the moment dyadic of the system (29). Kinetic energy will usually be represented as $K = K_{trans} = mv \cdot \frac{dv}{dt}$ where v now represents the velocity of the center of gravity of the system relative to stationary coordinates.

$\sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt}$:

$\Delta\tilde{H}_{Rk}$ = the molal heat of reaction of the kth reaction (FL/n)

$d\xi_k/dt$ = the change in extent of the reaction as discussed in Section A.

The symbol $\dot{\Delta M}$ will often be used to represent this term.

$\Sigma \Delta\tilde{H}_{Rk} d\xi/dt$ is the energy transformed due to reactions occurring within the system, the chemical portion of the internal energy. By including this term, several physiological functions may be analyzed, such as the ingestion of energy substrates by the system, the metabolic activity of both resting and active systems, and the depletion of energy sources and the limitations that this condition imposes. It is worthwhile to note that in the physiology literature this term is often evaluated as an energy expenditure. It is more appropriate to view $\dot{\Delta M}$ as the consumption of energy necessary to fuel a process. Because this term does play a variable role in describing the chemical internal energy of the system, further discussion is warranted.

The combustion of substrates as "fuel" is a straightforward application. Several reactions occurring within the system deplete the internal energy transforming it to heat, work, thermal internal energy, or other forms of energy. For an exothermic reaction k, $\Delta\tilde{H}_{Rk}$ is negative. The reactants are being depleted so that $d\xi_k/dt = \nu_i^{-1} dn_i/dt$ is positive since both ν_i and dn_i/dt are negative for reactants. If the progress of a reaction product is followed, ν_i and dn_i/dt are both positive. Both

situations give the appropriate sign, $\Delta\tilde{H}_{Rk}\ d\xi_k/dt = \Delta\dot{M} < 0$, to describe the depletion of internal energy.

Conversely, a fully fueled system, one with energy stores, has a higher internal energy than when fuel has been expended. Therefore, the process of food ingestion, or "refueling," should increase internal energy, indicated by a positive $\Delta\tilde{H}_{Rk}d\xi_k/dt$. This implies that, for most exothermic reactions that represent the metabolism of the living system, $d\xi_k/dt$ should be negative during refueling. Refueling replenishes reactants, so that dn_i/dt is positive for a reactant, but ν_i is negative. The change in extent, $d\xi_k/dt$, is a negative term making $\Delta\dot{M}$ positive. It is important to note that the change in extent is negative due to the addition of reactants and not because of a shift in chemical equilibrium. This term may also be used to describe changes in the state of aggregation of a system. This will be illustrated in the subsequent discussion.

3. Special cases

It is instructive to consider special cases of the first law expression as predecessors to the final overall equation capable of describing the many physiological conditions of living systems.

1. Nonphysiological conditions

A. Isolated, constant mass, reacting system

$$\frac{dU}{dt} = m\hat{C}_P \frac{dT}{dt} + \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = 0 \qquad (24a)$$

Integrated over a time increment Δt,

$$m\hat{C}_p(T_2 - T_1) = \sum_k \Delta\tilde{H}_{Rk}(\xi_{k_1} - \xi_{k_2})$$

$$m\hat{C}_p\Delta T = - \sum_k \Delta\tilde{H}_{Rk}\Delta\xi_k$$

By definition and as shown in this reduced first law expression, an isolated system does not interact with its surroundings. Total internal energy does not change, but is reallocated between the thermal and chemical portions.

B. Isothermal, constant mass, closed, reacting system

$$\frac{dU}{dt} = \sum_k \Delta\tilde{H}_{Rk}\frac{d\xi_k}{dt} = \dot{Q} - \dot{W} \qquad (24b)$$

$$\sum_k \Delta\tilde{H}_{Rk}\Delta\xi_k = Q - W$$

The reaction energy is entirely transformed into either heat and/or work. To illustrate the limitations of the first law, this expression suggests that a system may be energetically refueled by either having work performed upon it or by absorbing heat. No distinction is made between reversible and irreversible processes.

C. Open, steady state, constant mass, adiabatic system

$$\frac{dU}{dt} = 0 = \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j - \dot{W} \qquad (24c)$$

$$\sum_j \hat{H}_j \, \Delta m_j = W$$

where $\hat{H}_j$ is the average enthalpy of the jth stream.

This expr ssion is often used to describe adiabatic shaft work. However, in living systems work cannot usually be accomplished by flows alone. Although steady state exists and the entire left side of the first law expression is zero, reactions may be occurring at a steady rate. This would occur if reactants were being supplied at the same rate at which they were being consumed. In this case, the energy from the ongoing reactions would appear as changes in enthalpies and masses of the flow streams and as the energy of work.

None of the above examples are entirely physiologically realistic, but represent some aspects of actual physiological energy balances and appear in various combinations below.

2. Physiological conditions

A. Constant mass, maintenance steady state, fueled continuously, isothermal

$$\text{Mass balance:} \quad \sum_j \sum_i \dot{\omega}_{ij} \delta_j = 0$$

$$\text{Energy balance:} \quad \frac{dU}{dt} = 0 = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij} \dot{\omega}_{ij} \delta_j \qquad (24d)$$

This is similar to example 1.C, since the reactions within the system do not appear explicitly, but their energy contributions appear in each of the existing terms. The expressions may be integrated and rewritten to account for the reactive and passive flows,

$$\sum_j \sum_i m_{ij}\delta_j = 0$$

$$\Delta U = 0 = Q - W + \sum_j [(\sum_i \hat{H}_{ij} m_{ij}\delta_j)_R + (\sum_i \hat{H}_{ij} m_{ij}\delta_j)_P]$$

This is an idealized approximation to a living system being fueled at a rate equivalent to its fuel consumption, so that mass and extent of reaction remain constant.

B. Constant mass, nonisothermal, fueled continuously

$$\sum_j \sum_i \dot{\omega}_{ij}\delta_j = 0$$

$$\frac{dU}{dt} = m\hat{C}_P \frac{dT}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j \qquad (24e)$$

Integrated,

$$\sum_j \sum_i m_{ij}\delta_j = 0$$

$$m\hat{C}_P(T_2 - T_1) = Q - W + \sum_j \sum_i \hat{H}_{ij} m_{ij}\delta_j$$

The situation is similar to example 2.A, but the thermal energy may vary due to temperature changes.

C. Approximately constant mass, open, no fueling, isothermal

$$\sum_j \sum_i \dot{\omega}_{ij}\delta_j = 0$$

$$\frac{dU}{dt} = \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j \qquad (24f)$$

Stored chemical energy is being depleted to supply the terms on the right. The internal energy is decreasing since the extent of reaction is positive. These equations describe a living system between fuelings, e.g., a normal, resting human between meals.

D. Approximately constant mass, fueled periodically, isothermal

$$\sum_j \sum_i \dot{\omega}_{ij}\delta_j \simeq 0$$

$$\frac{dU}{dt} = \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j$$

The integrals of the expression are not continuous because of the nature of the fueling. During fueling the change in extent is negative, while after fueling, the extent is positive for a metabolically functioning system.

This expression may represent the daily functioning of a living system including periods of fuel consumption (meals).

E. A better description of a normal human system is given if the mass is allowed to vary. Then the equation becomes

$$\hat{H} \frac{dm}{dt} + \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j \qquad (24g)$$

with $\sum_j \sum_i \dot{\omega}_{ij}\delta_j$ not necessarily equal to zero. The integral is again discontinuous.

F. Growing, continuously fueled, isothermal system

$$\hat{H}\frac{dm}{dt} + \sum_k \Delta\tilde{H}_{Rk}\frac{d\xi_k}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j$$

The presence or absence of the reaction term is determined by relative rates of fueling and reaction. The change in mass is now representative of the addition of mass to the system by growth, the building of new system matter from chemical reaction products. Fuel storage may also increase the system mass. The equation may be approximately related to a growing mammalian fetus being constantly supplied with fuel by its mother.

G. Growing, fueled periodically, isothermal

$$\hat{H}\frac{dm}{dt} + \sum_k \Delta\tilde{H}_{Rk}\frac{d\xi_k}{dt} = \dot{Q} - \dot{W} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j$$

The expression is the same as that of example F except that the integral is not continuous. This expression characterizes a homiothermic "grower."

H. Constant mass, constant temperature, changing state of aggregation.

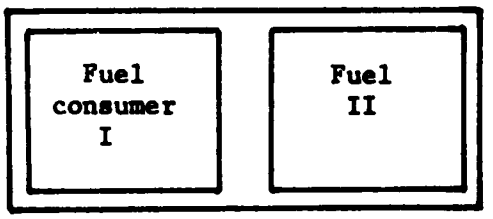
$$\sum_k \Delta\tilde{H}_{Rk}\frac{d\xi_k}{dt} = \dot{Q} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j \qquad (24h)$$

This situation arises when the relative concentrations of the constituents of a system are changing. The effects are included in the reaction term. Since the reference for the heat of reaction is usually

pure elements at the reference temperature and pressure, a reaction which changes the state of aggregation because the reaction products vary with time will have a heat of reaction that varies with the product composition. The changes in component concentrations are also included in the extent of reaction term, $d\xi_k/dt$. In biological systems, reactions which change the state of aggregation are known as biosynthetic reactions. Their heats of reaction are usually endothermic.

I. Variable mass, internally fueled, nonisothermal.

This system is best analyzed in two sections, the growing, reacting system and the fuel supply.



Exchange of mass and energy between the two subsystems is necessary and allowable.

Subsystem I:

$$\frac{dU_I}{dt} = (m\hat{C}_P \frac{dT}{dt})_I + (\hat{H} \frac{dm}{dt})_I + \Delta\dot{M}_I = \dot{Q}_I - \dot{W}_I + \Sigma_j(\Sigma_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j)_I$$

Subsystem II:

$$\frac{dU_{II}}{dt} = (m\hat{C}_P \frac{dT}{dt})_{II} + (\hat{H} \frac{dm}{dt})_{II} = \dot{Q}_{II} + \Sigma_j(\Sigma_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j)_{II}$$

The fuel source, II, is continuously depleted and so constantly loses mass. The fuel consumer, I, is continuously fed with fuel. The existence of the reaction term for I depends on whether or not it is operating at steady state. Both subsystems I and II exchange mass with the surroundings and with each other. Usually, these flows cannot be externally distinguished one from the other and must be accounted for in a general flow term. If $T_I = T_{II}$, the remaining equation is

$$\hat{H}_I \frac{dm_I}{dt} + \hat{H}_{II} \frac{dm_{II}}{dt} + (m_I \hat{C}_{P_I} + m_{II} \hat{C}_{P_{II}}) \frac{dT}{dt}$$

$$= \dot{Q}_I + \dot{Q}_{II} - \dot{W}_I + \sum_j (\sum_i \hat{H}_{ij} \dot{\omega}_{ij} \delta_j)_{TOT}$$

This expression best characterizes the energy balance around a developing egg. The embryo utilizes fuel sources within the system and respires, metabolizes, and exchanges heat with the surroundings. It is incapable of performing work until the developed embryo hatches from within its rigid system boundaries.

The preceding has been a demonstration of how the general first law expression may be applied to open or closed, steady state or transient, variable-mass systems. It is adaptable to and useful for analysis of experimental data and the interpretation and quantification of traditional physiological concepts. As discussed earlier, the general energy relation along with the material balance serve as the groundwork for the investigation of second law relationships. A more detailed discussion of several

of the terms of the first law equation and examples of mass and energy balances applied to living systems in various thermodynamic states will be presented later.

C. The Entropy Account

As shown in the previous examples, the first law analysis can only balance energy accounts after changes have occurred. It has no ability to predict the relative distribution of system energies and it can estimate only minimum energy requirements. Also, the first law balance does not distinguish between types of energy or irreversible conversions from one to another; a simplistic view could imply that a human body might be chemically refueled by exposure to a radiant energy source or by performing work on the body. Clearly, the first law is limited in its application. The second law is now introduced with the intent of complementing and augmenting first law analyses.

1. Development

The second law is often introduced as a formulation describing the limitations of cyclic processes. This leads to two important results known as Carnot's theorems dealing with cyclic efficiency and process reversibility. Although the ideas of cycles, heat engines, and efficiencies are useful in understanding the concept of entropy, a more general approach to the second law is needed for this study.

The second law quantitatively defines the directional tendencies of natural and spontaneous processes towards an equilibrium state. Dissipation of the motive forces is inevitable in natural processes. As an

example, this is illustrated by the equation for the change in Gibbs' free energy of chemical reactions, ΔG.

In general, in an isothermal process,

$$\Delta G = \Delta H - T\Delta S.$$

Of the total energy change for a reaction, ΔH, only ΔG is available for useful work. The remainder, $T\Delta S$, is unavoidably lost. This lost energy appears as heat, and for reversible processes,

$$dS = \frac{\delta Q}{T} \text{ and } \Delta S = \int \frac{\delta Q}{T}$$

where ΔS = the change in entropy

δQ = the heat transferred

T = the isothermal temperature of the system.

The description of entropy change becomes more complicated when irreversible processes are involved.

Onsager developed the basic theory of irreversible thermodynamics in 1931. The development involved the use of classical thermodynamics, linear laws relating flows to forces, $J_\ell = \sum_m L_{\ell m} X_m$, and the Onsager reciprocal relations for the phenomenological coefficients, $L_{\ell m} = L_{m\ell}$.

Irreversible processes are always accompanied by the production of entropy,

$$\frac{d_i S}{dt} = \frac{1}{T} \sum_m J_m X_m \qquad (25)$$

Each of the terms, J_m, represents a flow or flux which, along with its conjugated driving force, X_m, contributes to the rate of entropy production in a system, d_iS/dt. The fluxes and forces are related through the phenomenological coefficients, $L_{\ell m}$ such that $J_\ell = \sum_m L_{\ell m} X_m$.

To maintain the linearity of this relationship, and to justify the use of equilibrium thermodynamics quantities, the processes are confined to regions very close to equilibrium.

Living organisms exchange mass and energy with their environment and, therefore, represent open systems. This implies that the entropy of a system may be changed by entropy production within the system boundaries or by the flow of entropy across system boundaries (80). The rate of entropy production of a system may then be written

$$\frac{dS}{dt} = \frac{d_eS}{dt} + \frac{d_iS}{dt} \tag{26}$$

where d_eS represents entropy flow through exchange with the surroundings and d_iS is the internal entropy production. Equation 26 becomes

$$\frac{dS}{dt} = \frac{\dot{Q}}{T} + \sum_j \sum_i \hat{s}_{ij} \dot{\omega}_{ij} \delta_j + \frac{1}{T} \sum_n J_m X_m \tag{27}$$

with $$\frac{d_eS}{dt} = \frac{\dot{Q}}{T} + \sum_j \sum_i \hat{s}_{ij} \dot{\omega}_{ij} \delta_j$$

and $$\frac{d_iS}{dt} = \frac{1}{T} \sum_m J_m X_m$$

where S = entropy content of the system

T = absolute temperature

$\hat{s}_{ij}$ = specific entropy of species i crossing the system boundary in stream j referenced to pure species at a reference temperature T_o.

According to the second law of thermodynamics, the entropy production due to irreversible processes is always positive

$$\frac{d_i S}{dt} > 0.$$

For an isolated system, ($d_e S/dt = 0$), it follows that

$$\frac{dS}{dt} > 0.$$

In a closed system, where exchange is confined to heat transfer,

$$\frac{d_e S}{dt} = \frac{\dot{Q}}{T}$$

and therefore,

$$\frac{dS}{dt} > \frac{1}{T} \dot{Q}$$

For an open system, the entropy flow may be positive, negative, or zero and, as a consequence, dS/dt may also be positive, negative, or zero. This permits situations in which a system's total entropy could decrease by proper regulation of entropy flows to and from the environment.

Unlike internal energy and enthalpy, entropy is not a conserved quantity. It is a function of state and it is, therefore, worthwhile to consider the development of expressions to describe the forces and fluxes in terms of measurable state variables.

The evaluation of the forces and fluxes is dependent upon the characteristics of the system. In the case of living organisms, coupled heat transfer-temperature gradient, mass transfer-concentration gradient, and chemical reaction velocity-affinity products are the main contributions included in the force-flux summation. The major internal contribution arises from the reaction velocity, v_k (a flux J_m), and the chemical reaction affinity, A_k (a force X_m).

As shown by Prigogine (80), the affinity of the kth reaction may be expanded as follows:

$$A_k = - \left(\frac{\partial G}{\partial \xi_k}\right)_{P,T} = - \left(\frac{\partial H}{\partial \xi_k}\right)_{P,T} + T\left(\frac{\partial S}{\partial \xi_k}\right)_{P,T} \tag{28}$$

The Gibbs' free energy, G, represents the maximum amount of reaction energy which can be utilized. If the reaction energy is to be used to perform work, Gibbs' free energy equals the work maximum. As shown previously, $(\partial H/\partial \xi_k)_{P,T}$ is equivalent to the heat of reaction of the kth reaction, $\Delta\tilde{H}_{Rk}$. The term $(\partial S/\partial \xi_k)_{P,T}$ may be considered to represent an entropy of rearrangement caused by the change in entropy with reaction extent, ξ_k, expressed as $\sum_k \Delta S_{Rk}\, d\xi_k/dt = \Delta\dot{S}$. For the purposes of entropy production calculation, only extent changes due to reaction will be considered.

Equation 27 may be rewritten by expanding the internal force-flux summation with these known terms.

$$\frac{dS}{dt} = \frac{\dot{Q}}{T} + \sum_j \sum_i \hat{s}_{ij} \dot{\omega}_{ij} \delta_j - \frac{1}{T} \sum_k \Delta \tilde{H}_{Rk} \frac{d\xi_k}{dt} + \sum_k \Delta S_{Rk} \frac{d\xi_k}{dt} + \frac{1}{T} \sum_P J_P X_P \tag{29}$$

The same result is obtained using a continuum approach to entropy as described by Katchalsky and Curran (61) and Bree and Beevers (17). They relate the total rate of increase of internal system entropy to the volume integral of the local entropy production, σ.

$$\int_V \sigma \, dV = \frac{d_i S}{dt}$$

The calculation of σ is based on the existence of local equilibrium. The ability to calculate $d_i S/dt$, then, rests on the evaluation of σ. The final result is

$$\sigma = \underset{\sim}{J}_q \cdot \text{grad}\left(\frac{1}{T}\right) + \sum_{i=1}^{n} \underset{\sim}{J}_i \cdot \text{grad}\left(\frac{-\mu_i}{T}\right) + J_{ch} \frac{A}{T}$$

where $\underset{\sim}{J}_q$ = local heat flux

$\underset{\sim}{J}_i$ = local flux of chemical species i

$J_{ch} = d\xi/dt$, the reaction velocity

A = reaction affinity

μ_i = chemical potential or specific Gibbs' free energy

T = absolute temperature

and the flow of entropy, $\underset{\sim}{J}_s$, is

$$\underset{\sim}{J}_s = \frac{\underset{\sim}{J}_q - \Sigma \mu_i \underset{\sim}{J}_i}{T}$$

The rate of change of total system entropy, dS/dt, is obtained by integrating the local specific entropy change, $\partial s_v/\partial t$, where

$$\frac{\partial s_v}{\partial t} = - \nabla \cdot \underset{\sim}{J}_s + \sigma.$$

Then

$$\frac{dS}{dt} = \int_V \frac{\partial s_v}{\partial t} \, dV.$$

2. Discussion of terms

The evaluation of the entropy production of living things begins with the interpretation of the terms present in Equation 29 with the aid of the first law. The terms and their dimensions are discussed below

$$\frac{dS}{dt} = \frac{\dot{Q}}{T} + \Sigma\Sigma_{ji} \hat{s}_{ij} \dot{\omega}_{ij} \delta_j - \frac{1}{T} \sum_k \tilde{\Delta H}_{Rk} \frac{d\xi_k}{dt} + \sum_k \Delta S_{Rk} \frac{d\xi_k}{dt} + \frac{1}{T} \sum_P J_P X_P$$

M = mass, F = force, T = temperature, t = time, n = moles, L = distance

$\dot{Q}/T$ (FL/tT):

$\dot{Q}$ = rate of heat gain by the system (FL/t)

T = temperature at which $\dot{Q}$ is transferred (T)

This is the same heat energy term as is present in the first law energy balance. It is usually a negative quantity for living systems.

$\sum_j \sum_i \hat{s}_{ij} \dot{\omega}_{ij} \delta_j$ (FL/tT):

$\hat{s}_{ij}$ = specific entropy of species i entering or leaving the system in stream j referenced to T_o, P_o, and pure materials (FL/MT)

$\dot{\omega}_{ij}$ = the mass flowrate of species i entering or leaving the system in stream j

δ_j = +1 for inputs, -1 for outputs.

The entropy flow term is analogous to the enthalpy flow term of Equation 24. It is usually negligible. This and the previous term make up the external entropy exchange.

$\frac{1}{T} \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt}$ (FL/tT):

Except for the factor of 1/T, this has the same form as the reaction term found in the first law balance. It was taken to represent the metabolic activity of living systems and will have the same meaning in this expression, so that

$$\frac{1}{T} \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \frac{\Delta\dot{M}}{T} .$$

$\sum_k \Delta S_{Rk} \frac{d\xi_k}{dt}$ (FL/tT):

This term accounts for the entropy changes due to reaction and has been considered as the entropy of molecular rearrangement. The entropy of rearrangement term is referenced to the same conditions as the heat of reaction. As shown in Equation 28, both the entropy change and the heat of reaction arise from the chemical affinity-reaction velocity force-flux pair.

$\frac{1}{T} \sum_p J_p X_p$(FL/tT):

This summation accounts for the internal dissipation due to the remaining forces J_p and their corresponding fluxes X_p. Their contribution to entropy production arises from gradients in state variables such as temperature, concentration mechanical force, or electrical charge. External measurements alone cannot determine the magnitude of these terms. However, since $\frac{1}{T} \sum_p J_p X_p$ is part of the internal entropy production rate,

$$\frac{d_i S}{dt} = - \frac{1}{T} \sum_k \tilde{\Delta H}_{Rk} \frac{d\xi_k}{dt} + \sum_k \Delta S_k \frac{d\xi_k}{dt} + \frac{1}{T} \sum_p J_p X_p$$

and since the second law mandates that this quantity must be equal to zero or positive, the term $\frac{1}{T} \sum_p J_p X_p$ must contribute to the positiveness of the internal entropy production rate.

Erickson and Patel (40) have calculated the mean entropy change for the combustion of 253 large biological molecules and have found that

$T\Delta\dot{S}_{Rk}$ is less than three per cent of the mean value of the heat of combustion for those same molecules. Therefore, since the entropy of rearrangement contributes so little to the internal entropy production and since the heats of reaction for living systems are usually negative, $\frac{1}{T}\sum_{P} J_P X_P$ must be positive.

The external entropy exchange is related to the constraints imposed by the environment and can usually be measured. Therefore, since $d_e S/dt$ may be determined and at least the sign of $d_i S/dt$ is known, a reasonable estimate of the total system entropy production rate may be made.

Of further interest is the relationship between the terms in the external entropy exchange rate and terms in the internal entropy production rate for living systems. According to the first law, the system's metabolism and its rate of heat gain (or loss) are always related. As was shown in Equation 24g, for an isothermal, nonworking, unsteady state, growing organism, the first law expression is

$$\hat{U}\Delta m + \Delta M = Q + \sum_{j}\sum_{i} \hat{H}_{ij} m_{ij} \delta_j$$

Flows will be assumed to be negligible. As growth ceases and steady state is achieved, the expression simplifies to

$$\Delta M \cong Q.$$

The approach to steady state involves an approach to equivalence between metabolism and heat exchange.

When this fact is viewed in the context of the entropy production rate expression of Equation 29 in which entropy flows are negligible,

$$\frac{dS}{dt} = \left(\frac{\dot{Q}}{T} - \frac{\Delta\dot{M}}{T}\right) + \sum_k \Delta S_{Rk} \frac{d\xi_k}{dt} + \frac{1}{T} \sum_P J_P X_P \qquad (30)$$

whether dS/dt is positive or negative can be determined from values of $\dot{Q}$ and $\Delta\dot{M}$ since the sum of the last two terms on the right must be positive.

The heat loss is usually a by-product of metabolism, and is an end result of inefficient conversion processes. In growing systems, a portion of the metabolic energy is eventually stored in the new matter of the system. This amount does not appear as thermal energy or heat loss. The difference between $\dot{Q}$ and $\Delta\dot{M}$ is, in this case, a positive number. In general, unless a system experiences the effects of an external energy source which causes thermal energy to be gained by the system and as long as the energy source of the system is indigenous, $\dot{Q}$ can never be larger in magnitude than $\Delta\dot{M}$. Therefore, the grouping of the difference, $\dot{Q}-\Delta\dot{M}$, must be greater than or equal to zero. As long as entropy flows may be considered to be negligible, for the usual functioning of a living organism, the total entropy production rate must be positive or zero.

In order to determine a system's total entropy over any time period, the entropy production rate is integrated between limits as shown below:

$$\int_{S_o(t=0)}^{S(t)} \left(\frac{dS}{dt}\right) dt = S - S_o = \Delta S \qquad (31)$$

Since S_o may be chosen as a constant reference value for the state function S, and since $dS/dt \geq 0$ as time progresses, ΔS must also be ≥ 0.

It may therefore be concluded that living systems may experience increases in entropy and may do so without violating the second law of thermodynamics. This hypothesis will be tested using the first and second law expressions in the analyses of the energy and entropy flows of the microbial culture and avian egg systems.

3. Entropy and living systems

Living things are open, irreversibly operating systems that often exist in a dynamic steady state. They are composed of lifeless molecules but have the ability to maintain a high level of morphological and physiological organization and complexity. They are capable of extracting and transforming energy from the environment in order to develop and maintain their structural organization, whereas inanimate matter eventually decays to a more random state when it absorbs energy.

Living organisms operate on a principle of maximum economy of parts and processes; metabolism is an efficient linkage of many parallel and consecutive organic reactions where energy is transferred between steps of complex biochemical pathways. Energy containing substrates are taken in from the environment, broken down, and utilized in precise patterns for the synthesis of system components and of enzymes with which these reactions are catalyzed.

Reactions may be categorized as either biosynthetic (anabolic) or degradative (catabolic). Biosynthetic and degradative pathways are not

generally the same, since if this were so, no stable structures could result from biosynthesis. Biosynthesis is a genetically programmed process that produces complex multicellular products from relatively simple precursors. This process gives living things the ability to reproduce and allows the formation of order and structure from relative disorder. Thus, living organisms appear to have evaded the limits imposed by the second law of thermodynamics. Their highly organized nature has apparently, for a naive observer, violated the tendency of matter to spontaneously decay to a state of disorder and increased entropy.

Prigogine and Wiame (83) were among the first to suggest that the concepts of irreversible thermodynamics could be applied to the development and growth of living organisms. They stated that, in the stationary state with unchanging external parameters, the rate of system entropy production is constant and minimal. This is an important application for living systems because they often exist in such a state. In steady state processes all properties of a system are independent of time. Since entropy is a single-valued function of the parameters of the system, the rate of change of system entropy is zero. In this instance the exchange of entropy with the surroundings balances the system's internal entropy production and it is possible to evaluate the entropy production of a living organism.

Prigogine's hypothesis further states that, if the final stationary state occurs at minimal entropy production with respect to all other previous states of the system, then the approach to this state must

necessarily be along a path of a continually decreasing, but possibly fluctuating, rate of specific internal entropy production. If $Td(S_i/m)/dt \tilde{=} \psi$, the dissipation function (m is the mass of the system), then this means that $d\psi/dt < 0$.

Zotin (123) has suggested that living systems experience two types of stationary states. Basal metabolism is a level of minimal metabolism of an animal in a resting state. This corresponds to a homeostatic stationary state. It is altered by changing environmental or internal factors causing the system to operate at unsteady state conditions (increased oxygen uptake, increased system temperature) until the system can eventually act to return its functioning to steady state and a local minimum entropy production.

On a larger time scale, the final stationary state to which all organisms must inevitably proceed is the equilibrium following death. The small-scale oscillations about a homeostatic steady state which may cause a temporary increase in internal entropy production are superimposed upon the overall trend for the decrease of the rate of entropy production over the time scale spanning the organism's lifetime. It is the "openness" of living things which allows many of them to regulate their entropy production rates and survive the fluctuations of internal and external parameters. Many of the processes of life may be characterized by physical, chemical, electrical, and biochemical descriptions. It has been demonstrated that the first law of thermodynamics can be successfully applied to quantify these descriptions. Difficulties arise in the attempt to determine absolute values for entropy production rates since

many of the internal forces and fluxes necessary to completely evaluate entropy production are impossible to measure directly.

These restrictions notwithstanding, it is still of great interest to determine a method of approach in which approximating system entropy production rates is physically and physiologically practical. This approach should determine whether some of what occurs internal to a system can be deduced from external parameter variations. Some portion of the dissipation occurring within a system must eventually appear at the system boundary. From measurements taken at the boundary it may be possible to at least determine the direction or to calculate an estimate of system entropy.

The properties of maintained system heterogeneity and self-organization are unique to living systems and therefore of possible consequence in entropy calculations. These will be considered.

Finally, this approach may help determine whether entropy and entropy production rate can serve as a distinguishing measure between living and nonliving systems.

In order to establish a basis from which to begin the development of the approach described above, in this research entropy will be considered as a measure of a system's progress toward equilibrium. In complex systems such as living organisms the system's total entropy or total entropy production rate will be viewed as a summation of the entropies or entropy production rates, respectively, of each of the subsystems comprising the whole. The assumptions of local equilibrium and linear force-flux dependence will be considered valid. Without these

assumptions and simplifications, the analysis of the entropy flows of living systems would extend beyond the realm of practicality and manageability. This will not significantly detract from the conclusions reached.

With the first law providing a good understanding of the energy flows of living systems, it is a major intent of this study to gain a similar understanding of entropy flows of living systems by parallelling first and second law analyses.

D. Efficiency

Efficiency is a measure of the departure from ideality or the wastefulness of an energy conversion process. As a result of the second law of thermodynamics, a certain measure of inefficiency in spontaneous processes is a direct consequence of entropy production.

1. Thermodynamic efficiencies

Efficiencies have been evaluated in two general ways. One method defines efficiency as the units of useful energy obtained per unit of total energy expended. This is often called mechanical efficiency. A second approach is to evaluate the ratio of the real process function to the ideal. This is denoted as a thermodynamic efficiency.

These approaches may be viewed in the context of either the first or the second law of thermodynamics.

First law efficiencies involve the evaluation of physical work obtained per unit of supply energy. A common physiological definition

for efficiency, η, is

$$\eta = \frac{\dot{W}}{\Delta\dot{M}} \times 100 \tag{32a}$$

where $\dot{W}$ = the work rate

$\Delta\dot{M}$ = the change in metabolic rate to accomplish $\dot{W}$.

In the context of Equation 24, this is written

$$\eta = \frac{\dot{W}}{\sum_k \Delta\tilde{H}_{Rk} d\xi_k/dt} \times 100 \tag{32b}$$

Second law efficiencies, or Carnot efficiencies, compare the way in which heat and work effects are split by heat engines. They are a direct result of the second law which disallows the total conversion of heat to work in cyclic processes.

The second law efficiency is not entirely descriptive of isothermal biological systems. Biological systems do not generally operate as heat engines. In a system at uniform temperature, it is impossible that the only type of energy conversion is from heat to work. Heat is, in general, an end product rather than a motive power of living processes. One exception to this is the photosynthetic conversion of solar thermal energy to chemical energy as discussed by Erickson and Patel (40).

The second law does make further contribution to several particular means of evaluating efficiency. In the example of physicochemical systems where chemical energy is converted to mechanical work, the total energy given up by a reaction, ΔH, is not all available for work. Only the

change in Gibbs' free energy, ΔG, is utilizable. In fact, the theoretically maximum amount of work is obtained if all of ΔG is converted.

Then, as shown by Wilkie (119), efficiency is given by

$$\eta = \frac{W}{\Delta H - T\Delta S} \times 100$$

$$\eta = \frac{W}{\Delta G} \times 100$$

$$\eta = \frac{W}{W_{max}} \times 100 \qquad (33)$$

The evaluation of efficiency by Equation 33 results in values higher than the efficiency given by Equation 32b. The latter is in most frequent use in physiological efficiency studies.

Caplan (23) has written a generalized entropy production rate expression for an energy converter with one input and one output force-flux pair.

$$T \frac{dS}{dt} = J_1X_1 + J_2X_2$$

where J_1X_1 represents the output and J_2X_2 represents the input. Caplan has used this to describe the mechanicochemical functioning of muscle, so that

$$-J_1X_1 = F\upsilon, \; J_2X_2 = Av$$

where $F\upsilon$ = the force-velocity product describing physical work

Av = the affinity-reaction velocity product describing the energy source.

The efficiency is then written in terms of the force-flux pairs,

$$\eta = -\frac{J_1 X_1}{J_2 X_2} \tag{34}$$

These expressions have been used by several authors (13,14,15,121) as an irreversible thermodynamic description of working muscle. Using phenomenological equations to describe the force-flux relations,

$$J_1 = L_{11}X_1 + L_{12}X_2, \qquad J_2 = L_{21}X_1 + L_{22}X_2$$

a degree of coupling between the input, J_2X_2, and the output, J_1X_1, is defined by Caplan as

$$q = \frac{L_{12}}{\sqrt{L_{11}L_{22}}} \quad \text{(Onsager symmetry assumed, } L_{12} = L_{21}\text{)}$$

Then the maximum efficiency and the efficiency at maximum output result and are written as

$$\eta_{max} = \frac{q^2}{[1 + \sqrt{1 - q^2}]^2} \tag{35}$$

$$\eta_{max\ output} = \frac{1}{2}\,[2/q^2 - 1] \tag{36}$$

2. Biochemical efficiencies

The coupling of mechanical and chemical processes involve a more detailed examination of biochemical energy transformations and their efficiencies. In most biochemical cycles, there exists an intricate

series of coupled reactions. Many of the important reactions along the biochemical pathway of the oxidation of foodstuffs are not spontaneous, that is, the Gibbs' free energies of reaction, ΔG_R, are positive. These endothermic reactions are coupled with exothermic reactions such that the progress of the exothermic reaction feeds and pulls to completion the endothermic reaction. As long as the sum of Gibbs' free energy changes for both reactions is a positive number, the coupling will result in the forward progress of the coupled reactions.

Consider the following example of a reaction (1) which is not spontaneous, coupled with a reaction (2), which is spontaneous.

$$(1)\ X + Y \longrightarrow XY \qquad \Delta\mu_1 > 0$$

$$(2)\ H_2O + ATP \longrightarrow ADP + P_i \qquad \Delta\mu_2 < 0$$

where $\mu_i = (\frac{\partial G}{\partial n_i})_{T,P,n_j}$, the specific Gibbs' free energy or chemical potential of species i, and $\Delta\mu = \sum_i \nu_i\mu_i$. The stoichiometric coefficient, ν_i, is positive for reaction products and negative for reactants.

If the sum $dG = \Delta\mu_1 d\xi_1 + \Delta\mu_2 d\xi_2$, where $d\xi_i = \frac{dn_i}{\nu_i}$, is positive, the reactions will proceed forward.

This discussion gives rise to an <u>efficiency of coupling</u> expressed by

$$\varepsilon = -\frac{\Delta\mu_1 d\xi_1}{\Delta\mu_2 d\xi_2} \tag{37}$$

This efficiency is pertinent in this study because of its importance in the chemical-mechanical energy conversions in active muscle tissue.

The direct source of energy for muscular contraction is the hydrolysis of ATP. It is a product of the complex oxidation-reduction reactions of glycolysis, fatty acid oxidation, and the tricarboxylic acid cycle (6). The phosphorylative coupling efficiency, η_p, is an overall coupling efficiency for the entire biochemical pathway.

$$\eta_p = \frac{\text{free energy conserved as ATP}}{\text{free energy of oxidized foodstuff}} \times 100$$

This efficiency is typically estimated at 60% (68).

The contraction coupling efficiency, η_c, is the efficiency describing ATP energy conversion to the mechanical work of muscle contraction

$$\eta_c = \frac{\text{mechanical work output}}{\text{free energy of ATP hydrolysis}} \times 100$$

and is estimated by Whipp and Wasserman (115) at 48% for human muscle. Since these two efficiencies are independent events occurring in series, the overall total efficiency is then equal to the product of η_p and η_c (115).

$$\eta_{TOT} = [(\eta_p/100) \times (\eta_c/100)] \times 100 \approx 29\%$$

which is a typical value found for the overall mechanical efficiency of muscle contraction.

3. Physiology and efficiency

The above discussion has illustrated the importance of recognizing system boundaries to aid in the identification of the energy source and the resulting work output that a particular efficiency is used to describe. Physiological processes pose additional alternatives in the choice of evaluating efficiency. Stainsby et al. (107) have defined several physiological efficiencies. In addition to the phosphorylative coupling and contraction coupling efficiencies described earlier, they define a frequently used overall efficiency, the external work accomplished per free energy of oxidized foodstuff. Gross efficiency is the external work per total energy expenditure whereas net efficiency is defined as the external work accomplished per energy expenditure above the resting energy expenditure. Delta efficiency is the ratio of incremental work to the corresponding incremental energy expenditure. All of these efficiencies involve quantities integrated over the time of the event. They are different from and should not be confused with instantaneous efficiency relating instantaneous work rate to instantaneous energy expenditure.

Additional variations in efficiency calculations occur because of the choice of baselines for energy expenditure. The frequent choice made by physiologists is the resting metabolic rate, referred to as the basal metabolism. External work accomplished raises the metabolic rate. The change between working and resting metabolism is used as the energy expenditure value. It is important to recognize that a large portion of the increased energy consumption goes to support unmeasured "work," the internal processes that operate to support the accomplishment of external

work. These may include increased heart and ventilation rates, acceleration and deceleration of limbs, and the transporting of ions against electrochemical gradients. An efficiency used in such a manner, then, is a process efficiency, and should not be compared to the actual muscle efficiency.

Another commonly used baseline is a modification of the previous one. The baseline is set as the energy consumption level during unloaded exercise in which limb movements are allowed to occur, but in which no external load is carried. The implications of using this baseline are similar to those discussed above. This is a process efficiency rather than an isolated muscle efficiency.

To obtain an efficiency to measure changes in energy consumption for the performance of external work alone, the only reasonable approach is to isolate the subsystem which is responsible for the performance of the external physical work. This is accomplished by *in vitro* and *in situ* studies of muscle contraction which are then true muscle efficiencies. However, it should be noted that any measure of efficiency, when used with an understanding of its limitations, provides a convenient method by which to compare systems.

4. General efficiency and efficacy expressions

The efficiency proposed in this work is an overall efficiency relating changes in work energy to the chemical or metabolic energy consumed from the energy source available to the system. The possibility of the storage of elastic energy for reuse has been considered. This is accounted for by the symbol W', defined as the energy stored in elastic

fibers when previous work is done on them by stretching. If this term is neglected, it increases the apparent efficiency, which then no longer accounts for solely chemical to mechanical energy conversion. Several authors (2,4,5,27,71) have measured the apparent efficiency in order to illustrate the contribution of elastic energy in exercise.

The definition of efficiency, η, given here is intended to maintain consistency for the purposes of this and future studies.

$$\eta = \frac{W}{\int_0^t \Delta\dot{M}dt - W'} \times 100 \qquad (38)$$

W = the external work done by the system

W' = the energy stored as elastic energy. It is related to the work previously done on the system by an efficiency of conversion.

$\Delta\dot{M}$ = the change in the metabolism above the resting, or basal, value (or some other appropriate baseline)

t = the end of the time interval over which metabolic changes are a direct response to mechanical changes. The time over which mechanical changes occur may not correspond exactly with the time, t, over which metabolic changes occur.

When no physical work is performed, efficiency is no longer a useful concept. However, muscular activity which does not result in the performance of physical work still consumes energy. To evaluate the

effectiveness of energy conversion, the term efficacy, introduced by Caplan (24), will be used and expanded upon.

Efficacy is a measure of the effectiveness of energy utilization when the resultant output is a force without a flux or a flux without a force. The flux efficacy is then defined by Caplan as ε_{J_1}:

$$\varepsilon_{J_1} = J_1/J_2X_2 \tag{39}$$

where J_1 is the output, and J_2 and X_2 are inputs. The force efficacy is:

$$\varepsilon_{X_1} = -X_1/J_2X_2 \tag{40}$$

where X_1 is the output force. The force efficacy is useful in studies of isometric muscle contraction in which a force is maintained, but no work is performed.

In addition to these expressions, situations often occurring in exercise physiology require a third definition of efficacy in which energy conversion for purely mechanical state changes are considered. The potential or kinetic energy change efficacy is defined as: $\varepsilon_{\Delta\phi,\Delta K}$:

$$\varepsilon_{\Delta\phi,\Delta K} = \frac{|\Delta\phi + \Delta K|}{\int_0^t \Delta\dot{M}dt - W'} \tag{41}$$

where $\Delta\phi$ = the change in potential energy of the system from Equation 24

ΔK = the change in kinetic energy of the system from Equation 24

W', $\Delta\dot{M}$, and t represent the same quantities as previously.

This expression evaluates the energy required to perform some objective, usually mechanical changes of the system.

It is best to consider several cases as examples.

A. In running uphill at a constant velocity, no physical work is done, but the subject is expending energy to raise himself in a potential field. The possibility of reusing stored elastic energy is considered. The potential energy change efficacy is then

$$\varepsilon_{\Delta\phi} = \frac{|\Delta\phi|}{\int^{t} \Delta\dot{M}dt - W'} \times 100$$

B. In running uphill with acceleration, increases in both $\Delta\phi$ and ΔK terms are the objective of the energy expenditure. Therefore, the efficacy of acceleration is

$$\varepsilon_{\Delta\phi,\Delta K} = \frac{|\Delta\phi + \Delta K|}{\int^{t} \Delta\dot{M}dt - W'} \times 100$$

C. Some difficulties arise when the subject is lowered in a potential field. In running downhill, the objective of the runner is to prevent free-fall. The muscles act as a braking mechanism. The effectiveness of accomplishing this objective or the efficacy of deceleration, then, is the difference between the kinetic energy change that would occur if

the potential energy change was entirely transformed into kinetic energy and the actual apparent kinetic energy change.

If no acceleration occurs, the observed kinetic energy change $\Delta K_{obs} = 0$. The kinetic energy change of free-fall, ΔK_{ff}, would occur if the system's potential energy were converted entirely to kinetic energy

$$\Delta\phi = - \Delta K_{ff}$$

so that the efficacy of this potential energy change becomes

$$\varepsilon_{\Delta\phi} = \frac{|\Delta K_{ff} - \Delta K_{obs}|}{\int_0^t \Delta\dot{M}dt - W'} \times 100, \text{ and since } \Delta K_{obs} = 0,$$

$$\varepsilon_{\Delta\phi} = \frac{|\Delta K_{ff}|}{\int_0^t \Delta\dot{M}dt - W'} \times 100$$

$$\varepsilon_{\Delta\phi} = \frac{|-\Delta\phi|}{\int_0^t \Delta\dot{M}dt - W'} \times 100$$

If acceleration occurs, ΔK_{obs} is nonzero and positive, but can never be greater than ΔK_{ff}. Then the efficacy of downhill acceleration is

$$\varepsilon_{\Delta K} = \frac{|\Delta\phi - \Delta K_{obs}|}{\int_0^t \Delta\dot{M}dt - W'} \times 100$$

If deceleration occurs such that $\Delta K_{obs} < 0$, the body is braking more than is needed to prevent acceleration and requires more energy utilization than in the previous case. If the data of Margaria (71) are analyzed in this manner, the calculated efficacy of running up a ten per cent grade at a constant speed is $\varepsilon_{\Delta\phi} = 0.16$. The efficacy of walking up a ten per cent grade, which requires smaller energy expenditure, is $\varepsilon_{\Delta\phi} = 0.20$. The efficacies of running and walking downhill on a ten per cent grade are 0.39 and 0.94, respectively. These values of efficacy demonstrate the relative ease of accomplishing changes in the mechanical state of the system. Running uphill is the most difficult and requires the largest energy consumption to accomplish the potential energy change. Walking downhill requires little effort, and the potential energy changes and the energy consumption are almost equal.

The definition of efficacy avoids the use of negative efficiencies as calculated by Margaria (71) and Davies (33) and avoids the use of the work definition when no physical work is being performed.

Efficiencies and efficacies are useful, dimensionless quantities for performing comparisons. The definitions given here accommodate situations in which energy conversions result in the performance of work and situations in which energy is converted to a force or flux or to achieve a change in state. A summary is given in Table 1.

The analysis of subsystem efficiencies as they contribute to the overall system serves as a means of identifying the location of major inefficiencies that limit total system performance. This is exemplified by the phosphorylative coupling and contraction coupling efficiencies.

Table 1. A summary of the efficiency and efficacy definitions presented in this section

Efficiency or efficacy	Definition	Reference
Physiological work efficiency	$\frac{W}{\Delta M} \times 100$	In general use
Efficiency based on work maximum	$\frac{W}{\Delta H - T\Delta S} \times 100$	(118)
	$= \frac{W}{W_{max}} \times 100$	
Efficiency of an energy converter	$- \frac{J_1 X_1}{J_2 X_2}$	(23)
- degree of coupling	$q = L_{12}/\sqrt{L_{11}L_{22}}$	
- maximum efficiency	$q^2/(1 + \sqrt{1 - q^2})^2$	
- efficiency at maximum output	$\frac{1}{2}(2/q^2 - 1)$	
Efficiency of biochemical coupling	$\varepsilon = - \frac{\Delta\mu_1 d\xi_1}{\Delta\mu_2 d\xi_2}$	(68),(76)
Phosphorylative coupling efficiency	$\eta_P = \frac{\text{Free energy conserved as ATP}}{\text{free energy oxidized as foodstuff}} \times 100$	(115)
Contraction coupling efficiency	$\eta_C = \frac{\text{mechanical work output}}{\text{free energy of ATP hydrolysis}} \times 100$	(115)
Gross efficiency	$\frac{\text{external work}}{\text{total energy expenditure}} \times 100$	(107)

Table 1 (Continued)

Efficiency or efficacy	Definition	Reference
Net efficiency	$\frac{\text{external work}}{\text{energy expended above resting levels}} \times 100$	(107)
Delta efficiency	$\frac{\text{incremental work}}{\text{incremental energy expenditure}} \times 100$	(107)
Instantaneous efficiency	$\frac{\text{instantaneous work rate}}{\text{instantaneous energy expenditure}} \times 100$	(107)
Mechanicochemical efficiency	$\eta = \frac{W}{\int_0^t \Delta\dot{M}dt - W'} \times 100$	this work
Flux efficacy	$\varepsilon_{J_1} = \frac{J_1}{J_2X_2}$	(24)
Force efficacy	$\varepsilon_{X_1} = \frac{-X_1}{J_2X_2}$	(24)
Potential and/or kinetic energy change efficacy	$\varepsilon_{\Delta\phi,\Delta K} = \frac{\lvert\Delta\phi + \Delta K\rvert}{\int_0^t \Delta\dot{M}dt - W'} \times 100$	this work

The total organism efficiency could never be expected to exceed the product of the subsystem efficiencies. Efficiencies can predict extremes of performance, whether the system is a mechanical process or a world-record holding athlete.

IV. APPLICATIONS

In this section, several examples of the applications of the mass balance and the first and second law expressions in the study of biology and physiology will be discussed. A separate section will discuss the mechanical, biochemical, and molecular aspects of muscle contraction. Special attention will be devoted to the thermodynamics of growth and development. This will be followed by a definition and description of physical work and the calculation of system energy consumption.

A. Mass Balances

As has been previously discussed, oxygen consumption serves as a direct measure of a system's metabolic level. An example of this calculation will be given for the daily oxygen consumption rate of man. Recalling Equations 3 and 4,

$$\dot{V}_{O_2} = \frac{\sum_j \dot{\omega}_{O_2 j} \delta_j \, RT_o}{\tilde{M}_{O_2} P_o} = \frac{RT_o}{P_o} \left(\frac{dn_{O_2}}{dt} - \sum_k \nu_{O_2 k} \frac{d\xi_k}{dt} \right)$$

At steady state $dn_{O_2}/dt = 0$ and in most situations is negligible.

An average human at rest breathes approximately twelve times per minute inspiring 500 ml/breath of air. Dry air contains 21 mole percent oxygen and 79 percent nitrogen. A typical expired air analysis at rest (48) shows 15.1% O_2, 3.7% CO_2, 6.2% H_2O, and the remainder N_2. The total volume of gases expired is 527 ml/breath

$$\dot{V}_{O_2} = (\dot{\omega}_{O_2 in} - \dot{\omega}_{O_2 out}) \frac{RT_o}{\tilde{M}_{O_2} P_o}$$

$$= \left(\frac{500 \text{ ml}}{\text{breath}}\right)\left(\frac{12 \text{ breaths}}{\text{min}}\right)0.21 - \left(\frac{527 \text{ ml}}{\text{breath}}\right)\left(\frac{12 \text{ breaths}}{\text{min}}\right)0.151$$

$$\dot{V}_{O_2} = 305 \text{ ml } O_2/\text{min (STP)}$$

The mass rate of oxygen consumption is

$$\left(\frac{305 \text{ ml}}{\text{min}}\right)\left(\frac{32 \text{ g}}{\text{mole}}\right)(1 \text{ atm})\left(\frac{1}{273 \text{ K}}\right)\left(\frac{\text{K mole}}{82.06 \text{ ml}\cdot\text{atm}}\right) = \frac{118.9 \text{ g } O_2}{\text{min}}$$

This amount of oxygen is being utilized by the body in its basal metabolic activities.

A similar example illustrates that the human body loses mass during breathing because expired air is humidified to saturation.

$$\frac{dm_{H_2O}}{dt} = \sum_j \dot{\omega}_{H_2Oj}\delta_j + \sum \tilde{M}_{H_2O}\nu_{H_2Ok}\frac{d\xi_k}{dt}$$

If the production of metabolic water is neglected,

$$\frac{dm_{H_2O}}{dt} = \sum_j \dot{\omega}_{H_2Oj}\delta_j$$

If dry air is breathed, $\Sigma\dot{\omega}_{in} = 0$. Using data of the previous example,

$$\Sigma \dot{\omega}_{H_2O \text{ out}} = (0.062)(527)(12)\left(\frac{18 \text{ g}}{\text{mole}}\right)\left(\frac{1 \text{ atm}}{310 \text{ K}}\right)\left(\frac{\text{mole K}}{82.06 \text{ ml}\cdot\text{atm}}\right)$$

$$= 0.28 \text{ g/min}$$

$$\frac{dm_{H_2O}}{dt} = -\frac{0.28 \text{ g}}{\text{min}}$$

During the course of one 24-hour day, the body's mass loss by this process amounts to 0.4 kg or about 0.88 lbm.

Knowledge of the average mass or molar flows of the substrates, or food, consumed by a human coupled with a general stoichiometric description of the reactions in which these substrates participate leads to an interesting calculation of the metabolic water produced by the human. The amount of water produced in physiological oxidation reactions is approximated by equating the stoichiometric coefficients of the carbon dioxide and water products. This is a reasonable estimate as shown by the following combustion reactions for glucose and palmitic acid.

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

$$\text{palmitic acid} + 23O_2 \rightarrow 16CO_2 + 16H_2O$$

An average, moderately active 70-kg man consumes a typical diet described in Table 2.

Table 2. Average 24-hour fuel utilization by an adult male (68)

Compound	Grams	Moles O_2 consumed	Moles CO_2 produced	R
Carbohydrates	200	7.5	7.5	1.00
Protein	70	3.0	2.4	0.80
Fat	60	5.25	3.8	0.72

Therefore, the moles of water produced in a 24-hour period is approximately equal to the moles of CO_2 produced, or

$$(7.5 + 2.4 + 3.8)\text{moles } CO_2 \times 1 \text{ mole } H_2O/\text{mole } CO_2 = 13.7 \text{ moles } H_2O$$

$$= 246.6 \text{ g } H_2O$$

The data of this example may also be used to calculate the respiratory quotient for the diet shown.

$$R_{ave} = -\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = \frac{(7.5 + 2.4 + 3.8)\text{moles } CO_2/\text{day}}{(7.5 + 3.0 + 5.25)\text{moles } O_2/\text{day}}$$

$$R_{ave} = 0.87$$

The respiratory quotient, then, is a function of the proportions of carbohydrate, protein, and fat intake.

The use of mass balances as a means of analyzing reactant consumption and product manufacture from system chemical reactions is an

invaluable technique for the study of energy consuming processes in living systems. Energy consumption measurements are discussed in the next section.

B. Energy Consumption Measurements

The metabolic term $\sum_k \Delta\tilde{H}_{Rk} d\xi_k/dt$ or $\Delta\dot{M}$ of the first law energy balance is a measure of a large portion of the energy with which a living system supplies its functions. In complex organisms, distinguishing and separating the contributions of every chemical reaction taking place within the organism would be difficult. Several methods are used which simplify this task.

1. Traditional techniques

One method of evaluating system metabolism involves measuring all other terms of the energy balance and calculating the metabolism term by differences. Experimentally this is achieved in calorimetric studies by measuring the heat exchange rate and evaporative losses. For example, for a fully grown homoiothermic organism at rest and between fuelings, the first law expression is

$$\sum_k \Delta\tilde{H}_{Rk} v_k = \sum_j \sum_i \hat{H}_{ij} \dot{\omega}_{ij} \delta_j + \dot{Q}$$

The metabolism, or the rate of use of stored chemical internal energy, is balanced by the heat exchange with the surroundings and the enthalpy difference between the entering and exiting streams. This

resting metabolism represents the fueling of internal energy consuming processes and the eventual transformation of this energy to heat. For humans, the basal metabolism is about 1.7 kcal/kg·hr (6). The basal value is used to determine the absolute value of additional energy requirements of increased physical activity.

A second approach utilizes the fact that oxygen, while contributing a minimal amount to the enthalpy flow term, is the major oxidant of all biological fuels. Its consumption rate can be used to approximate the reaction velocity term, v_k, from Equation 4a

$$\dot{V}_{O_2} = - \frac{RT_o}{P_o} \Sigma \nu_{O_2 k} v_k$$

Using the total reaction velocity, $v_k = v_C + v_F + v_P$, together with an average heat of reaction for carbohydrates, proteins, and fats per volume of oxygen consumed (68),

$$\Delta\tilde{H}_{RC}/V_{O_2} = -5.47 \text{ kcal/liter } O_2$$

$$\Delta\tilde{H}_{RP}/V_{O_2} = -4.23 \text{ kcal/liter } O_2$$

$$\Delta\tilde{H}_{RF}/V_{O_2} = -4.60 \text{ kcal/liter } O_2$$

$$\Delta\tilde{H}_{ave}/V_{O_2} = -4.825 \text{ kcal/liter } O_2$$

the approximate value for the energy consumption is

$$\Delta\dot{M} = \sum_k \Delta\tilde{H}_{Rk} v_k = \dot{V}_{O_2} \times - 4.825 \text{ kcal/l } O_2$$

with $\dot{V}_{O_2}$ in liters per minute.

2. The electron balance technique

In their recent work with microbial cultures, Erickson (37, 38), Erickson and Patel (40, 41), and Erickson et al. (42) have contributed to the development of material and energy balances based on the available electron concept and several regularities of microbial culture biochemistry. Their work is summarized below.

The reactions of microbial growth are viewed as a series of electron transfers between the compounds involved in the reactions. According to Erickson and Patel (40), growth is represented by the equation

$$CH_mO_\ell + a\ NH_3 + b\ O_2 \rightarrow y_c CH_pO_nN_q + zCH_rO_sN_t + cH_2O + dCO_2 \qquad (42)$$

where CH_mO_ℓ is the elemental composition of organic substrate, $CH_pO_nN_q$ is the elemental composition of biomass, and $CH_rO_sN_t$ represents the elemental composition of the extracellular product. The coefficients y_c, z, and d are the fractions of organic substrate converted to biomass, products, and carbon dioxide, respectively.

The reductance degree, the number of equivalents of available electrons per g-mole of carbon, of each compound is then calculated according to the following equations:

substrate: $\gamma_s = 4 + m - 2\ell$

product: $\gamma_p = 4 + r - 2s - 3t$

biomass: $\gamma_b = 4 + p - 2n - 3q$

The reductance values are based on the electrons available for each element as follows: C = 4, H = 1, O = -2, N = -3. The highly reduced substrate transfers electrons to oxygen, to biomass, and to products. On a fractional basis relative to γ_s, the electrons available in the substrate, the fractions transferred are symbolized by ε, the fraction transferred to oxygen, η, the fraction transferred to biomass, and ξ_p, the fraction transferred to products. Since the total numbers of electrons must be conserved

$$\gamma_s + b(-4) = y_c\gamma_b + z\gamma_p \tag{43}$$

and

$$\varepsilon + \eta + \xi_p = 1. \tag{44}$$

Associated with each equivalent of electrons transferred is heat evolution Q_o. Each term in Equation 43 is multiplied by Q_o giving an electron energy balance

$$Q_o\gamma_s + Q_o b(-4) = Q_o y_c\gamma_b + Q_o z\gamma_p \tag{45}$$

The first term on the right side of Equation 45 represents the energy incorporated into the biomass and the second, the energy in the products. The term $4Q_o b$ is the heat evolution and the energy associated with electrons transferred to oxygen is evolved as heat. The term ε may be written as

$$\varepsilon = \frac{4b}{\gamma_s} = \frac{4bQ_o}{Q_o\gamma_s} = \frac{Q_{tot}}{Q_o\gamma_s} \tag{46}$$

accounting for the fraction of energy in the organic substrate evolved as heat. This heat is a result of energetic inefficiencies in maintenance requirements, in cell growth, and in product formation. Analogously, η is the fraction of energy stored in biomass and ξ_p, the energy contained in products.

Many experiments have shown that Q_o is relatively constant at about 26.5 kcal per g-equivalent of electrons transferred (37). Furthermore, the number of available electrons per carbon atom is a relatively constant value at 4.291 and the weight fraction of carbon in biomass is generally found to be equal to 0.462 (40). These regularities are the basis for the general application of the electron and energy balances. The application of these balances in the analysis of experimental results has proven to be a viable method of testing data consistency (37, 40,41,42).

It is significant to note that when the units for Q_o = 26.5 kcal/g-equiv are converted to units of kcal/liter of oxygen, Q_o = 4.821 kcal/liter O_2. This value is virtually the same quantity as that used in physiological energetics studies for the energy equivalent of oxygen. In exercise physiology studies, oxidative reactions are of major importance for energy supply. The generalized reaction is written below (41):

$$CH_pO_nN_q + \frac{\gamma_b}{4} O_2 \rightarrow CO_2 + q\ NH_3 + \frac{1}{2}(p - 3q)H_2O \qquad (47)$$

where γ_b is the reductance degree of the substrate, $\gamma_b = 4 + p-2n-3q$. For example, the oxidation of glucose, $C_6H_{12}O_6$, is represented when p = 2, n = 1, q = 0, and γ_b = 4,

$$CH_2O + O_2 \rightarrow CO_2 + H_2O$$

and the energy produced per mole of glucose combusted is calculated by

$$\left(\frac{26.5 \text{ kcal}}{\text{g·equiv}}\right) \times \left(\frac{4 \text{ g·equiv}}{\text{mole } O_2}\right) \times \left(\frac{6 \text{ moles of } O_2}{\text{mole of glucose}}\right) = \frac{636 \text{ kcal}}{\text{mole of glucose}}$$

which corresponds well to the commonly used value for the heat of combustion of glucose, -673 kcal/mole, a difference of only -5.5% (40).

Using oxygen consumption as a measure of heat production is further justified by the fact that oxygen is almost entirely absent from the biosynthetic processes of biochemical pathways. It enters the biochemical cycle at the end of oxidative phosphorylation to produce energy as heat.

It may be concluded that the use of the energy equivalent of oxygen, 4.821 kcal/liter O_2, is a good way of assessing metabolism in nongrowing, steady state organisms. However, when growth and development are dominant phenomena, the principles of the available electron balance should be used to calculate the energy allocated to growth and to product formation. Oxygen consumption then becomes a measure of heat production. An example of the use of the energy equivalent for oxygen in the first law balance is shown below.

An average person inhales about 300 ml of O_2/min. The metabolic rate is calculated

$$\Delta\dot{M} = \sum_k \Delta\tilde{H}_{Rk} v_k = - \dot{V}_{O_2} \times 4.821 \text{ kcal/l } O_2$$

$$= - 1.45 \text{ kcal/min}$$

If the only flows across the boundaries of the body are the air inhaled and exhaled, the enthalpy flow term, with reference at 25°C, is found to be

$$\sum_j \hat{H}_j \dot{W}_j \delta_j = \Sigma \dot{W}_j \hat{C}_{P_j} (T_j - T_{ref}) \delta_j = - 0.021 \frac{\text{kcal}}{\text{min}}$$

The total balance shows that the resting heat loss for an inactive person should then be

$$\Delta\dot{M} + \dot{H}_{out} = \dot{Q}$$

$$- 1.43 \frac{\text{kcal}}{\text{min}} = \dot{Q}$$

In particular, this illustrates the small contribution that flow terms make in an overall energy balance.

C. Thermodynamics of Growth and Development

Prigogine and Wiame (83) first suggested that irreversible thermodynamics might be applicable to the study of growth and development of animals. The consequences of a thermodynamic approach are not only of theoretical significance but have practical importance as well. The

analysis of the driving forces and fluxes in development and growth may be logically extended to studies of malignant growth, ageing, and wound healing.

Since 1946, the research dealing with the application of irreversible thermodynamics in biology has been active, but published results have often been contradictory. The apparent cause of this has usually been the misinterpretation of the thermodynamic meaning of experimentally measured quantities. This section is intended to clarify the interpretation of terms in the entropy account and to apply this in the analysis of well-defined systems.

1. Growth and development

Growth and development is an unsteady state period during the life of an organism in which the biosynthetic reactions dominate the biochemical pathways of an organism's metabolism. In the thermodynamic sense, it is a period in which a system's externally measurable parameters are changing. During growth these are generally mass, dimension, and state of aggregation. These changes are fairly rapid relative to the lifespan of the organism. The changes that occur in a healthy adult organism are largely replacement and repair, imperceptible when viewed on the macroscopic level. The adult stage is therefore characterized thermodynamically as a steady state.

The study of growth and development provides an opportunity to investigate the changes in energy utilization and allocation as an organism matures.

It is generally agreed that adenosine triphosphate, ATP, or some intermediate formed from its participation is the energy-coupling device between the exothermic reactions of oxidative metabolism and the endothermic processes of cell biosynthesis. Although the detailed biochemical mechanisms and substrates used vary from organism to organism, the ultimate requirements of biosynthesis are mainly the synthesis of proteins, nucleic acids, and lipids. These similarities between organisms provide a sound reason for studying periods of growth and development in well-defined living systems such as bacterial cultures and avian eggs, for using these results to make general comments about possible trends in all living systems, and to suggest avenues for further investigation.

2. Analyses of the microbial culture system

The thermodynamic study of growth energetics has been of recent importance in biotechnology. Material and energy balances have been applied to microbial growth and product formation as a means of understanding energy and product yields, important aspects of bioengineering process development (see 34, 37, 88). The methods developed and the data obtained have been an extremely useful addition to the analysis procedures described herein.

When unicellular organisms are provided with adequate nutrients and proper temperature and pH, they will grow. The cells increase in number thereby increasing the amount of living matter, or biomass. Associated with the growth process are the uptake of material from the cell's environment and the release of metabolic end products, many of which are industrially desirable.

Biomass may be grown in either a batch or a continuous (chemostat) culture. The discussion here will deal mainly with batch cultures such as fermentors.

A typical batch growth curve is represented in Figure 1.

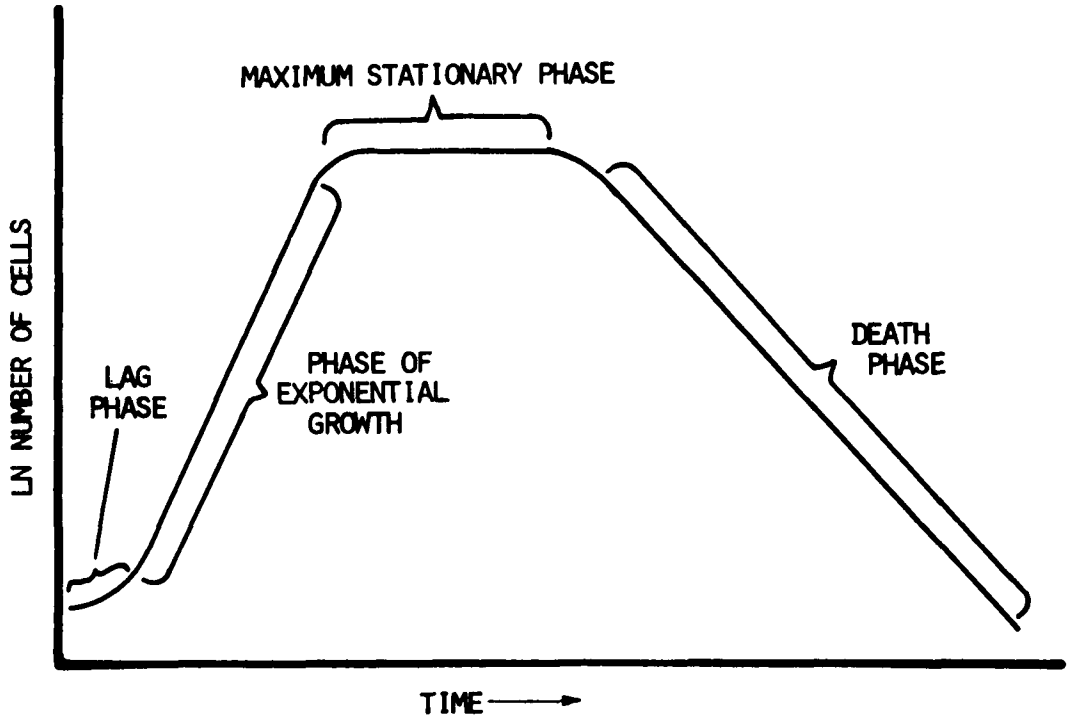
After the lag phase during which the inoculated organisms are adjusting to their environment, exponential growth begins. The maximum stationary phase is reached either when the substrate has been consumed or when further growth is inhibited by toxic products. The ensuing death phase has not been extensively studied as it is no longer industrially profitable. It is assumed to be exponential.

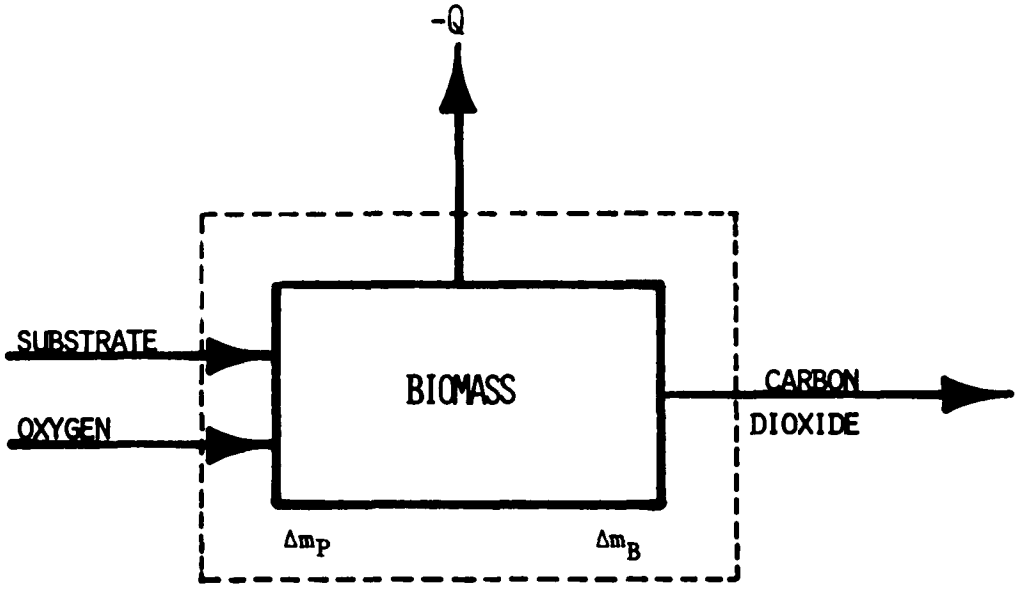
The general pattern of the batch culture growth curve is of interest because its shape and the significance of each phase resemble the general nature of the lifespan growth curves of other living organisms. In addition, the relatively short culture times, and the availability of fairly accurate methods of the monitoring of biomass, product, and heat production suggest that a batch culture may be a convenient system to use experimentally in the study of energy and entropy flows over the lifetime of the system. A batch culture portrays diversity in cell population and the interdependence between individual cells within the culture, thus promising to be an excellent model of a living organism.

a. The first law analysis Data taken by Selga et al. (100) have been cited and analyzed by Erickson et al. (42). Brevibacterium was grown in a batch culture containing molasses, corn extract, and other nutrients. Lysine was the extracellular product of this fermentation. The measured variables were biomass productivity, lysine productivity,

Figure 1. A typical batch growth curve of a microbial culture (8)

Figure 2. The material and energy flows of the microbial culture system (Δm_P and Δm_B represent system growth due to products and biomass, respectively)


MAXIMUM STATIONARY PHASE
LN NUMBER OF CELLS
LAG PHASE
PHASE OF EXPONENTIAL GROWTH
DEATH PHASE
TIME


-Q
SUBSTRATE
OXYGEN
BIOMASS
CARBON DIOXIDE
Δm_P
Δm_B

oxygen consumption rate, heat evolution rate, substrate consumption, and respiratory quotient. Erickson et al. (42) calculated η, ξ_p, and ε from these data. The data for Selga's Experiment 1 and the calculated efficiencies are presented in Table 3.

Table 3. Measured values of biomass productivity, lysine productivity, oxygen consumption, heat evolution, substrate consumption, carbon dioxide production, and efficiencies of energy transformation as reported in (42) for the data of Selga et al. (100) for Brevibacterium, experiment 1, total volume = 2.9×10^3 liters, and initial mass = 11.3 g/liter

Measured variable	Time period (hrs)			
	0-12	12-24	24-36	36-48
Biomass productivity				
g/liter·hr	0.292	0.366	0.258	0.125
(g/hr) x 10^{-3}	0.85	1.1	0.75	0.36
Lysine·HCℓ productivity				
g/liter·hr	0.200	0.417	0.279	0.434
(g/hr) x 10^{-3}	0.58	1.2	0.81	1.3
Oxygen consumption				
g/liter·hr	0.40	1.57	1.78	1.85
(moles/hr) x 10^{-3}	36	140	160	170
Heat evolution				
kcal/liter·hr	0.60	4.25	5.75	6.50
(kcal/hr) x 10^{-3}	1.7	12	17	19
Substrate consumption				
g/liter·hr	0.417	1.410	2.580	2.90
(g/hr) x 10^{-3}	1.2	4.1	7.5	8.4
Carbon dioxide production				
(moles/hr) x 10^{-3}	39	150	170	180
Fraction of substrate transformed to:				
biomass, η	0.38	0.19	0.14	0.07
product, ξ_p	0.24	0.20	0.14	0.21
oxygen, ε	0.38	0.61	0.72	0.72

The system to be analyzed is the biomass plus the products it forms. The system consumes organic substrate by metabolism, produces additional biomass and products (grows), and expels wastes and heat. The growing system is depicted in Figure 2. The process is isothermal.

The first law expression used in analyzing the system energy flows is an expanded version of Equation 24g,

$$\hat{H}_P \frac{dm_P}{dt} + \hat{H}_B \frac{dm_B}{dt} + \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \dot{Q}$$

where the growth rate of the system is represented in two portions, dm_B/dt, the growth rate of biomass, and dm_P/dt, the production rate of lysine.

An example of the calculations for the first 12-hour period is shown below.

The fraction of energy consumed from the substrate that is evolved as heat is given as $\varepsilon = 0.38$. The heat evolved is $\dot{Q} = 1.7 \times 10^3$ kcal/hr. The total metabolic rate, or the energy consumed in the substrate, is the energy per gram·equivalent of available electrons transferred (g·equiv a.e.) times the number of electrons in the substrate consumed hourly, $Q_o\gamma_s$. The term γ_s is calculated from Equation 46,

$$\varepsilon = \frac{Q}{Q_o\gamma_s} , \qquad (46)$$

so that

$$\gamma_s = \frac{\dot{Q}}{Q_o \varepsilon} = \frac{-\ 1.7 \times 10^3 \text{ kcal/hr}}{\left(-\ 26.5 \dfrac{\text{kcal}}{\text{g·equiv a.e.}}\right)(0.38)}$$

$$= 170 \frac{\text{g·equiv a.e.}}{\text{hr}}$$

The total metabolic rate is then,

$$\sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \Delta\dot{M} = Q_o \gamma_s$$

$$= -\ 4500 \frac{\text{kcal}}{\text{hr}}$$

From Equation 45, the products contain the amount of energy $Q_o z\gamma_p$. The fraction of substrate energy contained in the products is $\xi_p = 0.24$.

$$\xi_p = \frac{\dot{Q}_o z\gamma_p}{\dot{Q}_o \gamma_s} = \frac{z\gamma_p}{\gamma_s} \tag{45}$$

Since γ_s and ξ_p are known, $\gamma_s \xi_p = z\gamma_p$, and the rate of energy storage as products is given by

$$\hat{H}_p \frac{dm_p}{dt} = \dot{Q}_o \gamma_s \xi_p$$

$$= \left(26.5 \frac{\text{kcal}}{\text{gequiv a.e.}}\right)\left(170 \frac{\text{gequiv a.e.}}{\text{hr}}\right)(0.24)$$

$$= 1080 \frac{\text{kcal}}{\text{hr}}$$

Lastly, the rate of energy storage as biomass is the total consumption rate of substrate times the fraction stored as biomass, or $\Delta\dot{M}\eta$, so that

$$\hat{H}_B \frac{dm_B}{dt} = (4500 \frac{kcal}{hr})(0.38)$$

$$= 1710 \frac{kcal}{hr}$$

Since the data analysis performed by Erickson et al. (42) is consistent because $\eta + \xi_p + \varepsilon = 1.0$, as a consequence, the energy account must balance.

$$\hat{H}_p \frac{dm_p}{dt} + \hat{H}_B \frac{dm_B}{dt} + \Delta\dot{M} = \dot{Q}$$

$$1080 \frac{kcal}{hr} + 1710 \frac{kcal}{hr} + - 4500 \simeq - 1700 \frac{kcal}{hr}$$

The calculated values for each 12-hour measurement period are listed in Table 4. The mass, $\bar{m}$, is a mean value for the biomass plus products for each time period.

Table 4. The specific rates of energy storage and transformation calculated for Brevibacterium in units of kcal/g·hr. (Data from (42, 100))

Period (hrs)	$\bar{m}$ (g)	$\Delta\hat{\dot{M}}$	$(\hat{H}_p\ dm_p/dt)/\bar{m}$	$(\hat{H}_B\ dm_B/dt)/\bar{m}$	$\hat{\dot{Q}}$
0-12	41300	-0.11	0.03	0.03	-0.04
12-24	63500	-0.31	0.06	0.06	-0.19
24-36	86500	-0.28	0.04	0.04	-0.20
36-48	106000	-0.25	0.05	0.02	-0.18

b. Second law analysis The first law analysis has made available the quantities necessary to estimate the entropy production rate of the system, i.e. heat loss and metabolism energies.

Although no information about temperature was provided by Selga et al. (100), a system temperature of 25°C is assumed. It is within a range reasonable for the growth of Brevibacterium. In this case, the entropy flow term is negligible since flows enter and leave at the same temperature, which may be chosen as the reference state.

In order to test Prigogine's hypothesis, the entropy production rate in Equation 29 will be written for specific rates in units of energy per time (t) · temperature (T) · unit mass (m).

$$\frac{\hat{dS}}{dt} = \frac{\hat{\dot{Q}}}{T} - \frac{\Delta\hat{\dot{M}}}{T} + \Sigma\, \Delta\hat{S}_{Rk} \frac{d\xi_k}{dt} + \frac{1}{T \cdot m} \Sigma\, J_P X_P \qquad (48)$$

The last term cannot be evaluated, but it is known that it has a positive value.

As pointed out previously, for biological molecules, the entropy change of reaction, or the entropy of rearrangement, is small. It will be neglected leaving the following simplification of Equation 48

$$\frac{\hat{dS}}{dt} \simeq \frac{\hat{\dot{Q}}}{T} - \frac{\Delta\hat{\dot{M}}}{T} + (\text{positive number})$$

Using the data provided in the first law analysis and shown in Table 4, the calculated specific entropy production rate for the system, $\hat{dS}/dt$, is shown in Table 5. A plot of these values is presented in Figure 3. The rates are mean values for each time period.

Table 5. An approximation of the specific entropy production rate of the Brevibacterium system (42). (T = 25°C, units of dS/dt in kcal/g·hr·°C)

Period	$\hat{\dot{Q}}/T$	$\hat{\Delta\dot{M}}/T$	$\hat{dS/dt} \cong (\hat{\dot{Q}} - \hat{\Delta\dot{M}})/T$
0–12	-1.6×10^{-3}	-4.4×10^{-3}	2.8×10^{-3}
12–24	-7.6×10^{-3}	-1.2×10^{-2}	4.4×10^{-3}
24–36	-8.0×10^{-3}	-1.1×10^{-2}	3.2×10^{-3}
36–48	-7.2×10^{-3}	-1.0×10^{-2}	2.8×10^{-3}

The total system entropy can be approximated by assuming some initial system entropy, S_o, and integrating the total entropy production rate over each time period. The total entropy production rate is simply the product of the specific entropy production rate for each period and the mean value of the mass of the system for the same period. These results are shown in Table 6 and Figure 4.

Table 6. An approximation of the total system entropy change per measurement period for the Brevibacterium system (42, 100) (units of total system entropy change are in kcal/°C, average mass, $\bar{m}$, in grams, specific rates in kcal/g·hr·°C, and total rates in kcal/hr·°C)

Period (hrs)	$\bar{m}$	$\hat{dS/dt}$	dS/dt	$\Delta S = \int_t^{t+1} \left(\frac{dS}{dt}\right) dt$
0–12	41300	2.8×10^{-3}	116	1390
12–24	63500	4.4×10^{-3}	279	3350
24–36	86500	3.2×10^{-3}	277	3320
36–48	106000	2.8×10^{-3}	297	3560

Figure 3. The specific entropy production rate in kcal/g·hr.°C versus time period for Brevibacterium culture at 25°C (42, 100)

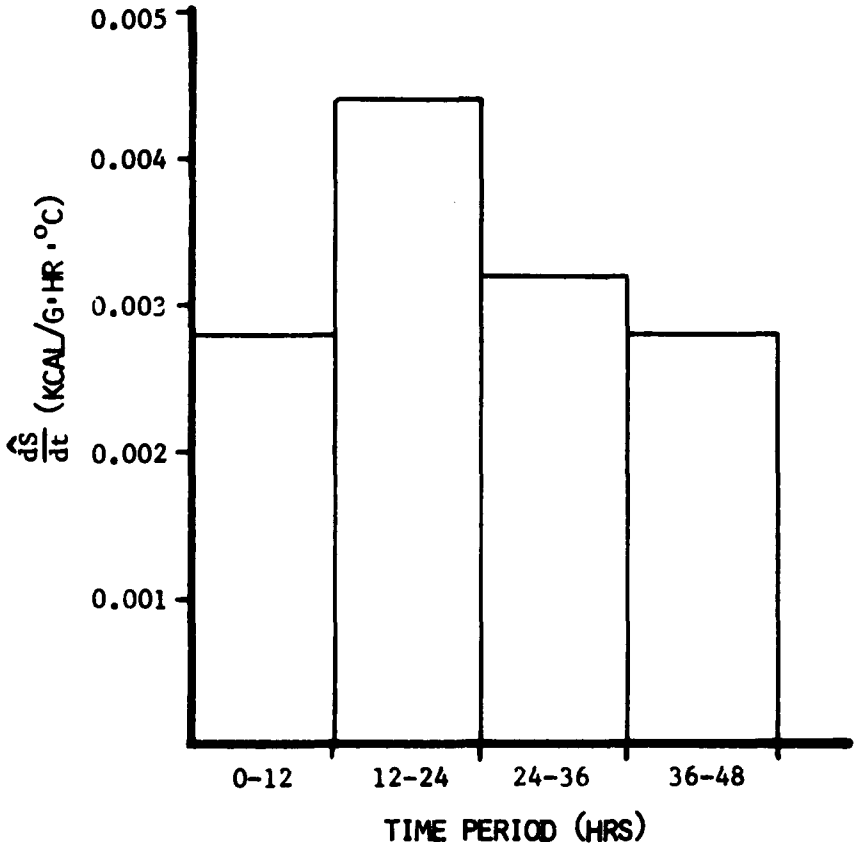
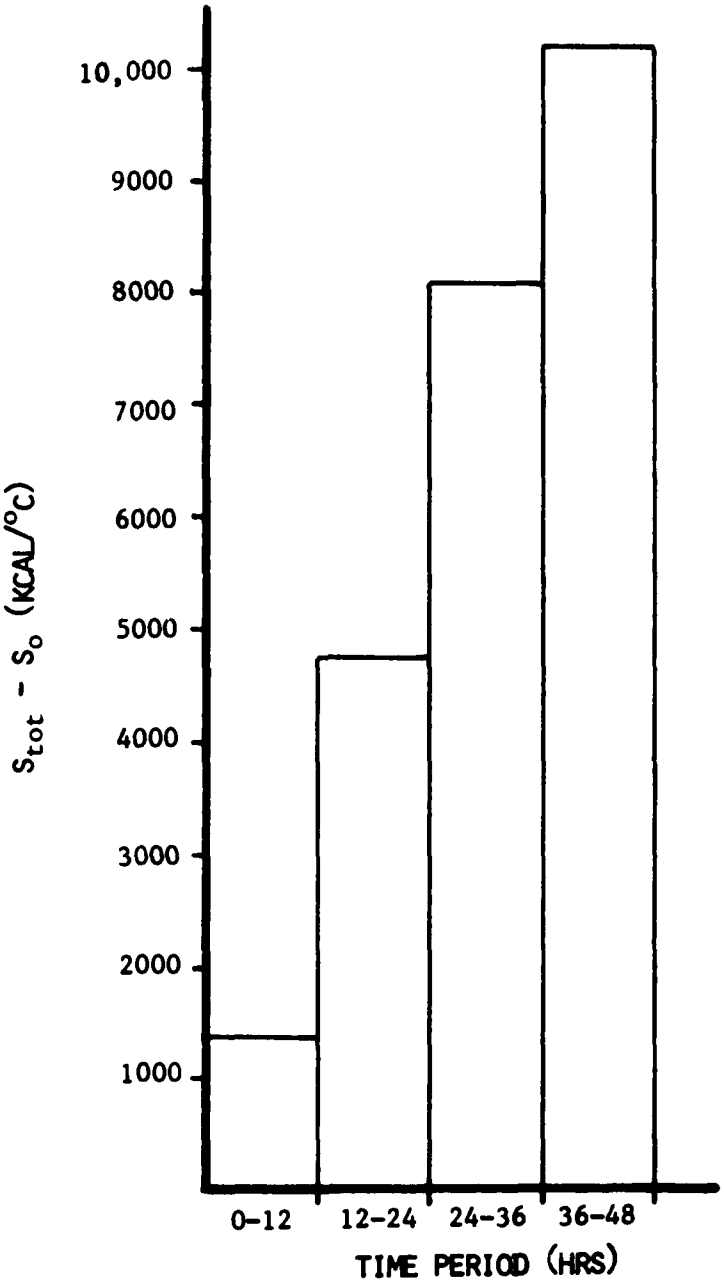

0.005
0.004
0.003
0.002
0.001
$\hat{\frac{dS}{dt}}$ (KCAL/G·HR·°C)
0-12
12-24
24-36
36-48
TIME PERIOD (HRS)

Figure 4. The cumulative change in total system entropy ($S-S_o$) in kcal/°C versus time period for Brevibacterium culture at 25°C


10,000
9000
8000
7000
6000
5000
4000
3000
2000
1000
$S_{tot} - S_o$ (KCAL/°C)
0-12
12-24
24-36
36-48
TIME PERIOD (HRS)

The cumulative value for system entropy is S_o + 11600 kcal/°C. This represents a minimum since the contribution from the remaining internal forces and fluxes has been neglected.

From this analysis it is apparent that total system entropy is a large positive value that is increasing for the duration of this experiment.

3. Analyses of the avian egg system

Avian eggs have been the subjects of extensive study by embryologists, geneticists, biochemists, and, lately, biophysicists. The system is well-defined. This allows its energy exchange with the environment to be readily measured. The system's energy source is self-contained; therefore, the system is regarded as semi-closed, since only the flows of gaseous reaction products, reactants, and inerts are present.

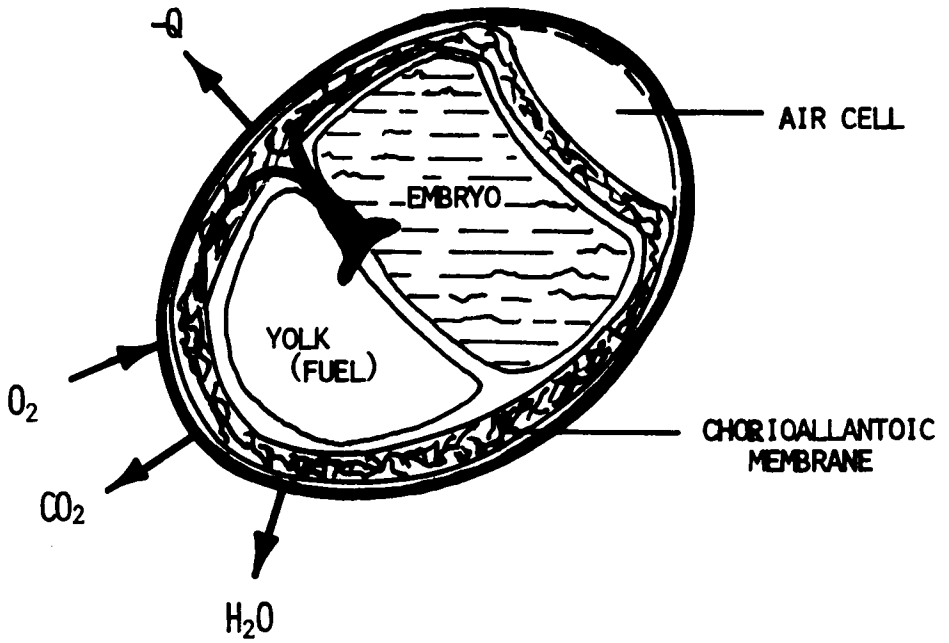
The egg system contains the developing embryo, the egg albumen, the egg yolk, the chorioallantoic membrane, which is the chief organ of respiration and heat exchange, and other structures. These structures are depicted in Figure 5a. The embryo is the chief metabolizing portion of the egg. Chemical compounds are selectively transported within the egg, transformed by synthesis, and incorporated into the tissues of the embryo. The mass of the embryo increases throughout the 21 day period of incubation and the mass of the remaining portions decreases yielding an overall mass loss for the whole egg.

The system's chief means of heat dissipation appears to be water vaporization. The exact physical mechanism of water loss is not

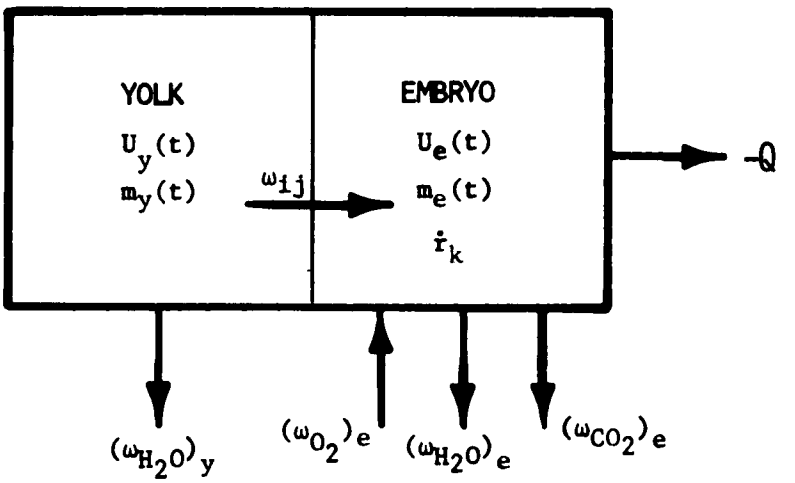
Figure 5. The physiological and thermodynamic depictions of the energy flows of avian eggs

a) as suggested by (87)
b) as viewed in a first law analysis

(A)


-Q
AIR CELL
EMBRYO
YOLK
(FUEL)
O_2
CO_2
H_2O
CHORIOALLANTOIC
MEMBRANE

(B)


YOLK
$U_y(t)$
$m_y(t)$
ω_{ij}
EMBRYO
$U_e(t)$
$m_e(t)$
$\dot{r}_k$
-Q
$(\omega_{H_2O})_y$
$(\omega_{O_2})_e$
$(\omega_{H_2O})_e$
$(\omega_{CO_2})_e$

completely understood, but it is clear that eggs of most avian species lose approximately sixteen per cent of their original system mass in water (86). Gas enters to replace the lost water and forms an air cell, which serves as the primary chamber for the pre-hatch chick's attempts at lung-breathing.

a. First law analysis The developing embryo is the real system of interest since it is the portion of the egg that is living and metabolizing. The goal is to ultimately determine the entropy production rate of the living tissue in the analysis of Brevibacterium.

As before, the analysis begins with the first law. Figure 5b is an analytically descriptive illustration of the egg system. The available electron balance technique will be applied. This is done first for the entire egg system. Data are available from several sources. The most complete is provided by Romijn and Lokhorst (92) for eggs of White Leghorn and Blue North Holland hens. However, the data have been misinterpreted by the authors because metabolism has apparently been calculated from oxygen consumption. This energy equivalent does not apply to growing systems. A value for η, the fraction of total metabolic energy incorporated into biomass, is required. Brody (19) has found this to be $\eta = 0.63$ for chick embryos. It is questionable whether η is constant for the entire incubation period, but the value of 0.63 will be used since it is the only one presently available. The number does show good agreement with values of energy storage and losses obtained by Tangl (111). He combusted a fertile chicken egg and a fully developed chicken embryo with its remaining yolk. The fertile egg contained approximately 88 kcal.

The pre-hatch embryo contained 36 kcal and the remaining yolk, 28 kcal. Thus, the pre-hatch egg held a total of 64 kcal and 24 kcal had been lost during incubation. The total amount of substrate expended equal to the metabolism was 88-28 = 60 kcal. The value of $\eta = 0.63$ would predict a biomass energy storage of 60 x 0.63 = 38 kcal. This is in very close agreement with the experimental value of 36 kcal.

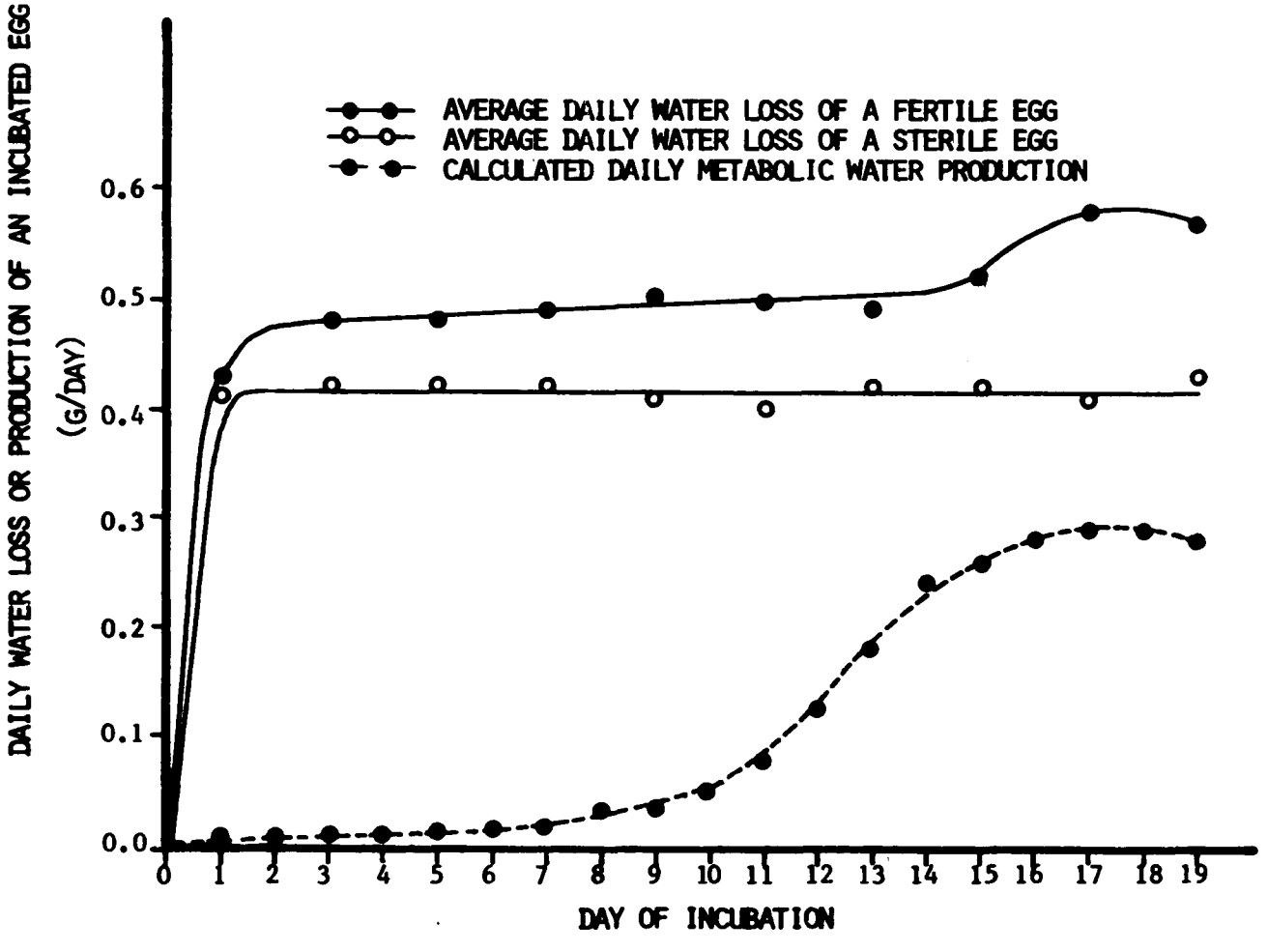
To evaluate the utility of predicting theoretical heat production of a chick embryo from oxygen uptake, the predicted value will be compared to the heat loss as calculated from experimental values of water vaporization from the egg. These values are generally calculated for the entire egg system, both living and nonliving portions. In order to isolate the heat loss by water vaporization from the embryo, some estimate of the water losses between sterile and fertile eggs must be used. Bywaters and Roue (21) have measured this difference for sterile and fertile eggs under the same incubation conditions. For the sterile eggs, the daily losses were approximately thirteen per cent of the initial egg masses. The fact that the daily losses of the sterile eggs are constant suggests that this water loss may be dependent upon the system's environmental conditions, which were held virtually constant, and may be a desiccation process. For fertile eggs, the daily losses varied, increasing past the ninth day of incubation, and averaged to about sixteen per cent of the initial mass. This is in agreement with the results of Rahn and Ar (86).

The "live" water losses found by taking the difference between the average fertile and sterile egg water losses account for the remaining three per cent of the initial mass lost. With the data currently

available, the water actually lost by the embryo cannot be determined. However, an estimate of this value is made if the "live" losses are attributed to the embryo and the water loss for the whole egg is visualized as the "live" losses added to the sterile losses, the latter of which are assumed to be lost from the nonliving portions of the egg.

That the extra water losses of the fertile egg above the losses of the sterile egg are required as a means of metabolic heat dissipation may be justified as follows. As was demonstrated earlier in the section describing the use of the mass balance, the knowledge of the respiratory quotient and the general stoichiometry of the system reactions allows the calculation of an estimate of the metabolic water production. The metabolism of a chicken embryo is fueled largely by lipids such as oleic and stearic acid. The combustion of these compounds generally produces equal molar yields of water and carbon dioxide, so that carbon dioxide production may be used to calculate water production. As shown in Figure 6, the general trend of the rate of "live" water loss resembles the trend in the increase of metabolic water production. Although the embryo water loss may not arise directly from the metabolic water produced, Figure 6 serves to illustrate the parallel between increased metabolic activity and increased embryo water loss. Moreover, data from Romanoff (89) show that the percentage of solids in the embryo increases past the seventh day of incubation. The total water loss required to maintain an increase in the solids concentration cannot be calculated from the data. However, since the embryo is also producing metabolic water, a "live" water loss seems necessary. If this loss is then equated to the water

Figure 6. A comparison between the average sterile and average fertile egg daily water losses (data from (21)) contrasted with the metabolic production of water


AVERAGE DAILY WATER LOSS OF A FERTILE EGG
AVERAGE DAILY WATER LOSS OF A STERILE EGG
CALCULATED DAILY METABOLIC WATER PRODUCTION
DAILY WATER LOSS OR PRODUCTION OF AN INCUBATED EGG
(G/DAY)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
DAY OF INCUBATION

vaporized by the embryo, an estimate of the heat loss from the embryo alone is obtained. The heat of vaporization at 39°C is used in the calculation, $\Delta\hat{H}_v$ = -0.575 kcal/g H_2O. The water loss heat flux is compared to the heat loss predicted from oxygen consumption in Figure 7 and Table 7.

Table 7. Comparison between the theoretical heat loss predicted from oxygen consumption (89) and the experimental heat loss calculated from water loss data (21)

Day	"Live" water loss (g in 24 hrs)	$-\dot{Q}_{H_2O}$ (kcal/hr)	$-\dot{Q}_{O_2}$ (kcal/hr)	Unaccounted heat loss $(-\dot{Q}_{O_2}) - (-\dot{Q}_{H_2O})$
1	0.02	4.8×10^{-4}	3.3×10^{-4}	-1.5×10^{-4}
3	0.06	1.44×10^{-3}	7.8×10^{-4}	-6.6×10^{-4}
5	0.06	1.44×10^{-3}	1.78×10^{-3}	3.4×10^{-4}
7	0.07	1.68×10^{-3}	4.81×10^{-3}	3.1×10^{-3}
9	0.07	1.68×10^{-3}	8.41×10^{-3}	6.0×10^{-3}
11	0.10	2.40×10^{-3}	1.84×10^{-2}	1.6×10^{-2}
13	0.07	1.68×10^{-3}	3.65×10^{-2}	3.5×10^{-2}
15	0.10	2.40×10^{-3}	6.41×10^{-2}	6.2×10^{-2}
17	0.18	4.31×10^{-3}	8.10×10^{-2}	7.7×10^{-2}
19	0.14	3.35×10^{-3}	1.00×10^{-1}	9.7×10^{-2}

It is readily apparent that a difference exists. The value of the difference between the predicted (by oxygen consumption) and the measured (by water loss) values is plotted in Figure 8. Along with this curve is shown the temperature gradient between the incubating egg and the

Figure 7. A comparison of the theoretical heat loss from oxygen consumption data (89) with experimental heat loss from water vaporization data (21)

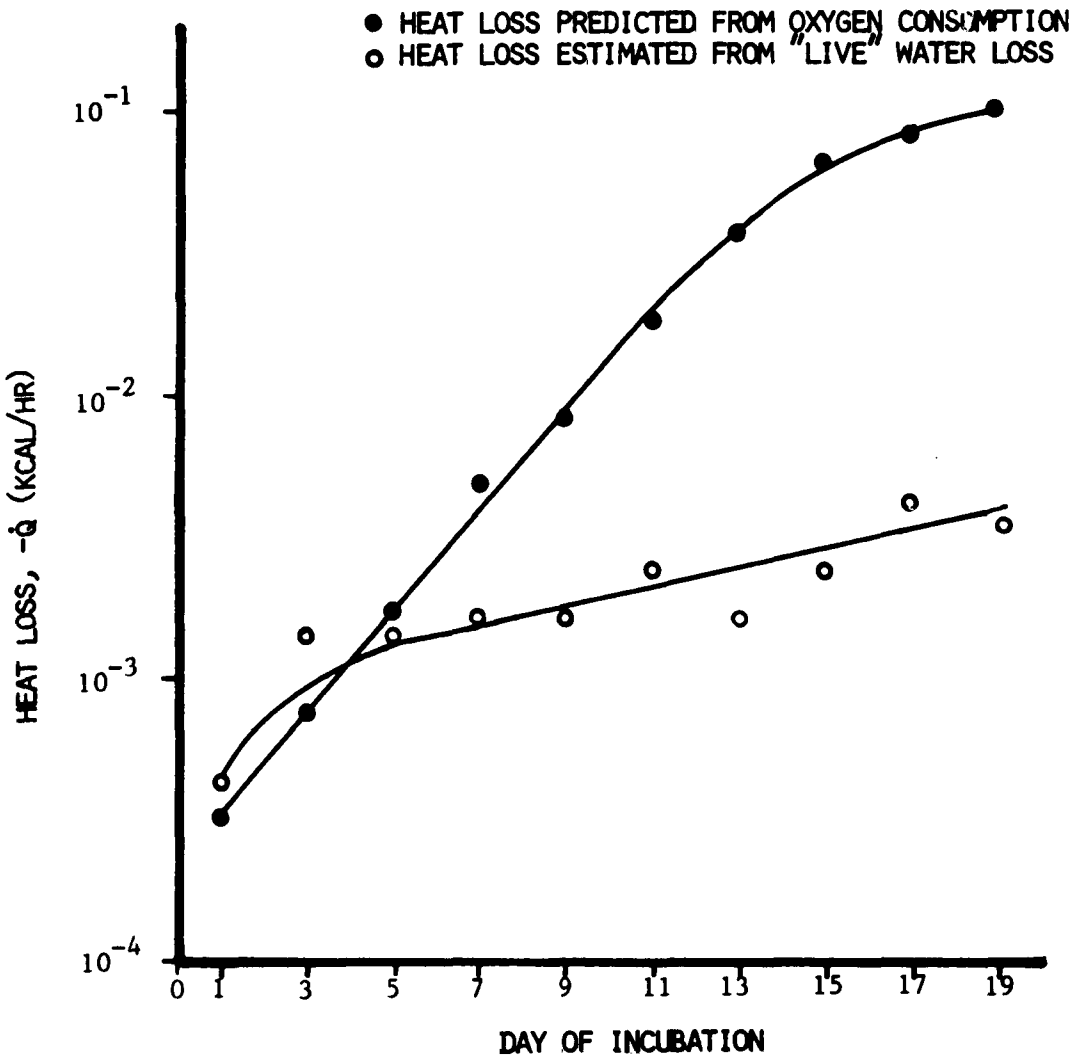
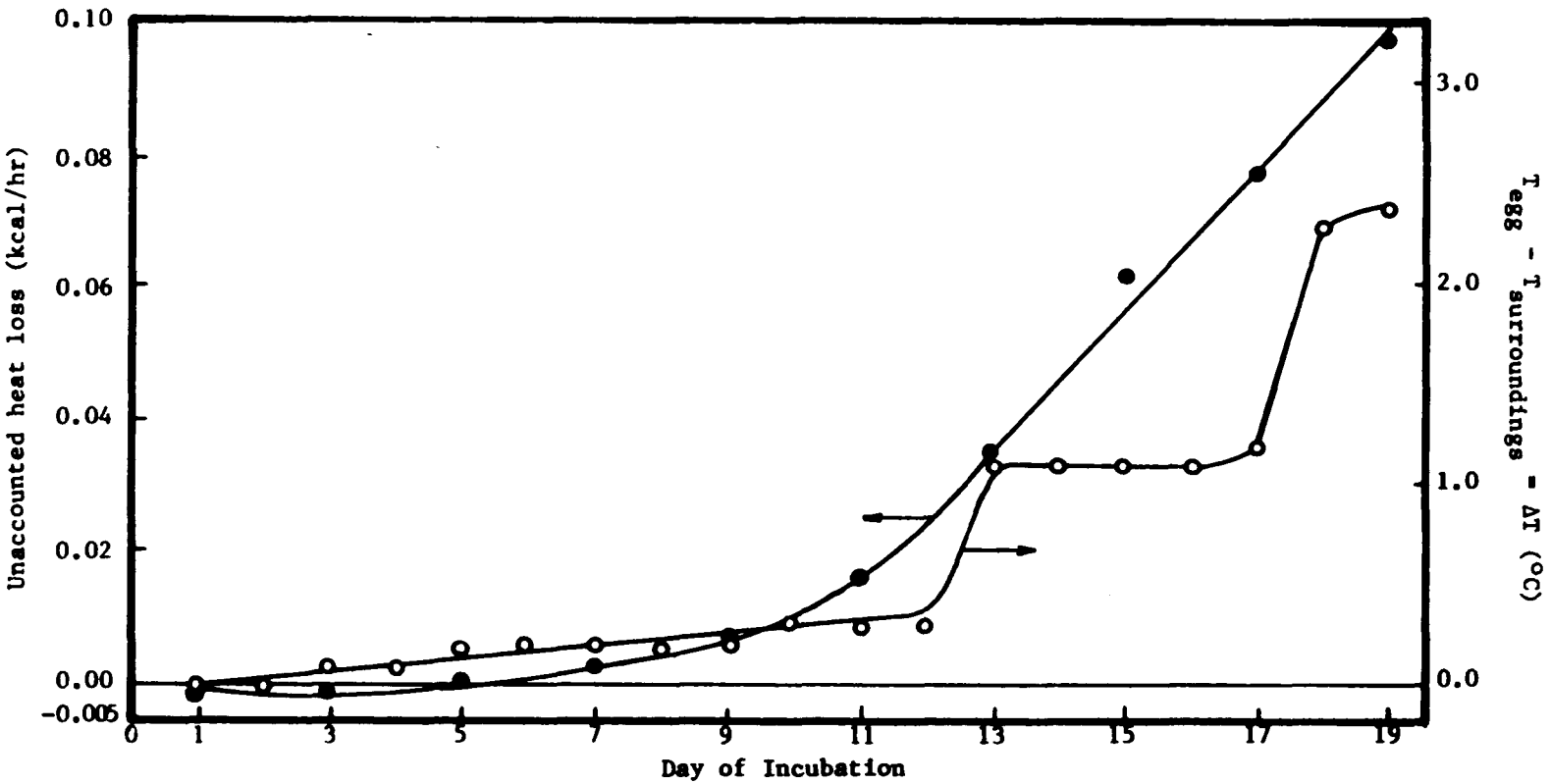

● HEAT LOSS PREDICTED FROM OXYGEN CONSUMPTION
o HEAT LOSS ESTIMATED FROM "LIVE" WATER LOSS
HEAT LOSS, -Q̇ (KCAL/HR)
10^-1
10^-2
10^-3
10^-4
0 1 3 5 7 9 11 13 15 17 19
DAY OF INCUBATION

Figure 8. The unaccounted heat loss, $-\dot{Q}$, versus day of incubation and the temperature gradient between the egg and its surroundings versus day of incubation


0.10
0.08
0.06
0.04
0.02
0.00
-0.005
Unaccounted heat loss (kcal/hr)
0
1
3
5
7
9
11
13
15
17
19
Day of Incubation
3.0
2.0
1.0
0.0
$T_{egg} - T_{surroundings}$ = ΔT (°C)

incubating chamber which is the driving force for convective heat transfer from the egg. It can now be shown that the heat losses unaccounted for by water vaporization are due to convective losses to the egg's immediate surroundings.

The expression for the overall heat transfer coefficient is, from (12),

$$h = \frac{\dot{Q}}{A\Delta T} \tag{49}$$

where $\dot{Q}$ is the total heat loss rate, A is the area for heat loss, and ΔT is the temperature gradient. Using the unaccounted heat loss difference of Day 19 as an example, the corresponding $\Delta T = 2.4°C$, and the surface area of a 60-gram egg, $A = 0.0074\ m^2$, the predicted total heat transfer coefficient is $h = 5.46\ kcal/m^2 \cdot °C \cdot hr$.

Whether this is within reason for the conditions of incubation can be assessed by evaluating the Nusselt number heat transfer correlation for free convection from a sphere (12),

$$Nu = \frac{hD}{k} = 2 + 0.60(Gr)^{1/4}(Pr)^{1/3} \tag{50}$$

where Gr is the Grashof number, Pr is the Prandtl number, and k is the thermal conductivity of the sphere material.

Using the physical properties of air from Kreith (64) and an equivalent spherical diameter for the egg of D = 5cm, the overall heat transfer coefficient predicted by this correlation for the conditions of incubation is $h = 4.8\ kcal/hr \cdot m^2 \cdot °C$. This agrees well with the overall

heat transfer coefficient obtained from experimental data and Equation 49. The experimental value may be larger due to the presence of some forced convection as well. Therefore, since the discrepancy between theoretical and experimental heat loss can be successfully accounted for, calculations using oxygen uptake and the energy equivalent of oxygen give good estimates of the system's total heat loss.

Romijn and Lokhorst (92) have provided good oxygen consumption data for the entire egg system. In order to analyze the energy flows of the embryo alone, however, the oxygen consumption for the embryo available from Romanoff (89) will be used. Employing the available electron balance techniques described in the previous section, the oxygen consumption becomes a measure of heat evolution. Assuming that no extracellular products are formed by the embryo, only biomass production and heat evolution consume the available substrate. Therefore, $\varepsilon + \eta = 1$ and, since η is known to be 0.63, $\varepsilon = 0.37$. Knowing ε, η, oxygen consumption data, and the energy equivalent of oxygen, all remaining terms of the first law balance are calculable. An example of such a calculation for the embryo follows.

The measured values are $\eta = 0.63$, $\varepsilon = 0.37$, and $\dot{V}_{O_2} = 2.98 \times 10^{-2}$ liters of oxygen/24 hours. The heat loss, $-\dot{Q}$, is the energy equivalent of the consumed oxygen, so that

$$\dot{Q}_{embryo} = \frac{2.98 \times 10^{-2} \text{ liters } O_2}{24 \text{ hrs}} \times \frac{4.821 \text{ kcal}}{\text{liter } O_2}$$

$$= -5.99 \times 10^{-3} \text{ kcal/hr}$$

Since this is 37% of the total metabolic energy transformed, the metabolic rate is

$$\Delta\dot{M} = \frac{-5.99 \times 10^{-3} \text{ kcal/hr}}{0.37}$$

$$= -1.62 \times 10^{-2} \text{ kcal/hr}$$

The energy storage is 63% of the metabolism since $\eta = 0.63$. Then

$$\hat{H}\Delta m = \eta \times \Delta\dot{M}$$

$$= 0.63 \times 1.62 \times 10^{-2} \frac{\text{kcal}}{\text{hr}}$$

$$= 1.02 \times 10^{-2} \frac{\text{kcal}}{\text{hr}}$$

The original data and the calculated first law terms are shown in Table 8. The data are taken for 19 days rather than 21, since, after the nineteenth day, the embryo begins lung breathing from the air cell and thus alters its enthalpy flows. The egg also experiences a temperature rise, but, relative to the other contributions to system energy, that due to stored thermal energy is negligible.

b. Second law analysis The mass specific quantities required in the second law analysis are listed in Table 9.

The entropy flows, $\sum_j \sum_i \hat{s}_{ij}\dot{\omega}_{ij}\delta_j$, account for less than 5% of the total entropy change and will be neglected. Upon applying the same reasoning as in the previous section in which $\Delta S_{Rk} d\xi_k/dt$ is negligible and by temporarily disregarding the positive contribution of the internal

Table 8. Pertinent data for an incubating chicken egg (oxygen uptake and mass data from 89 and 92)

Day	m_{egg} (g)	m_{embryo} (g)	$\dot{V}_{O_2 egg}$ (ml/24 hrs)	$\dot{V}_{O_2 embryo}$ (ml/24 hrs)	$\dot{Q}_{embryo}$ ($\frac{kcal}{hr}$)	$\Delta\dot{M}_{embryo}$ ($\frac{kcal}{hr}$)	$\hat{H}\Delta\dot{m}_{embryo}$ ($\frac{kcal}{hr}$)
1	63.3	0.0002	1.92	1.63	3.27×10^{-4}	8.85×10^{-4}	5.58×10^{-4}
2	62.6	0.003	3.12	2.35	4.72×10^{-4}	1.28×10^{-3}	8.08×10^{-4}
3	62.01	0.021	5.52	3.89	7.81×10^{-4}	2.11×10^{-3}	1.34×10^{-3}
4	61.4	0.060	8.88	6.51	1.31×10^{-3}	3.53×10^{-3}	2.23×10^{-3}
5	60.73	0.160	13.44	8.84	1.78×10^{-3}	4.75×10^{-3}	2.97×10^{-3}
6	60.10	0.34	22.32	14.56	2.93×10^{-3}	7.91×10^{-3}	4.97×10^{-3}
7	59.46	0.64	34.80	23.92	4.81×10^{-3}	1.30×10^{-2}	8.19×10^{-3}
8	58.82	1.07	44.64	29.82	5.99×10^{-3}	1.62×10^{-2}	1.02×10^{-2}
9	58.18	1.56	62.40	41.87	8.41×10^{-3}	2.27×10^{-2}	1.43×10^{-2}
10	57.55	2.39	88.80	61.16	1.23×10^{-2}	3.32×10^{-2}	2.09×10^{-2}
11	56.82	3.49	123.36	91.73	1.84×10^{-2}	5.0×10^{-2}	3.16×10^{-2}
12	56.12	5.04	174.48	136.55	2.74×10^{-2}	7.41×10^{-2}	4.67×10^{-2}
13	55.4	7.05	221.76	181.64	3.65×10^{-2}	9.86×10^{-2}	6.21×10^{-2}
14	54.66	9.86	291.37	248.63	4.99×10^{-2}	1.35×10^{-1}	8.51×10^{-2}
15	53.91	12.50	360.72	319.08	6.41×10^{-2}	1.73×10^{-1}	1.01×10^{-1}
16	53.19	15.06	397.68	358.21	7.20×10^{-2}	1.95×10^{-1}	1.23×10^{-1}
17	52.41	18.31	441.12	403.41	8.18×10^{-2}	2.20×10^{-1}	1.39×10^{-1}
18	51.66	22.09	446.80	417.74	8.39×10^{-2}	2.27×10^{-1}	1.43×10^{-1}
19	50.94	25.79	520.50	497.48	0.10	0.27	1.7×10^{-1}

Table 9. Specific energy flows and the estimated entropy production rates of the chicken embryo

Day	$\hat{\dot{Q}}$ ($\frac{kcal}{g\ hr}$)	$\Delta\hat{\dot{M}}$ ($\frac{kcal}{g\ hr}$)	m_{embryo} (g)	$T\hat{dS}/dt \simeq \hat{\dot{Q}} - \hat{\dot{M}}$	TdS/dt
1	-1.635	-4.425	0.0002	2.79	5.6×10^{-4}
2	-0.157	-0.427	0.003	2.70×10^{-1}	8.1×10^{-4}
3	-0.037	-0.101	0.021	6.40×10^{-2}	1.3×10^{-3}
4	-0.022	-0.059	0.060	3.70×10^{-2}	2.2×10^{-3}
5	-0.011	-0.030	0.160	1.90×10^{-2}	3.0×10^{-3}
6	-0.009	-0.023	0.34	1.40×10^{-2}	4.8×10^{-3}
7	-0.008	-0.020	0.64	1.20×10^{-2}	7.7×10^{-3}
8	-0.0056	-0.015	1.07	9.4×10^{-3}	1.0×10^{-2}
9	-0.0054	-0.0146	1.56	9.2×10^{-3}	1.4×10^{-2}
10	-0.0052	-0.0139	2.39	8.7×10^{-3}	2.1×10^{-2}
11	-0.0053	-0.0143	3.49	9.0×10^{-3}	3.1×10^{-2}
12	-0.0054	-0.0147	5.04	9.3×10^{-3}	4.7×10^{-2}
13	-0.0052	-0.014	7.05	8.8×10^{-3}	6.2×10^{-2}
14	-0.0051	-0.0137	9.86	8.6×10^{-3}	8.5×10^{-2}
15	-0.0051	-0.0138	12.50	8.7×10^{-3}	1.1×10^{-1}
16	-0.0048	-0.013	15.06	8.2×10^{-3}	1.2×10^{-1}
17	-0.0044	-0.012	18.31	7.6×10^{-3}	1.4×10^{-1}
18	-0.0038	-0.010	22.09	6.2×10^{-3}	1.4×10^{-1}
19	-0.0039	-0.010	25.79	6.1×10^{-3}	1.6×10^{-1}

forces and fluxes, the specific entropy production is presented in Figure 9. The total entropy production rate and the integrated entropy change for the chicken embryo is presented in Table 10. The cumulative change in total minimal system entropy is depicted in Figure 10 and has a value of S_o + 0.6 kcal/°C.

The general trend of the estimated minimum entropy production rate for the chicken embryo system is a decrease from a relatively high initial value. As before, the actual value of the entropy production rate is unknown since the internal forces and fluxes represented in Equation 29 by the term $\frac{1}{T}\sum_P J_P X_P$ cannot be measured. The highly irreversible nature of the internal processes of growth and development suggest that these unmeasured contributions must be positive. The changes in a system that are caused by these processes are largest at the beginning of the growth period and, therefore, their positive contribution to internal entropy production is likely to be largest then also. By definition from (80), at steady state, the total system entropy production rate is nearly zero and internal entropy production is approximately balanced by entropy exchange with the surroundings, so that from Equation 26

$$\frac{-d_e S}{dt} = \frac{d_i S}{dt}$$

For a normally functioning organism at steady state with wholly indigenous energy generation, $d_e S/dt$ is usually negative, and so $d_i S/dt$ must be positive. Since $d_i S/dt$ is positive at steady state, its value in the initial unsteady state phases of growth and development should be an even larger positive number. Furthermore, the internal entropy

Figure 9. The approximate specific entropy production rate versus day of incubation for the chicken embryo (data from (89))

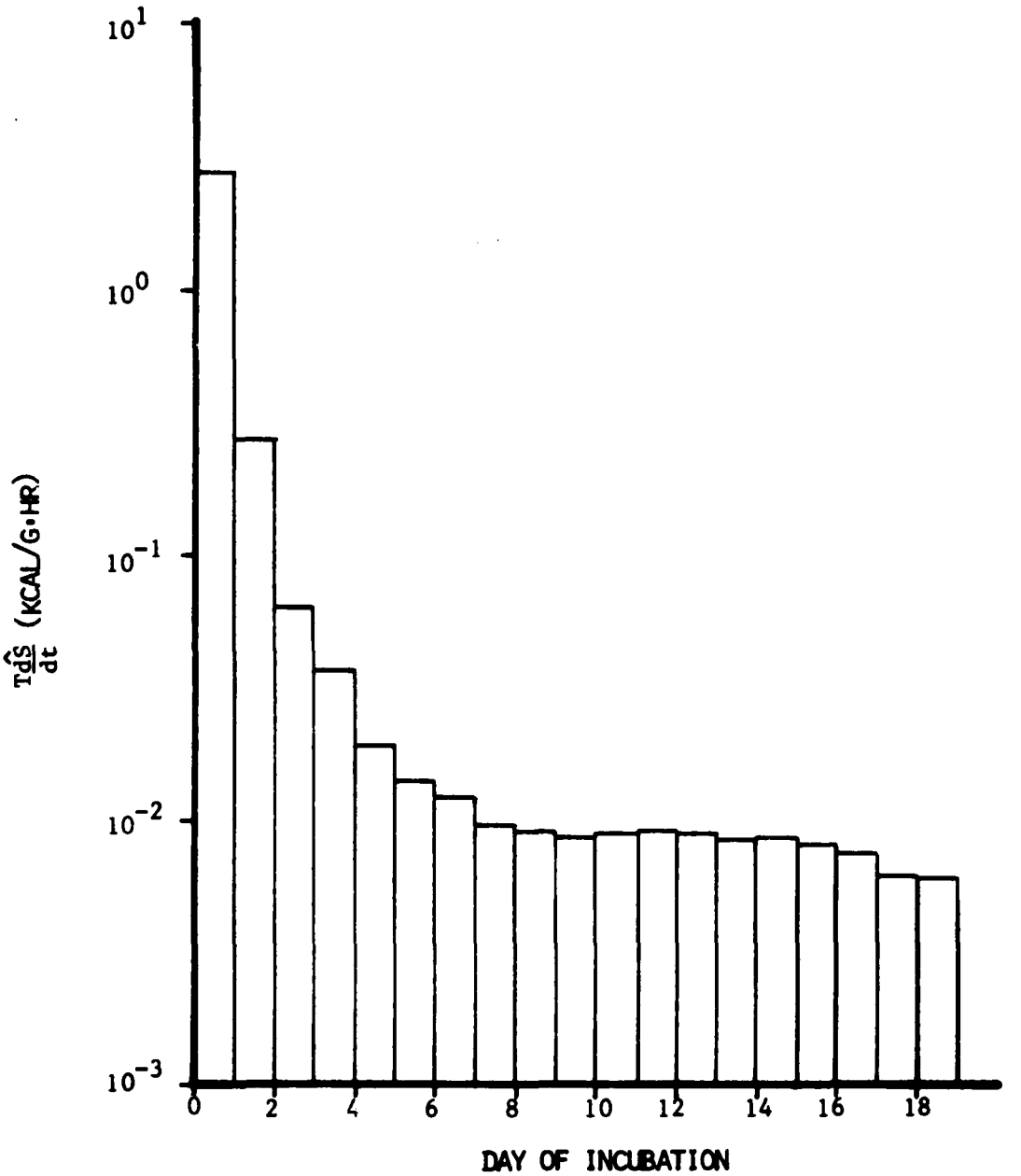
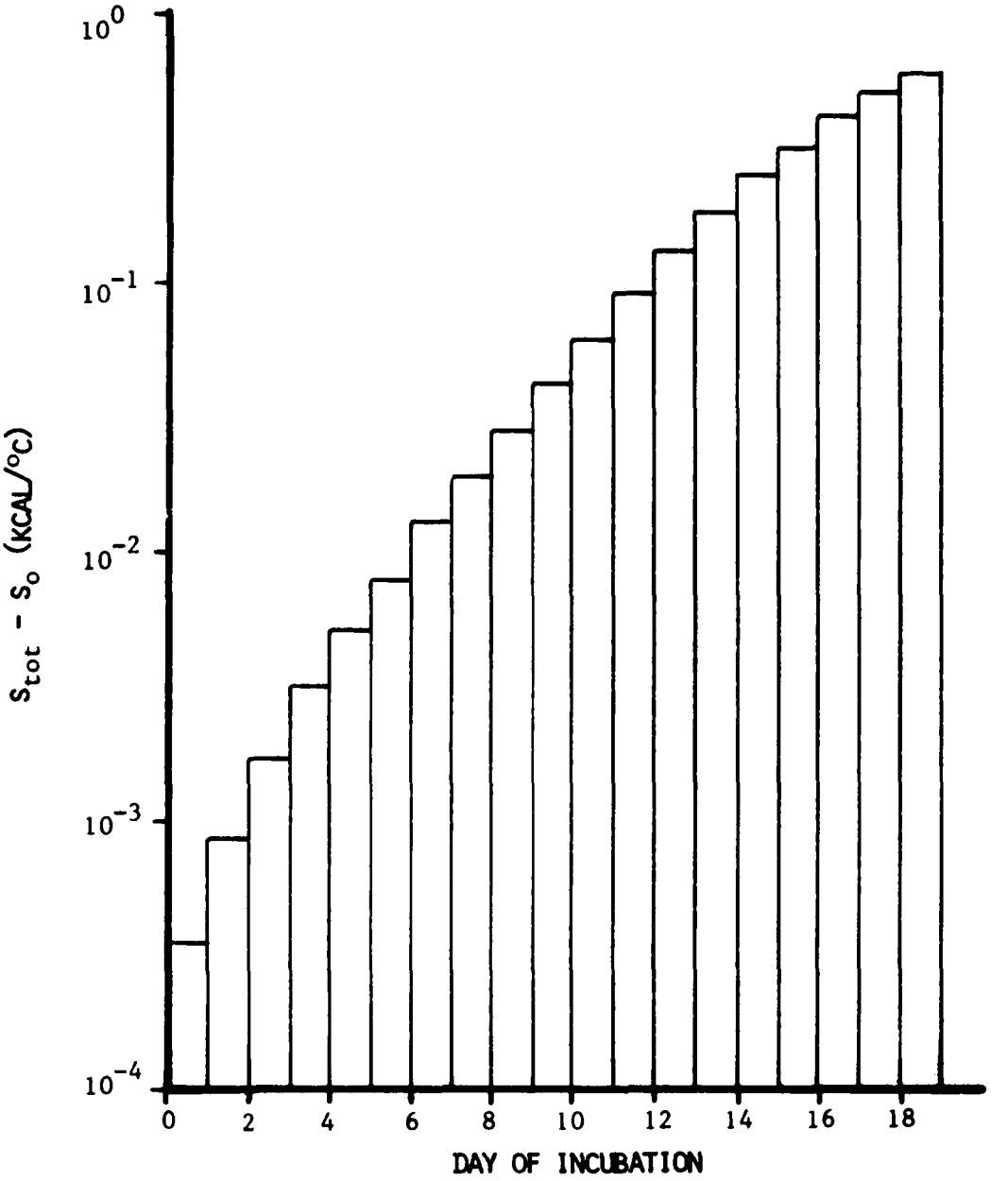

10^1
10^0
10^{-1}
10^{-2}
10^{-3}
$T\frac{d\hat{S}}{dt}$ (KCAL/G·HR)
0
2
4
6
8
10
12
14
16
18
DAY OF INCUBATION

Table 10. The total entropy production rate and the integrated total entropy change for the chicken embryo (temperature data from (91))

Day	T_{embryo} (°C)	dS/dt (kcal/hr °C)	$\Delta S = \int_{t}^{t+1} (\frac{dS}{dt}) dt$
1	37.7	1.5×10^{-5}	3.6×10^{-4}
2	37.7	2.1×10^{-5}	5.2×10^{-4}
3	37.8	3.4×10^{-5}	8.3×10^{-4}
4	37.8	5.8×10^{-5}	1.4×10^{-3}
5	37.9	7.9×10^{-5}	1.9×10^{-3}
6	37.9	1.3×10^{-4}	3.0×10^{-3}
7	37.9	2.0×10^{-4}	4.9×10^{-3}
8	37.9	2.6×10^{-4}	6.3×10^{-3}
9	37.9	3.7×10^{-4}	8.9×10^{-3}
10	38.0	5.5×10^{-4}	1.3×10^{-2}
11	38.0	8.2×10^{-4}	2.0×10^{-2}
12	38.0	1.2×10^{-3}	3.0×10^{-2}
13	38.8	1.6×10^{-3}	3.8×10^{-2}
14	38.8	2.2×10^{-3}	5.3×10^{-2}
15	38.8	2.8×10^{-3}	6.8×10^{-2}
16	38.8	3.1×10^{-3}	7.4×10^{-2}
17	38.9	3.6×10^{-3}	8.6×10^{-2}
18	40.0	3.5×10^{-3}	8.4×10^{-2}
19	40.1	4.0×10^{-3}	9.6×10^{-2}

Figure 10. The change in the total cumulative system entropy, $S_{TOT} - S_o$, in kcal/°C versus day of incubation for the chicken embryo


10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
$S_{tot} - S_o$ (KCAL/°C)
0
2
4
6
8
10
12
14
16
18
DAY OF INCUBATION

production rate must be zero at death. These facts suggest that Prigogine's hypothesis, which states that $\hat{d_i S}/dt > 0$ and that $\hat{d_i^2 S}/dt^2 \leq 0$, is correct, although absolute proof cannot be given.

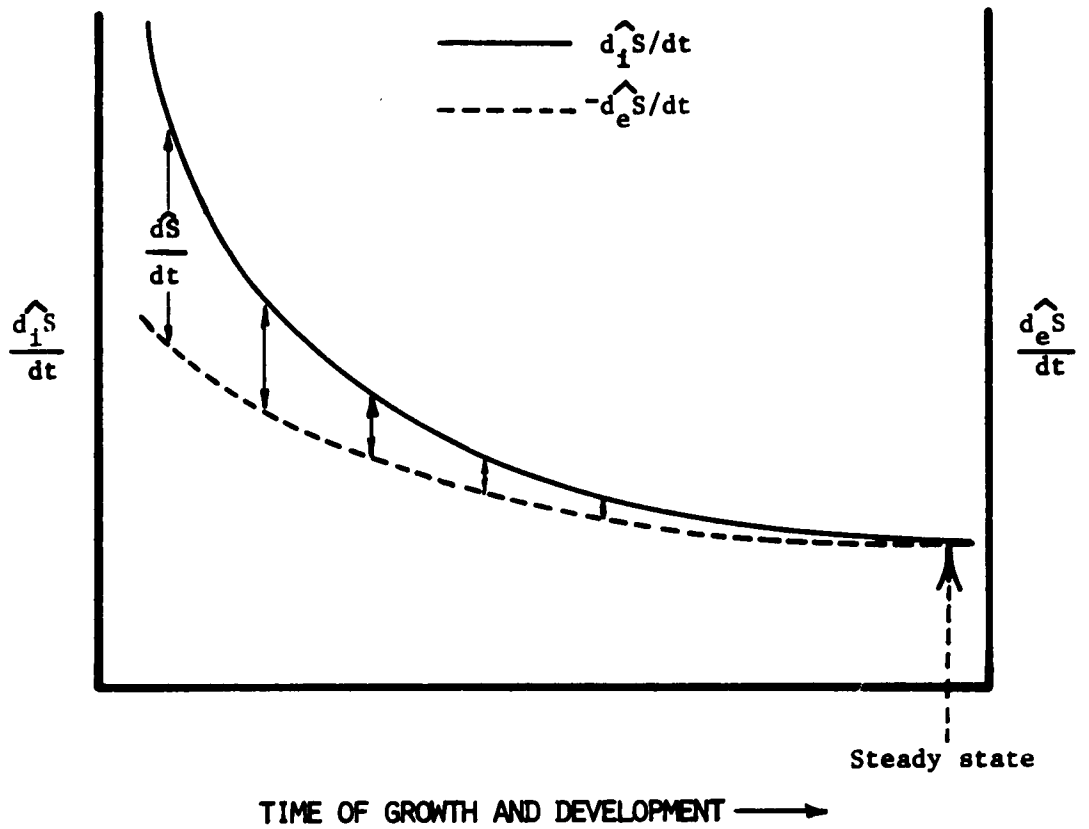
The results of this research demonstrate that a similar trend is found to occur for the specific rate of the minimal system entropy production, $\hat{dS}/dt$, as well. The term $\hat{dS}/dt$ represents the difference between entropy lost by the system by exchange with the surroundings, $-\hat{d_e S}/dt$, and the internal entropy produced by the system, $\hat{d_i S}/dt$. As the system begins developing, the difference is a large, positive number. As growth and development progress, $-\hat{d_e S}/dt$ and $\hat{d_i S}/dt$ approach equivalence and, consequently, $\hat{dS}/dt$ becomes smaller as depicted in Figure 11. If a steady state is achieved by the system, $\hat{d_i S}/dt = -\hat{d_e S}/dt$. Therefore, it may be concluded that, for the period of growth and development in living systems, the specific rate of minimal system entropy production is positive and decreasing, or

$$\frac{\hat{dS}}{dt} > 0 \tag{49}$$

$$\frac{\hat{d^2 S}}{dt^2} \leq 0 \tag{50}$$

The total system entropy of the chicken embryo is shown to increase over the incubation time. The expected leveling trend in the value of the total system entropy change due to the effect of the decreasing rate of entropy production is apparent in Figure 10. This was not obvious for the Brevibacterium system entropy since the time of data measurement was much shorter than for the chicken embryo data.

Figure 11. The decreasing rate of the specific rate of system entropy production; the comparison between the specific rate of the internal entropy production and the specific rate of entropy exchange as the system grows, develops, and approaches a steady state


$d_i\hat{S}/dt$
$-d_e\hat{S}/dt$
$\frac{d\hat{S}}{dt}$
$\frac{d_i\hat{S}}{dt}$
$\frac{d_e\hat{S}}{dt}$
Steady state
TIME OF GROWTH AND DEVELOPMENT ⟶

The results of this section have demonstrated the utility of techniques which couple first and second law analyses in the study of energy and entropy flows in living systems. The techniques have been successful in estimating minimal values of both the entropy production rates and the total system entropy change. Living systems do not violate the second law of thermodynamics during the period of growth and development.

In order that these techniques be developed, several assumptions have been made. The most fundamental is that the concept of local equilibrium, which is basic to the development of nonequilibrium thermodynamics, applies. This cannot be tested directly, but it is reasonable to hypothesize that even macroscopically unsteady state nonequilibrium systems can be divided into small enough subsystems so that, at some level, equilibrium operation is achieved.

Another assumption deals with the linear relationships between force-flux pairs of the Onsager expression for dissipation. Nicolis and Prigogine (78) have used the reaction affinity-reaction velocity force-flux pair as an example where such linearity may not exist. The nature of the biochemical pathways in living systems are such that the individual reactions which compose the pathways may be operating within the linear range and at equilibrium. When the system reactions are viewed as a sum of the constituent linear reactions, the assumption of overall linearity is acceptable for the purposes of the analyses of this study.

The contributions to total values of the entropy change due to the rearrangement of molecules and the entropy change due to material flows

have not been included. Calculations performed on presently available data and the discussion on entropy and organization to follow, suggest that these values are very small. It has been a goal of this work to be able to rigorously calculate the values of the minimum entropy production rates and the total system entropy. The assumptions which have been made do not apparently detract from the achievement of this goal.

It is interesting to extend the analysis techniques that have been developed to periods before and beyond those which have been investigated here. The study of the entropy production of living systems during stages previous to growth and development requires study of the energy flows and energy transformations as the organism is conceived. At this time, the system is ill-defined and the energy changes are difficult to assess. It may be hypothesized that the highly irreversible nature of the conception of an organism results in a sharp increase in the rate of entropy production to reach the high value from which the rate then decreases as the system begins to develop and grow. Some evidence of this initial rise is demonstrated in the entropy production rate plot of Brevibacterium (Figure 5).

Beyond the period of growth and development a system enters what has been called a steady state period of adulthood. However, as discussed by Zotin (123), ageing processes begin soon after physical maturity is achieved. On an hourly or daily basis, changes in the system parameters are not perceptible, but when viewed over larger portions of the organism's lifespan, macroscopic changes become obvious. This suggests that no true steady state is reached and that the total entropy production

rate of a living system never quite reaches a steady state level of zero, which has been presumed by Katchalsky and Curran (61) and Zotin (123). It may be hypothesized that, in accordance with Prigogine's hypothesis, the entropy production rate of a living system, except for local fluctuations, decreases continually over the system's lifetime until it reaches a minimum at maximum lifespan. Consequently, the total entropy of the system continues to increase toward a maximum value as ageing occurs. These hypothesized trends are depicted in Figures 12a and 12b.

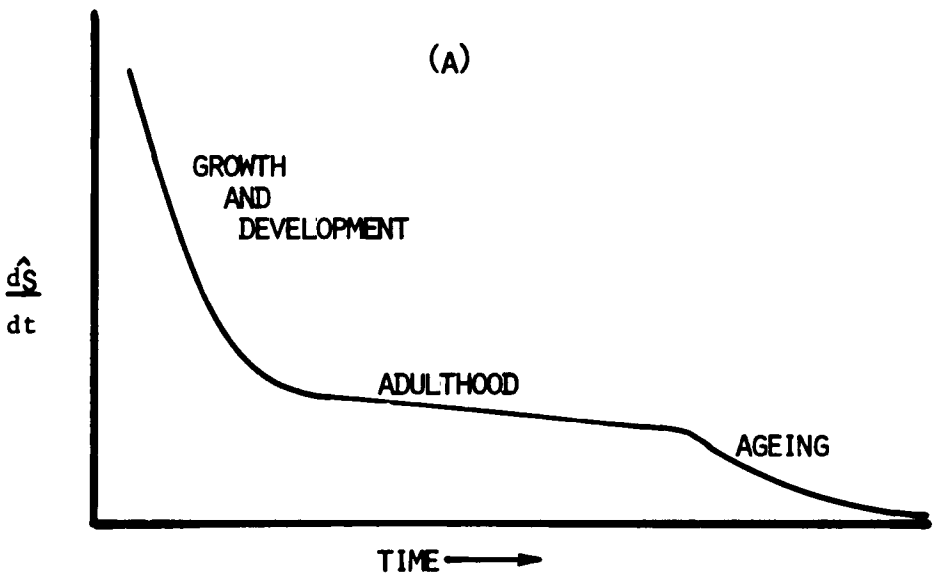
Since living organisms are not in violation of the laws of thermodynamics, a comparison between living and nonliving systems suggests an aspect by which the entropy production in living systems differs from the entropy production in nonliving systems. Unlike nonliving systems, living systems seem capable of regulating their entropy production rate. This regulation occurs at two main levels, as suggested by Zotin (123). Living organisms exercise homeostatic regulation which involves autonomic neural and hormonal controls that maintain system functioning within definite limits around the system's basal operating level. An example of this is the complicated mechanism of homeostatic regulation during exercise. As the muscles perform work, they require metabolic energy to fuel this process. As discussed on page 53, this and similar diversions of metabolic energy upset the steady state balance between internal metabolic energy production and heat loss, so that the performance of work results in a fluctuation in the total system entropy production rate.

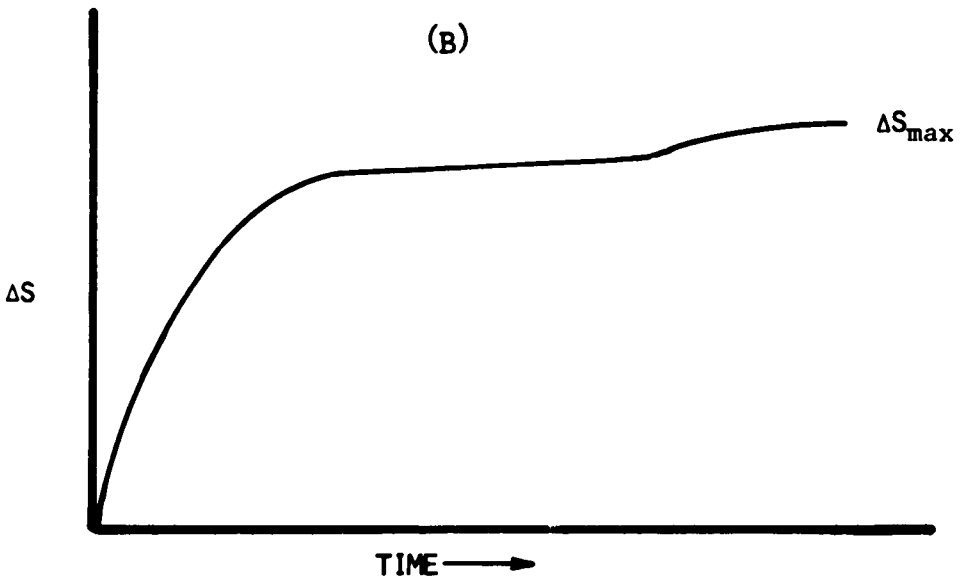
The second level of control is the regulation of entropy production rate over the lifetime of the organism. Nonliving systems do not

Figure 12. Hypothetical entropy production patterns over the lifespan of an organism

a) The specific minimal entropy production rate, $\hat{dS}/dt$, versus time

b) The minimal total system entropy, ΔS, versus time


(A)
GROWTH
AND
DEVELOPMENT
$\frac{d\hat{S}}{dt}$
ADULTHOOD
AGEING
TIME


(B)
ΔS_{max}
ΔS
TIME

demonstrate the ability to survive unassisted against adverse gradients imposed by their surroundings and usually decay to higher states of disorder as a result of energy transformations within the system. Living systems are capable of prolonging their decay by self-organization and self-replication which maintain their system integrity and pseudo-steady-state functioning over much longer periods of time. Living systems are open to both material and energy flows and these flows are either autonomically or consciously regulated. This seems to be instrumental in the system's control over its entropy production rates.

Entropy production rates are directly related to chemical reaction rates and process rates that constitute the functioning of a living organism. Recent literature has suggested that these rates may regulate the lifespan of an organism. For example, Günther (50) has suggested that each species is given an approximate number of breaths and an approximate number of heartbeats per lifetime. These conclusions have been the result of the dimensional analysis of a wide range of rate data. The rate at which the system uses its "allotment" determines its lifespan. Furthermore, Kuehn (65) has suggested that, if a human heart is destined to beat a given average number of times, the increase in heart rate which an athlete experiences during exercise temporarily consumes some portion of the given total number of heartbeats, but has longterm effects that cause bradycardia and therefore lengthen the athlete's life. Rahn and Ar (86) have found a similar generality in the water loss of incubating eggs. Almost all avian eggs lose about sixteen per cent of their initial mass in water. The length of the incubation period for a particular avian

species is dependent upon the daily rate of water loss, so that the total loss of sixteen per cent is achieved regardless of the incubation environment.

An analogy may be drawn between process rates of living systems and entropy production rates. Since death represents a state of maximum entropy, it is suggested that the entropy production rate in living systems is a factor which determines longevity. In the same manner as a system uses heartbeats and breaths, each system may be specified a certain pattern of entropy production, such as achieving a maximum entropy level at equilibrium. Although such a hypothesis requires extrapolation of present knowledge, it suggests opportunities for further investigation into the importance and possible omnipotence of entropy in the processes of life.

4. Entropy and organization

Forrest and Walker (47), Morowitz (76), Schrödinger (97), and others have attempted to describe the contribution that the organization of matter in a living system has on the system's total entropy, referred to as the entropy of rearrangement, ΔS_R. It is the ability of living things to self-organize molecules into morphological units that separates them from nonliving systems and has been believed to be the major contribution to their internal entropy production.

The concepts of sequence and order have led to the use of information theory in biology. Information theory was first applied in the communications industry to provide a measure of the information contained in ordered and random sequences of symbols (102). Its application to the

analysis of physical systems deals with the random distribution of microstates within the system. The prediction of the macroscopic properties of the system is done by averaging all possible microstates of the system. The distribution of microstates is related to distributions which are derived from statistical mechanics. A brief summary of these arguments follows.

A system is viewed as an ensemble containing N particles. The system is completely described by specifying the position and properties of each of these particles. The time trajectory of the ensemble is found by specifying these properties with time. However, any macroscopic measurement made on the ensemble is a time average of the changing properties of the N particles. For large ensembles and long time trajectories, these two representations approach each other. This postulate is known as the ergodic hypothesis. Simply stated, it suggests that macroscopic measurements can be predicted by the microstate average over the ensemble. At equilibrium, the ensemble average of a measurable property will be the same as the time average of that property for a given system.

It has been shown by Shannon and Weaver (102) that the information obtained from an ensemble by knowing the microstate or quantum state of the system is given by

$$I = - \Sigma f_j \, \ell n_2 f_j \tag{51}$$

where the f_j are normalized probability distributions of the states of particle j. This is similar in form to the expression for entropy derived in statistical mechanics

$$S = -k\Sigma f_j \ell n f_j \tag{52}$$

where for very large numbers of particles

$$f_j = N_j/N \tag{53}$$

and N_j is the number of particles in the jth quantum state, N is the total number of particles, and k is Boltzmann's constant. In a rigorous derivation, f_j is the normalized probability distribution

$$f_j = \frac{e^{-E_j/kT}}{\sum_j e^{-E_j/kT}}$$

where E_j is the energy of the jth particle. This expression is simplified as shown above to illustrate the comparison between information and entropy.

Then, since the distributions f_j are the same for large N in both Equation 51 and Equation 52, entropy is related to information content by Equation 54

$$S = 0.693\ kI \tag{54}$$

It is further observed that both Equations 51 and 52 are similar in form to the entropy of ideal mixing given by Modell and Reid (75),

$$\Delta S^{ID} = -R \sum_{j=1}^{n} x_j \ell n\ x_j \tag{55}$$

where R = the gas constant = kN_{Av}

N_{Av} = Avogadro's number, 6.023×10^{23}

x_j = the mole fraction of the jth component

For an N-particle or N-mole system,

$$x_j = \frac{N_j}{N}$$

and the entropy of mixing becomes

$$\Delta S^{ID} = -R \sum_{j=1}^{n} \frac{N_j}{N} \ln \frac{N_j}{N} \tag{56}$$

As the number of particles present in the system increases, i.e. $f_j \rightarrow N_j/N = x_j$, the expression for the entropy of mixing becomes the same as the expression for the entropy evaluated from information content. Equation 55 is on a molar basis and Equation 54 is on a particle basis.

As a means of testing the applicability of this approach in biological systems at the level of cellular organization, the following calculation is performed.

A "typical" cell can be shown to weigh approximately 5.6×10^{-10} grams. This average is obtained by dividing the mass of the cellular matter of a human by the estimated total number of cells present, 100 trillion (51). Assuming that the typical cell mass does not change appreciably from human to chicken, the number of cell types in each major body compartment of the chick is calculated (Table 11).

Table 11. The distribution of cell number in the major body compartments of the chick (mass data from (89))

Body compartment	Compartment mass (mg)	Approximate number of cells per compartment
Fat	3000	5×10^9
Bone	1100	2×10^9
Intestine	2900	5×10^9
Gizzard	1650	3×10^9
Brain	1000	2×10^9
Liver	950	2×10^9
Eyes	450	8×10^8
Heart	250	5×10^8
Lungs	200	4×10^8
Kidneys	200	4×10^8
Blood	2400	4×10^8
Skin	1500	3×10^9
Noncellular	8400	

The total number of cells in the chick is approximately 3×10^{10} cells. The entropy of rearrangement at the cellular level is approximated by finding the entropy of mixing of the given amount of each cell type into one mixture containing all cells. In this model of cellular arrangement, the entropy of rearrangement is evaluated as the reverse of mixing, i.e. the original state becomes the mixture of cells which are then

organized according to cell type, the reversal of the mixing process. When this calculation is performed employing Equations 55 and 56, the resultant entropy of ideal mixing is 18 J/mole of cells·K. However, the chick contains only about 5×10^{-14} moles of cells. Therefore, the entropy change of mixing for the system is only 9×10^{-13} J/K. The entropy change of rearrangement, ΔS_R is the opposite of the entropy of mixing so that

$$\Delta S_R = -\Delta S^{ID} = -9 \times 10^{-13} \text{ J/K}$$

$$= -2 \times 10^{-16} \text{ kcal/K}$$

When evaluated according to this model, the contribution to the entropy change of the chick embryo during the incubation period is very small compared to the value obtained from the effects of energy transformations.

Since the development of this method is rooted in the ensemble approach and the theories of quantum states, the evaluation of entropy in this way requires the knowledge of the states of a very large number of particles. Clearly, even knowledge of the location of 3×10^{10} cells is too small of a number to successfully utilize this method.

Since the biochemical reactions of living organisms, which have been discussed earlier, deal with interactions of molecules, it is appropriate to consider the rearrangement effect at a second hierarchal level, the molecular level.

The composition of a representative cell is as shown in Table 12 from data for Escherichia coli (68). Although these bacteria are

Table 12. The average molecular composition of a representative cell (data from (89))

Molecular species	Weight per cent	Average molecular weight	Weight per cell	Moles per cell
Water	70	18	4×10^{-10}	2×10^{-11}
Protein	15	10^6	8×10^{-11}	8×10^{-17}
DNA (deoxyribonucleic acid)	1	10^9	6×10^{-12}	6×10^{-21}
RNA (ribonucleic acid)	6	10^6	3×10^{-11}	3×10^{-17}
Carbohydrates	3	200	2×10^{-11}	8×10^{-14}
Lipids	2	225	1×10^{-4}	5×10^{-14}
"Building block" molecules	3	150	2×10^{-11}	1×10^{-13}

relatively simple cells, their molecular composition will be assumed to be a typical average for other cell types. The total moles of molecules in a cell is then calculated to be about 2.2×10^{-11} moles/cell. Using Equation 55 and the same model of rearrangement utilized previously, the entropy of rearrangement is now substantially larger, $\tilde{\Delta S}_R = -0.5$ J/mole of molecules·K. If the effect of rearrangement is assumed to be an additive property over all cells of the organism, the total system entropy change due to rearrangement is $\Delta S_R = -8 \times 10^{-5}$ kcal/K for the organism containing 3×10^{10} cells. This change occurs over the entire incubation period. When this value is compared to the minimal total system entropy change for the chick embryo, $S_o + 0.6$ kcal/°C, ΔS_R is, at

the most, less than one per cent of the total minimal value. For the purposes of this example, ΔS_R may apparently be assumed negligible.

A comparison between the values of ΔS_R obtained for cellular organization, in which 3×10^{10} cells or "particles" were accounted for, and the ΔS_R evaluated for molecular organization, in which the effect of 4×10^{23} molecules was considered, results in an increase of eleven orders of magnitude in the estimate of entropy change for an increase of thirteen orders of magnitude in particle number. This suggests that, in order that a significant value of ΔS_R relative to the minimal total system entropy be calculated, the knowledge of particle distributions at some submolecular level would be required. This type of analysis would not be practical in the macroscopic study of living systems.

The model of molecular organization presented here considers the original mixture as completely random with no tendencies for segregation within the mixture. The quasichemical approximation to the total entropy of mixing (79) suggests that, if such tendencies exist, the mixture is not entirely random and the entropy of nonrandom mixing is smaller than the entropy of ideal mixing. According to the model proposed here, the entropy of rearrangement would then become smaller as well. If the attractive forces between the molecules are large enough such that they cause the molecules to act as supramolecular units, thereby reducing the effective number of particles, the entropy of rearrangement would decrease. Further, if bonding occurs between the rearranged molecules by exothermic reactions, as ultimately happens in living systems, the entropy of rearrangement for an isothermal system would decrease due to

heat loss. Consequently, it appears that the factors which have been neglected would only lower the estimate of ΔS_R.

Since the evaluation of system entropy in this research has been concerned largely with macroscopically measurable energy transformations, the entropy of rearrangement, which may only become significant at sub-molecular levels, is not significant. The goodness of the evaluation of ΔS_R by this method is uncertain. Therefore, the effects of the entropy of rearrangement will be neglected. This does not qualitatively alter the results and conclusions of this study, since the remaining terms of the internal entropy production rate must cause the sum of all terms of $d_i S/dt$ to be positive.

D. The Thermodynamics of Muscles and Muscle Systems

The analysis of the energy flows of a contracting muscle system is an interesting study of a combination of biochemical, electrical, thermal, and mechanical effects.

Determining the work done by a system is potentially the most perplexing aspect of the first law analysis. Physical work has been a largely misunderstood and misrepresented quantity. The intent here is to define and classify work so that its determination for the purposes of an energy balance is consistent for any and all systems considered. A general discussion of the work definition will precede its application to the specific system.

1. Work and muscles

Work occurs at the boundaries of the system and serves as one means of energy exchange between the system and its surroundings. Work is performed when a force external to the system, X_i, is exerted on or is acted upon by the system causing a change in an external system parameter a_i such that the quantity of work performed is $\delta W = \sum_i X_i da_i$ (61). X_i and da_i must occur in proper conjugated pairs. In particular, examples of these pairs are

$$\delta W = PdV + Fdx - \mathcal{E}de - fd\ell$$

The term PdV represents the classical expansion work, the change in volume dV against a pressure P. $\mathcal{E}de$ describes the electrical work performed when a quantity of charge de is given off by a system across an electrical potential $\mathcal{E}$. The time rate of change of this term, electrical power, is $\mathcal{E}de/dt = \mathcal{E} \cdot I$, where I is electrical current.

The two remaining terms are directly suited for applications to muscle systems. The term $fd\ell$ is the general term for the work of deformation, where $d\ell$ is the deformed length experiencing a force f. For the muscle, $fd\ell$ can represent the work done by a contracting muscle when $d\ell$ is negative referenced to the resting length ℓ_o, or the work done on a stretched muscle when $d\ell$ is positive.

The remaining work term, Fdx, is unique. It can represent the change in the position of the system in a nonconservative force field such as in situations when work is performed against friction (drag). This type of work results in the dissipation of energy which often appears as thermal

energy. This term may also be used to represent the commonly defined physical work when a force acts through a distance, or

$$W = \underset{\sim}{F} \cdot \underset{\sim}{x}$$

where $\underset{\sim}{F}$ = the force vector

$\underset{\sim}{x}$ = the distance vector.

The dot product notation indicates that in order for work to be performed, some components of force and of distance must be parallel.

The rate of doing work, $\dot{W}$, is then

$$\dot{W} = \underset{\sim}{F} \cdot \frac{d\underset{\sim}{x}}{dt} = \underset{\sim}{F} \cdot \underset{\sim}{v}$$

where $\underset{\sim}{v}$ is velocity.

Forces may be and often are exerted with no external work being done. Work is performed only on deformable or moveable surroundings. For example, if running into the wind, lifting weights, and walking in loose sand are evaluated for the human body as the system, these all represent forms of physical work, whereas climbing up stairs, running on a hard surface, and jumping do not. However, if the balance is taken around the human leg segment as the system, climbing up stairs, running, and jumping are also examples of the legs doing work as they lift and lower the body torso.

In the next step of the hierarchy of subsystems from limb to muscle, the isolated muscle can be easily visualized as doing work whenever it contracts to move a load. It is important that the system boundaries are

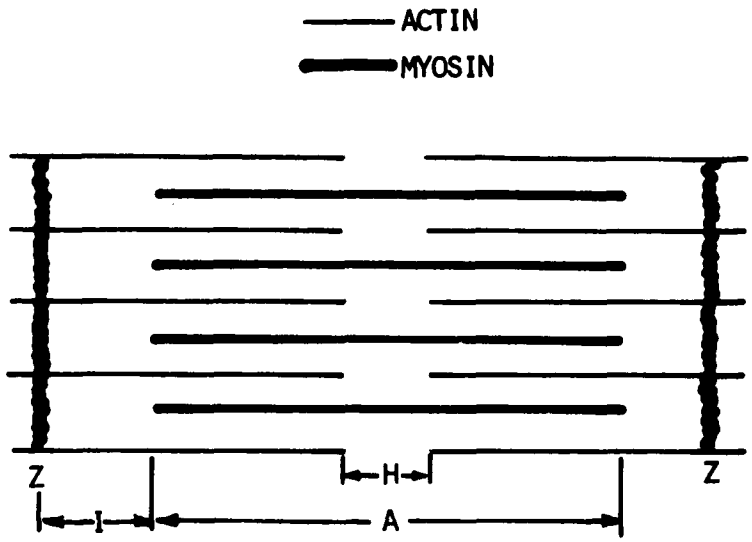
well-defined since the work, whether it is done by or on the system, must occur at these boundaries.

Since the active muscle initiates all physical work performed by the human body, it is worthwhile to consider a description of its characteristics and operation. The research done on single muscles, its relation to this study, and the evaluation of muscle energy sources will be discussed.

a. Contraction A single muscle is a bundle of thousands of muscle fibers. Each single muscle fiber is made up of myofibrils which are the basic contractile element of the entire muscle. The striated appearance of muscles is due to the partially overlapping arrays of the two main myofibril types, the myosin filament and the thinner actin filament. The striations are classified according to bands as depicted in Figure 13. The unit from Z-line to Z-line is called a sarcomere. The contraction of muscle is brought about by relative sliding between these fibrils. In activated muscle the myofibrils shorten. If the ends of the muscle are fixed, no overall shortening occurs; the contraction is isometric. When the muscle length shortens, the contraction is concentric or isotonic. If the muscle lengthens while contracting, the contraction is eccentric.

Huxley (60) and others have given strong evidence for the cross-bridge and sliding filament theory. The sliding of filaments is accomplished by individual myosin molecules which each possess a protruding "head," the site of the force-generating mechanism. These heads are made up of heavy meromyosin arranged in pairs at regular intervals

Figure 13. A graphical illustration of the overlapping arrays of myosin and actin filaments in muscle (from (6))


ACTIN
MYOSIN
Z
H
Z
I
A

along the myosin filament, each rotated 120° from the neighboring pair. The heads are pointed in one direction along one half of the myosin filament and in the other direction along the other half.

The heavy meromyosin has an affinity for a certain active site on the actin molecule. This active site is protected by troponin when the filaments are not contracting. When a nerve impulse initiates an action potential in the muscle, Ca^{++} is released into the spaces between the myofibrils. Ca^{++} binds to troponin thus uncovering the active site on the actin molecule. When the meromyosin head contacts the active site and forms the cross-bridge, adenosine triphosphetase, an enzyme, is activated and ATP is hydrolyzed to ADP causing conformational changes in the meromyosin. The result is a relative sliding of the two fibers. Since the meromyosin heads in the other half of the myosin strand are oriented in the opposite direction, the sliding in both halves causes the muscle to contract.

Meanwhile, the Ca^{++} has been actively transported away from the actin, the troponin again protects the site, and the muscle relaxes. Since myosin-actin filaments can only contract 100 Å per movement of the meromyosin head, and a muscle on the macroscopic scale can contract over 30% of its resting length, muscular contraction must be accomplished by repeated sliding movements.

The interdependence of these chemical and mechanical effects may be diagrammatically portrayed as the parallel occurrence of cyclic mechanical events and cyclic chemical events. This interpretation is presented in Table 13 and Figures 14a and 14b modified from a similar description

Table 13. Idealized representation of the cyclic events at the molecular level of muscle contraction

Cycle phase	Chemical event	Mechanical event
1 to 2	Ca^{++} in; actin-myosin cross-bridges form	Development of tension
2 to 3	ATP hydrolyzed; conformational changes in cross-bridge orientation	Muscle contraction
3 to 4	Ca^{++} out	Tension released
4 to 1	ATP replaced	Original length restored

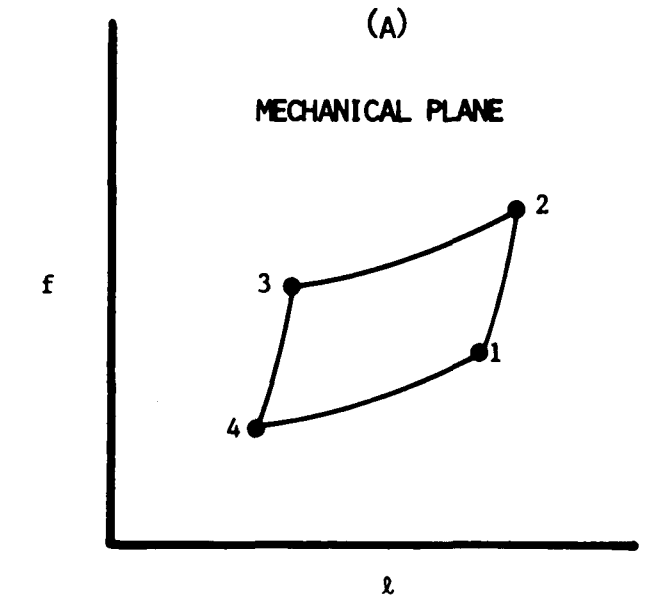
suggested by Katchalsky and Curran (61). The description is somewhat idealized in that it may not represent accurately the sequence of chemical-mechanical events during a contraction. It is offered as a method of stepwise analysis of the contraction process. It will be assumed that for the single cycle of contraction, heat production is negligible and that ATP serves as the major source of energy substrate.

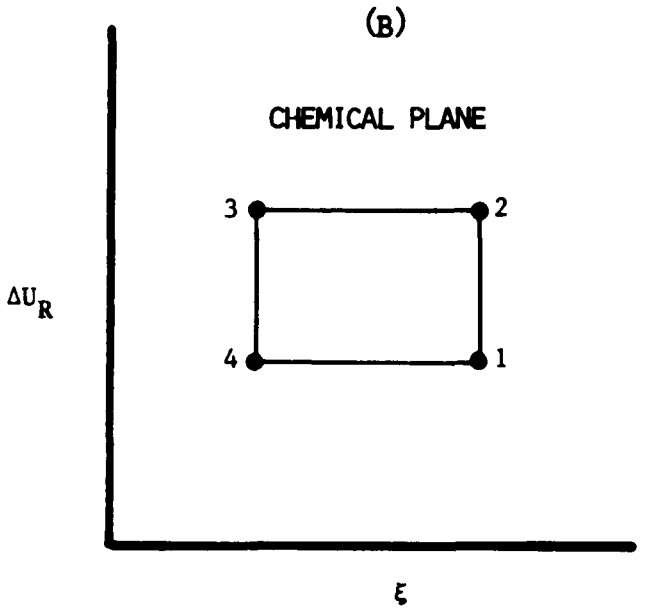
The term "reaction" or "chemical potential" will be used interchangeably with the internal energy change of reaction. This is valid because, when the chemical potential is defined to be $\mu_i = \frac{\partial \mu}{\partial n_i}$, it can be shown that $\sum_k \Delta U_{Rk} d\xi_k = \sum_i \mu_i dn_i$.

Figure 14. A diagrammatic representation of the idealized cyclic nature of muscle contraction without afterload in

(a) the mechanical plane and

(b) the chemical plane (modified from (61))


(A)
MECHANICAL PLANE
f
2
3
1
4
ℓ


(B)
CHEMICAL PLANE
ΔU_R
3
2
4
1
ξ

A microscopically viewed muscle contraction begins at the resting length, ℓ_o, resting tension, and at the state of internal energy corresponding to the resting conditions. These conditions are a suitable choice for the reference state and are designated as point 1 on both Figures 14a and 14b.

The release of Ca^{++} into the space surrounding the myofibrils, its reaction with troponin, and the initial interaction between actin and myosin are viewed as a change in the internal energy from point 1 to point 2. This event is considered to occur in parallel with the development of tension in the muscle as the actin-myosin cross bridges form.

The internal energy changes of the myofibril system for this step are described by a simplified first law balance of Equation 24 in which the internal energy of reaction has been substituted for heat of reaction. The change in internal energy from point 1 to point 2, $\Delta U_{1,2}$, is due to the flow of ions into the system which act to change ΔU_{Rk}. The internal energy change of reaction may be viewed as a change in reaction potential.

$$\int_1^2 dU = \int_1^2 \sum_k \xi_k d(\Delta U_{Rk}) = \int_1^2 \hat{H} dm_{in}$$

$$\Delta U_{1,2} = \Delta \sum_k \Delta U_{Rk} \xi_k = \hat{H} \Delta m_{in}$$

As the ATP in and around the myofibrils is hydrolyzed, conformational changes take place which cause myofibril contraction. As the fibrils shorten the tension decreases. The performance of work is driven by the hydrolysis of ATP.

$$\int_2^3 dU = \int_2^3 \Delta U_{Rk} d\xi_k = \int_2^3 f d\ell = -W_{2,3}$$

$$\Delta U_{2,3} = \sum_k \Delta U_{Rk} \Delta \xi_k = -W_{2,3}$$

As Ca^{++} is released from the system the muscle releases its tension. The reaction potential drops to its reference value so that ΔU_{Rk} of step 1 to 2 is equal and opposite to ΔU_{Rk} of step 3 to 4.

$$\int_3^4 dU = \int_3^4 \sum_k \xi_k \, d(\Delta U_{Rk}) = \hat{H} m_{out}$$

$$\Delta U = \Delta \sum_k \Delta U_{Rk} \xi_k = \hat{H} \Delta m_{out}$$

To restore the system to its initial state, the reaction extent is changed by the addition of the energy substrate ATP. The myofibrils return to their original positions and the muscle is again at resting length.

$$\int_4^1 dU = \int_4^1 \Delta U_{Rk} \, d\xi_k = \int_4^1 (\hat{H} dm)_{ATP}$$

$$\Delta U_{4,1} = \sum_k \Delta U_{Rk} \Delta \xi_k = (\hat{H} \Delta m)_{ATP}$$

The sum of the internal energy changes over the cycle are zero, as required. The remaining effects of the cycle are the performance of work by the system on the surroundings exchanged for the consumption of substrate by the system from the surroundings.

This model presents a method of analyzing muscle operation as a chemical engine that consumes substrate to produce work. It is unrealistic in that dissipation and the effects of cycle inefficiencies have not been considered. It does demonstrate the utility of the first law energy balance in analyzing the functioning of systems, even at the microscopic level. A similar approach will be used in a macroscopic muscle analysis for the design of muscle experiments.

b. Force-velocity relationships Several authors have studied the mechanics of isometric, concentric, and eccentric contractions and their effect on the heat generation of muscle. Hill (55) was one of the first to characterize the force-velocity relationships of muscle. He has shown that the tension exerted by a frog sartorius muscle depends on the initial muscle length. The tension decreases as the muscle shortens and as the speed increases. The maximum isometric tension, P_o, occurs when the muscle can no longer lift the load. The muscle contracts with the maximum velocity, v_o, when no load is carried. Hill has also shown that the shape of the force-velocity curve is governed by the way in which energy is released during shortening. This simple relationship has resulted:

$$(P + a)(v + b) = (P_o + a)b$$

P = force of contraction

v = velocity of shortening

P_o = isometric force

a = heat of shortening per resting length, a constant

b = constant proportional to the maximum velocity of shortening.

Wilkie (117) has studied the isotonic force (P) and velocity (v) in elbow flexions and has found the curve for the human muscle to fit the Hill equation, after correction for the inertia of the arm.

The heat effects of working muscle were further studied by Hill (54, 57, 58), Hill and Howarth (59), Fenn (43, 44), Wilkie (120), Curtin et al. (32), Edwards et al. (36), and others.

The major result of each of these studies has shown that the activation of muscle fibers increases heat production. If the contraction is isometric, extra energy is liberated as heat. If the contraction is isotonic, energy is consumed to do work, with a large portion also used to either increase thermal internal energy or be lost as heat. This is in agreement with the changes described by the first law and the inefficiencies of chemical-mechanical energy conversions.

Although the absolute values of energies measured in the early experiments by Hill and Fenn are questionable, the effects they have shown are qualitatively correct and have served as noteworthy predecessors to later work. Both Hill (54) and Fenn (43, 44) have shown that the length of the muscle has a great effect on the energy expenditure. Small changes in length produce small changes in energy expenditure. The heat production (the actual value measured has been stored thermal energy, $m\hat{C}_p\Delta T$, and not Q) also increases with greater loads. So heat production, which serves as an indication of energy consumption, was found to be proportional both to load and to muscle length, and consequently proportional to work.

In studies dealing with energy consumption and work output, the evaluation of efficiency arises. Hill (56) has used the results of his earlier work to evaluate the mechanical efficiency of frog muscle. He has used the characteristic equation for muscle to calculate maximum efficiency and the velocity of contraction and load at which this occurs. The maximum efficiency was found to be 40.5% at an optimum velocity 0.18 times the maximum unloaded velocity and the optimum load at 0.475 times the isometric load. The efficiency of the whole contraction including recovery was found to be 20%. His experimental results have verified these conclusions; however, the accuracy of the heat measurements is questionable.

Hill and Howarth (59) have studied the effects of stretching muscle and have found that the heat production, $(m\hat{C}_p\Delta T - Q) = H$ was often exactly equal to the work done on the muscle, W_n, over a cycle. This in itself is not surprising. However, they have observed that the net energy, $H - W_n$, where W_n is the integrated work done on the muscle exclusive of the stored elastic energy, could drop to large negative values. This seems to imply that the energy of the work done on the muscle up to any point in time is greater than what appears as heat. Yet over the cycle, the values would balance. These authors have claimed that the only explanation can be that the work done on the muscle can act to reverse the chemical reactions to return the chemical species to their original states.

Although it is possible to convert work energy to chemical energy in electrochemical cells, the mechanism for this transformation in living

systems is unknown. The authors do not provide enough information to completely define the state of the system. Nothing is said about the changes in internal chemical energy or whether the muscle is being provided with any enthalpy flows that could provide substrates to refuel the system. The addition of this type of information would allow a complete first law analysis to be performed to determine what effect, if any, the work has on the chemical reactions.

Hill (57) has further studied the effects of load on the heat of shortening, the constant "a" found in the force-velocity equation. He has found that the heat of shortening is not constant, but a function of load and that "a" is only a mechanical parameter of the force-velocity curve. The true heat of shortening, α, is related to, but not equal to a. This error had arisen because the loads used in his first experiments were small, and the dependence of heat of shortening on load was not discernible. However, the experiments that Hill has used to support his theory have used the comparison between heat given off during muscular shortening versus the heat of isometric contraction. This comparison is not legitimate because the isometric heat is a poor baseline for isotonic contraction. The mechanisms of contraction are quite different, as pointed out by Stainsby et al. (107).

As the next step, Hill (58) has used these new results to recalculate the dependence of muscular efficiency on load. As in previous experiments, Hill has used an isolated frog muscle. A thermopile was used to measure the temperature change of the muscle. The heat term, ΔH, was calculated from the temperature changes of the muscle corrected for heat loss. In

terms of the first law expression, $\Delta H = m\hat{C}_p\Delta T - Q$. The work done by the muscle was ΔW. Then efficiency was calculated from $(\Delta W / (\Delta H + \Delta W) \times 100$. If the enthalpy flows are negligible, $\Delta H + \Delta W = \Delta M$, and the previous expression is actually the usual efficiency, $\Delta W/\Delta M \times 100$.

Hill has concluded that the efficiency of a muscle is independent of length, but highly dependent upon the relative load, P/P_o. Using the new definition of heat of shortening, the maximum efficiency, 43%, was obtained at relative loads of about 0.32. The relative velocity at this load, v/v_o, is also approximately equal to 0.32. These efficiencies when applied to exercise conditions can predict the velocities and loads which will maximize performance. As shown by Seabury *et al.* (98) and Diprampero *et al.* (35), the optimum cycling frequency is around 60 rpm. The maximum velocity for unloaded pedalling is about 180 rpm. Using Hill's result for the relative velocity at maximum efficiency, $v/v_o = 0.33$, the optimal cycling frequency is found to be approximately 60 rpm $\tilde{=}$ (180 rpm) x (0.32).

These studies have provided very significant and useful results about the thermodynamic and mechanical aspects of muscle contraction. It seems that much speculation would have been eliminated had a first law balance been used in the analyses. The energy balance leaves no doubt about accounting of terms and gives straightforward results about the relationship between heat and work.

Several researchers have studied the chemical changes of muscle as they relate to the type of contraction and the heat produced. Wilkie (120) measured the heat production, the $m\hat{C}_p\Delta T$ term corrected for heat, and related it to the changes in phosphocreatine concentration (PCr) in the

muscle. His intent was to determine the in vivo heat of reaction of phosphocreatine breakdown. His results showed a close coupling between chemical and thermal events in the muscle. He was also able to quantitatively support the previous results that showed that the energy consumption increases when physical work is performed by the muscle.

Edwards et al. (36) have measured the concentration changes of PCr, ATP, and lactate in isometrically contracted muscle and have related them to the thermal energy changes of the muscle. Their data appear to be consistent, as will be discussed in the next section.

Because the measurement of substrate concentration changes in muscle by biopsy is an invasive technique, Kushmerick and Paul (67) have performed experiments on frog muscle to relate substrate consumption and oxygen consumption. They have found them to be directly related. This fact may be useful in determining live, in situ muscle internal energy changes.

c. Muscle energy sources and their evaluation In an earlier example, the consumption of energy by an entire human body was estimated from oxygen uptake. If we narrow our viewpoint to a less complicated system, the isolated muscle, the actual changes in concentrations of the energy substrates in the muscle can be used to determine reaction velocities. These are measured using needle biopsy techniques as in the work done by Curtin et al. (32) and Edwards et al. (36). The results can be evaluated for consistency using a first law balance.

The immediate source of energy for muscular contraction is adenosine triphosphate (ATP). Muscles possess a high energy compound that can be

utilized anaerobically for the rapid generation of ATP. In vertebrate muscle, this mechanism operates through phosphocreatine by the following reaction:

$$PCr + ADP \rightleftarrows Creatine + ATP$$

The enthalpy of reaction is given by Edwards et al. (36) as + 3 kcal/mole. The PCr is hydrolyzed to ATP which is then an immediate energy source for the mechanism of muscular contraction. The enthalpy for the overall reaction is - 7.89 kcal/mole as shown below.

		H (kcal/mole)
Aerobic	$ATP \rightarrow ADP + P_i$	-11
	$PCr + ADP \rightarrow ATP + C$	+ 3
	Net reaction: $PC \rightarrow C + P_i$	- 8 (-7.89)

Anaerobic 1/2 glycosyl unit → lactate + 1-1/2 ATP - 6 kcal/mole

If the muscle is forced to operate in completely anaerobic conditions, a second store of ATP energy becomes available. These energy demands are satisfied by glycolysis of glycogen to lactic acid. These possible pathways are illustrated in Figure 15.

The data taken by Edwards et al. (36) are used in the following example.

The system considered was a single leg of a human.

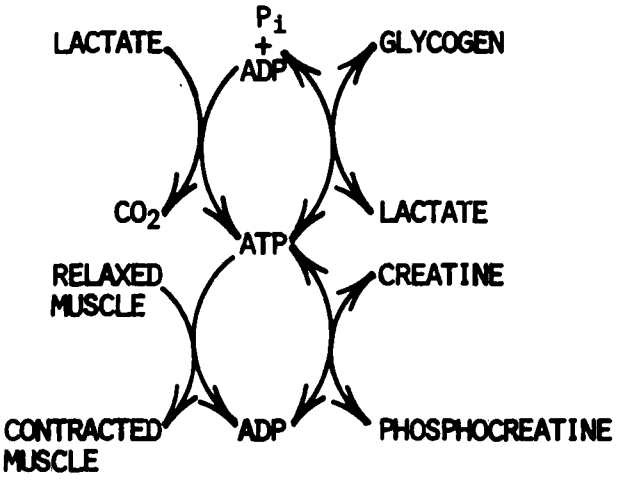
Subject data:

Body mass = 75 kg

Mass of leg segment = 15 kg

Body surface area = 1.9 m^2

Figure 15. The pattern of the utilization of energy sources in contracting muscle (from (116))


P_i
+
ADP
LACTATE
GLYCOGEN
CO_2
LACTATE
ATP
RELAXED
MUSCLE
CREATINE
CONTRACTED
MUSCLE
ADP
PHOSPHOCREATINE

Specific heat of muscle and surrounding tissue, $\hat{C}_p = 0.896 \frac{kcal}{kg\,°C}$

Experimental procedure:

Isometric contraction of the quadriceps muscle over a 74-second time span.

Variables measured:

1) The rate of temperature change of the muscle, $\Delta T/\Delta t$ = 0.257°C/min

2) Changes in muscle substrate concentrations, Δ = (final - initial),

ΔATP = 4.3 μmoles/g dry muscle

ΔPCr = -74.4 μmoles/g dry muscle

ΔLactate = -24.5 μmoles/g dry muscle

Assuming that these are the significant reactions occurring in the muscle, the sum of the integrated reaction terms, $\sum_k \Delta\tilde{H}_{Rk}\Delta\xi_k$, is

$$\text{PCr:}\quad \Delta\tilde{H}_R\Delta\xi_{PCr} = \left(-\frac{74.4 \times 10^{-6}\ \text{moles}}{\text{g dry muscle}}\right) \times \left(-\frac{7.89\ \text{kcal}}{\text{mole}}\right)$$

$$= +\ 5.87 \times 10^{-4}\ \frac{kcal}{g}$$

$$\text{Lactate:}\quad \Delta\tilde{H}_R\Delta\xi_{Lact} = \left(-\frac{24.5 \times 10^{-6}\ \text{moles}}{\text{g dry muscle}}\right) \times \left(-\frac{6.21\ \text{kcal}}{\text{mole}}\right)$$

$$= +\ 1.521 \times 10^{-4}\ \frac{kcal}{g}$$

ATP from this source used in muscle contraction:

$$\Delta\tilde{H}_R\Delta\xi_{ATP} = -\left(\frac{24.5 \times 10^{-6} \text{ moles lactate}}{\text{g}}\right) \times \left(\frac{1.5 \text{ moles ATP}}{\text{mole lactate}}\right)$$

$$\times \left(-\frac{11 \text{ kcal}}{\text{mole ATP}}\right) = 4.043 \times 10^{-4} \frac{\text{kcal}}{\text{g}}$$

$$\text{ATP:} \quad \Delta\tilde{H}_R\Delta\xi_{ATP} = \left(\frac{4.3 \times 10^{-6} \text{ moles ATP}}{\text{g}}\right) \times \left(-\frac{11 \text{ kcal}}{\text{mole}}\right)$$

$$= -0.473 \times 10^{-4} \frac{\text{kcal}}{\text{g}}$$

The sum of these terms is

$$\sum_k \Delta\tilde{H}_{Rk}\,\Delta\xi_k = \frac{10.96 \times 10^{-4} \text{ kcal}}{\text{g dry muscle}}$$

Muscle tissue is 77% water by weight. To find the total integrated metabolic heat,

$$\sum_k \Delta\tilde{H}_{Rk}\Delta\xi_k = \Delta M = \left(\frac{10.96 \times 10^{-3} \text{ kcal}}{\text{g dry muscle}}\right) \times \left(\frac{0.23 \text{ g dry}}{\text{g wet muscle}}\right)$$

$$\times (15{,}000 \text{ g wet muscle}) = 4.12 \text{ kcal}$$

The temperature increase was measured to be 0.257°C/min.

The term

$$m\hat{C}_P\Delta T = (15 \text{ kg}) \times \left(\frac{0.896 \text{ kcal}}{\text{kg °C}}\right) \times \left(\frac{0.257°\text{C}}{\text{min}}\right) \times (1.23 \text{ min})$$

$$= 4.26 \text{ kcal}$$

Although the heat transferred from the limb, Q, was not measured, a reasonable approximation of this value is possible using the equation for conductive heat transfer

$$Q = -\int_0^t (kA \frac{dT}{dn})dt$$

$$\tilde{=} - kA \frac{\Delta T}{\Delta n} \Delta t$$

where ΔT is the difference between the muscle temperature and the skin temperature, $\Delta n = 2.23$ cm (103) is the distance from the muscle to the skin surface, k is the thermal conductivity of the tissue involved and equals 1.3×10^{-3} cal/cm·°C as given by Shitzer (103), and Δt is the time interval of the event.

It is necessary to calculate the increase in heat transfer due to the activity Q = Q(active) - Q(resting).

The temperature of resting muscle is about 36°C, while the active muscle reaches about 36.3°C. Assuming a constant skin temperature of 30°C, Q is found to be -0.05 kcal.

Then the overall balance is

$$m\hat{C}_p \Delta T + \Sigma \Delta \tilde{H}_R \Delta \xi_k = Q$$

$$4.26 \text{ kcal} + (-4.11 \text{ kcal}) \tilde{=} -0.05 \text{ kcal}$$

The difference between the thermal internal energy gain of the muscle and the metabolic energy is 0.15 kcal, which compares favorably with the estimated Q. Although the conditions of this experiment have

minimized the effect of neglecting Q, this example illustrates the desirability of measuring all terms of the first law balance, if possible, or of providing some means by which they may be estimated. When the purpose of an experiment is the accurate measurement of the internal energy changes due to reaction, the consistency of the data, the accuracy of the measurements, and the validity of the conclusions is assured only if all possible paths of energy flow have been accounted for. These possible paths are clearly listed in the first law expression.

d. In situ studies The majority of the studies described have been performed on or applied to in vitro isolated muscle. These conditions bring about the question of how data from in situ muscle would compare to in vitro results. Stainsby (105, 106) has performed oxygen consumption measurements on contracting dog skeletal muscle in situ. He was able to measure the oxygen difference between the arterial supply and the venous return of a working muscle. He has made such measurements for isometric, isotonic, and eccentric contractions. As did researchers before him, he also has concluded that oxygen uptake increases with load and decreases when work is done on the muscle. His second group of experiments (106) have shown that oxygen uptake increases with load up to the isometric load, and then decreases as the muscle is stretched. However, in his first study (105), he had plotted oxygen uptake against load for isometric and isotonic contractions. The results suggest that oxygen uptake is dependent only upon load and not upon work, which is in contradiction with all previous results.

The factor that Stainsby has excluded from his plots is the effect that muscle length has on oxygen consumption. Purely anatomical considerations indicate that the length of the muscle has a direct effect on the juxtaposition of cross-bridges and, further, electromyographic techniques have shown that the oxygen consumption reflects the number of active cross-bridges. The results of Aubert and Gilbert (7) and Matsumoto and McPhedran (73) indicate a strong dependence of muscle energy consumption on length. In Stainsby's work, although the loads may have been the same for each type of contraction, the muscle lengths were not. In general, for a given tension, the isometric length was much shorter than the average isotonic length. Also, the amount of work performed was small, with the muscle contracting to only about 5% of its resting length. Therefore, the results of Stainsby's work (105) are inconclusive.

2. Approaches to muscle experimentation

The previous section has illustrated the lack of consistency in many experimental studies of muscle behavior and muscle energetics. Two approaches will now be presented which are useful in the design of experiments which are thermodynamically and physiologically complete.

a. The contraction cycle The operation of a muscle may be viewed as a cyclic process in which the muscle begins from rest, prepares to contract, contracts, releases, and recovers. This approach is similar to that discussed earlier for the muscle cross-bridges, however, the considerations here deal with a macroscopic approach over the whole muscle system.

Although the physical mechanism of contraction may not correspond exactly to the steps of the cycle to be discussed, the model is a

convenient way in which to view the energy and entropy flows of muscle. Since the contraction is to be considered as a cyclic process, the initial and final states of the muscle should be identical. This concept helps identify the energy conversions and energy flows that must be accounted for over the cycle in order that the system be returned to its initial state.

1. The muscle system begins at rest. This state is described by Equation 24. The resting conditions will serve as a baseline or reference for subsequent calculations. The steady system is isothermal, unstretched, and its total entropy production must be zero

$$\text{Energy:} \quad \dot{M}_{rest} = \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} = \dot{Q}_{rest} + \sum_j \hat{H}_j \dot{W}_j \delta_j$$

$$\text{Entropy:} \quad \frac{TdS}{dt} \cong 0$$

The muscle is assumed to have sufficient energy stores with which to supply the contraction energy requirements.

2. The muscle prepares to contract. Although no work is done by the whole muscle, on the microscopic level, the cross-bridges have engaged and are developing tension. The metabolism increases somewhat above resting. The muscle temperature may rise slightly as blood flow is constricted by the developing tension, but this amount will be neglected. Since the blood supplies the muscle's nutrients and removes its wastes, these material flows are prevented and the muscle operates as a closed system. The entropy production increases as new gradients are established within the system and as reactions proceed more rapidly.

Energy: $\Delta\dot{M}_{1,2} = \dot{Q}_{1,2}$

Entropy: $\frac{TdS_2}{dt} > 0$

3a. The muscle contracts and work is performed. The muscle temperature may rise since the heat energy produced due to the inefficiencies of energy conversions cannot be immediately convected and/or conducted from the system.

Energy: $m\hat{C}_p \frac{dT_{2,3}}{dt} + \Delta\dot{M}_{2,3} = \dot{Q}_{2,3} - \dot{W}_3$

Entropy: $\frac{TdS_3}{dt} > 0$

Entropy is produced as metabolic energy is used to perform work, since $\dot{Q} - \Delta\dot{M} = m\hat{C}_p \frac{dT_{2,3}}{dt} + W_3 > 0$, thus, from Equation 30,

$$\frac{TdS}{dt} = \dot{Q} - \Delta\dot{M} + \Delta\dot{S}_R + \sum_m J_m X_m > 0.$$

3b. If the contraction is isometric, no work is done, but a definite temperature increase is observed due to the muscle cross-bridge activity. The entropy production is likely to increase because of the "internal" work performed by the cross-bridges.

Energy: $m\hat{C}_p \frac{dT'_{2,3}}{dt} + \Delta\dot{M}'_{2,3} = \dot{Q}'_{2,3}$

Entropy: $\frac{TdS'_3}{dt} > 0$

4. The muscle releases the load by an eccentric contraction. Work is done on the system if the muscle length extends beyond the resting length. In this case, elastic energy may be stored.

$$\text{Energy:} \qquad f_s \frac{d\ell_s'}{dt} + \Delta\dot{M}_{3,4} = \dot{Q}_{3,4} - \dot{W}_4 \qquad (\dot{W}_4 < 0)$$

$$\text{Entropy:} \qquad \frac{TdS_4}{dt} < \frac{TdS_3}{dt}$$

Entropy production drops because the system is absorbing energy.

If the muscle is released from tension without an eccentric stretch, this step is not included in the cycle.

5. The muscle recovers as energy stores are replenished and gradients are restored to their initial state. If the muscle has operated anaerobically, lactate will diffuse from the muscle into the blood where it will be transported to the liver. Stored thermal energy is lost to the surroundings.

$$\text{Energy:} \qquad m\hat{C}_p \frac{dT_5}{dt} + \Delta\dot{M}_{4,5} = \dot{Q}_{4,5} + \sum_j H_j \dot{W}_j \delta_j$$

$$\text{Entropy:} \qquad \frac{TdS_5}{dt} < \frac{TdS_4}{dt}$$

Entropy production decreases as thermal energy is lost and gradients are restored.

6. The muscle returns to rest and the cycle is complete

$$\dot{M}_6 = \dot{M}_{rest} = \dot{Q}_{rest} \qquad \frac{TdS}{dt} = 0$$

Because steps 1) through 6) describe a cycle, certain relationships must exist between the terms. These may serve as a test of data consistency and as a guide to distinguishing the paths of energy flows and the character of energy transformations.

All of the stored thermal, stored elastic, and metabolic energies must eventually appear either as heat or work. If the work done by the muscle and the work done on the muscle are of equal magnitude, only heat effects should be observed.

The flows during the recovery phase include the flow of oxygen and glucose to the muscle and the flow of metabolic wastes from the muscle. Although these represent relatively negligible quantities as enthalpy flows, they represent a means of determining internal chemical energy transformations. For example, since the reactions which provide energy for muscle contraction are oxidation reactions, oxygen consumption is a measure of this reaction rate. If the muscle is forced to operate anaerobically, the removal of lactate from the muscle indicates the extent to which glycogen and glucose, the primary energy substrates in muscle, are broken down anaerobically.

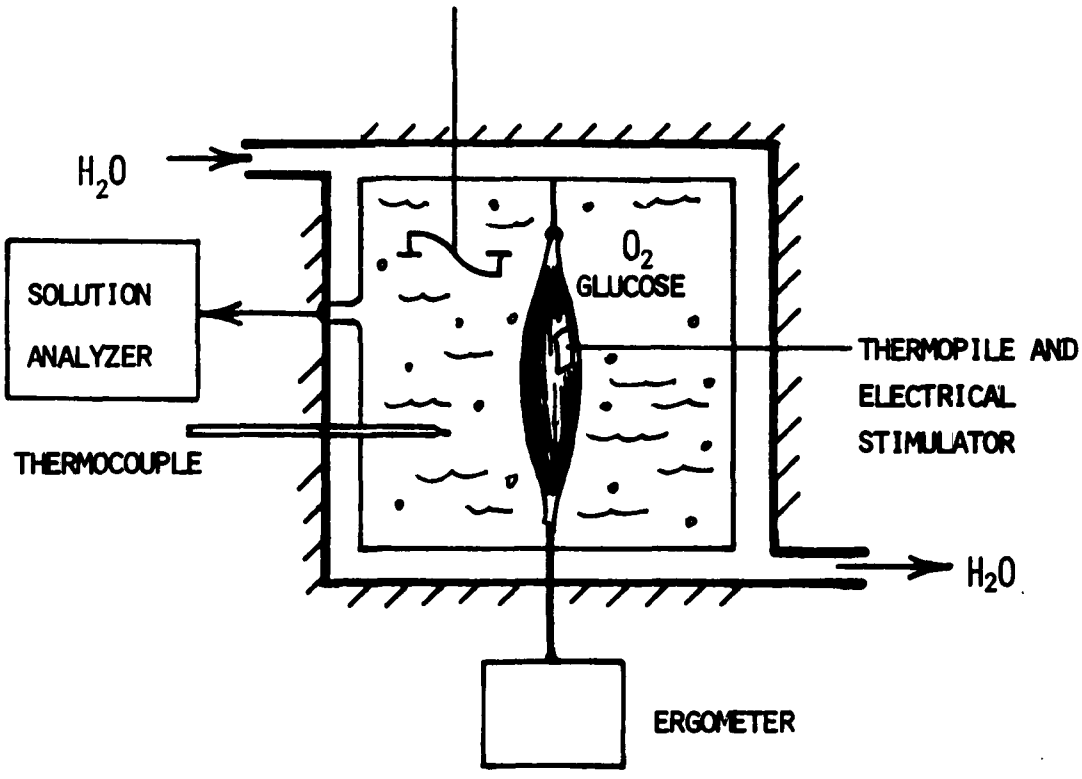
Although the evaluation of entropy has been qualitative, it appears as if the entropy production rate increases from the resting value as the muscle contracts and decreases as the muscle relaxes and recovers. These changes in the entropy production rate represent the local fluctuations which are regulated by homeostatic control.

Suggestions for the design and use of a muscle-testing chamber in which the phases of the cycle are physically realized are discussed below.

The suggested apparatus in which the muscle system is contained is simply a jacketed reactor. The muscle is bathed in a well-stirred nutritive solution containing known concentrations of oxygen and an energy substrate such as glucose. This solution is analyzed before and after experimentation to determine the uptake of oxygen and glucose and the production of carbon dioxide and lactate. The operating temperature should be held within a physiological range. The temperature of the muscle may be recorded with a thermopile as described by Wilkie (120). The muscle is linked with an ergometer with which the work done by or on the muscle may be recorded. The length changes of the muscle should be recorded. Such an apparatus is depicted in Figure 16.

The physical measurements and the thermodynamic quantities which they represented are listed as follows: the thermopile reading represents the thermal energy storage of the muscle, $m\hat{C}_p\ dT/dt$; the oxygen consumption of the muscle from the solution is a measure of the energy consumption of the muscle, $\Delta\dot{M}$; the glucose uptake represents an enthalpy flow into the muscle which should account for the replacement of depleted chemical energy stores; the load imposed on the muscle represents the isometric tension if the muscle does not shorten or the work term, W, if the muscle shortens (work done by the muscle), if the muscle lengthens (work done on the muscle), or the recovery of stored elastic energy; the temperature change of the jacket fluid and the temperature change of the nutritive solution are used to calculate the heat loss from the system so that the heat gained by the jacket fluid and by the solution are equal to $-\dot{Q}_{muscle}$.

Figure 16. An apparatus for the calorimetric study of muscle mechanico-chemical relationships


H_2O
SOLUTION
ANALYZER
THERMOCOUPLE
O_2
GLUCOSE
THERMOPILE AND
ELECTRICAL
STIMULATOR
H_2O
ERGOMETER

This stepwise, cyclic approach to muscle activity in which an energy balance is written for each phase of muscle contraction assumes that all of the energy flows and transformations described for each phase are accomplished before the next phase begins. This is a simplification, however, the sequence of steps describes all possible forms of energy consumption and dissipation as a guide to the design of experiments and the analysis of data. By making the proper choice of experimental conditions and measuring the appropriate thermodynamic variables, almost all macroscopic aspects of muscle contraction may be investigated.

b. Oxygen consumption as a function of state In an attempt to describe the oxygen consumption, which is proportional to the reaction velocity, of the muscle system, $\dot{V}_{O_2}$ is written as a function of state, $\dot{V}_{O_2} = \dot{V}_{O_2}(\ell, P, PV)$ such that

$$d\dot{V}_{O_2} = \left[\frac{\partial \dot{V}_{O_2}}{\partial \ell}\right]_P (\ell - \ell_R) + \left[\frac{\partial \dot{V}_{O_2}}{\partial P}\right]_\ell (P - P_R) + \frac{1}{\eta} P \frac{d\ell}{dt} \qquad (57)$$

where P_R = resting muscle tension

ℓ_R = resting muscle length

P = muscle tension

ℓ = muscle length

η = efficiency of transforming chemical to mechanical energy.

The term $d\dot{V}_{O_2}$ represents changes above the reference oxygen consumption at the chosen ℓ_R and P_R. From the research of Kushmerick and Paul (67), Stainsby (106) and others, it is known that muscle metabolism, or the overall reaction velocity of the muscle system, is proportional to

oxygen uptake. When work effects are accounted for, heat production is also a direct measure of metabolic energy. Therefore, in the discussion to follow, heat production, oxygen uptake, and metabolism will be considered equivalent.

In work done by Aubert and Gilbert (7), the reaction velocity measured proportional to heat production was shown to be 40% greater at lengths shorter than resting relative to lengths greater than resting for the same tension. This trend is qualitatively depicted in Figure 17a.

In the in vivo muscle studies performed by Stainsby (105) tension effects on oxygen uptake were investigated in conditions of approximately constant muscle length. A definite trend towards an increasing reaction velocity with increasing tension was demonstrated.

These length and tension dependences suggest a set of experiments in which oxygen uptake or heat production is measured as a function of length for several choices of constant tension. Length variation should be held to within physiologically significant lengths -- from 0.7 to 1.2 times the resting length. Such experiments would result in a family of curves as depicted in Figure 17b.

The maximal static load that a muscle can hold is related to length as shown in Figure 17c. This curve represents the limiting case of length tension interdependence and corresponds to the uppermost curve of Figure 17b. The chemical reaction rate at any particular point on the length-tension curve can be located on the P_{max} curve of Figure 17b.

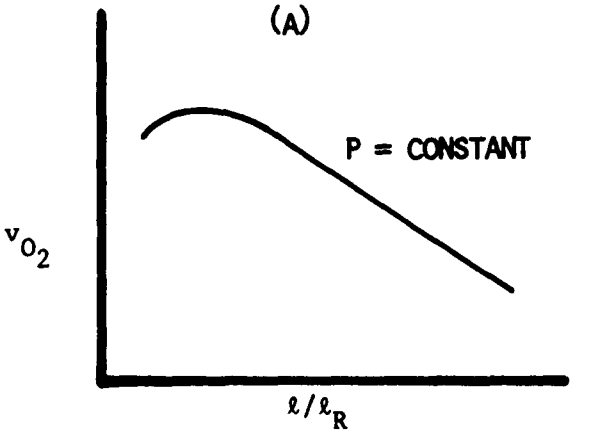
The conditions described above are static. They now must be related to dynamic condition of concentric muscle contraction.

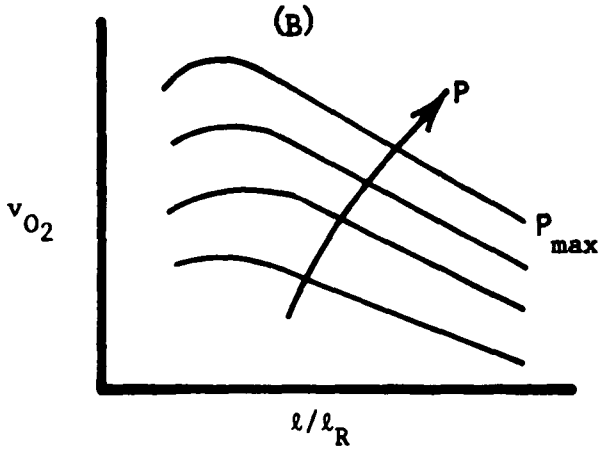
Figure 17. The qualitative relationships between muscle energy consumption (oxygen uptake), muscle length, and muscle load

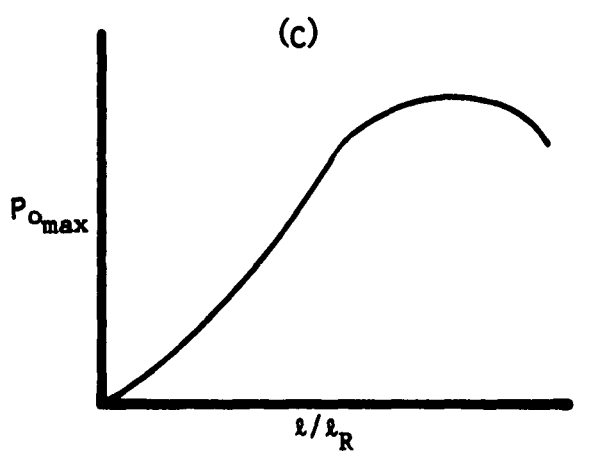
a) Oxygen uptake as a function of relative muscle length at a constant load

b) Oxygen uptake as a function of relative muscle length for several values of constant load

c) The maximal static load as a function of relative muscle length


(A)
P = CONSTANT
$\dot{V}_{O_2}$
ℓ/ℓ_R


(B)
P
P_{max}
$\dot{V}_{O_2}$
ℓ/ℓ_R


(C)
$P_{O_{max}}$
ℓ/ℓ_R

Many investigators (36,57,58,66) have endeavored to discriminate between the heat effects of various types and stages of muscle contraction. In general, their intent has been to find the source or sources of the energy for the various energy-consuming phenomena of contraction. Heat effects have usually been divided in the following manner:

$$E = M + W + \alpha x \tag{58}$$

where E is the total energy appearing during muscular activity, M is the activation or maintenance heat, W is the work performed by the shortening muscle, α is the heat of shortening, and x is the distance shortened.

The majority of studies done in muscle energetics have measured "heat production," h, as the rate of temperature change of the muscle corrected for heat lost to the surroundings. Written in terms of the first law expression for a system closed to flows,

$$\Delta U = m\hat{C}_p\Delta T + \Delta M = Q + (-W) \tag{59}$$

and heat production, $h = [m\hat{C}_p\Delta T + (-Q)]$ is the experimentally measured variable. Then metabolism, which is proportional to reaction rate, is

$$[-h + (-W)] = \Delta M$$

or when no work is done,

$$-h = \Delta M$$

As shown, metabolism is calculated by difference or by direct measurement. Researchers have also measured the changes in substrate concentrations to determine ΔM (32, 120).

The interpretation of the oxygen consumption model of Equation 57 and its application to the measurements obtained in muscle contraction experiments will be discussed in relation 1) to the first law energy balance, 2) to the heat terms described in muscle energetics studies, and 3) to phenomenological expressions for reaction rates for muscle obtained by Bornhorst and Minardi (14,15).

Caplan (24) has suggested the following first law interpretation of Equation 58. First, for an isometrically contracting muscle

$$\dot{U}_o = \dot{Q}_o$$

where heat in is positive.

When work is performed,

$$\dot{U} = \dot{Q} + PV$$

where P = tension, V = velocity.

The values for the rates of internal energy must actually represent changes above a reference and $PV = -\dot{W}$. The integrated expression then becomes

$$\Delta U = Q - W$$

A quantity α is introduced such that

$$\alpha = (\dot{Q} - \dot{Q}_o)/V$$

Upon combination and rearrangement Caplan obtains

$$\dot{U} = \dot{Q}_o + PV + \alpha V$$

and after integration,

$$\Delta U = Q_o - W - \alpha x \tag{60}$$

Caplan suggests that Q_o must be the maintenance heat and αx the shortening heat. The quantity Caplan labels Q_o is usually experimentally measured as the heat production, $h_o = m\hat{C}_p\Delta T_o + (-Q_o)$ for an isometric contraction. Then x becomes the extra heat production above the isometric level present during a contraction (referred to as the Fenn effect), $h = m\hat{C}_p\Delta T + (-Q)$.

The expression for the change in chemical reaction rate or metabolism becomes

$$\Delta M = -h_o - W - (-h)$$

$$\Delta M = -m\hat{C}_p\Delta T_o + Q_o - W - [(-m\hat{C}_p\Delta T + Q)] \tag{61a}$$

For convenience and clarity energy losses are equated to a positive energy production so that the loss of internal energy is equal to the production (loss) of heat (thermal) and work energy symbolically represented as follows:

$$-h_o = +h_o' \ , \quad -W = W' \ , \quad -h = +h',$$

so that

$$\Delta U = \Delta M = h_o' + W' + h' \tag{61b}$$

Equations 61a and 61b relate experimentally measured quantities to the first law and to the various heat effects described in Equation 60.

The choice of the isometric values as a baseline for calculating added heat effects due to shortening has been questioned (107). Experiments to be suggested that will utilize the oxygen uptake expression of Equation 57 as a model will resolve this question.

Equation 57 is rewritten as

$$d\dot{V}_{O_2} = \dot{V}_{O_2} - \dot{V}_{O_2}\Big|_R = \Delta\dot{V}_{O_2} = \frac{\partial \dot{V}_{O_2}}{\partial \ell}(\ell-\ell_R) + \frac{\partial \dot{V}_{O_2}}{\partial P}(P-P_R) + \frac{1}{\eta} P \frac{d\ell}{dt} \tag{62}$$

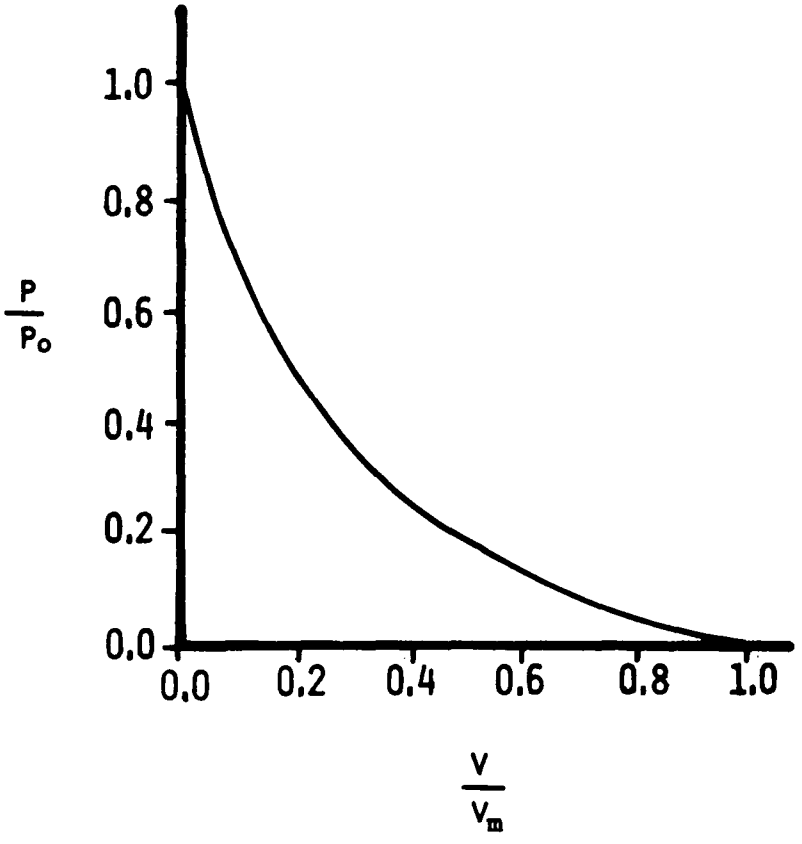
where the resting oxygen consumption, length, and tension are chosen as references. The first two terms of the right hand side of the expression are static terms. They are evaluated at a point of a curve rather than along its path. The third term represents the effect of the dynamic contribution or work on muscle metabolism.

The dynamic relationship between tension and velocity is represented by the classic Hill force-velocity curve (55) shown in Figure 18. The curve is described by the equation

$$\frac{P}{P_o} = \frac{a}{P_o} \frac{\left(1 - \frac{V}{V_m}\right)}{\frac{a}{P_o} + \frac{V}{V_m}} \tag{63}$$

where P_o is the isometric tension, the intercept on the ordinate, V_m is the maximum velocity of contraction, the intercept on the abscissa, and a and b are mechanical constants such that $b/V_m = a/P_o$.

Figure 18. The maximal static load as a function of relative muscle velocity modified from (6)


1.0
0.8
0.6
0.4
0.2
0.0
P/Po
0.0
0.2
0.4
0.6
0.8
1.0
V/Vm

First, parallels are drawn between Equations 58, 61b, and 62 rewritten on a rate basis below:

$$\Delta\dot{M} = \dot{M} + \dot{W} + \dot{\alpha x}$$

$$\Delta\dot{M} = \dot{h}'_o + \dot{W}' + \dot{h}'$$

$$\Delta\dot{V}_{O_2} = \frac{\partial\dot{V}_{O_2}}{\partial\ell}(\ell-\ell_R) + \frac{\partial\dot{V}_{O_2}}{\partial P}(P-P_R) + \left[\frac{Pd\ell(t)}{dt} + \left(\frac{1-\eta}{\eta}\right)\frac{Pd\ell(t)}{dt}\right]$$

The original term of Equation 62, $\frac{1}{\eta} P \frac{d\ell}{dt}$, has been rewritten as the last two terms of the last expression. Correspondences between the thermodynamic description of the first two expressions and the physical-mechanical description in the third expression are suggested below:

$$\dot{M} = \dot{h}'_o = \frac{\partial\dot{V}_{O_2}}{\partial\ell}(\ell - \ell_R) + \frac{\partial\dot{V}_{O_2}}{\partial P}(P - P_R) \tag{64a}$$

$$\dot{W}' = P(t)\, d\ell(t)/dt \tag{64b}$$

$$\dot{\alpha x} = \frac{1-\eta}{\eta} P(t) \frac{d\ell(t)}{dt} \tag{64c}$$

Equation 64b is given by definition. Equation 64a is reasonable because for an isometric contraction $P\, d\ell(t)/dt = 0$, leaving $\Delta\dot{V}_{O_2} = (\partial\dot{V}_{O_2}/\partial\ell)(\ell-\ell_R) + (\partial\dot{V}_{O_2}/\partial P)(P-P_o)$ and $\Delta\dot{M} = \dot{h}'_o = \dot{M}$. The remaining term results in Equation 64c and says that the heat of shortening is an "inefficiency" term.

Once the accuracy of experimental energy measurements is assured, the following procedure is suggested to test for the existence of maintenance heat that is distinct from heat due to mechanicochemical energy conversion inefficiencies during contraction. The question of whether isometric heat and maintenance heat during contraction are one and the same may also be resolved.

Maintenance heat, if it exists, must be due to the inefficiencies of energy consuming processes of maintaining the physical characteristics of the system in a state other than resting. This energy should be in excess of work energy and heat loss due to contraction inefficiencies.

A series of static experiments such as those described earlier, in which the oxygen uptake is measured as a function of muscle length with load as a parameter, are performed for isometric contractions. These data are then compared to oxygen uptake or heat production values in concentric contraction experiments performed in the same range of loads and muscle lengths. The instantaneous length of the muscle must be measured through each contraction. Comparisons will determine a) whether maintenance heats exist and, if they do, b) whether isometric contractions are related to maintenance heat as described by Equations 62a and 64a.

To test these hypotheses, dynamic muscle contraction must first be considered to be a set of infinitesimal isometric contractions summed to produce an actual concentric muscle shortening. This implies that at some physiological level, the mechanism of contraction is the same whether the contraction is isometric or concentric. This is most likely

to be anatomically true at the cross-bridge level.

The data for oxygen consumption in a concentric contraction, the P-V relationship, and the length vs. time relationship are necessary data. As long as both tension and length are known for every instant of time during the contraction, an instantaneous reading of reaction rate can be obtained from data of Figure 17b. The entire P-V curve is then represented by differential changes in tension and length. The reaction rate changes predicted by the integration of these point values are then compared to the work energy, $Pd\ell/dt$. In summary, the same effects that cause reaction rate changes during isometric contractions, namely length and tension, are assumed to act instantaneously during a concentric muscle reaction. If the maintenance energy as predicted by summation of the length-tension dependent reaction rates exactly equals the experimental value of reaction rate during a "working" contraction and/or, equivalently, the calculated value of $\frac{1}{\eta} Pd\ell(t)/dt$, the maintenance effect is either small or nonexistent. If the experimental value of reaction rate is greater than the integrated data, since $\frac{1}{\eta} P\ d\ell/dt$ can be calculated explicity (η is known (58)), this suggests that the maintenance heat does exist and is evaluated by difference. Then, the accuracy of the oxygen uptake model as a predictor for evaluating maintenance heat can be determined, the validity of using an isometric baseline established, and a possible physiological explanation for the maintenance heat considered.

A quantitative discussion is not possible at this time since required data are not presently available. Furthermore, the questions and discrepancies in existing muscle energetics literature often seem to be due

to erroneous definition and use of thermodynamic terminology. It is suggested that, when dealing with potentially small differences in energies, accurate measurement of all possible heat losses should be taken. The heat loss, -Q, is the primary candidate for sources of error since, of all papers reviewed in this work, not one had measured it directly. The implementation of adiabatic test chambers with accurate temperature measurement of both the muscle and its immediate surroundings within the system as described earlier is suggested. This, along with more accurate accounting of the enthalpy flows of energy substrates and waste products entering and leaving the system, as per the first law expression, and a precise definition of the boundaries of the system to be considered, will aid in distinguishing between the various energy flows of muscle contraction.

3. Nonequilibrium thermodynamics of muscle

Muscle behavior has recently been a major focus of nonequilibrium thermodynamics. This introduces an opportunity to study a system which has been analyzed in terms of both classical and nonequilibrium thermodynamics.

Caplan (23) has used irreversible thermodynamics to model the muscle as a linearly coupled energy converter regulated by feedback. The output is regulated so that its force and flow characteristics are identical to the Hill force-velocity expression. The input flow is the chemical reaction velocity and the input force is the chemical affinity. Caplan has defined the degree of coupling between the input and the output and

used it to determine the maximum efficiency and maximum output (see Equations 34, 35, and 36).

Caplan was able to show that the force-flux relationship fit Hill's equation exactly with the proper choice of the regulator function. However, Wilkie and Woledge (121) have shown that, since the phenomenological coefficients must be constants, the relation between the rates and the affinities of the driving reactions must vary well beyond experimentally measured values and that the regulator is therefore required to act as a dissipator to reduce the energy supplied to the converter to an acceptable level. They have concluded that the muscle does not operate as the energy converter described by Caplan.

Bornhorst and Minardi (14, 15) have proposed a modified phenomenological theory for contracting muscle based on irreversible thermodynamics and the sliding filament theory. The theory has been applied to the subunits of the muscle, the cross-bridges. The transport coefficients of the phenomenological equations have been shown to be functions of the number of activated cross-bridges. Several important but reasonable assumptions have been made in their derivation: 1) the cross-bridges are linear energy converters, 2) the number of active cross-bridges is a function of velocity of contraction and load (tension), 3) the chemical affinity, the driving force for contraction, is constant for each cross-bridge, and 4) the Hill force-velocity curve is valid for any muscle length. They then have derived reaction velocity expressions at a given length and, in the second paper, have accounted for generalized length variations. The results of this second paper seem to be directly related to the oxygen uptake model proposed in Equation 62. In view of this

apparent relationship, the two expressions will be compared.

Bornhorst and Minardi have written reaction velocity, v, as a function of intrinsic load, P_s, contraction velocity, V, and the number of active cross-bridges, n, which are all functions of muscle length, ℓ. These dependences are shown in Equation 27 of reference 15, rewritten below as Equation 65a

$$\frac{v^{\ell}}{v_o^{\ell_o}} = \frac{P_s^{\ell}}{P_{o_s}^{\ell_o}} + \left(\frac{n^{\ell}}{n_o^{\ell}} \right) \left(\frac{n_o^{\ell}}{n_o^{\ell_o}} \right) \frac{n_o^{\ell_o}}{n_m^{\ell_o}} \frac{v_m^{\ell_o}}{v_o^{\ell_o}} \frac{V}{V_m^{\ell_o}} \tag{65a}$$

The "o" subscripts indicate isometric values, the "m" subscripts are values during unloaded contraction, and the "ℓ" superscripts indicate a function of length, while the "ℓ_o" superscripts represent the variable evaluated at the resting length ℓ_o. Furthermore n^{ℓ}, v^{ℓ} & P_s^{ℓ} are functions of velocity as well as length, n_o^{ℓ} is a function only of length since the subscript indicates an isometric contraction, and $n_o^{\ell_o}$, $n_m^{\ell_o}$, $v_o^{\ell_o}$, $v_m^{\ell_o}$, $P_{o_s}^{\ell_o}$, and $V_m^{\ell_o}$ are all constants. Substituting expressions for these various constants and functions given in their paper, Equation 65a becomes

$$\frac{v^{\ell}}{v_o^{\ell_o}} = \frac{P_s^{\ell}}{P_{o_s}^{\ell_o}} + \frac{a^{\ell_o}}{P_o^{\ell_o}} F(\ell) \left(1 + \frac{P_o^{\ell_o} V_m^{\ell_o}}{A v_o^{\ell_o}} \right) \left(\frac{1}{b+V} \right) V \tag{65b}$$

where $F(\ell)$ is a function of length that allows Hill's force-velocity relationship to be applied at the cross-bridge level. To simplify, if

$$\left(1 + \frac{P_o^{\ell_o} V_m^{\ell_o}}{Av_o^{\ell_o}}\right) = K, \text{ a constant, then}$$

$$\frac{v^{\ell}}{v_o^{\ell_o}} = \frac{P_s^{\ell}}{P_{o_s}^{\ell_o}} + [(a^{\ell_o}/P_o^{\ell_o})\,]F(\ell)\,\frac{1}{b+V}\,V \tag{65c}$$

The oxygen consumption model of Equation 62 has also been written as a function of load, length, and velocity. The maximum isometric tension is achieved at a length very close to resting. Therefore, the oxygen consumption for an isometric contraction is

$$v_{O_{2o}} = \left(\frac{\partial v}{\partial P}\right)^{\ell_o}_{P_o^{\ell_o}}$$

where now $\dot{dV}_{O_2}$ is written as v_{O_2}. Assuming that at the cross-bridge level $\left(\frac{\partial v}{\partial P}\right)^{\ell} = \left(\frac{\partial v}{\partial P}\right)^{\ell_o}$ (or, alternately, that the relationship between v & P is linear) the ratio of $v^{\ell}_{O_2}/v^{\ell_o}_{O_{2o}}$ becomes

$$\frac{v^{\ell}_{O_2}}{v^{\ell_o}_{O_{2_o}}} = \frac{\left(\frac{\partial v}{\partial \ell}\right)^{\ell}_{P_o}\ell}{\left(\frac{\partial}{\partial}\right)^{\ell}_{P_o}} + \frac{\left(\frac{\partial v}{\partial P}\right)^{\ell}_{P}}{\left(\frac{\partial v}{\partial P}\right)^{\ell_o}_{P_o}} + \frac{1}{\eta}\;\frac{PV}{\left(\frac{\partial v}{\partial P}\right)^{\ell}_{P_o}} \tag{66a}$$

where ℓ and P represent the distance from resting, $(\ell-\ell_R)$ and $(P-P_R)$, respectively.

Simplifying,

$$\frac{v^{\ell}_{O_2}}{v_{O_{2o}}} = \frac{\partial P}{\partial \ell}\frac{\ell}{P_o} + \frac{P}{P_o} + \frac{1}{\eta\left(\frac{\partial v}{\partial P}\right)\ell}\frac{P}{P_o}V \qquad (66b)$$

Substituting the Hill force-velocity relationship, in which length changes have been accounted for, into the term P/P_o,

$$\frac{v^{\ell}_{O_2}}{v_{O_{2o}}} = \frac{1}{P_o}\left(P + \frac{\partial P}{\partial \ell}\ell\right) + \frac{1}{\eta\left(\frac{\partial v}{\partial P}\right)\ell}F(\ell)\frac{a^{\ell_o}}{P_o^{\ell_o}}\left(\frac{V_m^{\ell_o}-V}{b+V}\right)V \qquad (67)$$

When Equations 67 and 65b are compared,

$\frac{P^{\ell}_{s}}{P_{o_s}}$ is represented by $\frac{1}{P_o}\left(P + \frac{\partial P}{\partial \ell}\ell\right)$, which is

a reasonable first order approximation of the dependence of tension on length.

Comparing the second groups of terms;

$$\kappa\frac{a^{\ell_o}}{P_o^{\ell_o}}F(\ell)\frac{V}{b+V} \leftrightarrow \frac{1}{\eta\left(\frac{\partial v}{\partial P}\right)\ell}F(\ell)\frac{a^{\ell_o}}{P_o^{\ell_o}}\frac{V}{b+V}(V_m^{\ell_o} - V)$$

which implies, under the assumptions described, that

$$\left[1 + \frac{P_o V_m}{A\, v_m^{\ell_o}}\right] = \frac{1}{\eta\left(\frac{\partial v}{\partial P}\right)^{\ell}} \quad (V_m^{\ell_o} - V) = \text{a constant.}$$

The reaction velocity, v, contained on the right side of the equality represents the oxygen consumption, $d\dot{V}_{O_2}$, which is a measure of the metabolic energy of the system. If this term is rewritten so that the partial derivative of tension appears in the numerator, the result is a ratio of efficiencies,

$$\frac{1}{\eta}\,\frac{\partial P}{\partial v}\quad (V_m^{\ell_o} - V) = \frac{1}{\eta}\,\frac{\partial P(V_m^{\ell_o} - V)}{\partial (d\dot{V}_{O_2})}$$

which the formulation implies would be constant.

The analysis of the energy consumption of the muscle as a function of state appears to be consistent with the phenomenological relationship offered by Bornhorst and Minardi. The proposed model (Equation 62) suggests physiological interpretations of the phenomenological expressions which may be evaluated by experimentation to give an improved understanding of the underlying phenomena of energy consumption in muscle contraction.

4. Work classification

At the level of the isolated muscle, the work performed by the system is a relatively simple determination. Certainly in the studies and experimental techniques described in earlier sections, the calculation of work done has been the most facile portion of the analyses. As the system

increases in complexity, the investigation becomes somewhat more complicated and the calculation of work is no longer a clear, straightforward procedure.

The classification of work types when the body is chosen as the system can be facilitated through the use of mechanics. Three general divisions become apparent and are summarized with examples in Table 14.

These categories are not intended to be absolute and often a particular form of work will fall into more than one category. They are a convenient guide for the types of work to be considered here.

a. Exercise without work Running or walking at a constant velocity on a nondeformable surface with the analysis performed for whole body as the system is described by Equation 24. Since the systems to be discussed are isochoric and isobaric, specific enthalpy will be used in place of specific internal energy and $\hat{C}_p$ in place of $\hat{C}_v$.

$$m\hat{C}_p \frac{dT}{dt} + \frac{\hat{H}dm}{dt} + \Delta\dot{M} = \dot{Q} + \sum_j \sum_i \hat{H}_{ij}\dot{\omega}_{ij}\delta_j$$

Depending upon the severity of the exercise, the system temperature may or may not rise, so $m\hat{C}_p\, dT/dt \geq 0$. The energy consumption, $\Delta\dot{M}$, measured from oxygen uptake and oxygen debt, is a negative quantity. The mass of the body will not change during short bouts of exercise, but in running over extended periods of time, such as in marathons, weight loss may be significant. The enthalpy flow terms due to respiration are usually negligible. The heat exchange term is negative and is represented by convective, radiative, and evaporative heat transfer.

Table 14. The classification of physiological work forms

	Work in a gravitational field		Work of propulsion		Work against drag
System	Body	Legs	Body	Legs	Body
Work examples	Weight lifting	Lifting the torso in a running or walking stride	Throwing a projectile	Accelerating the torso in a stride	Swimming; Running Cycling into a wind

Costill (30) has presented data on changes in the physiological state of a male human during running on a treadmill. Data for oxygen uptake, rectal temperature changes, and weight loss are given. Integrated values for the duration of the 101 minute run are

$$\int_0^{101} (\hat{H} \frac{dm}{dt}) dt = -3.2 \text{ kcal}$$

$$\int_0^{101} (m\hat{C}_P \frac{dT}{dt}) dt = +123.4 \text{ kcal}$$

$$\int_0^{101} (\sum_k \Delta\tilde{H}_{Rk} d\xi_k/dt) dt = -1664.1 \text{ kcal}$$

Heat loss data are not given. Use of the first law balance indicates that the heat loss value should be

$$Q = \hat{H}\Delta m + m\hat{C}_P\Delta T - \sum_k \Delta\tilde{H}_{Rk}\Delta\xi_k$$

$$Q = -3.2 \text{ kcal} + 123.4 \text{ kcal} - 1664.1 \text{ kcal}$$

$$= -1550 \text{ kcal.}$$

To justify this, if the body weight loss, $\Delta m = 3$ kg, is due to sweating, the total heat loss from the evaporation of this amount of sweat is (heat of vaporization at the skin temperature, $\Delta\tilde{H}_v(30°C) = -580$ kcal/kg water)

$$Q_E = (3 \text{ kg}) \times (-580 \text{ kcal/kg})$$

$$= -1740 \text{ kcal.}$$

Any unevaporated sweat does not contribute to this heat loss and, while all of the weight loss may not be due to sweating, the value predicted and the value calculated are in close agreement.

For the convective heat loss, Shitzer (103) has given a formula for the overall heat transfer coefficient, h_c, as a function of air velocity.

$$h_c = 7.5 \times v^{0.67} \tag{68}$$

where h_c is in the units of kcal/m^2·°C·hr and the velocity is in meters/second. If the subject is running in still air, his running velocity becomes the relative air speed. With v = 5 m/s, the body surface area = 1.9 m^2, h_c = 22 kcal/m^2·°C·hr, the skin temperature, T_s = 30°C, and the air temperature, T_{air} = 25°C,

$$Q_c = h_c A(T_{air} - T_s)\Delta t$$

$$= (22) \times (1.9) \times (25 - 30) \times (101 \text{ min}) \times (\text{hr}/60 \text{ min})$$

$$= -350 \text{ kcal.}$$

The sum of convective heat transfer and the maximum evaporative heat loss, $Q_E + Q_C$, is equal to -2090 kcal. This is in reasonable agreement with the first law value for heat loss calculated by difference.

Similar data have been given by Pugh *et al.* (85) for athletes participating in a marathon race (42 km). Although the conditions are not as controlled as they are in treadmill experiments, the energy data provided balance remarkably well.

The following are data and the integrated values over the entire 158 minute run:

Subject:

Initial weight = 74.4 kg

DuBois surface area = 1.9 m^2

Height = 178 cm

Average running speed = 16 km/hr

Weight loss = 5.23 kg

Rectal temperature change = 2°C

Calculated values:

$\hat{H}\Delta m$ = - 9.0 kcal

$m\hat{C}_p\Delta T$ = 247 kcal

ΔM = - 3000 kcal

Q = - 2600 kcal + 275 kcal (the second number is the authors' estimate of radiation heat transfer)

$\Sigma \hat{H}_{ij} m_{ij} \delta_j$: negligible

$$\hat{H}\Delta m + m\hat{C}_p\Delta T + \Delta M = Q$$

The balance yields

- 2762 kcal $\tilde{=}$ - 2325 kcal.

The 16% difference in these values may be a result of the inability to account for the total heat loss from the body and low value for the heat of vaporization of sweat used by the authors (see 104). However, the first law expression has again provided a good comparison between

physiological data and the thermodynamic quantities they represent and has reasonably satisfied the overall balancing of these data.

b. Leg segment analysis To illustrate the analysis of a situation where work is performed, the subsystem to be considered is the leg segment. The active muscles during running are largely the leg muscles and an analysis of the work performed by the leg subsystem on the torso has been done for running and walking on a per stride basis (26, 27).

In the first half-stride, one leg works to change the potential and kinetic energies of the torso. The torso is lifted and accelerated. During the second half-stride, the second leg prepares to duplicate the actions of the first. The original working leg becomes passive and acts as a brake, absorbing and/or dissipating the energy transmitted to it by the falling and decelerating torso. The energy may be taken up as internal thermal energy, partially absorbed in the stretching of muscle fibers as elastic energy, or dissipated to the surroundings. The energy balances to describe the activity of the legs are taken from Equation 24

$$m\hat{C}_p \, dT/dt + \sum_k \Delta\tilde{H}_{Rk} \, d\xi_k/dt = \Sigma \, \hat{H}_{ij}\dot{\omega}_{ij}\delta_j + \dot{Q} - \dot{W}$$

for the first half-stride and

$$m\hat{C}_p \, dT/dt + f_s \frac{d\ell'}{dt} + \sum \Delta\tilde{H}_{Rk} \, d\xi_k/dt = \Sigma \, \hat{H}_{ij}\dot{\omega}_{ij}\delta_j + \dot{Q}$$

for the second half-stride.

The values calculated by Cavagna et al. (27) for the work done to raise and accelerate the body must be slightly modified to account for the difference between total body mass used in the calculations done by the authors, and torso weight, which is the actual mass supported by the legs. The torso is taken to have 60% of the total body mass. Then the lifting and accelerating work rates are 18 cal/kg body mass•min and 30 cal/kg body mass•min, respectively. The legs of a 75 kg man running for 158 minutes perform about 570 kcal of work. During heavy exercise such as running, the legs receive 87% of the total blood flow (48). Consequently, a reasonable estimate of the energy consumption of the leg system would be to assume that the legs also consume 87% of the total body oxygen uptake. Using oxygen consumption data from Pugh et al. (85) as an estimate, the energy consumption of the leg segment is about 2600 kcal for the 158 minute period.

To account for the other terms in the first law balance, several estimates are required. The temperature rise of working muscle follows rectal temperature rise, but the absolute value of the muscle temperature is 1-2°C lower (94). Therefore, the rectal temperature data of Pugh et al. (85) is utilized to find $m\hat{C}_p\Delta T = 53$ kcal. The average specific heat of the leg system is $\hat{C}_p = 0.84$ cal/g•°C, calculated by using the weighted average of specific heats of muscle, bone, blood, and skin from Shitzer (103).

The convective heat transfer due to the increased blood flow to and from the deep tissue of the legs is not significant because of the negligible change in blood temperature between the inlet and outlet of

the leg system. The blood vessels at the skin surface, however, are significant as heat exchangers as they raise the temperature of the skin to facilitate heat loss. The external heat transfer can be estimated from the expression for convective heat transfer from (12), $Q = \int_0^t h_c A(T_s - T_{air})dt$. The heat transfer coefficient for the leg system may be derived from values given for the whole body by comparing the Nusselt number for the body as a cylinder to the Nusslet number for the legs as cylinders. The results of this calculation predict that the heat loss from the legs will be 45% of the total heat loss. The value obtained in this manner is similar to the 40% derived from merely taking a ratio of surface areas. The heat loss from the legs is then found to be approximately 1425 kcal.

The total integrated balance now yields

$$m\hat{C}_p\Delta T + \Sigma\, \Delta\tilde{H}_{Rk}\Delta\xi_k = Q - W$$

$$53 \text{ kcal} - 2600 \text{ kcal} = -1425 \text{ kcal} - 570 \text{ kcal}$$
$$- 2550 \text{ kcal} \cong - 2000 \text{ kcal}$$

which is within reasonable agreement considering the approximations made and the various sources of data. This example shows that the work performed is actually a very small portion of the energy consumption and energy transformation during exercise. The overall efficiency of the working legs, neglecting elastic energy storage, is approximately 22%.

This is in good agreement with typical exercise efficiency values found in the exercise physiology literature.

It is worthwhile to further consider several familar forms of exercise and to evaluate their contribution to individual terms of the first law balance.

c. Work against drag Cavagna et al. (25) have studied the mechanics of sprinting. Their data allow the calculation of the work done to overcome air resistance and to change the kinetic energy of the body. Sprinting is one of the few forms of exercise where the translational kinetic energy term is present in the first law balance.

In still air, the drag increases as the square of the sprinting velocity, v, and, therefore, the power output is proportional to v^3. The situation changes somewhat when running into a wind. This will be illustrated subsequently.

The drag is evaluated from the expression from (108),

$$D = \frac{1}{2} C_D A \rho v^2 \tag{69}$$

where D = drag in Newtons

C_D = drag coefficient, a function of body shape and velocity (here $C_D = 0.8$)

A = projected body surface area

ρ = density of air.

The total work done against drag in accelerating from rest to a velocity of 9.4 m/s was calculated by Cavagna et al. (25) to be 0.12 kcal. The

kinetic energy change of the 68 kg subject was calculated to be 0.454 kcal. The changes are small, but they occur over a time interval of only 4.5 seconds, so that the increase in power output is 0.15 hp.

An important point to consider in evaluating the energy consumption in short, transient exercises such as sprinting is that a large portion of the energy sources may be anaerobic. Therefore, the $\Delta\dot{M}$ measured from oxygen uptake over the work period alone may be too small. Åstrand and Rodahl (6) point out that, in work times of up to two minutes, the anaerobic energy is more important than the aerobic. For durations of 10 seconds or less, the anaerobic contribution can amount to 85% of the total energy consumption. The data of Fenn (45) and Sargent (95) support this. Fenn has calculated the proportion of energy used in producing "useful work" (potential energy changes, velocity changes, acceleration and deceleration of limbs) and has found it to be almost 23% of the total energy requirement. The total energy is 40% anaerobic, consumed largely for the "useful work" and its inefficiencies, with the remaining aerobic 60% used in the recovery period. Sargent has shown that the energy consumption in a series of 120 yard sprints and the subsequent recovery periods could not possibly be supplied by aerobic sources alone. Therefore, it is important to measure oxygen consumption for any type of exercise, but especially for the short, intense activity such as the sprinting described above, from initiation of the exercise until recovery is complete.

d. Overcoming wind resistance The calculation of the work to overcome drag is similar to that in the previous section. In the case

of an opposing wind, drag is calculated from

$$D = \frac{1}{2} C_D A \rho u^2$$

where u is now the relative velocity between the wind and the running athlete.

The data of Pugh (84) can be used to calculate the work to overcome drag and to calculate the expected heat loss with the overall energy balance.

The wind velocity for the chosen example is 18.5 m/s. The drag coefficient used by Pugh is $C_D = 1.04$ and the projected surface area of the runner is 0.5 m^2. For a running velocity of v = 4.5 m/s, the rate of doing work is found to be

$$\dot{W} = \frac{1}{2} C_D \rho u^2 A v \qquad (70)$$

$$= 0.147 \text{ kcal/s} \cong 0.82 \text{ hp.}$$

The corresponding change in oxygen uptake was measured to be 5.0 liters/min. Then the energy consumption $\Delta\dot{M}$ is

$$\Delta\dot{M} = \left[\frac{5.0\ \ell O_2}{\text{min}}\right] \times \left[\frac{-4.82 \text{ kcal}}{\ell O_2}\right] \times \left[\frac{\text{min}}{60\text{s}}\right]$$

$$= - 0.40 \text{ kcal/s.}$$

If both the thermal internal energy change and the flow terms are neglected, the $\dot{Q}$ determined by difference is

$$\dot{Q} = \dot{W} + \Delta\dot{M} = - 0.25 \text{ kcal/s}$$

Davies (33) has performed similar experiments and has determined that the energy cost of overcoming air resistance is 7.8% of the total energy consumption required in sprinting, 4% for middle distance running, and 2% in marathons. However, his calculations of the work used drag as proportional to (wind velocity)^3 rather than the correct (relative wind velocity)^2 x (running velocity). It is important to distinguish the two velocities used in drag power calculations. The velocity used to calculate the drag force depends on the velocity of the object relative to the fluid in which it moves. The velocity used to calculate the power, $\dot{W} = \underset{\sim}{F} \cdot \underset{\sim}{v}$, is the velocity of the object relative to fixed coordinates.

If the sprinter is considered as the system, and the starting line as the coordinate system origin, the drag force is proportional to u^2, where u is the relative velocity between the runner and the wind, so that

$$\underset{\sim}{u} = \underset{\sim}{v} - \underset{\sim}{v}_w$$

where $\underset{\sim}{v}$ is the running velocity and $\underset{\sim}{v}_w$ is the wind velocity. The drag force is then

$$D = \frac{1}{2} C_D \rho A u^2$$

and the power becomes

$$\dot{W} = D \cdot \underset{\sim}{v}$$

When running into the wind, the runner must exert a force equal and opposite to the drag and therefore performs work.

When running with the assistance of the wind, work may be done on the system. This occurs when the relative velocity, $\underset{\sim}{u} = \underset{\sim}{v} - \underset{\sim}{v}_w$, is negative; i.e. the wind velocity is greater than and in the same direction as the running velocity. Since the value of $\underset{\sim}{u}$ will be squared in the drag calculation and since the value for work must be negative, this situation requires that a new proportionality constant, c', be defined that is negative when $\underset{\sim}{u}$ is negative. This type of modified or "reverse" drag coefficient has been discussed by Davies (33).

When the wind velocity and the running velocity are in the same direction but $\underset{\sim}{v} > \underset{\sim}{v}_w$, the runner has effectively "outrun" any wind assistance and the drag coefficient for running in still air at a velocity of $\underset{\sim}{u}$ is used to calculate drag.

Another example of work against drag is the work done by a cyclist. The mechanics and energetics of cycling have been well studied by Diprampero *et al*. (35). Their definition of work has been for the man-cycle system. The analysis discussed here will be for the man alone.

Cycling requires the performance of physical work. Each leg of the cyclist must apply a force on the pedals to push them through a half-rotation, thereby satisfying the classical definition of work. The magnitude of the force required to achieve a particular cycling velocity is a function of several variable, viz. a) the frictional resistance in the pedals, the chain, and the gears, b) the frictional or rolling resistance of the tires on the cycling surface, c) the incline of the cycling

surface, and d) the wind resistance.

If the mechanical friction in the moving parts of the bicycle is neglected, the total resistance to forward motion, R_{TOT}, is expressed by Diprampero et al. (35) is

$$R_{TOT} = R_R + D \tag{71}$$

with R_R = rolling resistance (includes the effects of surface incline)

D = drag = $\frac{1}{2} C_D \rho \dot{x}^2 = k\dot{x}^2$, where k is a constant and x represents ground speed.

The equation for power has then been written as

$$\dot{W} = R_{TOT}\dot{x} \tag{72}$$

and the work done is

$$\int \dot{W} = \int R_{TOT}\dot{x}dt.$$

If the analysis is performed on the rider, however, the use of $\dot{x}$, the ground speed, is not entirely correct. If d is the distance through which the pedals move in each half-rotation, this distance is related to the distance x that the bicycle covers through the gear ratio, f, so that $d = fx$. The distance x is appropriate in determining the work done to overcome wind drag, but the pedal rotation distance, d, should be used

to calculate the work performed against rolling resistance.

Therefore, the modified equations for power and work become

$$\dot{W} = R_R\dot{d} + D\dot{x} \tag{73a}$$

$$= (fR_R + D)\dot{x}$$

and $$W = (fR_R + k\dot{x}^2)x \tag{73b}$$

Diprampero and his co-workers have measured the rolling resistance R_R and the constant k as

$$R_R = (\frac{4.5 \times 10^{-2} N}{kg \text{ body wt}} + 9.8 \sin\theta)P$$

where θ = the angle of the incline of the surface

P = the body mass in kg

$k = 0.19 \text{ N/m}^2 \cdot \text{s}^2$

The rolling resistance is specifically calculated for the conditions of the experiment and is dependent upon such variables as the inflation pressure of the tires and the posture of the cyclist.

e. Projectiles and propulsion In the case of throwing projectiles, the analysis is similar to the leg segment problem in which the legs accelerated the torso in every stride. Work is done by the body in accelerating a mass, m, through a distance, x. If the initial work of lifting the object to the "launching" position is neglected, work is calculated from

$$W = \int_{x_o}^{x} F dx = \int_{v_o}^{v} mv dv$$

where v is the projected object's velocity, $v = dx/dt$.

If the applied force, F, is considered to be constant throughout the distance, x, then

$$W = F(x - x_o) = \frac{mv^2}{2g_c} - \frac{mv_o^2}{2g_c}$$

For force-mass conversion constant, g_c, is included to maintain consistent units. The force applied for a distance $(x - x_o)$ imparts a kinetic energy to the projectile and the work is measured from the resultant change in the kinetic energy of the object.

If the initial distance, x_o, and the initial velocity, v_o, are both chosen to equal zero,

$$W = Fx = mv^2/2g_c$$

For example, if the mass of the projectile (a softball) is 0.5 kg and it departs the hand of the thrower at v = 70 mph = 31.4 m/s, the work done by the thrower is

$$W = \frac{1}{2} \frac{(0.5kg)(31.4\ m/s)^2}{1\ Ns^2/kg \cdot m} = 246\ N \cdot m = 0.06\ kcal$$

If the distance over which the force is applied can be measured, the force applied may be calculated. For example, if x = 1 m, then F = 246 N. The power output is $\dot{W} = F\,dx/dt = F\int_0^t a\,dt$ where a is the acceleration of either the throwing arm or of the ball. If the force is applied over 1 m, the final velocity attained is 31.4 m/s and the total time of the force application, t, can be found.

From the mechanics relations for acceleration, velocity, distance, and time,

$$v = v_o + at \qquad v_o = 0$$

$$x = x_o + \frac{1}{2}at^2 \qquad x_o = 0.$$

Solving for time, $t = 2x/v = 0.064$ s. The average acceleration is $a = (31.4\ \text{m/s})/(0.064\ \text{s}) = 493\ \text{m/s}^2$. Then the power at any time is

$$\dot{W} = 246\ \text{N} \int_0^\tau \frac{493\ \text{m}}{\text{s}^2}\,dt$$

and the value for the power output for the entire throw is

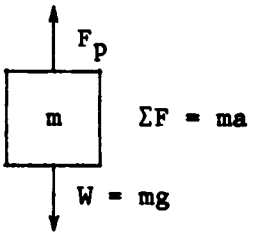
$$\dot{W}_{TOT} = 7761.5\ \text{N m/s} = 1.86\ \text{kcal/s} = 10.4\ \text{hp}.$$

f. Work in a gravitational field The lifting and lowering of weights is often analyzed in the literature with the calculation of negative work. The work calculation for the lifting of weights is simply evaluated by a force times distance expression. However, when weights are lowered, they perform work on the body. In the energy balance, W

is in this case a negative number, hence, the misleading term, negative work, has been commonly used.

When work is done on the body, the resulting energy flows should reflect the gain of energy by the system. This situation and the concept of negative work are best analyzed through an example of the mechanics of weight lifting.

If a free-body diagram is drawn for the weight with the positive direction designated as upward, Newton's second law says that the effect of the sum of the forces should appear in the acceleration of the mass,



where F_p = the force applied by the person

m = the mass of the weight

$\underset{\sim}{g}$ = gravitational acceleration

$\underset{\sim}{a}$ = acceleration of the mass.

Then, to solve for the force applied by the subject, F_p,

$$\Sigma F = m\underset{\sim}{a}$$

$$\underset{\sim}{F}_p + \underset{\sim}{W} = m\underset{\sim}{a}$$

$$\underset{\sim}{F}_p = m\underset{\sim}{a} - \underset{\sim}{W} = m\underset{\sim}{a} - m\underset{\sim}{g}$$

In general,

$$\underset{\sim}{F}_P = m\frac{d\underset{\sim}{v}}{dt} - m\underset{\sim}{g}$$

where acceleration has been written as the time derivative of velocity. For lifting, $\underset{\sim}{a}$ is positive and opposite to $\underset{\sim}{g}$.

$$\underset{\sim}{F}_P = m\underset{\sim}{a} - m\underset{\sim}{g}$$

$$= m(a + g)\underset{\sim}{e}$$

where $\underset{\sim}{e}$ is the unit vector in the positive direction. The power output during lifting can then be expressed using the velocity of lifting, $\underset{\sim}{v}$,

$$\underset{\sim}{F}_P \cdot \underset{\sim}{v} = m(\frac{dv}{dt} + g)\underset{\sim}{e} \cdot \underset{\sim}{v}$$

and work, W, over the time, τ, becomes

$$W = \int_o^\tau \underset{\sim}{F}_P \cdot \underset{\sim}{v}\, dt = \int_{v(0)}^{v(\tau)} m\underset{\sim}{v} \cdot d\underset{\sim}{v} + \int_0^\tau m\underset{\sim}{g} \cdot \underset{\sim}{v}\, dt$$

Since velocity is the time derivative of distance, $\underset{\sim}{v} = d\underset{\sim}{x}/dt$,

$$W = \int_{v(0)}^{v(\tau)} m\underset{\sim}{v} \cdot d\underset{\sim}{v} + \int_{x(0)}^{x(\tau)} m\underset{\sim}{g} \cdot d\underset{\sim}{x}$$

$$= \frac{1}{2} m(v(\tau)^2 - v(0)^2) + mg(x(\tau) - x(0))$$

If initially velocity and distance are set equal to zero,

$$W = \frac{1}{2} mv(\tau)^2 + mgx.$$

The work done on the weight will be manifested in its potential and kinetic energy changes. Specifically, if $d\underset{\sim}{v}/dt = 0$, then the work done by the subject is expressed as $W = mgx$.

The analysis is slightly more complicated for the lowering of the weight. Using the same sign convention and the same free-body diagram,

$$\underset{\sim}{F}_P = m(\underset{\sim}{a} - \underset{\sim}{g})$$

with $\underset{\sim}{a}$ now in the negative direction $\underset{\sim}{a} = a(-\underset{\sim}{e})$.

$$\underset{\sim}{F}_P = m(a(-\underset{\sim}{e})-g(-\underset{\sim}{e}))$$

$$\underset{\sim}{F}_P = m(g - a)\underset{\sim}{e}$$

The power output of the person is

$$\underset{\sim}{F}_P \cdot \underset{\sim}{v} = m(g - \frac{dv}{dt})\underset{\sim}{e} \cdot \underset{\sim}{v}$$

$$\dot{W} = - mgv + mv\ dv/dt$$

This expression shows that the body absorbs energy. To find the work done by the subject,

$$W = \int_0^\tau \dot{W} dt = \int_0^\tau \underset{\sim}{F}_P \cdot \underset{\sim}{v}\, dt = \int_0^\tau mg\underset{\sim}{e} \cdot \underset{\sim}{v}\, dt - \int_{v(0)}^{v(\tau)} m \frac{dv}{dt} \underset{\sim}{e} \cdot \underset{\sim}{v}\, dt$$

$$= \int_{x(0)}^{x(\tau)} mg\underset{\sim}{e} \cdot dx(-\underset{\sim}{e}) - \int_{v(0)}^{v(\tau)} m\underset{\sim}{e} \cdot v(-\underset{\sim}{e})dv$$

$$= - mg(x(\tau) - x(0)) + \frac{1}{2} m(v^2(\tau) - v^2(0))$$

If the mass is lowered at a constant velocity, $d\underset{\sim}{v}/dt = 0$, or if the initial and final velocities are zero, $W = -mgx$. Clearly, work is done on the body by the weight. This has often been misleadingly interpreted as the subject doing negative work.

The body receives the largest amount of energy in the shortest time when the weight is allowed to fall freely onto the body. If $\underset{\sim}{v}(0) = 0$, the potential energy of the weight will be transformed into kinetic energy which will enable the weight to do work on the body as it is suddenly brought to a halt by its impact with the body. The effects of a large kinetic energy change are eliminated if the weight is lowered differentially. Then the work done on the body is dissipated or absorbed at each increment of lowering, and the effects on the body are not nearly as drastic as in the first case. The rate of doing work is minimized. Real situations lie between these two extremes.

The rate at which work is done on the body may appear in the energy balance of Equations 23 and 24 in one or more terms. The energy could be entirely dissipated, so that

$$\dot{Q} = \dot{W},$$

or the system could transform the power input into thermal energy,

$$m\hat{C}_p \, dT/dt = - \dot{W}.$$

If the system is capable of energy storage in a manner similar to a spring, elastic internal energy storage is possible,

$$\sum_s f_s \frac{d\ell'_s}{dt} = - \dot{W}.$$

The work done on the system may also be transformed into changes in the kinetic and/or potential energies of the system. An example of this is the effect of the impingement of a high velocity air stream on a ping-pong ball causing a change in its translational and rotational kinetic energy and/or its potential energy.

Because of the inefficiencies of energy transformation, the most likely form of the first law expression to describe a situation in which work is done on the system may include each of the terms described above,

$$\frac{d\phi}{dt} + \frac{dK_{TOT}}{dt} + m\hat{C}_P \frac{dT}{dt} + \sum_k \Delta\tilde{H}_{Rk} \frac{d\xi_k}{dt} + \sum_s f_s \frac{d\ell'_s}{dt} = \dot{Q} - \dot{W} \qquad (74)$$

The necessity of including the metabolic term is justifiable in the following sense. We again consider the extremes of power input into the body, the freely falling weight and the differentially lowered weight.

The muscles of the body modulate the energy uptake that accounts for the difference between these extremes as they lower the weight. This requires muscle contraction in what may be approximated as a series of infinitesimal isometric contractions at constantly varying muscle lengths. Although the positive work performed is not obvious in a macroscopic evaluation of the body muscles as the system, on a microscopic level, there is some subunit of the muscle that is performing work to modulate the energy transformation and to maintain the series of isometric contractions. The muscle cross-bridges may be the subunits that function in this way. Therefore, some energy consumption is always necessary and the oxygen consumption of lowering the weight will be greater than that at rest. However, this value will be lower than that in a macroscopic isometric or isotonic contraction in which the weight is held or lifted, respectively.

Asmussen and Bonde-Petersen (4) have provided data on the effects of negative work on the subsequent amount of positive work performed. Subjects jumped from a squatting position without preparatory movements in which work could be done on the muscles of the subject. They were then allowed to jump using a) a preparatory counter-movement or b) after jumping down from a specified height. Situations a) and b) were designed to stretch the muscles used in jumping to allow them to take advantage of stored elastic energy.

The results showed that the subjects were actually able to jump higher with some preparatory motion except when jumping from the highest height of 0.690 m. The situation may be analyzed by considering, again, the leg segment as the system. The effect of jumping down onto the legs

or of the counter-movement is to convert potential energy of the torso into stored elastic energy in the leg muscles.

The energy balance for the torso for this step is

$$\Delta\phi = - W_{torso}$$

and the torso does work on the legs so that $W_{legs} = - W_{corso}$.

The balance for the legs before the jump upwards is

$$m\hat{C}_p\Delta T + f_s(\ell - \ell_o) = Q - W_{legs} = Q + W_{torso} = Q + -\Delta\phi_{torso}$$

If we further assume that the metabolic energy consumed in each jump upward is the same regardless of previous events, the efficacy between the conditions with and without negative work may be compared. The increase in apparent efficacy due to negative work will result in the achievement of a greater height in jumping. If the differences between the thermal energy changes and heat losses between both conditions are negligible, the stored elastic energy is assumed to account for the difference.

Energy balances on the leg segments are:

without elastic energy:

$$(m\hat{C}_p\Delta T)_1 + \Delta M_1 = Q_1 - W_1$$

with elastic energy:

$$f_s(\ell - \ell_o) + (m\hat{C}_p\Delta T)_2 + \Delta M_2 = Q_2 - W_2$$

If

$$(m\hat{C}_p\Delta T)_1 \cong (m\hat{C}_p\Delta T)_2,\ \Delta M_1 \cong \Delta M_2,\ \text{and}\ Q_2 \cong Q_1$$

$$f_s(\ell - \ell_o) = W_1 - W_2$$

The use of a preparatory counter-movement allowed the recovery of the greatest amount of negative work as stored elastic energy, 23%. Jumping from increasing heights gave conversion efficiencies of 13%, 10.5%, and 3.3% in order of increasing height. This suggests that more energy is dissipated when the conversion occurs more abruptly and the legs act as shock absorbers. The counter-movement is a smoother motion and less energy is dissipated.

The counter-movement and each of the succesive preparatory jumps increased the overall efficacy of the jumping movement by 5%, 8%, 12%, and 6% of the original value, respectively.

Cavagna et al. (28) have done studies of negative work on the efficiencies of isolated muscle. They stretched initially relaxed muscle and then stimulated it to allow it to shorten with 3.94 g·cm of work done by the muscle. The same muscle was stretched during an isometric contraction by performing 40 g·cm of work on the muscle. The tension was allowed to subside slightly before the muscle shortened to perform 4.65 g·cm of work. Lastly, the conditions were the same as just described, except that the tension was not allowed to subside completely. The amount of work done then was 13.04 g·cm.

The efficiencies of elastic energy conversion in the latter two experiments were 11.6% and 32.6%. If the first experiment is used as a baseline with minimal preparatory work, the original overall efficiency is increased by 18% and 331% by the negative work done. The first value is in reasonable proximity to the results from the Asmussen and Bonde-Petersen data (4). The magnitude of the second efficiency is anomalous. The tension achieved in the muscle is much greater than in the first two experiments and therefore the positive work performed should not be compared to the first experiment as a baseline.

Asmussen and Bonde-Petersen (5) and Margaria (71) have studied the negative work performed in exercises such as running and walking and have shown that the use of stored elastic energy increases the apparent overall efficiency. Asmussen and Bonde-Petersen also conducted running, walking, and bicycling experiments on a treadmill. The subject performed these exercises while trying to overcome a constant horizontal resistance. The power output ($\dot{W}$) was the product of the resistance and the velocity. The power output was compared to the increase in metabolic rate ($\Delta\dot{M}$) measured at the exercising steady state above the basal rate. The efficiencies were found to be 53.8% for running, 32.3% for walking, and 25.1% for cycling. Since overall efficiencies are typically 25%, the mechanics of running seems to enable the muscles to take the most advantage of stored elastic energy, while the mechanics of walking apparently are such that less work is done on the muscles or the efficiency of conversion is in itself lower. Bicycling does not seem to involve negative work.

The decrease in apparent efficiency for walking as compared to running can be explained by the work done by Cavagna et al. (26, 27). The transformation of work done on the legs to stored elastic energy occurs more readily in running because the fall of the potential energy of the torso occurs just prior to the acceleration and lift phase of the stride. The stored elastic energy is immediately utilized to do work. In walking, the sequence of events is not as favorable for the reuse of elastic energy because the transfer of the potential energy of the torso to the legs is out of phase with the eventual increase in kinetic energy of the torso. The progression of the body forward comes during the fall of the torso downward.

The efficiencies of the Asmussen and Bonde-Petersen locomotion experiments are much higher than those given in their jumping experiments. This is probably due to the abrupt change in direction experienced by the jumpers that may dissipate much of the energy of the work done on the muscles. The runner goes through a smooth transition from the negative to the positive work phases, while the abruptness of transition for a walking subject lies somewhere between the two.

In summary, it has been shown that the first law can be successfully applied in the analysis of many systems in a variety of energy states. The first law allows the calculation of the minimum changes in energy necessary for changes in the energetic state of the system. It cannot be used to theoretically calculate the absolute values of these terms at a particular energy state nor can it predict the apportionment of energy

among the terms when changes do occur. These changes must be experimentally determined. However, in such cases, the first law remains the ultimate test of data consistency.

V. CONCLUSIONS

This work has resulted in several conclusions which may be divided into general and specific categories.

A. General

1. Comprehensive forms of material and energy balances for open, periodically supplied, growing systems operating far from equilibrium have been developed and successfully applied in the analysis of energy flows of living systems.

2. Physiological interpretation of the thermodynamic terms of the energy balance has lead to the development of an entropy account which facilitates the rigorous calculation of the entropy production rate and minimal total system entropy.

3. The corrected interpretation of oxygen consumption and water loss data from avian egg experiments has lead to the development of a relationship between oxygen consumption and heat loss and the understanding of changing energy flows and energy storage during periods of growth and development.

4. The rate of specific system entropy production has been shown to be positive but decreasing during periods of growth and development. The minimal system entropy is increasingly positive during this period.

5. The results of the calculation of entropy production rates have been in general agreement with Prigogine's hypothesis.

6. Generalized expressions for physiological efficiency and efficacy have been developed and have been shown to be conducive to the reinterpretation of previously used anomalous efficiency definitions.

B. Specific

1. The minimal entropy production rate of a living system may be more properly determined by comparing the system's heat loss and metabolic energy conversion levels, as opposed to reaching conclusions based on either quantity alone.

2. The entropy production due to changing the molecular organization of living systems may be estimated and shown to contribute negligibly to total system entropy change.

3. Material balances, generalized reaction stoichiometries, and system respiratory quotients may be used as indirect measures of internal system processes and in analyzing the patterns of reactant consumption and product formation.

4. Muscle contraction may be described as a cyclic operation both at the cross-bridge level and the macroscopic level. These cyclic representations are a useful guide in the design of muscle contraction experiments and in the design of muscle testing apparatus.

5. Oxygen uptake requirements for muscle may be expressed as a state function dependent upon muscle length, tension, and the amount of work performed. This model produces a direct physiological interpretation of nonequilibrium phenomenological expressions for muscle contraction and serves as a classification device for muscle experiments.

6. Characterization of physiological work performed by muscles and muscle systems can be improved by classification into three categories; work in a gravitational field, work of propulsion, and work against drag.

VI. RECOMMENDATIONS

1. The methods of energy and entropy flow analysis developed in this work should be extended to the study of living systems which may be experimentally monitored over the natural lifespan of the system to permit comparative investigation of the entropy production during growth and development, maturity, and ageing. Expanded studies of microbial cultures seem promising as systems of study for this purpose.

2. The changes in the rates of processes occurring within a living system under stressed and unstressed conditions should be investigated in order to determine what significance entropy production patterns and the principle of maxima at equilibrium may have on lifespan.

3. The approaches described above may be used specifically in the study of entropy production changes caused by malignant growths.

4. The generalized first law expressions, the efficiency and efficacy definitions, and the classification of work developed in this research should be used as guides in the design of apparatus and experiments in the study of bioenergetics.

5. Further experimentation should be performed to study the energy conversion patterns during growth and development in a variety of species of living systems. This should include a more accurate determination of the efficiencies of metabolic energy transformation into biomass, products, and heat.

6. Additional work should be done in order to further substantiate the proportionality between oxygen uptake and heat loss.

7. Investigation into the water transport phenomena of incubating avian eggs is desirable, possibly accomplished by radioactive labelling of the oxygen consumed by the egg system and the subsequent analysis of the constituents of the embryo mass and of the gases released by the embryo during incubation.

8. Further muscle experimentation should be done to more precisely determine the relationships between energy consumption, muscle length, muscle tension, and work performed. This investigation should also evaluate the mechanicochemical similarities or differences between isometric and isotonic contractions.

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