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Caloric Restriction, Metabolic Rate, and Entropy

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Caloric restriction increases life span in many types of animals. This article proposes a mechanism for this effect based on the hypothesis that metabolic stability, the capacity of an organism to maintain steady state values of redox couples, is a prime determinant of longevity. We integrate the stability-longevity hypothesis with a molecular model of metabolic activity (quantum metabolism), and an entropic theory of evolutionary change (directionality theory), to propose a proximate mechanism and an evolutionary rationale for aging. The mechanistic features of the new theory of aging are invoked to predict that caloric restriction extends life span by increasing metabolic stability. The evolutionary model is exploited to predict that the large increases in life span under caloric restriction observed in rats, a species with early sexual maturity, narrow reproductive span and large litter size, and hence low entropy, will not hold for primates. We affirm that in the case of humans, a species with late sexual maturity, broad reproductive span and small litter size, and hence high entropy, the response of life span to caloric restriction will be negligible.

AGING can be defined as the progressive decline in the physiological capacity of vital organs, a process concomitant with an increase in age-specific death rate (1). A powerful indication that the process is subject to regulation is the observation that life span can be extended by caloric restriction (CR)—a phenomenon first observed in laboratory rats (2), but now documented in flies, yeast, and worms (3). The problem addressed in this article is: Is the effect of dietary restriction on life span a universal phenomenon with a comparable response for different species, or does the effect depend critically on the life history of the organism? This issue is particularly pertinent in current efforts to determine whether the large changes in mean life span induced by CR in rodents, a species characterized by early sexual maturity, narrow reproductive span and large litter size, would also obtain in humans, a species described by late sexual maturity, broad reproductive span and small litter size [see (4)].

Caloric restriction essentially induces a change in the metabolic activity of the organism. Thus, any effort to elucidate the effect of CR on life span must necessarily analyze the relation between metabolic processes and the rate at which an organism ages. There now exist a body of empirical results that point to certain relations between metabolic activity and species life span. Cutler (5) has observed that cells from longer lived species are intrinsically more resistant to the effects of mutagenic—like agents of endogenous origin that are known to destabilize the differentiated state of cells. Kapahi and colleagues (6), in a comparative study of stress resistance in primary cultures of mammalian skin fibroblasts, noted that cell stress resistance is positively correlated with species life span. These observations suggest that the capacity of cells to resist the effect of perturbations of endogenous or environmental origin may be a critical factor in regulating life span.

We will appeal to this argument to propose a class of analytic models of the aging process based on the following hypothesis: *metabolic stability, the ability of the cells of an organism to maintain steady state values of redox couples in the face of random fluctuations in enzymatic reaction rates, is a prime determinant of longevity.*

The stability–longevity hypothesis postulates that the senescence-related loss of function is due to the dysregulation of the steady-state values of redox couples, and the concomitant impairment of homeostasis. This model of the aging process contends that deviations from redox poise are an intrinsic property of all metabolic processes. These deviations derive from chance perturbations in chemical reaction rates, which characterize all metabolic systems where the concentrations of reacting species are extremely low. We postulate that the effect of these perturbations will accumulate over time and lead ultimately to the dysregulation of the developmental process, and cell death. Accordingly, senescence is the result of spontaneous changes in the metabolic condition of the cell during normal developmental. In the context of this model, longevity will be determined by processes acting to maintain homeostatic regulation.

I will invoke the stability–longevity hypothesis to propose a new theory of aging, which provides both a proximate mechanism for aging, and an evolutionary rationale for the large variability in life span observed between species. This stability theory of aging is then applied to: (a) analyze the effect of metabolic rate on the rate of aging; (b) propose a mechanism for the action of CR on life span; (c) investigate the effects of the life-history of an organism on the response of life span to CR.

The three main predictions that this new model generates are as follows:

- **I(a)** In species subject to similar ecological constraints and having equivalent body size, longer life span is

associated with a correspondingly *higher* standard metabolic rate.

- **I(b)** Prolongation of life span by regimes such as caloric restriction is associated with an increase in metabolic stability.
- **I(c)** The effect of CR on life span is constrained by the life history or the demographic entropy of the species. In high entropy species—organisms characterized by late age of sexual maturity, broad reproductive span, and small litter size—the effect of caloric restriction on life span will be negligible; whereas in low entropy species—organisms described by early age of sexual maturity, narrow reproductive span, and large litter size—the effect of caloric restriction on life span will be large.

The predictions I(a) and I(b) underscore the claim that the metabolic stability model of senescence specifies both a proximate mechanism for aging—the ultimate collapse of homeostatic regulation; Item (c) indicates that the entropic theory provides an evolutionary rationale of species variation in life span. The new theory thus stands in sharp contrast to the rate of living theory, an early model of aging proposed by Pearl (9). The rate of living theory was inspired by empirical observations that noted an inverse correlation between species longevity and mass-specific metabolic rate (10). This correlation was only observed within a small group of nonprimate mammals, and hence highly restrictive. Pearl however, went beyond these limited observations and proposed the general thesis that animal life span should be inversely correlated with the rate at which physicochemical processes occur. This proposition can be expressed by the following tenet: *Mass-specific metabolic rate is a prime determinant of longevity.*

This alleged primacy of metabolic rate as the factor regulating longevity has two main implications:

- **II(a)** Longer life span in species with equivalent body size is associated with a correspondingly *lower* standard metabolic rate.
- **II(b)** Prolongation of life span by regimes such as caloric restriction is associated with a reduction in mass-specific metabolic rate.

The rate of living theory does not provide an evolutionary rationale for aging. It does, however, offer a proximate mechanism, based on the accumulation of oxygen free radicals generated during metabolism. As a mechanistic model, the free radical theory has had considerable appeal and influence, as the review in (11) indicates. However, its main predictions are not consistent with empirical data. Cross-species comparisons, as reported in (12), are in conflict with II(a). These studies show that longer life span in species with equivalent body size is associated with a *higher* standard metabolic rate. Empirical studies of the effects of CR on mice, as reported for example in (13), indicate that CR may increase, decrease or have no significant effect on mass-specific metabolic rate, an observation that conflicts with II(b). The studies of Austad and Fischer (12) and Masoro and colleagues (13) and related empirical work have thus tended to undermine the notion that the rate of energy expenditure drives the senescent process. The stability theory of aging proposed in this article is partly driven by an effort to explain the large body of empirical studies which are now agreed to be inconsistent with the rate of living theory. The stability-longevity theory relates features such as metabolic stability, a molecular property, with species life span, a population level characteristic. The theory integrates principles from two classes of analytic models: quantum metabolism (7), which pertains to processes at the molecular level, and directionality theory (8), which deals with processes at the population level. To facilitate the reading of this paper, I will give a brief synopsis of the main ideas that underlie quantum metabolism and directionality theory, and then describe their implications to the study of aging.

Quantum metabolism recognizes that energy transduction in metabolic systems is determined by the movement of electrons and protons through a series of carriers in biological membranes—the plasma membrane in bacteria, the inner membrane in mitochondria, and the thylakoid membrane in plants. The model assumes that the metabolic energy generated by the flow of electrons between redox centers in the biomembrane is quantized, that is, the energy produced is transmitted in discrete bundles. The methods of quantum statistics were then invoked to express the total metabolic energy generated by the electron transfer process as a function of the metabolic cycle time, the mean time it takes electrons to flow from donor to acceptor states within the cell membrane. This fundamental relation between metabolic energy and cycle time was then exploited to study metabolic organization in multicellular organisms. We showed that the metabolic rate, P, which is defined as the rate of energy expenditure, is allometrically related to body size, W, according to the equation (7),

$$P = \alpha W^{\frac{4\mu-1}{4\mu}}. \quad (1)$$

The quantity μ is the metabolic efficiency, the ratio of the rate of ADP phosphorylation to the rate of the electron transport process. The proportionality constant, α, depends on properties such as the proton conductance and the electrochemical potential of the biomembrane.

Directionality theory is an analytical model of the evolutionary process that integrates demography and Mendelian genetics to study genotypic and phenotypic changes of populations under different ecological constraints (8). In this theory, Darwinian fitness, the parameter that describes the outcome of competition between mutant and ancestral types in a population, is measured by demographic entropy, denoted H, and given by (8),

$$H = -\frac{\int_0^\infty p(x)\log p(x)dx}{\int_0^\infty xp(x)dx} \equiv \frac{S}{T}$$

Here $p(x)dx$ is the probability that a female in the age range $(x, x + dx)$ bears a child.

The function S describes the uncertainty in the age of the mother of a randomly chosen newborn. The quantity T represents the generation time, the mean age of mothers at the birth of their offspring.

Demographic entropy H is positively correlated with demographic stability, the capacity of a population to maintain steady state values of population numbers in spite of small variations in the individual birth and death rates (8). The main predictions of directionality theory derive from the analytical fact that entropy, and its correlate demographic stability, are the principal measures of selective outcome, and hence the main determinants of genotypic and phenotypic change under natural selection.

Directionality theory postulates that the outcome of selection will be regulated by ecological factors, such as resources, which impose constraints on the intensity of selection. Accordingly, it distinguishes between two classes of ecological constraints (i) *bounded* growth—this condition pertains to populations described by a stationary size, or a size that fluctuates around some constant value; (ii) *unbounded* growth—this property describes populations which spend the greater part of their life-history in an exponential growth phase. The main tenets of the theory are principles that describe evolutionary changes in entropy under bounded and unbounded growth constraints.

This article is organized as follows: I will first describe the ideas that underlie the model (quantum metabolism) that is invoked to derive the allometric relation given by Eq. [1]. I will then apply this allometric law and analogous relations to predict that metabolic potential, estimated as the total amount of energy consumed per gram of body weight during the life span of the organism, is not a universal constant, as assumed in Pearl (9), but is highly dependent on factors such as taxonomic status and ecological constraints. This dependency, which is supported by empirical data, is shown to provide one of the strongest arguments against the rate of living theory. I will then describe the longevity–stability hypothesis and invoke this condition to develop the stability theory of aging and its applications to the study of CR on life span. This study revolves around directionality theory. I will recall the basic tenets of this evolutionary model, and apply it to explain the large variability in life span observed in mammalian populations, and also to investigate the role of life history in determining the response of life span to CR. The article concludes with a commentary on empirical considerations—in particular an analysis of the quantitative response of life span to CR.

The entropic formalism exploited in this article pertains to demographic entropy. Considered as a functional property, demographic entropy describes the capacity of a population of reproducing organisms to maintain its steady state condition in the face of perturbations in the individual birth and death rates. Statistically, entropy is a measure of the variability in the age of replicating individuals in the population, and can therefore be considered as a descriptor of demographic diversity or complexity.

Entropic considerations have often been cited in qualitative studies of the aging process [see, e.g., (14), p. 10]. These heuristic models revolve around the parameter thermodynamic entropy. Considered as a functional property, thermodynamic entropy characterizes the capacity of a material aggregate to maintain its equilibrium condition in the face of fluctuations in the position and velocity of the individual particles that comprise the aggregate. Statistically, thermodynamic entropy describes the variability in the energy states of the molecules in the aggregate, and can therefore be considered a measure of molecular disorder. The relationship between demographic entropy, a property that has its origin in studies of the flow of metabolic energy within a population of replicating organisms, and thermodynamic entropy, a property that derives from studies of heat flow in material objects, will be delineated in the Appendix.

Allometric Relations: Metabolic Rate and Body Size

The standard metabolic rate of an organism is the rate of heat production under conditions that minimize known extra sources of energy use. This is usually measured by the rate of oxygen consumption since the two quantities are closely related. Empirical studies that go back to Kleiber (15), show that the standard metabolic rate, P, is allometrically related to body size, W, with a scaling exponent which is highly dependent on ecological constraints, and a proportionality constant that varies with phylogeny. A mechanistic explanation of this scaling relation and the range of values assumed by the scaling exponent is central to any analysis of the relation between metabolic processes and life span. Influential efforts to address this problem (16,17) implicitly ignore the molecular events that drive energy transduction. These models are based on processes at the macroscopic level of biological organization, and do not apply to the diversity of metabolic patterns that define unicells, plants, and animals.

Quantum Metabolism

A new class of models, applicable to organisms at all levels of biological organization was proposed in Demetrius (7). Quantum metabolism, the term we introduced to describe this class of models, is concerned with processes at the molecular level. The models appeal to the methods of quantum statistics to study the biochemical events that regulate energy transduction in biomembranes (7). Quantum metabolism draws from the chemiosmotic theory of bioenergetics (18) and postulates that the production of ATP, the energy currency of living organisms, is mediated by the coupling of two dynamical events:

(a) The movement of electrons and protons through a series of carriers within biological membranes,
(b) The phosphorylation of ADP.

The analysis proceeds by studying the energy transduction process within plasma membranes in unicells, and then extending this study to multicellular organisms.

The dynamics of energy transfer at the unicellular level was based on the following parameters: (i) The energy flux, denoted $\tilde{U}$, associated with ADP phosphorylation, (ii) the metabolic efficiency, denoted μ, which defines the coupling between the electron transport and ADP phosphorylation, (iii) the metabolic cycle time, τ, which is defined as the mean time it takes the electrons to flow from donor to acceptor states within the cell membrane. The methods of quantum statistics were applied to express the energy flux, $\tilde{U}$, in terms of the metabolic cycle time and metabolic efficiency. We have (7),

$$\tilde{U} = \tilde{\alpha}\tau^{4\mu}. \quad (2)$$

The proportionality constant $\tilde{\alpha}$ is a product of two factors: (i) the proton conductance of the cell membrane (ii) the proton motive force, a thermodynamic measure of the extent to which an ion gradient is removed from equilibrium.

The standard metabolic rate $\tilde{P}$, the rate at which chemical reactions occur within the cell is given by $\tilde{P} = \tilde{U}/\tau$, and we have

$$\tilde{P} = \tilde{\alpha}\tau^{4\mu-1}. \quad (3)$$

The relations [2] and [3] can be integrated to derive scaling relations for the cycle time τ, and the metabolic rate $\tilde{P}$, as a function of cell mass $\tilde{W}$. The argument given in (7) assumes that the total energy $\tilde{U}$ is proportional to cell mass $\tilde{W}$. This yields the allometric relation,

$$\tilde{P} = \tilde{\alpha}\tilde{W}^{\frac{4\mu-1}{4\mu}}. \quad (4)$$

Equation [4] refers to unicells. In order to determine the scaling relations for the standard metabolic rate, P, of a multicellular organism, as a function of body size, W, we consider the multicellular organism, as an aggregate of interacting unicells. By appealing to a conservation of energy flow argument through the network of cells that describe the multicellular organism, we showed that the total metabolic rate, P, will satisfy a scaling relation analogous to Eq. [4]. This yields the allometric law expressed by Eq. [1].

The relation between metabolic flux and cycle time given by [2] can also be used to derive a scaling relation for the maximum life span, denoted L, which is defined as the mean life span of an organism in a protected environment. The quantity L can be considered as the time period over which the total metabolic energy can be consumed. We have, as shown in (7), the following relation between life span, L, and body size W,

$$L = \alpha W^{1/4\mu}. \quad (5)$$

The relations given by Eq. [1] and Eq. [5] show that the properties metabolic rate and life span depend not only on body size, but are determined by the metabolic efficiency, μ, and a proportionality constant α.

The metabolic efficiency, μ, can be expressed in the form, $\mu = qZ$. Here q is a measure of the degree of coupling between electron transport and proton phosphorylation, and Z is the stochiometric parameter, which is equal to the ATP/electron flux ratio. The proportionality constant α can be written as $\alpha = k\theta\Delta p$, where θ denotes the proton conductance and Δp the proton motive force, properties that depend on the permeability of biological membranes [see Nicholls and Ferguson (19)]. The proton conductance, θ, for example, depends on the phospholipid composition of the biological membrane. Proton conductance increases with the incorporation of polyunsaturated fatty acids, the greater the number of double bonds, the greater the proton conductance. Phospholipid composition differs between homeotherms and heterotherms: the former typically have more polyunsaturated phospholipids forming the bilayers of their membrane. Accordingly, proton conductance is greater in homeothermic than in heterothermic tissues when compared at constant body temperature (20).

Metabolic Potential and Life Span

The allometric relation described by Eq. [1] pertains to the standard metabolic rate, P, that is the total energy production of the organism over a set period of time: We can use this equation to determine an allometric relation for the mass-specific metabolic rate, denoted P^*, and defined as the total metabolic rate per unit mass. The function P^* is given by, $P^* = P/W$. From Eq. [1], we now have,

$$P^* = \alpha W^{-1/4\mu}. \quad (6)$$

The mass-specific rate, in contrast to the standard metabolic rate, is a decreasing function of body mass.

The scaling relations given by Eq. [5] and Eq. [6] can be used to derive a relation between P^* and L. We have:

$$P^*L = C. \quad (7)$$

The quantity C can be considered to be proportional to the energy expended per unit mass during the lifetime of the organism. Thus C describes the lifetime metabolic expenditure, or metabolic potential of the organism. In view of the expressions for P^* and L, we note that C will be determined by the proportionality constant α.

The range of values assumed by α is constrained by the structural properties of the biomembrane. As we observed earlier, the proportionality constant α is a product of the proton motive force, and the proton conductance. Proton conductance, as noted in Hulbert and Else (20), assumes different values in homeothermic and heterothermic tissues when compared at constant body temperature. Proton conductance also varies with body size (21). These observations imply that the parameter α will vary within and between species. Consequently the metabolic potential, C, is not a biological invariant, as postulated in the rate of living theory, but a parameter which is highly dependent on phylogenetic status and on ecological constraints.

Metabolic Rate, Metabolic Stability, and Longevity

The inverse relation between metabolic rate and longevity, which Eq. [7] describes, was first formalized on empirical grounds by the German physiologist Max Rubner (9). Rubner measured metabolic rate in several species of mammals and observed that in spite of the large differences in longevity, the product of mass-specific metabolic rate and longevity (the metabolic potential) was constant. Pearl (8) expanded on this empirical observation. He assumed that the metabolic potential was the same across all species, and on the basis of this assumption proposed the rate of living hypothesis.

Pearl's theory and its derivatives have been influential in both theoretical and empirical studies of the aging process for the last seven decades. However, its fundamental assumption—energy expenditure per life span is approximately the same across species—is not supported by analytical studies as Eq. [7] indicates. These studies show that the metabolic potential, C, is highly dependent on the proportionality constant α, a quantity which varies with the structure and composition of biomembranes—a species-specific property. The assumption is also inconsistent with empirical data. Various phylogenetic groups have different metabolic potential. Lifetime energy expenditures can assume a large

range of values: ~25 kcal in dipterian flies, ~200 kcal in nonprimate mammals, ~800 kcal in humans, and ~1500 kcal in birds. The constancy of metabolic potential, postulated in Pearl (9), does not even hold within mammalian orders. As reported in Austad and Fischer (12), energy expenditure per lifetime shows a 20-fold range of variation in studies based on 164 mammalian species. The range of variation is also significant in species of the same genus: Energy expenditure per lifetime shows a 10-fold range of variation among marsupials and a fourfold range among bats (12).

In this section, I will develop the stability theory of aging, a competing model, which among other things, explains, the large variation in metabolic potential observed both within and between species. Its central tenet, the stability–longevity hypothesis, asserts that metabolic stability is the prime determinant of aging, and that the senescence related loss of function is due to the breakdown in homeostatic regulation.

Metabolic Stability and Longevity

Metabolic stability describes the capacity of the metabolic system to resist chance perturbations in the reaction rates of enzymes in the metabolic networks, and to maintain constant steady state values of redox couples such as NAD/NADH. In highly stable systems the steady state concentrations of redox couples will be kept at levels that regulate the production rate, for example, of reactive oxygen species (ROS).

Unstable systems will be characterized by large deviations in the concentrations of redox couples from their steady state values. These deviations will induce fluctuations in certain metabolites, such as ROS species, with an attendant dysregulation of the signal transduction and other metabolic pathways.

Our analysis of the stability–longevity hypothesis will draw from some recent results on the complexity and stability of dynamical systems (22). These studies show that complexity, as measured by the entropy of the dynamical system, and stability, as measured by the rate at which perturbed states of the system return to the steady-state condition, are positively correlated. This analytic result is also applicable to dynamical systems describing cellular growth and metabolism (22). We will appeal to this result, and exploit relations between (i) the complexity and stability of cellular dynamical systems, (ii) metabolic rate and body size, to predict the following general property: *Among species subject to similar ecological conditions and with equivalent body size, the standard metabolic rate and longevity will be positively correlated.*

This new theory of aging predicts a coupling between metabolic rate and life span which is more complex than that proposed by the rate of living theory. The argument that underlies this coupling revolves around a new concept metabolic entropy. This property pertains to the diversity of the metabolic pathways that characterize intracellular processing of substrates and products. We will investigate relations between metabolic entropy and the properties metabolic stability, a property of the molecular network, and demographic entropy, a property of the population network. These relations will be exploited to establish the correspondence between metabolic rate and longevity, which we have enunciated.

Metabolic Entropy and Metabolic Stability

The concepts metabolic entropy and metabolic stability are analytical properties that characterize structural and dynamic properties of networks of metabolic reactions in cells [see (22)].

The model we consider will focus uniquely on the transformations from substrates to products that occur in the metabolic system. Our analysis recognizes that the large number of enzyme-catalyzed reactions in the cell do not take place independently of each other but are integrated into sequences of consecutive reactions with common intermediates. We will represent these coupled sequences of reactions in terms of a discrete dynamical system. We will be concerned only with the behavior of the system at steady state. In this case it can be represented by the equation

$$\bar{u}(t+1) = A\bar{u}(t).$$

Here $\bar{u}(t) = \{u_j(t)\}$ denote the vector of concentration of the metabolites. The matrix $A = \{a_{ij}\}$, where (a_{ij}) denote the rate at which an enzyme transform the substrate I_i into the product I_j.

We follow the analysis in Demetrius and colleagues (22), and we let $P = (p_{ij})$ be the Markov matrix associated with $A = (a_{ij})$, and $\pi = (\pi_i)$ the stationary distribution of P. Metabolic entropy pertains to the variability in the rates at which substrates are transformed into products during the metabolic process. Analytically, metabolic entropy, denoted H^*, is given by

$$H^* = \sum_i \pi_i H_i \tag{8}$$

Where

$$H_i = -\sum_j p_{ij} \log p_{ij}.$$

The quantity H_i represents the variability in the reaction rates of the set of enzymes that use I_i as a substrate. The number H^* describes the mean value of H_i, the mean obtained by averaging over the frequency distribution (π_i). The quantity H^* is a measure of the extent to which the system of sequential reactions are clustered around a few common intermediates. A high entropy system is characterized by a high degree of clustering, a low entropy system is described by few sequences of consecutive interactions sharing a common intermediate.

The term metabolic stability refers to the capacity of the cell to maintain steady state concentrations of metabolites in the face of perturbations in enzymatic reaction rates. An analytic characterization of metabolic stability derives from the following considerations. We first remark that perturbations in reaction rates due to events intrinsic to the metabolic process will induce variations in the distribution of metabolites and corresponding fluctuations in the concentration of the redox couples.

Let $P_n(\varepsilon)$ denote the probability that the concentration of redox couples at time n differs from the predicted concentration by more than ε. As n increases, it can be shown that $P_n(\varepsilon)$ will tend to zero (22). The fluctuation decay rate, denoted Q^*, is the asymptotic rate at which the

number $P_n(\varepsilon)$ tends to zero. The quantity $P_n(\varepsilon)$ can be interpreted as the probability that the sample mean of a metabolic observable defined at instant n, differs from the asymptotic mean by more than ε. We write

$$Q^* = \lim_{n\to\infty} -\frac{1}{n}\log P_n(\varepsilon).$$

The fluctuation-stability theorem (22) asserts that

$$\Delta H^* \cdot \Delta Q^* > 0. \quad (9)$$

The relation [9] implies that the larger the entropy, the more rapid the fluctuation decay rate, or the greater the ability of the network to resist chance perturbations in reaction rates and to maintain steady state values of redox couples.

Metabolic Entropy and Demographic Entropy

The quantity metabolic entropy, H^*, pertains to the complexity of the metabolic network. Demographic entropy, S, refers to the complexity of the reproduction-survivorship cycle. Now changes in the metabolic properties of the organism will induce changes in the individual life cycle and hence changes in individual survivorship and fecundity. This will result in a variation in population properties, such as demographic entropy. We will now investigate the relation between these changes in metabolic and demographic entropy, respectively.

We first observe that fluctuations in the reaction rates of the enzymes in the metabolic network are an inherent property of metabolic systems. These fluctuations, which derive from the intrinsic random variations in molecular processes, will induce variations in metabolic activity, and hence changes, ΔH^*, in the metabolic entropy. Furthermore, variations in metabolic activity will cause perturbations in the reproduction and mortality components, with a corresponding change, ΔS, in demographic entropy. We will now show that the changes ΔH^* and ΔS are positively correlated. We write

$$\Delta H^* \cdot \Delta S > 0. \quad (10)$$

The correlation described by Eq. [10] derives from the following argument: Since the intrinsic fluctuations at the demographic level (demographic stochasticity), are driven by stochastic events at the metabolic level (metabolic stochasticity), the fluctuation decay rates Q and Q^* of population numbers and metabolic concentration, respectively, will be positively correlated. Analytically, we have

$$\Delta Q \cdot \Delta Q^* > 0. \quad (11)$$

Now, according to the fluctuation–stability theorem (22), changes in entropy and changes in the fluctuation decay rate are positively correlated. Hence we have $\Delta H^*\ \Delta Q^* > 0$, and $\Delta S\ \Delta Q > 0$. We can therefore conclude from Eq. [11] that the change, ΔH^*, in metabolic entropy, and the change ΔS in demographic entropy will be positively correlated—a condition that is expressed by Eq. [10].

Demographic Entropy and Life Span

The stability–longevity hypothesis implies a positive correlation between metabolic stability and longevity. In view of the fluctuation–stability theorem (see Eq. [9]), we can infer that metabolic entropy and longevity will also be positively correlated. We can therefore invoke the relation between changes in metabolic entropy and changes in demographic entropy to predict that demographic entropy and life span will be positively correlated. We write

$$\Delta S \cdot \Delta L > 0. \quad (12)$$

Equation [12] implies that a long life span will be positively correlated with a broad variation in the net-reproductive schedule.

Empirical support for Eq. [12] is provided by cross species comparisons. Among mammals of equivalent body size, large entropy species (bats), defined by late sexual maturity, broad reproductive span, and small litter size are relatively long lived; low entropy species (rats and mice), characterized by early sexual maturity, narrow reproductive span, and large litter size are short lived.

Metabolic Rate and Longevity

The correlation given by Rubner (10), and the scaling relation for metabolic rate, Eq. [1], can now be used to predict certain relations between metabolic rate and longevity. Two crucial items will be considered in this analysis. The first is the relation between changes in demographic entropy, ΔS, and changes in metabolic rate, ΔP. We have (7,23),

$$\Delta S = T\,\Delta P. \quad (13)$$

Here T denotes the generation time, the mean age of mothers at the birth of their daughters.

The second item is the scaling relation for generation time,

$$T = \tilde{\alpha} W^{1/4\mu}, \quad (14)$$

Equation [14] can be derived by appealing to the same set of arguments used to express metabolic rate, P, as a function of body size [see (7)]. The generation time, T, is thus dependent on both $\tilde{\alpha}$, which is a function of the structure and composition of biomembranes, and μ, the metabolic efficiency, which will be determined by ecological and resource constraints.

The relations [12], [13], and [14] thus indicate that any coupling between metabolic rate and longevity will be highly contingent on factors such as metabolic efficiency, the structure and composition of biomembranes, and body size.

These observations can be expressed in terms of the following general tenet: *Among species with similar membrane composition, similar metabolic efficiency, and equivalent body size, the physiological properties metabolic rate, and the life-history property longevity will be positively correlated.*

We write

$$\Delta P \cdot \Delta L > 0. \quad (15)$$

There exists a large body of empirical data on longevity and metabolic rate for birds and mammalian species (24). The ecological conditions under which these species evolved are also well documented. I will appeal to this study to evaluate the coupling between metabolic rate and longevity as expressed by Eq. [15]. I will consider two classes of cross

species comparisons, namely (i) eutherians and marsupials and (ii) birds and mammals (12). The standard metabolic rates of marsupials are reported to be approximately 70% that of equivalent-sized eutherian mammals. However, marsupials are shorter lived. The standard metabolic rates of birds are much higher than that of equivalent sized mammals—birds, however, have a considerably greater maximum life span.

These cross-species comparisons are clearly consistent with the positive correlation between standard metabolic rate and life span expressed by Eq. [15], hence it offers support to the stability theory of aging. The empirical data, however, conflicts with the rate of living theory. As we observed in our earlier discussion, the rate of living theory predicts that relatively longer life span is associated with a correspondingly lower mass-specific metabolic rate. This implies, that in the case of species with equivalent body size, the standard metabolic rate and longevity will be negatively correlated. This prediction does not accord with the cross-species comparisons we have described.

Caloric Restriction and Life Span

Limiting the dietary intake of mammals is a method of extending life span, which goes back to the pioneering experiments on mice (2). There is now convincing evidence that the effect of CR on life span is coupled to metabolic events. However, the precise mechanism that defines this coupling remains to be elucidated. I will appeal to the stability theory of aging to propose the following mechanism: *Caloric restriction increases life span by increasing metabolic stability*. This claim will be shown to be a consequence of the stability–longevity hypothesis, and the proposition, which we now establish, that CR acts on the metabolic process by increasing the entropy of the metabolic network.

Caloric Restriction and Metabolic Entropy

We study the effect of CR on metabolic entropy H^* by considering a discrete dynamical system describing the metabolic process. We assume that the dynamical system is at steady state. Under steady state conditions, the system will now be described by the linear equation

$$\bar{u}(t+1) = A\bar{u}(t).$$

Here $A=(a_{ij}) \geq 0$ denote the transition matrix, where a_{ij} is the reaction rate of an enzyme transforming the metabolite I_i to I_j.

Under the steady-state assumption, we have $\lambda = 1$, where λ denotes the dominant eigenvalue of the matrix A. The constraint on λ entails that the elements $\{a_{ij}\}$ of the transition matrix will satisfy, $0 \leq a_{ij} < 1$.

Now CR is known to increase the efficiency of a number of key enzymes in intermediary metabolism (25). This increase in efficiency implies an increase in the reaction rates of the enzymes in the metabolic pathway to yield a new matrix, $\hat{A} = (\hat{a}_{ij}) \geq 0$, with $\hat{a}_{ij} \geq a_{ij}$.

Let ΔH^* denote the change in entropy induced by the action of CR on metabolic activity. The perturbation studies described in Arnold and colleagues (26) show that

$$\Delta H^* = -\sigma^2\delta.$$

Here σ^2, a positive quantity, denotes the demographic variance of the metabolic network, and δ, the magnitude of the changes in the reaction rates of the enzymes which the action of CR induces. The perturbation analysis indicates that, since $\hat{a}_{ij} > a_{ij}$, and $0 \leq a_{ij} \leq 1$, then $\delta < 0$. We conclude that $\Delta H^* > 0$, that is, CR will result in an increase in metabolic entropy.

We have shown, however, see Eq. [9], that metabolic stability and metabolic entropy are positively correlated. In view of the stability–longevity hypothesis, we can now infer that caloric restriction increases life span by increasing metabolic stability.

The increase in metabolic stability that the model predicts will be mediated through an increase in the efficiency of key enzymes in the metabolic pathways. These changes, as is characteristic of chemical processes, will be highly nonlinear. We predict that stability will increase under CR until a certain limiting value is attained, at which point the system becomes resistant to further changes.

The positive coupling between CR, metabolic stability and longevity which the model predicts is consistent with empirical studies of CR on three classes of model organisms: *Caenorhabditis elegans*, mice, and yeast.

Studies of the effect of CR on *C. elegans* (25) have observed an increased resistance to elevated temperature, a condition that reflects an enhanced production of heat shock proteins. The studies on mice indicate an increased rate of gluconeogenesis under the action of CR (27). The investigations in (28) on yeast reveal an increase in the NAD/NADH ratio, one of the prime determinants of metabolic regulation. These three classes of metabolic response correspond to an increased homeostatic capability of the cell, that is, an increase in the ability of the cell to maintain steady state concentrations of redox couples.

A general support for the prediction that CR increases life span by increasing metabolic stability is provided by the recent studies of a genome-wide microarray expression analysis of genes in the liver (29). The liver is the central organ for the regulation of glucose homeostasis. Accordingly, it has a major effect on metabolic regulation during aging. A common effect of aging in liver is the induced expression of a number of stress response genes—a condition that reduces the homeostatic capability of the organ. The experimental design reported in Cao and colleagues (29) showed that CR opposed the age-related induction of stress response genes and inflammatory genes. This action can be considered as an enhancement of homeostatic regulation, and hence an increase in the metabolic stability of the organ.

Caloric Restriction and Entropy: Evolutionary Considerations

The proposition that CR increases life span by increasing metabolic stability has important implications for evaluating the response of life span to caloric restriction in different species. The genus *Rattus* and *Mus* (laboratory rats and mice, respectively) have been the model organisms in studies of CR on life span. The problem we now address is: *Will the large increases in life span observed in laboratory rats and mice subject to CR also hold for humans?*

We will appeal to an evolutionary argument in addressing this question. Metabolic stability, as is the case with other

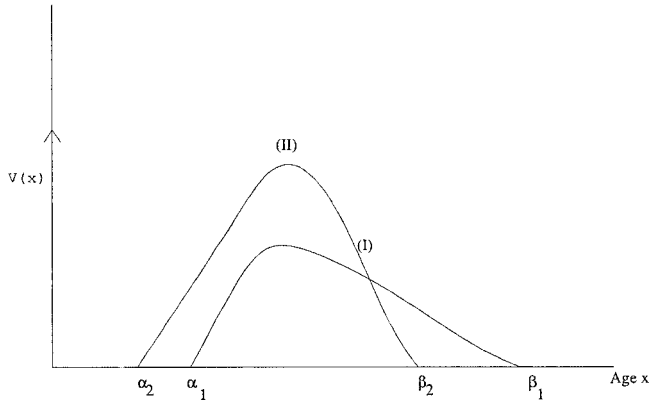

Figure 1. The relation between the shape of the net-reproductive function $V(x)$ and the entropy H. Model (I) = large entropy. Model (II) = small entropy. α = age of sexual maturity; β = age at which reproduction ceases.

physiological variables, has been subject to changes during the evolutionary history of the population. The pattern of these changes can be predicted by analyzing changes in demographic entropy under the forces of mutation and selection.

Demographic Entropy

The concept demographic entropy is a function of the age-specific and fecundity and mortality schedule, and is given by $H = S/T$ where

$$S = -\int_0^\infty p(x)\log p(x)dx; \quad \text{and} \quad T = \int_0^\infty xp(x)dx. \quad (16)$$

Here $p(x)$ denotes the probability density function of the age of reproducing individuals in the population. The function $p(x)$ is given by

$$p(x) = \exp(-rx)V(x).$$

The quantity r denotes the population growth rate. The function $V(x)$, the net-reproductive function at age x, is given by the product $l(x)m(x)$, where $l(x)$ is the probability that an individual born at age zero survives to age x, and $m(x)$ is the mean number of offspring produced by an individual age x. $V(x)$ can be qualitatively described in terms of three parameters: (i) the age of sexual maturity, (ii) the age at which reproduction ceases, and (iii) the net reproductive output.

The function S is a measure of the uncertainty in the age of the mother of a randomly chosen newborn. This quantity describes the spread of the net-fecundity function. The function T, the generation time, denotes the mean age of mothers at the birth of their offspring.

The function H, and concomitantly S, are functions of the life history of the organism, that is, the age-specific birth and death rates. The entropy parameters H and S, can be qualitatively described as follows (32):

(a) *Large entropy*: late sexual maturity, large reproductive span, small litter size.
(b) *Small entropy*: early sexual maturity, narrow reproductive span, large litter size.

The properties (a) and (b) can be derived from sensitivity analysis, the study of changes in entropy with respect to changes in the net-fecundity function $V(x)$. We have (30),

$$\frac{\partial H}{\partial V_x} = -\frac{\exp(-rx)}{T}Q(x) \quad (17)$$

where $Q(x) = W(x) - U$. Here $W(x) = -x\Phi + \log V(x)$; $U = \int_0^\infty xp(x)W(x)dx/T$.

In most natural populations the net-fecundity function $V(x)$ is a concave function of x. By taking the derivatives of $W(x)$ and $Q(x)$, we can easily show that $Q(x)$ will therefore be a convex function of x.

The qualitative properties (a) and (b) are the result of the sensitivity relation, Eq. [17], and the concavity and convexity of the functions $V(x)$ and $Q(x)$, respectively (30). The shape of the net-reproductive function, $V(x)$, for large and small values of entropy are given by Figure 1.

Directionality theory.—Directionality theory classifies populations according to the ecological forces that impinge on the population throughout its evolutionary history. It distinguishes between two classes of ecological constraints.

(a) *Bounded growth*: This pertains to populations (equilibrium species) existing in environments in which resources are limited but in constant supply. Population size under this constraint will be stationary or fluctuate around some constant value.
(b) *Unbounded growth*: This condition refers to populations (opportunistic species) existing in environments in which resources are ample but only intermittently available. Population size under this constraint will be characterized by prolonged and recurrent episodes of rapid increase followed by short periods of population decline.

The main tenets of directionality theory are a set of principles that relate the ecological constraints—bounded and unbounded growth—to changes in entropy under mutation and selection. Since evolutionary changes in the parameters H and S are positively correlated (23), the directionality principles pertain to both the entropy rate H, and the entropy function S. These tenets can be qualitatively annotated as follows.

- **A(1)** In populations subject to bounded growth constraints, evolution is described by a unidirectional increase in entropy.
- **A(2)** In large populations subject to unbounded growth constraints, evolution is described by a unidirectional decrease in entropy.
- **A(3)** In small populations subject to unbounded growth constraints, evolution is described by random, nondirectional changes in entropy.

Principles A(1), A(2), and A(3) pertain to evolutionary changes at the population level. These relations between ecological constraints and changes in entropy can be applied to infer trends in metabolic stability, the ability of cells in an organism to maintain steady state values of redox couples.

We first note that changes in demographic entropy, ΔH, and changes in metabolic stability ΔQ, are positively correlated (22). This correlation implies that evolutionary

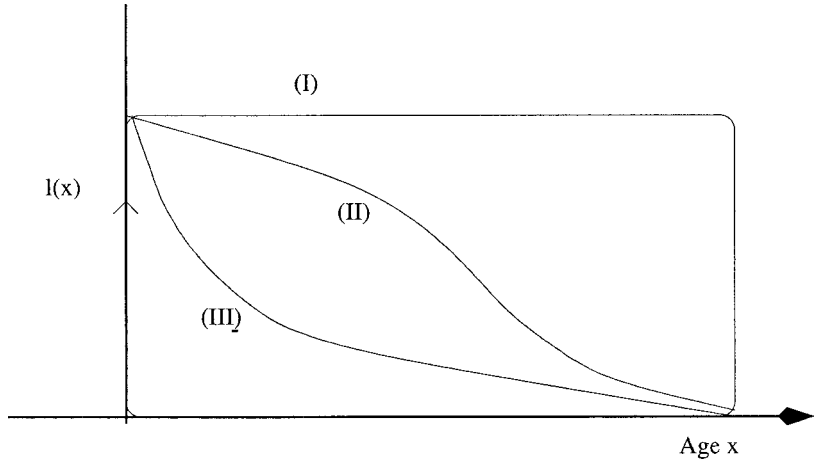

Figure 2. Three canonical survivorship curves. Type (I) $\tilde{H} = 0$, Type (II) $\tilde{H} = 1/2$; Type (III) $\tilde{H} = 1$.

changes in metabolic stability will also satisfy principles analogous to A(1), A(2), and A(3). We have:

- **B(1)** In populations subject to bounded growth constraints, evolution will be described by a unidirectional increase in metabolic stability.
- **B(2)** In large populations subject to unbounded growth constraints, evolution will be described by a unidirectional decrease in metabolic stability.
- **B(3)** In small populations subject to unbounded growth constraints, evolution will be described by random, nondirectional changes in metabolic stability.

The principles B(1), B(2), and B(3) imply that the physiological response of an organism to caloric restriction will be contingent on its evolutionary history. Caloric restriction, as the preceding analysis shows, increases metabolic stability. We can therefore infer from the evolutionary trends in metabolic stability that (B) delineates, that the response of metabolic stability to CR will depend on the life history of the organism. The metabolic stability of organisms whose evolutionary history is defined by bounded growth constraints will be close to its maximal value. Hence any further increase that CR may induce will be relatively small. However, in the case of organisms whose evolutionary history is described by unbounded growth constraints, caloric restriction should generate relatively larger changes in metabolic stability. This argument indicates that life span extension under CR in populations subject to bounded and unbounded growth constraints will be significantly different.

The responses of life span to CR in populations defined by bounded and unbounded growth constraints, and the correlation between metabolic stability and metabolic entropy, as expressed by Eq. [9], entail the following dependencies between demographic entropy and the response of life span to CR.

- **C(1)** Species with large demographic entropy will be characterized by a relatively weak response of life span to caloric restriction.
- **C(2)** Species defined by small demographic entropy will be characterized by a comparatively large response of life span to caloric restriction.

The predictions C(1) and C(2) are consistent with the qualitative arguments and empirical observations described in Austad (31). Evidence from cross-species studies indicate that net reproductive output influences longevity. In Austad (31), ecological arguments were exploited to propose that in species with reduced levels of reproduction (*K*-selected species), the effects of CR on life span will be negligible, whereas in species with high levels of reproduction (*r*-selected species), the effects of CR on life span will be pronounced. As we observed in the characterization of demographic entropy, *K*-selected species and *r*-selected species correspond to high and low entropy populations, respectively (22). This correspondence between demographic entropy and ecological constraints as defined by the *r*-*K*-selection model, indicates that the qualitative arguments advanced in Austad's study (31) are indeed consistent with the predictions of our analytical model.

Caloric Restriction and Entropy: Empirical Considerations

The principles C(1) and C(2) provide a qualitative description of the effect of life history and physiological properties on the response of life span to CR. We now proceed to develop a quantitative description by introducing the concept life table entropy.

The mean life span e_o of a population of organisms is given by

$$e_0 = \int_0^\infty l(x)dx$$

where $l(x)$ denote the age-specific survivorship function.

The effect of caloric restriction on a population of organisms can be described in terms of a transformation of the survivorship curve $l(x)$ to a new function $l^*(x)$. Caloric restriction is assumed to act on adult individuals in the

population, hence the change $l^*(x)$ will be described by a change in the slope of the survivorship curve. The induced change $g(x)$ in the slope of the survivorship curve will be given by

$$g(x) = \frac{\log l^*(x) - \log l(x)}{\log l(x)}.$$

The relative change in the mean life span is defined by $\Delta e_0 = e_0^* - e_0/e_0$: We have (32),

$$\Delta e_0 = \tilde{H}\psi. \tag{18}$$

The parameter ψ denotes the mean change in slope, that is, the mean value of the function $g(x)$. For example, if caloric restriction results in a decrease in mortality, say δ, which is independent of age, then $l^*(x) = l(x)^{1+\delta}$, and hence $\psi = \delta$.

The function $\tilde{H}$, which is called the life-table entropy, is given by Demetrius (33) and Keyfitz (34),

$$\tilde{H} = \frac{-\int_0^\infty l(x)\log l(x)dx}{\int_0^\infty l(x)dx}. \tag{19}$$

The function $\tilde{H}$ is a measure of the uncertainty in the age of death of an individual who has just died. As observed in Demetrius (32),

$$\tilde{H} \leq 1 + \log(\beta/e_0^2)$$

where $\beta = \int_0^\infty xl(x)dx$.

Hence, when $\beta < e_0^2$, a condition that empirical studies show is satisfied by most natural populations, we have

$$0 < \tilde{H} \leq 1.$$

The properties of $\tilde{H}$ can be illustrated by an analysis of three canonical survivorship curves (see Figure 2).

The Type (1) or rectangular distribution represents the situation where all individuals attain the maximum physiological longevity of the species. Here the maximum age at death and the mean life span coincide. We have $\tilde{H} = 0$. The Type (II) distribution is obtained by maximizing $\tilde{H}$, subject to a constraint on the variance of the age of death. The corresponding survivorship function is $l(x) = \exp[-\pi/4e_0^2]x^2$, and $\tilde{H} = 1/2$. The Type (III) life table describes a mortality curve that is independent of age. All individuals in the population have a constant chance of death. The distribution is given by $l(x) = \exp(-x/e_0)$, and $\tilde{H} = 1$.

The equation [18] asserts that the relative change Δe_0 in mean life span is a function of two variables, an *individual* property ψ, which depends on the intensity of CR, and a *population* property $\tilde{H}$, which reflects the variance in the age of death. We should note that the parameters that appear in Eq. [18] can be empirically evaluated. The quantity ψ can be estimated from the survivorship curves before and after caloric restriction. The function $\tilde{H}$ is given by Eq. [19] and is thus determined by the survivorship curve $l(x)$. Hence the empirical significance of Eq. [18] can be determined using life history data. The values assumed by Δe, the change in mean life span, depends on the range of variation of the parameters ψ and $\tilde{H}$. We now qualitatively characterize this range and exploit this property to describe the effect of life history on the response of life span to CR.

The parameter Ψ.—The mean value Ψ depends on the intensity of caloric restriction, ρ, and the metabolic stability Q. This dependency derives from the coupling between CR and metabolic stability we have proposed, namely: caloric restriction extends life span by increasing metabolic stability. In view of the nonlinear dependency of metabolic stability on caloric restriction, we can infer that for a given intensity of caloric restriction, ρ, the parameter Ψ will be relatively small for individuals with high metabolic stability, and relatively large for individuals with low metabolic stability. Since organisms subject to bounded growth constraints, are characterized by high metabolic stability, and organisms defined by unbounded growth constraints, have low metabolic stability, we can appeal to the correlation between demographic entropy and metabolic stability as established earlier, to compare the effect of CR on populations with different life histories. Our analysis implies the following dependencies.

- **C(i)** In high entropy populations, the changes in Ψ induced by CR will be small.
- **C(ii)** In low entropy populations, the changes in Ψ induced by CR will be large.

The parameter $\tilde{H}$.—The parameter $\tilde{H}$ is a function of the survivorship curve. Evolutionary changes in $\tilde{H}$ can be analyzed by evaluating the changes ΔH and $\Delta\tilde{H}$ induced by a perturbation of the net-reproductive function $V(x)$ (32,35). If we consider perturbations of the form

$$V^*(x) = V(x)^{1+\delta},$$

we obtain,

$$\Delta H = -\sigma^2\delta; \quad \Delta\tilde{H} = \omega\delta$$

Here σ^2 denotes the demographic variance; a positive quantity. The function ω is the third moment of the distribution $\ell(x)$ (35). Numerical studies show that, for typical life tables, $\omega > 0$. Hence we have

$$\Delta H \cdot \Delta H < 0. \tag{20}$$

Equation [20] asserts that evolutionary changes in demographic entropy, H, and the life table entropy $\tilde{H}$, are negatively correlated. Since evolutionary changes in the entropy parameters H and S are positively correlated, we can appeal to Eq. [20] to predict the following dependencies between the entropy function S and the life table entropy $\tilde{H}$.

- **D(i)** Species with large values for the entropy S, that is, species with life history described by late sexual maturity, long reproductive span and small litter size, will be characterized by a small life-table entropy, $\tilde{H}$.
- **D(ii)** Species with small values for the entropy S, that is, species with life history described by early sexual maturity, narrow reproductive span and large litter size, will be characterized by a large life-table entropy, $\tilde{H}$.

Empirical considerations.—Equation [18] and the dependencies described by (C) and (D) can be applied to quantitatively compare the effect of caloric restriction on rats and humans.

Wild populations of rats and mice will be subject to resource constraints that induce erratic or irregular bursts of rapid exponential growth (31). Hence, these populations can be described as opportunistic species. Laboratory rats and mice are not opportunistic species in the sense of their wild relatives. However, the ecological constraints they experience may result in demographic trends similar to that observed in the wild. Under laboratory conditions, resources are always ample, and hence rapid exponential growth will be the typical condition. Hence laboratory populations of these organisms will be described by what we have defined as unbounded growth constraints. When these constraints prevail, evolution will act to decrease demographic entropy (8). Laboratory rats and mice should therefore be described by a weak metabolic stability and a comparatively large value for the life-table entropy.

The demographic analysis of human populations, [36], suggest that these populations have been subject to bounded growth constraints throughout most of their evolutionary history. Directionality theory predicts, and the empirical studies show, that in human populations, the evolutionary trend will be towards an increase in demographic entropy [see (36)]. Modern human populations should therefore be described by a strong metabolic stability, and comparatively small values for the life-table entropy.

Table 1 gives certain demographic and physiological attributes of rats, mice and humans. Values for the life-table entropy are based on modern European populations for humans, and laboratory populations for rats and mice.

We can now apply Eq. [18], to compare the effect of caloric restriction on the life span of rats and humans. Now, age related diseases in mammals can be classified as chronic, which include neoplasia, cardiovascular disease, diabetes; or acute, which pertain to inflammatory diseases. Altered redox homeostasis is one of the hallmarks of the aging process (37). The stability–longevity hypothesis entails that both chronic and inflammatory diseases will be result of an increase in metabolic instability, and a concomitant decrease in redox homeostasis with age. To assess the effect of different diseases on life span, we will distinguish between metabolic instabilities according to their effect on the nonregulatory or regulatory metabolic events that drive cellular dynamics (5,37). We contend that fluctuations in steady-state concentrations of redox couples which result in changes in the nonregulatory elements of metabolic processes will lead primarily to changes in the concentration of certain metabolites without necessarily inducing a change in the developmental program. However, fluctuations which result in changes in the regulatory behavior of cells may result in a dysregulation of the redox control machinery with a corresponding change in the pattern of gene expression. We propose that chronic diseases, such as cardiovascular ailments and diabetes, are primarily associated with alterations in the concentration of certain specific enzymes. Consequently these diseases can be considered to be the outcome of instabilities in the nonregulatory gene expression mechanism. Equivalently, acute diseases that characterize inflammatory ailments derive primarily from alterations in the developmental program. Consequently these diseases can be considered to be the result of regulatory instabilities.

Table 1. Human Life History Traits Compared to Laboratory Mice and Rats

Trait	Mice	Rats	Humans
Age at first reproduction	35–50 days	35–50 days	13 years
Litter size	4–8	8–10	1
Maximum longevity (y)	4	4	120
Metabolic rate (KJ/day)	16	104	7,200
Life table entropy	0.25	0.25	0.12

Caloric restriction, as our model predicts, increases metabolic stability. In species such as laboratory rats with relatively weak metabolic stability, the increase in stability that CR induces will be relatively large. Consequently, the metabolic instabilities that are the natural result of the aging process will be significantly reduced. Such a reduction will mitigate the deviations from steady state induced by both the nonregulatory and the regulatory effects of metabolism. Accordingly, the incidence of both chronic and acute diseases will decrease. This will be reflected by a significant change in the shape of the survivorship curve, and a correspondingly large change in the parameter ψ. The change in life span is determined by the parameter ψ and the life table entropy $\tilde{H}$. Since rats have a relatively large life-table entropy $\tilde{H}$, the change in life span, as inferred by Eq. [18], will be large.

However, in species such as humans with a relatively high metabolic stability the increase in stability induced by CR will be relatively small. This increase may be sufficient to mitigate the effect of deviations induced by changes in the nonregulatory effects of metabolism; however, its effect on monitoring the regulatory action of metabolism—a more complex dynamic process—will be less pronounced. Hence, in humans subject to CR, the incidence of chronic diseases may decrease, however, the incidence of acute diseases may not be affected. This will be reflected in a less pronounced change in the shape of the survivorship curve under CR. Accordingly, changes in the sensitivity parameter Ψ under CR will be comparatively small. Humans, in view of their life history and evolutionary ancestry, are described by a small life-table entropy $\tilde{H}$. In view of these constraints on the parameters Ψ and $\tilde{H}$, we conclude that in humans the change in life span due to CR as predicted by Eq. [18] will be comparatively small.

This class of predictions of the effect of CR on human life span should be qualified by the observation that it applies uniquely to nonobese populations. Epidemiological studies show that the incidence of certain neurodegenerative diseases is lower in countries with low per capita food consumption, such as Japan, compared to countries with a high per capita food consumption such as the United States (38). Hence CR can induce significant changes in the reduction of acute diseases in comparatively obese humans. Consequently, in the case of obese human populations, CR may result in a significant increase in life span.

In 1987, the National Institute on Aging initiated a study to determine the effectiveness of CR on rhesus monkeys, an animal model closely related to humans. These studies are incomplete. However, preliminary evidence indicates a decreased incidence of risk factors for cardiovascular disease and diabetes. However, the control and caloric restricted

groups appear to be equally susceptible to acute conditions such as inflammation and infection (39). Studies by Keyfitz (34) on the effect of the eradication of certain diseases on life span using the parameter life-table entropy, show that a reduction in the incidence of chronic diseases such as heart ailment and diabetes will have small effects on human life span. Significant increases in life span will only result from a reduction in the incidence of inflammatory diseases. Since these acute conditions are weakly sensitive to CR, these preliminary findings suggest that the effect of CR on the life span of rhesus monkeys or humans will be much less pronounced than its effect on rats and mice CR.

Conclusion

Studies in a wide range of organisms including yeast, nematodes and mice, have repeatedly demonstrated that caloric restriction significantly reduces the rate of aging and increases life span. This article proposes a mechanism to explain this effect. The model provides analytic and empirical support for the hypothesis that caloric restriction increases longevity by increasing metabolic stability, the capacity of the organism to maintain steady state values of redox couples. We also show that the magnitude of the action of CR on life span is highly constrained by the life history of the organism. We exploit an evolutionary argument to show that the response of life span to CR is determined by demographic entropy, a measure of the variability in the age at which individuals in a population reproduce and die. We predict that in high entropy species, which consist of organisms described by late sexual maturity, broad reproductive span and small litter size, the increase in life span under caloric restriction will be negligible; whereas, in low entropy species, consisting of organisms defined by early sexual maturity, narrow reproductive span and large litter size, the increase in life span under caloric restriction will be significant.

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Appendix

Demographic Entropy and Thermodynamic Entropy

This appendix will delineate the analytic and conceptual relations between demographic entropy, the parameter used in this study, and thermodynamic entropy, a notion that is sometimes invoked in heuristic models of aging. The concepts demographic entropy and thermodynamic entropy have their origin in evolutionary theory and thermodynamic theory, respectively. Both theories have similar mathematical structures, and involve concepts that are analytically related when evaluated at the cellular level of biological organization. A detailed account of the analytic relationship between the two theories is described in Demetrius (8).

Evolutionary Theory

Evolutionary theory in its widest sense may be said to be concerned with understanding and interpreting the adaptive properties of populations of reproducing organisms, in so far as these properties are determined by changes in the generation time of the population. Demographic entropy, denoted S, a central concept in this theory, is defined by

$$S = -\sum_{j=1}^{d} p_j \log p_j. \qquad \text{A(1)}$$

Here p_j is the probability that the mother of a randomly chosen newborn belongs to age-class j. The quantity S thus describes the uncertainty in the age of the mother of a randomly chosen newborn. Annual plants, for example, have small entropy: These organisms reproduce at a single instant at approximately the same time in their life cycle. Perennial plants reproduce at several different stages in their life cycle, and have a comparatively large entropy.

Demographic entropy predicts the outcome of competition between a mutant population and a resident type. Entropy in the demographic context determines Darwinian fitness, and hence the direction of evolutionary change under mutation and natural selection.

Directionality theory is a mathematical model of the evolutionary process based on the parameter entropy as a measure of Darwinian fitness. The theory studies evolutionary changes in entropy under two classes of ecological constraints—bounded and unbounded growth. The theory predicts that, when population size is large, the following relations between ecological conditions, and the outcome of competition between the resident population and the rare mutant obtain:

- **A(i)** Mutants with increased demographic entropy will replace the ancestral 66 type, under bounded growth constraints.
- **A(ii)** Mutants with decreased demographic entropy will replace the ancestral type under unbounded growth constraints.

Thermodynamic Theory

Thermodynamic theory, in its widest sense, is concerned with understanding the properties of aggregates of material particles in so far as these properties are determined by changes in temperature, that is the mean kinetic energy of the molecules that constitute the material aggregate.

Thermodynamic entropy, $\tilde{S}$, the fundamental parameter in this theory, is defined by

$$\tilde{S} = -\sum_{j} \tilde{p}_j \log \tilde{p}_j. \qquad \text{A(2)}$$

Here $\tilde{p}_j$ is the probability that a randomly chosen particle is in energy state j.

The quantity $\tilde{S}$ describes the uncertainty in the energy state of a randomly chosen particle in the material aggregate. A crystalline solid, for example, has low entropy: The molecules occupy relatively fixed positions in the material aggregate. A liquid, by contrast has high entropy, since the constituent molecules have greater degrees of freedom. Thermodynamic entropy predicts the direction of heat flow when two material objects at different temperatures are brought into contact.

Statistical thermodynamics is an analytic theory that studies the changes in entropy that occur in aggregates of inanimate matter subject to different classes of constraints. The theory distinguishes between adiabatic processes according to the magnitude of their relaxation time, that is, the time it takes the system to return to its equilibrium state. Processes in which the reactions proceed rapidly relative to the relaxation time are called *irreversible*, whereas processes that occur in times long compared to the relaxation time are called *reversible*. The distinction between irreversible and reversible processes is central in describing the two fundamental tenets of the theory:

- **B(i)** In irreversible processes, thermodynamic entropy increases
- **B(ii)** In reversible processes, the thermodynamic entropy remains constant.

Relation Between Demographic Entropy and Thermodynamic Entropy

The properties metabolic rate P, the rate of heat production in an individual organism, and heat energy, Q, the thermal energy of an ensemble of interacting molecules, are central concepts in evolutionary theory and thermodynamic theory, respectively. The analytical relation between these two properties is the basis for the correspondence between demographic entropy and thermodynamic entropy, which we now specify.

We first consider a population of reproducing organisms. Adult individuals in the population can be characterized by their metabolic rate, denoted P. The population, which consists of individuals of different ages, can be described in terms of its demographic entropy, S. Assuming that the metabolic energy of adult individuals in the population is allocated uniquely to survivorship and reproduction, then small changes in the metabolic activity of the individual organisms will result in a change in metabolic rate, ΔP, and a change in entropy ΔS, which are related by the following equation (23)

$$\Delta S = T\,\Delta P. \qquad \text{A(3)}$$

Here T denotes the generation time.

Secondly, we consider a material aggregate, solid, liquid or gas, for example. This aggregate can be described in terms of its heat energy Q. The molecules in the aggregate vary in terms of their energy states. This variability in energy states can be characterized in terms of the thermodynamic entropy, denoted $\tilde{S}$. Thermodynamic theory predicts that small changes in the molecular behavior of the material aggregate will result in a change in heat energy ΔQ, and a change in entropy $\Delta\tilde{S}$, which are related by the equation

$$\Delta\tilde{S} = \left(\frac{1}{\tilde{T}}\right)\Delta Q, \qquad \text{A(4)}$$

The expressions A[3] and A[4] refer to evolutionary and thermodynamic systems, respectively. These systems, in general, have quite distinct macroscopic representations. There exist processes, however, which can be considered both in terms of an evolutionary and a thermodynamic formalism. The canonical model is a population of replicating cells.

A population of cells can be considered as an evolutionary system: The individual cells can be described in terms of their age, or the stage in their life cycle, at which they divide into daughter cells. The population of cells will now be described in terms of macroscopic parameters such as, the generation time, the mean age at which the cells divide, the demographic entropy, or entropy production rate, and the metabolic rate. These three demographic variables will be related by Eq. A[3].

A population of cells can also be considered as a thermodynamic system. The individual cells are characterized by their constituent molecules. The molecular aggregate is a thermodynamic system defined by a temperature, the mean kinetic energy of molecular units, the thermodynamic entropy and heat energy. The population of cells can be described in terms of these macroscopic variables, averaged over the values associated with the individual cells. The three thermodynamic variables will be related by Eq. A[4].

We have exploited the properties of the molecular organization that characterizes the individual cells in the population to show that the generation time, T, of the population considered as an evolutionary unit, is inversely related to the temperature, $\tilde{T}$, which describes the population considered as a thermodynamic system (8). These studies also show that changes in the metabolic rate, ΔP, will be proportional to changes in heat energy, ΔQ. The relations between temperature and generation time, and between metabolic rate and heat energy are given by Eq. A[5] (8). We have:

$$(i)\ T \sim \frac{1}{\tilde{T}} \quad (ii)\ \Delta P \sim \Delta Q. \qquad \text{A(5)}$$

In view of A[3], A[4], and A[5], we conclude that, in the case of a population of replicating cells, we have,

$$\Delta S = \tilde{k}\,\Delta\tilde{S}, \qquad \text{A(6)}$$

where k is a positive constant.

The equation A[6] expresses a fundamental relation between changes in the parameters, demographic entropy, and thermodynamic entropy. Its significance can be interpreted as follows. We consider a population of replicating cells characterized by a thermodynamic entropy $\tilde{S}$, and a demographic entropy S. A small change in the thermal energy content of the individual cells, will induce a change in heat energy ΔQ, and a corresponding change in metabolic rate ΔP. These changes, in view of the laws of chemical kinetics will result in a change in thermodynamic entropy, $\Delta\tilde{S}$, and a change in demographic entropy, ΔS. The expression A[6] asserts that the changes ΔS and $\Delta\tilde{S}$ are proportional to each other. In particular, an increase in thermodynamic entropy will necessarily entail an increase in demographic entropy.

The relation A[6] thus implies that the directionality principles for demographic entropy described in this article are the natural extensions of the directionality principles for thermodynamic entropy expressed by B(i) and B(ii).