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Biological Aging and Life Span Based on Entropy Stress via Organ and Mitochondrial Metabolic Loading

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Abstract: The energy for sustaining life is released through the oxidation of glucose, fats, and proteins. A part of the energy released within each cell is stored as chemical energy of Adenosine Tri-Phosphate molecules, which is essential for performing life-sustaining functions, while the remainder is released as heat in order to maintain isothermal state of the body. Earlier literature introduced the availability concepts from thermodynamics, related the specific irreversibility and entropy generation rates to metabolic efficiency and energy release rate of organ k, computed whole body specific entropy generation rate of whole body at any given age as a sum of entropy generation within four vital organs Brain, Heart, Kidney, Liver (BHKL) with 5th organ being the rest of organs (R5) and estimated the life span using an upper limit on lifetime entropy generated per unit mass of body, $\sigma_{M,life}$. The organ entropy stress expressed in terms of lifetime specific entropy generated per unit mass of body organs (kJ/(K kg of organ k)) was used to rank organs and heart ranked highest while liver ranked lowest. The present work includes the effects of (1) two additional organs: adipose tissue (AT) and skeletal muscles (SM) which are of importance to athletes; (2) proportions of nutrients oxidized which affects blood temperature and metabolic efficiencies; (3) conversion of the entropy stress from organ/cellular level to mitochondrial level; and (4) use these parameters as metabolism-based biomarkers for quantifying the biological aging process in reaching the limit of $\sigma_{M,life}$. Based on the 7-organ model and Elia constants for organ metabolic rates for a male of 84 kg steady mass and using basic and derived allometric constants of organs, the lifetime energy expenditure is estimated to be 2725 MJ/kg body mass while lifetime entropy generated is 6050 kJ/(K kg body mass) with contributions of 190; 1835.0; 610; 290; 700; 1470 and 95 kJ/K contributed by AT-BHKL-SM-R7 to 1 kg body mass over life time. The corresponding life time entropy stresses of organs are: 1.2; 60.5; 110.5; 110.5; 50.5; 3.5; 3.0 MJ/K per kg organ mass. Thus, among vital organs highest stress is for heart and kidney and lowest stress is for liver. The 5-organ model (BHKL and R5) also shows similar ranking. Based on mitochondrial volume and 5-organ model, the entropy stresses of organs expressed in kJ/K per cm^3 of Mito volume are: 12,670; 5465; 2855; 4730 kJ/cm^3 of Mito for BHKL indicating brain to be highly stressed and liver to be least stressed. Thus, the organ entropy stress ranking based on unit volume of mitochondria within an organ (kJ/(K cm^3 of Mito of organ k)) differs from entropy stress based on unit mass of organ. Based on metabolic loading, the brains of athletes already under extreme mitochondrial stress and facing reduced metabolic efficiency under concussion are subjected to more increased stress. In the absence of non-intrusive measurements for estimating organ-based metabolic rates which can serve as metabolism-based biomarkers for biological aging (BA) of whole body, alternate methods are suggested for estimating the biological aging rate.

Keywords: biological aging; entropy stress; mitochondria; life span; bio-markers

1. Introduction and Rationale

Living Biological systems (BS) are open systems exchanging mass, energy and entropy with the surroundings. The required energy for sustaining the life is released through the oxidation of glucose (carbohydrates, CH), fat (F) and proteins (P) (called macro-nutrients) carried by the blood stream to all the organs (a group of tissues which are self-contained and are specialized in performing a particular function) and a part of the chemical energy of nutrients is converted into another form of chemical energy, which is stored within Adenosine Tri-Phosphate (ATP) molecules, called the energy currency of the body and which can be readily used to deliver work (W, organized energy; e.g., lifting weights and placing them on shelve resulting in energy transfer in the form of work, which causes potential energy gain of weight) and/or supply cellular energy for endothermic biological reactions, active transport of species against adverse gradient (e.g., transport of glucose in intestines) and for repair/reproduce of cells for sustaining life functions while the remainder of the chemical energy is released as heat (Q, random energy) to overcome heat loss from the body and to maintain the normal body temperature.

One may define aging as an indication of decrease in physiological life sustaining functions, which leads to an increase in age related mortalities along with a decrease in reproductive functions [1]. Weinert et al. [2] presented a comprehensive review on aging and listed multiple trajectories for aging: evolutionary [3], molecular, cellular and whole body (system) levels including the environmental factors. Medvedev [4] listed more than 300 hypotheses on aging. The evolutionary concept outlined in [3] deals with genetic variants which cause Alzheimer′s disease are found to be less in people with longer lifespans (i.e., slower rate of aging), indicating that Darwin's natural selection at work allowing better ones (without genetic mutants) to survive. Lee et al. [5] studied the regulatory effects of nutrients on aging and suggested that the nutrient composition may be altered rather than using CR for improving life span. Kirkwood's theory on aging falls under evolutionary and cellular [6] trajectories and mostly relies on copying errors. The ROS theory falls under cellular mechanism. Under ROS theory, the aging is attributed to accumulated damage to the cells of various organs via the production of radical oxygen species (ROS) during oxidation process/electron transport chain, resulting in impaired functions of cells within organs in repairing and replacing dead cells and eventually result in its inability to overcome the adverse environmental factors. It is cautioned that there are many other factors and interventions that modulate speed of aging but not necessarily related to ROS production [7]. Thus, aging is a "multi-factor" process.

Rubner's rate of living theory (ROL) assumes a fixed amount of specific metabolic energy release. $q_{M,life}$ (≈835 MJ/kg body mass, a first law hypothesis, "live fast, die young" [2]) over life span irrespective of metabolic efficiency (i.e., proportional to ATP production per unit mole of oxygen consumption) for every living organism and falls under systemic trajectory. The biological aging rate (BAR) is based on how fast or slow one reaches $q_{M,life}$. Living systems are characteristics of systems being far from equilibrium and hence must generate entropy since birth/conception. Thus Silva and Annamalai [8,9] adopted the availability concepts from thermodynamics, showing that availability/exergetic efficiency in thermodynamics is almost same as metabolic efficiency (η_M), proposed the second law hypothesis on biological aging with a fixed amount of life span entropy generation/irreversibility, $\sigma_{M,life}$ (10,000 kJ/(K kg body mass)) for the whole body. Such a hypothesis is also consistent with Andresan's concept on constant total lifetime entropy production per unit body mass for all BS [10] except that Silva's hypothesis includes the effect of metabolic efficiency. Unlike Rubner's hypothesis, the energy release along with metabolic efficiency (i.e., ATP production efficiency) affects the entropy generation rate. Thus, BAR is based on how fast or slow one reaches $\sigma_{M,life}$. The $\sigma_{M,life}$ depends on the heat part, "Q_M" (= MJ of energy released as heat/kg body mass) of specific energy release rate, (SERR) or called as specific metabolic rate (SMR) in biology.

Apart from thermodynamics governing internal biological processes, there is a perpetual outflow of energy in the form of heat loss, Q and hence disposal of entropy generated within the whole body in the form of heat to the environment. In layman's language, the entropy generation within a system is a measure of how things can go wrong irreversibly [11].

There is striking similarity between the field of combustion science, which deals with oxidation at high temperature (order of 1200–1500 °C, without use of catalysts) [12], and the field of metabolism in BS where oxidation at low temperature (37 °C) is aided by enzymes. Thus, currently efforts are under way to translate, modify and link the extensive results from fields of thermodynamics and combustion science to the field of biology particularly in the following areas:

1. First and second Law and availability analyses of oxidation of nutrients: CH, F and P and their mixtures and the relation to life span of BS.
2. Adiabatic temperature rise in combustion of fuels [12] vs. maximum temperature rise of blood leaving the organs either from basic principles of nutrient oxidation or from allometric laws.
3. Oxidation of a single carbon particle and carbon particle temperature vs. oxidation of nutrients in cells and single cell temperature.
4. Adoption of literature on SERR from oxygen deficient carbon cloud in engineering [7] to specific energy release rate $SERR_k$ (W/(kg of organ k)) or specific metabolic rate of organ k (SMR_k) (k = Brain, heart, kidney, etc.), and bridging of gap between data on body mass independent SMR_k data of Elia [8] (but still depends on type of organ or its enzyme) with those of body mass-dependent SMR_k data of Wang [13] and Singer's data [10] in biology. The SMR_k will be a function of size of organ or mass of organ k when one of the following conditions are satisfied: (1) diffusion of oxygen dominates for large organ (i.e., there are a large number of cells within organ or abundant active enzymes are present in mitochondria); (2) the energy release rate is kinetically limited with first order (Michaelis Menten (MM)) kinetics (enzymes are limited or not active) SMR_k is independent of organ mass under zero order kinetics or when organ size is small which leads to Elia constant in biology [13].
5. Deduction of allometric laws/constant for organs and the whole-body Kleiber's law using Combustion Science and Thermodynamics [9,14–16].

The present work concerns the extension of availability analyses to mitochondrial level (Item 1), estimation of maximum possible temperature rise of blood from each organ (Item 2; i.e., non-ATP process) and presents methods of determining BAR. A brief literature review is presented summarizing previous work, followed by objectives and methodology adopted, a summary of results, and basic and derived allometric constants in tabular forms, quantitative results for ranking entropy stresses of organs and finally methods of estimating BAR.

2. Literature Review and Background

2.1. Second Law, Irreversibility Rate ($\dot{I}$) and Entropy Generation Rate ($\dot{\sigma}$)

Entropy generation occurs within the completely warm body (with control surface of control volume (CV) boundary just outside skin) due to internal and external irreversibilities. The internal irreversibilities include: (1) cells of organ k ($\sigma_{cl,m,k}$, J/(K kg of organ k) where vast number of irreversible chemical reaction and oxidation reactions occurs; (2) Interstitial fluid around cells where property gradients exist (O_2, CO_2, glucose, temperature); (3) Skeletal muscles where ATP is used to move muscle fibers against stationary muscles involving frictional process and heart muscles due to pumping action; and (4) pressure losses in circulation system, frictional/duct losses in breathing in and out etc. The external irreversibility occurs due to the property gradients between the skin of body and surroundings; they also influence internal irreversibilities; e.g., increased heat loss to colder ambience requires increased energy release rate $(\dot{q})$ thus increasing internal irreversibility. Of all the entropy generation sources, the major contribution to whole body entropy generation comes from internal irreversibilities where almost 2/3 of ERR is released as heat $(\dot{Q})$. If control surface of CV is selected just inside the skin, the body is almost isothermal at body temperature T_B. The life-sustaining gradients (e.g., Δg, Gibbs function difference required for reactions) within the body disappear when a biological system dies and decays into its non-living form. At this juncture or near death, rate of

entropy generation within body approaches almost zero and cumulative specific entropy generated by BS, $\sigma_{M,life}$ (J/(K kg body mass)) over life span reaches a maximum. This should not be confused with S_{max} principle for isolated system in engineering (i.e., fixed internal energy (U), volume (V) and mass (m) or fixed enthalpy (H), pressure (P), m), since BS does not have fixed U, V and m and the BS is not an isolated system. Rather it operates at fixed T and P. There were two approaches in estimating specific entropy generation of whole body ($\sigma_{M,life}$, kJ/(K kg body)):

1. **Homogeneous** where one considers whole body as homogeneous system and
2. **Heterogeneous** where the metabolic rate of whole body is considered to be a sum of metabolic rates of internal organs with each organ serving as system.

The two approaches are used in biology for estimating specific metabolic energy release (SMR, kJ/kg body) and specific entropy generation (σ_M, kJ/(K kg body)).

2.2. Homogeneous Approach

The thermodynamics literature present the entropy balance equation for an open engineering system (where mass crosses the boundary) for whole body of mass m_B as [12]:

$$\frac{dS}{dt} = \frac{\dot{Q}}{T_b} + \dot{m}_i s_i - \dot{m}_e s_e + \dot{\sigma} \quad (1)$$

where $\dot{Q}$ (random energy) is the rate of heat transfer across the boundary at boundary temperature T_b. The term dS/dt represents the entropy accumulation rate within body, $\dot{m}_i s_i$ input of entropy through mass intake (air, nutrients through mouth), and $\dot{m}_e s_e$ is entropy leaving through exhaust of waste products (CO_2, H_2O through nose).

Hershey and Wang [17] used second law and homogeneous approach and estimated average specific entropy generation rate as $\dot{\sigma}_M(t)$ $(= \dot{\sigma}(t)/m_B$, W/K per kg body mass) at given age t. The specific entropy generation over human life span ($\sigma_M(t)$, J/kg body mass K) is given as:

$$\sigma_M(t)\left[\frac{J}{\text{kg bodymass K}}\right] = \int_{t_{birth}}^{t} \dot{\sigma}_M(t)dt \quad (2)$$

In estimating, $\dot{\sigma}_M(t)$ they assumed that all the energy released $(\dot{q})$ via oxidation cause entropy generation and found that the advection terms $\dot{m}_i s_i - \dot{m}_e s_e$ is only about 2.5% of total entropy generation rate. Their work suggests that it is not the total entropy during lifespan, but the rate of change on entropy production that define the senile death. i.e., $\delta\sigma/dt$ (kJ/K per kg body mass) reaches zero.

Instead of entropy balance equation in estimating $\dot{\sigma}(t)$, Silva and Annamalai [9] adopted the availability balance equation for whole body as though it is homogeneous system:

$$\frac{d(E_{cv} - T_0 S)}{dt} = \sum_{n,Inlet} \dot{m}_{n,i}\Psi_{n,i} - \sum_{n,exit} \dot{m}_{n,e}\Psi_{n,e} - \dot{W} - \dot{I}, E = U + KE + PE = H - PV + KE + PE \quad (3)$$

where "n" represents the nutrients n (e.g., n = CH, F and P) U, internal energy, KE, kinetic energy of whole body (e.g., running) and PE, potential energy (e.g., climbing stairs), $\psi_{n,i} = h_{n,i}\ T_0 s_{n,i}$, stream availability (as per EU definition) of nutrient "n" at inlet, (e.g., availability in through intake of food intake), T_0 ambient temperature), $\psi_{n,e} = h_{n,e}\ T_0 s_{n,e}$, availability exiting (e.g., through waste products n = CO_2, H_2O, etc.), $\dot{W}$ all forms of work crossing the boundary, and $\dot{I}$ irreversibility rate. It is noted that exergy (as per EU definition; but called availability in US literature. EU notation is used here) is defined as $\psi_{n,i} - \psi_{n,i,0}$ where dead state availability is defined as $\psi_{n,i,0} = h_{n,i,0} - T_0 s_{n,i,0}$. The oxidative process/metabolism in BS involves energy release, $\dot{q}$ and a part of $\dot{q}$ is used in ATP production

($\dot{W}_{ATP}$) and remainder as heat $\dot{Q}$ (random energy) which is energy lost during electron transport and oxidative phosphorylation. The term $\dot{W}$ in engineering thermal systems does not contribute to entropy generation and they replaced $\dot{W}$ in Equation (3) by $\dot{W}_{ATP}$ (with assumption of reversible conversion of ADP to ATP) for all internal organs. When applied to human body the BS is almost isothermal within whole body at T_B and hence $T_i = T_e = T_B$, $\psi_n = h_n$, $T_0 s_n = h_n$, $T_B s_n = g_n$, Gibbs function (J/kg) of nutrient "n". It is the "Q" which contributes a major fraction of causes entropy generation rather than $\dot{q}$ as assumed by Hershey and Wang [17]. Ignoring KE and PE (e.g., resting). Equation (3) becomes:

$$\frac{dG}{dt} = \sum_{n,Inlet} \dot{m}_{n,i} g_{n,i} - \sum_{n,exit} \dot{m}_{n,e} g_{n,e} + P\frac{dV}{dt} - \dot{W}_{ATP} - \dot{I} \tag{4}$$

where $G = H - T_B S$ and $\dot{I} = T_B \dot{\sigma}$.

Ignoring P dV/dt (e.g., breathing work) and assuming quasi-steady state on daily basis,

$$0 = \sum_{n} \dot{m}_{n,reacted} |\Delta G_{c,n}| - \dot{W}_{ATP} - \dot{I},$$

Typically $g_{n,e} < g_{n,i}$ and hence $\Delta G_{c,n} < 0$ due to irreversible oxidation process involving species "n"; but above equation uses the absolute value of $\Delta G_{c,n}$. By setting $\dot{I} = 0$ in above equation one can show that total optimum work rate is equal to sum of optimum work of each macro-nutrient

$$\dot{W}_{ATP,opt} = \sum_{n} \dot{m}_{n,reacted} |\Delta G_{c,n}|, \text{ whole body, } n = CH, F \text{ and } P$$

where $\dot{m}_{n,reacted}$, the consumption rate of nutrients which could be less than $\dot{m}_{n,i}$ and unreacted Gibbs function of nutrients at inlet and exit cancel out. Silva and Annamalai [8] found that the availability efficiency (η_{Avail} = work delivered/optimum work) used in thermodynamics for an isothermal system is same as metabolic efficiency in biology. Thus, metabolic efficiency (η_{Met})

$$\eta_{Avail,n} = \eta_{Met,n} = \frac{W_{ATP,n}}{W_{ATP,n,opt}} = \frac{W_{ATP,n}}{|\Delta G_{c,n}|} \tag{5}$$

where the $\Delta G_{c,n}$ is maximum possible ATP work from nutrient "n". The irreversibility rate of a system of interest is equal to sum of irreversibility of each macro-nutrient:

$$\dot{I} = \dot{W}_{ATP,opt} - \dot{W}_{ATP} = T_B \dot{\sigma} = \sum_{n} \dot{m}_{n,reacted} |\Delta G_{c,n}| * (1 - \eta_{Met,n}) \tag{6}$$

Since the engineering studies for several fuels revealed that the ratio of change in Gibbs function to heating values of fuels/nutrients, $|\Delta G^{\circ}_{c,n}|/HV_n \approx C_g$, a constant $\approx 0.95 - 1.05$ [8,16] for most nutrients. Hence

$$|\Delta G_{c,n}| * (1 - \eta_{Met,n}) \approx C_g HV_n (1 - \eta_{Met,n})$$

where HV_n is the heating value of nutrient n. Thus, after dividing by m_B, Equation (6) becomes

$$i\left(\frac{\frac{kJ}{S}}{\text{kg body mass K}}\right) = \frac{\dot{I}}{m_B} = T_B \dot{\sigma}_M = \sum_{n} \frac{\dot{m}_{n,reacted}}{m_B} HV_n * (1 - \eta_{Met,n}) \tag{7}$$

where the term $\dot{m}_{n,reacted} HV_{n,i}$ is the energy release rate, SERR (see Section 2.2) and $\dot{m}_{n,reacted} HV_n \eta_{Met,n}$ is work part of energy used by body for pumping blood, work for breathing and for repair and creation of new cells thus maintaining the life functions. Aoki demonstrated that the heat part

$\{HV_n * (1 - \eta_{Met,n})\}$ plays major role in estimation of entropy generation of reacting system [16,18] while convective part of entropy change is negligible. The irreversibility rate "i" is a function of age "t" since energy consumption changes with age t. The inclusion of metabolic efficiency in the entropy generation concept reveals that lower ATP production (i.e., lower amount of work) should result in higher Q, and higher temperature rise around cells. The increased temperature rise (due to higher Q) can also cause increased ROS and along with decreased ATP energy available for repair and creation of new cells including the damage cause by environmental factors, and accumulation of damaged cells causing rapid aging and reduced life span. This is consistent with hypothesis of Kirkwood [6] who discounted theory of gene programming.

2.3. Heterogeneous Approach

Wang [19] adopted heterogeneous approach where the exponents in the completely body-allometric law for energy release rate (ERR) can be derived by summing of the metabolic rates of five organs: vital organs such as Brain (B), Heart (H), Kidney (K), and Liver and the rest of body (R5). This is termed as Wang-5 model. Later they included two additional organs: skeletal muscle (SM) and adipose tissue AT (which is fatty tissue packed between organs) which is termed as Wang-7 model [20] and improved the accuracy on prediction of whole body allometric law exponents. Annamalai and Silva adopted similar heterogeneous approach for entropy generation of whole body as a sum of entropy generation of the BHKLR for an isothermal body [8]. Thus, Equation (7) at organ level for k = B, H, K, L, R becomes

$$T_B\{K\}\dot{\sigma}_k\left\{\frac{\text{Watts}}{K}\right\} \approx \dot{q}_k(1-\eta_{Met,k}),\ k = \text{BHKLR}, \eta_{Met,k} = \sum_n \eta_{Met,n}\frac{\dot{q}_{k,n}}{\dot{q}_k}; n = \text{CH, F and P} \quad (8)$$

where $\eta_{Met,k}$ an energy is weighted average metabolic efficiency for whole organ k. Major nutrient (almost 100%) for brain is CH with higher metabolic efficiency and unity respiratory Quotient (RQ) while a mix of fat (about 70%) with lower metabolic efficiency and RQ = 0.7 and CH (about 20%) with higher metabolic efficiency is used in heart [21]; thus the organs may have different metabolic efficiencies. The term $\dot{q}_k$, is energy release rate from organ k due to oxidation of all nutrients within organ k, and $\dot{q}_k\eta_{Met,k}$ is energy used in ATP production by all nutrients that do not cause entropy generation just as work delivered in engineering device does not cause entropy generation. Dividing by organ mass m_k, the specific entropy generation rate is obtained as:

$$\dot{\sigma}_{k,m}\left\{\frac{\text{Watts}}{\text{K kg of k}}\right\} \approx \frac{\dot{q}_{k,m}\left\{\frac{\text{Watts}}{\text{kg of k}}\right\}(1-\eta_{Met,k})}{T_B\{K\}},\ k = \text{BHKLR}, \quad (9)$$

Since the number of cells per unit mass is approximately constant for various organs, the specific entropy stress at cell level is proportional to $\dot{\sigma}_{k,m}$. One uses allometric laws for organs to estimate $\dot{q}_{k,m}$ and known $\eta_{Met,k}$ in order to estimate the entropy generation rate of organ k.

2.4. Allometric Laws-Organs

$SMR_k\left(\dot{q}_{k,m}\right)$ Controversy exists on the relation between the SMR_k and body mass m_B. Elia's results show that SMR_k remains constant regardless of body mass (i.e., regardless of age). Wang's data fit for six mammalian species ranging from 0.5 kg (rabbit) to 70 kg (human) yields:

$$SMR_k = \dot{q}_{k,m}\left(\frac{W}{\text{kg of organ k}}\right) = e_k m_B^{f_k} \quad (10)$$

Thus, for Elia, $f_k = 0$ while for Wang $f_k \neq 0$. Elia's constant SMR_k data presumes that the rates are kinetically limited indicating that $SMR_k \propto \exp\left(-\frac{E}{RT_k}\right)$ where E, activation energy (J/kmol) for

oxidation, $\overline{R}$ universal gas constant and T_k, organ temperature $\approx T_B$, body temperature in K for a specified organ k. Since body temperature remains constant through growth of organ k, SMR_k must remain constant. However the extension of recent engineering literature on oxygen-deficient combustion to BS seems to indicate partial diffusion control of O_2 and hence SMR_k may depend on the size of organ or organ mass (m_k). These results explain why $f_k < 0$ [14] and confirm Singer's data [22] on SMR_k indicating oxygen deficiency for large organ.

The *k*th organ mass is given by the allometric law:

$$m_k = c_k {m_B}^{d_k} \tag{11}$$

where c_k and d_k are allometric constants at organ level. Further the previous work [8,23] converted the "body mass"-based allometric relation for each organ into "organ mass"-based allometric relation:

$$SMR_k = \dot{q}_{k,m} = \left(\frac{e_k}{{c_k}^{\frac{f_k}{d_k}}} \right) {m_k}^{\frac{f_k}{d_k}+1} \tag{12}$$

The exponents in Equation (12) satisfy in inequality relation: $-1/3 < (\frac{f_k}{d_k} + 1) < 0$ for most organs (see areas of research 4 and 5) [14,15].

Entropy Generation Rate: Equation (10) was used in Equation (9) to obtain specific organ entropy generation rate, $\dot{\sigma}_{k,m}(t)$ as a function of age t; then integrating over age "t" the organ-based specific entropy generation $\sigma_{k,m}$ is given as

$$\sigma_{k,m}(t) \left[\frac{J}{\text{kg organ mass K}} \right] = \int_{t_{birth}}^{t} \dot{\sigma}_{k,m}(t) dt, \; k = B, H, K, L \text{ (vital organs) and R} \tag{13}$$

and letting $t = t_{life}$, $\sigma_{m,life}$ can be obtained [16]. Using heterogeneous approach, the whole body specific entropy generation ($\sigma_M(t)$) as a function of age t is given as:

$$\sigma_M(t) \left[\frac{J}{\text{kg organ mass K}} \right] = \int_{t_{birth}}^{t} \sum_k \dot{\sigma}_{k,m}(t) \left(\frac{m_k(t)}{m_B(t)} \right) dt, \; k = B, H, K, L \text{ (vital organs) and R} \tag{14}$$

where $m_B(t)$ change with age t. Setting $t = t_{life} + t_{birth}$ in Equations (13) and (14), $\sigma_{k,m,life}$ and $\sigma_{M,life}$ were obtained; the earlier studies by Annamalai and Silva [8] revealed that heart has highest specific entropy generation ($H_{m,life}$) while liver ($L_{m,life}$) had the lowest.

Mitochondria: The oxidation occurs within the mitochondria of the cell. Mitochondria are known to be the main source of ROS due to electron transfer process. The ROS (also called as ROM, radical oxygen metabolites) within mitochondria is believed to be primary cause of mitochondrial DNA (mtDNA) damage in Alzheimer's disease patients via leak of electrons in the electron transport chain process [24]. If one assumes that mitochondrial densities (Mito volume % in each cell) are same in all organ, then ranking of vital organ based on entropy stress per cell must follow the same scaling as entropy stress per unit mitochondrial volume. However, allometric laws reveal that Mito volume fraction (vf_{Mito}) vary from organ to organ [25] and is given by allometric law:

$$vf_{Mito} = p_k {m_B}^{q_k} \tag{15}$$

Gemme et al. [24] indicated that there is better correlation between mitochondrial metabolic rate and mitochondrial free radical production rate and longevity (e.g., birds) than with the overall metabolic rate. Indeed, the mitochondrial rate of free radical production seems to have a much stronger correlation with maximum longevity. Thus, the organ stress based on mitochondrial metabolic loading could be different compared to average metabolic loading of organ.

2.5. Biological and Chronological Aging

The second law approach relies on entropy generation as one of the biomarkers for BAR. Improved metabolic efficiency (i.e., reduced amount of heat transferred to blood or lower temperature rise in blood) slows down the aging process and thus extends life span. Section 5.4 will show that temperature rise in blood when metabolic efficiency is reduced consistent with experimental data. Section 5.5 will show slower aging with increased metabolic efficiency validating 2nd law hypothesis.

The chronological aging (CA) is measured in terms of calendar years and most retirement planning are based on CA. Using the recommended nutrition data vs. age (calendar years) provided by Food and Nutrition board (FNB), Silva and Annamalai [9] estimated the cumulative entropy generation vs. calendar years (curves AM for Male and AF for female, Figure 1) and the slope will be denoted as calendar aging rate (CAR). If consumption is more than the amount recommended for indicated age group by FNB, the SMR will be much higher and hence cumulative entropy generated is faster and thus biological aging rate (BAR) is faster than CAR. One may be at age 50 but feels like age 80 (line AB, BAR > CAR) while others may be at age 80 but feels like 50's (line AC, BAR < CAR). Thus, Milevsky and his co-researchers recommend using BAR for retirement planning [26]. The biomarkers for BAR could be (1) energy release from unit mass of the body ($q_M(t)$) which follows Rubner's hypothesis (first law, homogeneous approach, ordinate in Figure 1 replaced by energy release in kJ/kg body mass); (2) energy release from unit mass of the vital organ ($q_{k,m}(t)$), first law, heterogeneous approach); (3) specific entropy generation from unit mass of the body, ($\sigma_M(t)$) which follows Silva and Annamalai's hypothesis (Figure 1, second law, homogeneous approach); and (4) specific entropy generation from unit mass of the vital organ ($\sigma_{k,m}(t)$), second law, heterogeneous approach). Thus, the BAR of organs differ from each other. Smaller animals undergo aging at much faster rate compared to large animals due to high Calorie consumption per unit mass of body (i.e., heart has to pump more blood per min or heart beats much faster in clock time for smaller animals). Similarly, animal spending more time outdoor ages faster than animal in door.

The biological aging rate of organs can be used to indicate how fast the organs approach chronic conditions. It has been reported that about 91% of older adults are above one chronic condition and 73% have 2 chronic conditions [27]. The top four chronic conditions that cause 2/3 of deaths are: heart disease, cancer, stroke (brain), and diabetes (kidney/liver). The organ-based second law approach predicts the top two stressed organs are heart and brain [8]. In the current work, the metabolic and entropy stress are extended to mitochondrial level to investigate whether same order is followed.

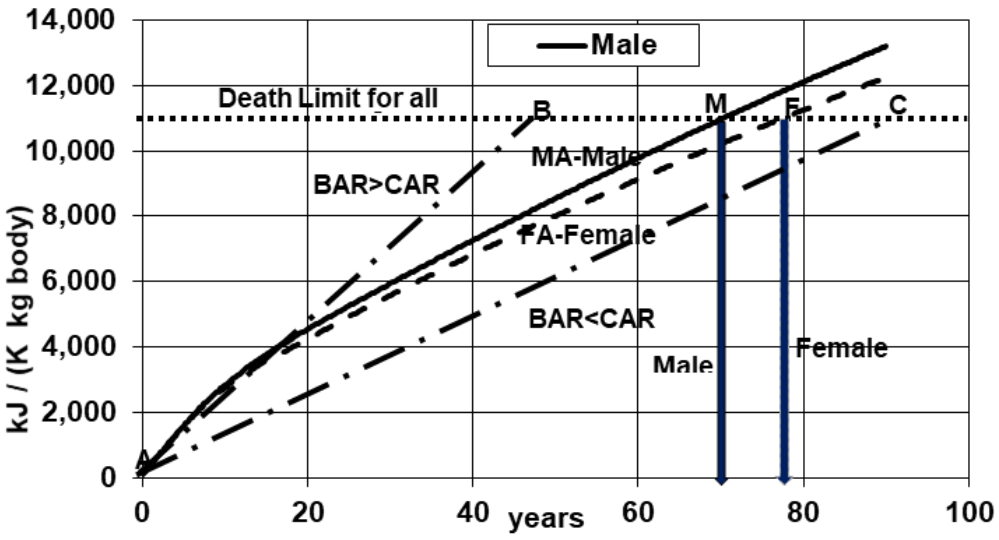

Figure 1. Entropy generation vs. aging in calendar tears (Chronological aging, CA based on recommended diet by Food and Nutrition Board, [8] for male and female. Curve AF: Female, Curve AM: Male. Within the upper limit of about 11,000 kJ per kg body mass, life span of man and woman are 70 (line AM) and 78 years (line AF). The slopes of AM and AF represent chronological aging rates (CAR) of male and female. With higher $SERR_M$ (kJ/kg body mass; uncontrolled diet, e.g., line AB), the biological aging rate, BAR > CAR (e.g., Reduced metabolic efficiency); under diet control (e.g., line AC, BAR < CAR [8]; (e.g., Increased metabolic efficiency). The BA lines are qualitative. Note that the BAR of cats, dogs, ants etc. are much faster compared to BAR of humans due to high SMR of whole body or high surface area to volume ratio. For Rubner's hypothesis based on first law, the ordinate could be replaced by specific metabolic energy; lines AB and AC refer to energy (calories) consumption per unit mass of body with line AC referring to "Calorific restriction", and AB refers to higher "calorific consumption". Further line AB may also correspond to energy released from smaller species indicating faster BAR for smaller species. Under similar metabolic efficiency throughout life span both the 1st and 2nd law hypotheses yield similar results.

3. Objectives and Methodology

3.1. Objectives

The overall goal of current aging research is to provide biomarkers for biological aging rate (BAR) using the second law approach. The objectives of the present study are as follows: (1) Couple BAR of whole body to organ aging using heterogeneous approach; (2) Extend the 5 organ (B-H-K-L-R) analysis of BS to 7 organ analysis by including the two additional organs: adipose tissue (AT) and skeletal muscle (SM) which are of importance to athletes; (3) Extend analysis to mitochondrial level; (4) Study the effects of proportions of nutrients being oxidized, (CH:F:P) which affect metabolic efficiencies as well as maximum temperature rise of blood and which relates to entropy generation; and (5) Compare the ranking of organs based on the lifetime specific entropy generation $\sigma_{m,k,life}$ (kJ/(K kg of organ k)) vs. mitochondrial volume-based specific entropy generation $\sigma_{m,k,life}$ (kJ/(K cm^3 of Mito within organ k)).

3.2. Methodology

In order to achieve the stated objectives, the following methodology is adopted:

1. Extend the 5 organ analysis (B-H-K-L-R5) to 7 organs/compartments (AT-B-H-K-L-R7-SM) and tissues (SM and AT) and residual mass (R7).
2. Calculate the specific metabolic rate, $\dot{q}_{k.m}$ (W/kg of organ k) and entropy generation rate within organ k, $\dot{\sigma}_{k,m}$ (W/(K kg of organ k)) (Equations (12) and (13) respectively, Section 2) as function of age(t).
3. Using allometric laws for mitochondrial density (Equation (15)), estimate Mito volume-based specific entropy generation rate per unit volume of mitochondria ($\dot{\sigma}_{v,k}$W/cm^3 of Mito within organ k).
4. Since body mass is not constant, then use body mass growth data with age and the SMRk relation in terms of body mass (Equation (8), Section 2) to estimate growth correction factor, GCF.
5. Using GCF, rank the organs based on mitochondrial metabolic loading (MJ in organ k over life/cm^3 of Mito) and entropy stress (MJ in organ k over life/(K cm^3 of Mito)).

4. Modeling and Relations for Specific Energy Release and Entropy Generation of Organs

This section presents brief derivations and explicit results obtained for several parameters of interest a few of which could serve as biomarkers for biological aging. Using the literature review section (Equation (9)),

$$\dot{\sigma}_{k,m} \approx \frac{\dot{q}_{k,m}(1-\eta_{Met,k})}{T_B\{K\}},\ k = BHKLR,$$

The lifetime energy release per unit mass of organ k $\left(q_{k,m,life}\right)$ over life span is given as:

$$q_{k,m,life}\left(\frac{kJ}{kg\ of\ organ\ mass\ k}\right) = \int_{b_{birth}}^{t_{st,1}} \dot{q}_{k,m}(t)dt + \int_{t_{st,1}}^{t_{st,2}} \dot{q}_{k,m}(t)dt + \int_{t_{st,2}}^{t_{life}+t_{birth}} \dot{q}_{k,m}(t)dt, \quad \text{where } k = B, H, K, L, AT, SM, R7 \tag{16}$$

where $\dot{q}_{k,m}(t)$ is a function of body mass $m_B(t)$ as given by allometric law (Equation (10)). The life span t_{life} is typically defined from birth to death; so $t_{life} = t_{death} - t_{birth}$.

4.1. Growth Correction Factor (GCF)

The relation for m_B can be found from data given in [28] and was curve fitted using

$$m_B(t) = m_{B,st}\left(\frac{t}{t_{st}}\right)^z \tag{17}$$

where "t" is age in years from day of conception so that $m_B = 0$ at $t = 0$, t_{st} is age required from conception to achieve steady body mass $m_{B,st}$ and as such organ masses which are related to body mass remain constant after t_{st}. It is noted that Wang et al. analyzed an existing database for organ weights of humans and found that the mass almost remains constant for most vital organs after 21 years [20]. The present analysis uses UK data for body mass vs. age, which is presented in Figure 2. The curve fit yields "z" when $t_{st,1} = 20$ years for female and $t_{st,1} = 30$ for male.

Period-I: for $t_{birth} < t < t_{st,1}$, $z = 0.75$ (mass increase period), $t_{st,1} = 20$ years for female and $t_{st,1} = 30$ for male;

Period-II: for $t_{st,1} < t < t_{st,2}$, $z = 0$ (steady mass period);

Period-III: for $t_{st,2} < t < t_{death}$, $z = -0.75$ (mass decrease period).

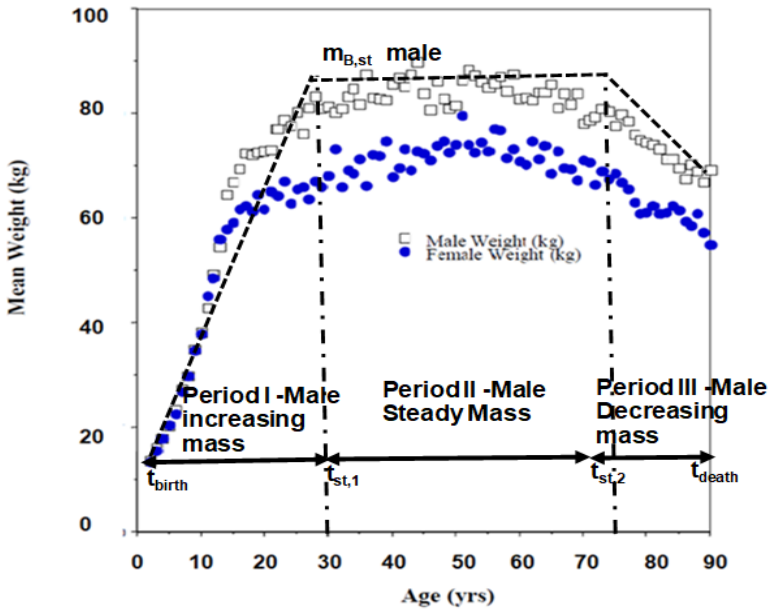

Figure 2. Population-Weighted Mean Weight for NHANES3 Subjects of Different **Ages** (2.6 months to 96 years) (adopted from [28] and modified). The body mass, m_B for humans is not constant and grows with age (t, since conception, Period I) until reaching steady mass $m_{B,st}$ at $t = t_{st,1}$, remains almost constant until $t = t_{st,2}$ (Period II) along with the rate of entropy production fixed and then it decreases $t_{st,2} < t < t_{death}$ (III). Current analysis ignores period III. Curve fit for growth for age 0 to 75 years: $0 < t < t_{st,1}$: $m_B = m_{B,st} * (t/t_{st})^z$, Male: $m_{B,st}$: 84 kg, $t_{st,1} = 24$ years, $t_{st,2} = 75$ years, $z = 0.75$ [8]; female: $m_{B,st} = 70$ kg, $t_{st,1} = 20$ years, $t_{st,2} = 75$ years, $z = 0.75$.

4.2. Lifetime Specific Energy Release of Organ

Letting $t^* = t/t_{death}$ where $t_{death} = t_{life} + t_{birth}$, using allometric laws $\dot{q}_{k,m}(t)$ given in terms of body mass $m_B(t)$ (Equation (10)) and Equation (17) for variation of $m_B(t)$ with age, Equation (16) is converted into non-dimensional form for $q_{k,m,life}$ as given below:

$$\begin{aligned}\frac{q_{k,m,life}}{t_{death} e_k {m_{B,st}}^{f_k}} &= \frac{q_{k,m,life}}{t_{death} e_k {m_{B,st}}^{f_k}} \left(\frac{kJ}{\text{kg of organ mass}k}\right) \\ &= \int_{t^*_{birth}}^{t^*_{st,1}} t^{*z f_k} dt^* + \int_{t^*_{st,1}}^{t^*_{st,2}} t^{*z f_k} dt^* + \int_{t^*_{st,2}}^{1} t^{*z f_k} dt^*\end{aligned}$$

The numerator of left hand side is actual specific metabolic energy over whole life span while denominator is specific metabolic energy over whole life span in case body mass remains constant. Thus, the right hand represents the growth correction factor (GCF_q) for lifetime metabolic energy since body mass is not constant. Integrating above equation

$$\frac{q_{k,m,life}}{t_{life} e_k {m_{B,st}}^{f_k}} = \frac{t^*_{st,1}\left(1 - \left\{\frac{t^*_{birth}}{t^*_{st,1}}\right\}^{g_k+1}\right)}{g_k + 1}(t^*_{st,2} - t^*_{st,1}) + \frac{t^*_{st,2}\left[\left|\frac{1}{t^*_{st,2}}\right|^{-g_k+1} - 1\right]}{(-g_k + 1)}$$

where $g_k = z\, f_k$ when computing life span metabolic energy released by unit mass of organ k. Ignoring period III, and hence $t^*_{st,2} = 1$.

$$\frac{q_{k,m,life}}{t_{life} e_k {m_{B,st}}^{f_k}} = GCF_q(t^*_{st,1}, t^*_{birth}, g_k) = \frac{t^*_{st,1}\left(1 - \left\{\frac{t^*_{birth}}{t^*_{st,1}}\right\}^{g_k+1}\right)}{g_k + 1} + (1 - t^*_{st,1}) \tag{18}$$

where GCF_q, represents growth correction factor for q (metabolic energy). When $f_k = 0$ (Elia data), $g_k = 0$. $GCF_k = 1$. For GCF derivations for other parameters (e.g., lifetime energy contribution by organ k to unit body mass), the "g_k" definition changes as shown in column 4 of Table 1. See Annamalai and Silva [8] and Nanda [29] for more details. The summary of algebraic relations for other biomarkers of interest for BAR is presented in Table 1.

4.3. Mitochondrial Metabolic Loading

There are a large number of mitochondria present within the cells of an organ and occupy certain fraction of volume of cells (vf_{Mito}) called mitochondrial density. Allometric law for vf_{Mito} is given as

$$vf_{Mito} = p_k {m_B}^{q_k} \tag{19}$$

Nutrients and oxygen enter the cells; but the oxidation occurs within mitochondria while glycolysis occurs outside the mitochondria (Figure 3). The oxidation produces significant amount of ATP and hence ATP due to less efficient anaerobic process (glycolysis) is neglected. The organ volume is a sum of cell volume and interstitial fluid volume. The organ metabolic rate and entropy generation rate are converted to rates at mitochondrial level using allometric law for mitochondrial volume fraction:

$$\begin{aligned}&\dot{q}_{k,v,Mito}\left(\frac{W}{cm^3 \text{ of Mito of organ k}}\right) \\ &= \dot{q}_{k,m}\left(\frac{W}{\text{g of organ k}}\right)\rho_k\left(\frac{\text{g of organ k}}{cm^3 \text{ of organ k}}\right)\frac{1}{vf_{cell,k}\left(\frac{cm^3 \text{ of cells in k}}{cm^3 \text{ of organ k}}\right)}\frac{1}{vf_{Mito}\left(\frac{cm^3 \text{ of Mito k}}{cm^3 \text{ of cell k}}\right)} \\ &= \frac{\rho_k e_k {m_B}^{f_k}}{vf_{cell} P_k {m_B}^{q_k}} = \left(\frac{\rho_k e_k}{vf_{cell} P_k}\right) {m_B}^{f_k - q_k}\end{aligned} \tag{20}$$

where $vf_{cell,k}$ volume fraction of cells = n_k ($\pi\, {d_{cell}}^3/6$), n_k, number of cells per cm^3 of organ k, d_{cell}, cell dia. For life span metabolic energy per unit volume of mitochondria $g_k = z\,(f_k - q_k)$ in Equation (18).

Table 1. Summary of Results Lifetime Entropy Generation of Whole body (Annamalai & Silva [23]).

#	Desired Variable	Non-Dimensional Form of Desired Variable	Growth Correction Factor, GCF Right Side of Equation (18); Note 2	Example for Heart, (Wang 5 Data $SERR_K$ Body Mass Depend; m_{Bst} = 84 kg, 75 years, $t_{st,1}$ = 24 years, RQ_{mix} = 0.80, η_{met} = 0.312, $m_{H,std}$ = 0.006 × $84^{0.98}$ = 0.46 kg, z = 0.75; t_{st2} = t_{life} = 75 years (Note 1))
1	Lifetime Specific metabolic energy release by organ k $\left(\frac{\text{kJ}}{\text{kg of organ mass k}}\right)$	$\frac{q_{k,m,life}}{t_{death}\ \dot{q}_{k,m,st}}$ or $\frac{q_{k,m,life}}{t_{life}\ e_k\ m_{B,st}{}^{f_k}}$	g_k in Figure 4 = z f_k; g_k = 0 with Elia data	z = 0.75, f_H = −0.12; g_H = zf_H = 0.75 × (−0.12) = −0.09, GCF from chart = 1.015 (Wang $SERR_k$), = 1 for Elia; $\dot{q}_{H.m,st}$ = 21 W/kg heart; $q_{H,m,Life,st}$ = 60.GJ/kg heart, $q_{H,m,Life}$ = 60 × 1.015 = 60.8 GJ/kg heart
2	Lifetime Specific Entropy Generation of organ k, $\left(\frac{\text{kJ}}{\text{K kg of organ mass k}}\right)$	$\frac{T\sigma_{k,m,life}}{t_{death}\ \dot{q}_{k,m,st}(1-\eta)}$ or $\frac{T_B\sigma_{k,m,life}}{t_{death}\ e_k\ m_{B,st}{}^{f_k}(1-\eta_k)}$	g_k in Figure 4= z f_k	GCF = 1.015, t_{life} e_k $m_{B,st}{}^{f_k}(1-\eta_k)/T_B$, $\sigma_{H,m,st}$ = 134 MJ/(K kg heart) $\sigma_{H,m,s}$ = 134 × 1.015= 135 MJ/(K kg heart)
3	Lifetime metabolic energy contribution by organ k to unit mass of body, $\left(\frac{\text{kJ by k}}{\text{kg of body mass}}\right)$	$\frac{q_{k,M,life}}{t_{death}\ \dot{q}_{k,M,st}}$ or $\frac{q_{k,m,life}}{\left(m_{k,st}q_{k,m,st,life}/m_{B,st}\right)}$	g_k in Figure 4 = z(f_k + d_k − 1)	g_H = z(f_H + d_H − 1)=0.75 × (−0.12 + 0.98 − 1) = −0.105, GCF = 1.02 $q_{H,M,Life,st} = t_{life}\ \dot{q}_{k,M,st}$ = 60 × 0.46/84 = 0.33 GJ by heart to 1 kg body mass, $q_{H,M,life}$ = 0.33 × 1.02 = 0.336 GJ to 1 kg body mass
4	Lifetime Entropy Generation contribution by organ k to unit mass of body $\left(\frac{\text{kJ by k}}{\text{K kg of body mass}}\right)$	$\frac{T\sigma_{k,M,life}}{t_{death}\ \dot{q}_{k,M,st}(1-\eta)}$ or $\frac{T\sigma_{k,m,life}}{t_{death}\ c_k e_k\ m_{B,st}{}^{f_k+d_k-1}(1-\eta_k)}$	g_k in Figure 4 = z(f_k + d_k − 1)	GCF = 1.02, $\sigma_{H,m,Life,st}$ = 0.33 × 1000 × (1 − 0.31)/310= 0.73 MJ/K by heart to 1 kg body mass; $\sigma_{H,m,Life}$ = 0.73 × 1.02 = 0.745 MJ/K by heart to 1 kg body mass
5	Lifetime metabolic energy contribution by organ k to whole body ($q_{k,life}$)	$\frac{q_{k,life}}{t_{death}\ \dot{q}_{k,m,st}}$ or $\frac{q_{k,m,life}}{\left(m_{k,st}q_{k,m,st,life}/m_{B,st}\right)}$	g_k in Figure 4 = z(f_k + d_k)	gH = z(f_k + d_k) = 0.75 × (−0.12 + 0.98) = 0.645, GCF = 0.874, $q_{H,Life,st}$ = 0.33 × 84 = 27.72 GJ st by heart to whole body $q_{H,Life,}$ = 27.72 GJ × 0.874 = 24.1 GJ by heart to whole body
6	Lifetime Entropy Generation contribution by organ k to whole body	$\frac{T\sigma_{k,life}}{t_{death}\ \dot{q}_{k,st}(1-\eta)}$ or $\frac{T\sigma_{k,m,life}}{t_{death}\ c_k e_k\ m_{B,st}{}^{f_k+d_k}(1-\eta_k)}$	g_k in Figure 4 = z(f_k + d_k)	$\sigma_{H,Life,st}$ = 27.72*(1 − 0.31) × 1000/310 = 61.34 MJ/K by heart to whole body at std mass; $\sigma_{H,Life,st}$ = 61 × 34 × 0.874 = 53.6 MJ/K to whole body over life span
7	Lifetime Specific metabolic energy release per m^3 mito within organ k $\left(\frac{\text{kJ}}{\text{m}^3\text{ of Mito within organ k}}\right)$	$\frac{q_{k,V,Mito,life}}{t_{death}\ \dot{q}_{k,V,st,Mito}}$ or $\frac{q_{k,V,Mito,life}}{t_{death}\left(\frac{1}{v_{f,cell}}\right)\left(\frac{\rho_k\dot{q}_{k,m,st}}{\rho_k m_{B,st}{}^{f_k}}\right)}$	g_k in Figure 4 = z (f_k − q_k)	f_H = −0.12 + 0.044 = −0.076; GCF = 1.015

Note 1: The Nallometric coefficients presume no AT, no SM; coefficients are from [23]. Note 2: When f_k = 0, F = 1; one obtains Elia's results; $\dot{q}_{k,m,st}$ or $SBMR_k$ are: 0.581, 11.622, 21.307, 21.307, 9.685, 0.630, 0.581 W/kg of k, where F is called growth correction factor.

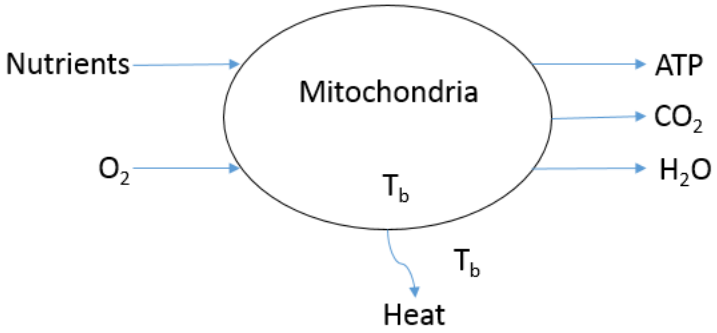

Figure 3. Schematic diagram of the thermodynamic system for estimation of metabolic loading based on mitochondrial volume; a large number of mitochondria within cell of given size results in increased mitochondrial volume (MiV) %.

Previous literature provided details on conversion of allometric laws from body mass m_B to organ mass k for various parameters of interest [23]. If cell density is equal to organ density, the allometric law for metabolic rate per unit mitochondrial volume in terms of $vf_{Mito,k}$ is given as:

$$\dot{q}_{k,Mito,vol}\frac{W}{cm^3\ Mito\ organ\ k} = r_k(vf_{Mito,k})^{t_k}, r_k = \frac{e_k\rho_k}{p_k^{\ fk/qk}vf_{cell,k}}, t_k = \frac{f_k - q_k}{q_k} = \frac{f_k}{q_k} - 1 \quad (21)$$

If $\frac{f_k}{q_k} > 1$, then $t_k > 0$, Mito volume-based metabolic rate (W/m^3 of Mito within k) will increase with increase in $vf_{Mito,k}$ but rate of increase will be different for different organs depending on $\frac{f_k}{q_k}$.

4.4. Maximum Possible Blood Temperature

The ROS production rate is extremely sensitive to temperature and is function of body temperature, oxygen concentration and activation energy. A part of the energy released is converted into work (ATP) and part is released as heat Q which controls the temperature rise and is also related to entropy generation; higher is Q, higher is temperature rise ΔT (of the order of 1 °C) and higher is σ. Thus, it is of interest to estimate maximum possible blood temperature rise estimated under zero work (i.e., no ATP production). Using conservation of energy for blood entering an organ and leaving an organ, the maximum rise in blood temperature is given as:

$$(T_{exit} - T_{in})_k = \frac{Y_{O_2in}OEF_kHV_{O_2}(1 - \eta_{Met,k})}{c_p}$$

where Y_{O_2in}, oxygen mass fraction in blood entering organ (about 300 ppm), c_p, specific heat of blood, OEF, oxygen extraction fraction, HV_{O_2}, energy released per g of O_2 consumed and $Y_{O_2in}OEF_kHV_{O_2}$ is energy released per g blood. If $\dot{V}_{Bl,k}$ is blood flow rate into organ k in volume units, then term $\frac{Y_{O_2in}OEF_kHV_{O_2}\ \rho_{Bl}\ \dot{V}_{Bl,k}\rho_{Bl}}{m_k}$ is SMR_k, which is given by allometric law for the organ. Thus, knowledge of OEF is not necessary.

$$(T_{exit} - T_{in})_k = \frac{\text{Energy released by nutrients oxidation per kg blood } \times \text{ fraction into heat}}{\text{heat capacity per kg blood}}$$

$$(T_{exit} - T_{in})_k = \frac{SMR_k m_k(1 - \eta_{Met})}{\dot{V}_{Bl,k}\rho_{Bl}c_p} \quad (22)$$

Using the allometric law for blood flow rates to organs $\dot{V}_{Bl,k}\left(\frac{\text{mL to organ k}}{s}\right) = h_k m_B(kg)^{i_k}$ and allometry for SMR_k, the allometric relation for temperature rise is derived as

$$\Delta T = (T_{exit} - T_{in}),\ ^\circ C = N_k m_B{}^{L_k},\ N_k = \left(\frac{c_k e_k}{h_k \rho_{bl} c_p}\right), L_k = f_k + d_k - i_k \tag{23}$$

Note that body mass changes with age and as such temperature rise and hence ROS production rates of organs will change with age. An approximate relation between cell death rate and/or ROS production rate, body temperature (TB) and k, bl (entropy generation within organ k, kJ/(K kg blood flow into organ) is derived in [29]; it shows a linear relation as presented below:

$$\begin{aligned} -\frac{d[n_{cell,k}]}{dt},\ \frac{\text{cells under disfunction}}{cm^3\ s} = \frac{d[ROS]_k}{dt} &\approx A\left(1 + \frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right)\exp\left(-\frac{E}{RT_B}\right) \\ &= A\left(1 + \frac{E}{\overline{R}T_B}\left(\frac{\sigma_{k,bl}}{c_p}\right)\right)\exp\left(-\frac{E}{\overline{R}T_B}\right) \end{aligned} \tag{24}$$

where E activation energy for production of ROS, $\overline{R}$ universal gas constant (kJ/K kmol), $\left(\frac{\sigma_{k,bl}}{c_p}\right) = \frac{SMR_k m_k(1-\eta_{Met})}{\dot{V}_{Bl,k}\rho_{Bl}T_B c_p}$, and A, pre-exponential factor; higher is heat part of energy released (which is higher when metabolic efficiency is low e.g., brain after concussion [30]), higher is temperature rise and higher is production rate of ROS.

5. Results and Discussion

Data input for thermal and chemical properties of nutrient are presented in Table 2 followed by basic allometric constants for Wang-5 organ and Wang-7 organ models where 5 and 7 denote number of organs considered in the model (Table 3). The derived allometric constants and blood temperature rise are summarized in Table 4. The results on entropy stress at organ and mitochondrial levels are then presented and compared. Finally, brief procedures are presented for use by medical professional in qualitative evaluation of the biological aging based on Calories/energy released.

5.1. Nutrient Properties and Body Mass Growth Data

The thermal and chemical properties of CH, F and P are presented in Table 2. It is seen that the HV_{O_2} is almost constant and $\Delta G^\circ/\Delta H^\circ$ is close to unity for most nutrients. Here m_{st} = 84 kg, z = 0.75, $t_{st,1}$ = 24 years and $t_{st,2} = t_{death}$ = 75 years for quantitative estimates (Equation (17)).

5.2. Basic Allometric Constants

The following basic allometric constants were used: (A) organ mass vs. body mass (m_B) based on Wang-5 model and body mass-dependent Wang-5 SMR_K data, (B) organ mass vs. body mass (m_B) for Wang-7 organ with Elia's body mass independent constant SMR_k; and (C) blood flow rate, and mitochondrial volume vs. body mass.

1. **Wang-5-Wang SMR_k or SMR_k (5 Organ Model)**: Here the whole body is divided into 5 organs: B, H, K, L, and R5 where R denotes residual mass and R5 denotes residual mass in the 5-organ model. Table 3 lists the basic allometric constants. The in vivo measurements of O_2 concentration differences between artery and vein, and blood flow rate measurement provided data on organ metabolic rates. Using data for 6 species (Rat, rabbit, cat, dog, human-1, human-2) (0.48–70 kg), Wang et al. presented allometric relation for body mass-dependent SMR_k and organ mass in terms of body mass and the basic allometric constants are listed (within parentheses) in Table 3 [19].
2. **Wang 7–Elia-SMR_k Model**: The allometric constants were presented by Wang et al. considering a body with 14 organs: four higher metabolically active vital organs: BHKL, two intermediate organs, AT and SM and eight low level metabolic organs with equal metabolic intensity: adrenal, blood, gut, lung, skin, skeleton, spleen and thyroid. For the current work, the whole body

is divided into 7 organs: BHKL, AT, SM and R7 (R7: Residual mass for 7-organ model). The allometric constants for SMR of R7 are different from R5 due to the following: body mass independent SMR_k throughout growth [13] i.e., constant irrespective of size/mass of selected vital organ, R7 mass is different and the R7 includes 8 sub-organs: adrenal, blood, gut, lung, skin, skeleton, spleen and thyroid. The allometric constant for R7 are curve fitted in terms of body knowing the constants for 8 sub-organs. Table 3 lists the basic allometric constants for Wang-7 organ model.

3. **Blood Flow Rate and Mitochondrial Volume Fraction (MiV)**: The basic allometric constants for blood flow rate to each organ (mL/s per kg organ k), and average mitochondrial volume fraction ($vf_{k,Mito}$, cm^3 of Mito/cm^3 of cells within organ k), etc are given in terms of body mass (m_B, kg) (Table 3).

5.3. Derived Allometric Constants

The body mass (m_B, kg)-based allometric relations for (1) SMR_k or $\dot{q}_{k,m}$, $\dot{q}_{k,V,Mito}$ (W/cm^3 of Mito for organ k); (2) blood flow rate into organ k (mL/s per kg organ k); (3) Mitochondrial volume fraction ($vf_{k,Mito}$, cm^3 of Mito/cm^3 of cells within organ k); (4) oxygen extraction fraction OEF_k (= oxygen used for energy release/oxygen supplied) in each organ k; and (5) maximum temperature rise ($T - T_B$, °C) for blood flow around an organ k can be re-derived in terms of organ mass (m_k, kg) and/or body mass m_B and/or $vf_{k,Mito}$. Derivations for the derived allometric relations are omitted here; for derivation details refer to thesis of Nanda [29]. Table 4 summarizes the derived allometric relations and lists the constants.

L_k (exponent for temperature rise allometry, Equation (23)) ≈ 0 for brain and kidney and hence temperature rise is fixed regardless of age. For heart $L_k > 0$ (Table 3), indicating increase in temperature rise with body mass which is an indication of increased ROS production while for liver $L_k < 0$ indicating decrease in temperature rise with body mass. If metabolic efficiency is reduced then there is further temperature rise.

Table 2. Properties of Nutrients. RQ mix = $(\nu_{CO_2,CH}X_{CH} + \nu_{CO_2,F}X_F + \nu_{CO_2,P}X_{CH,P})/(\nu_{O_2,CH}X_{CH} + \nu_{O_2,F}X_F + \nu_{O_2,P}X_{CH,P})$.

Nutrients	M, kg/kmol	St. O_2 kg/kg Nutrient (Mole per Mole Nutrient)	HHV MJ/kg (MJ/kmol) = $\lvert \Delta H_c^\circ \rvert$	RQ	HHV_{O_2} M J/kg of O_2	$\overline{\Delta G}^\circ_c$ MJ/kmol	$\overline{\Delta G}^\circ_M$ MJ/kmol	$\frac{\lvert\overline{\Delta G}^\circ_M\rvert}{\lvert\overline{\Delta H}^\circ_c\rvert}$	kmol O_2 Consumed per kmol ATP	Metabolic Efficiency (%)
Glucose(CH), $C_6H_{12}O_6$	180	1.066 (6 mole O_2/mole CH)	15.630 (2813 MJ/kmol)	1	14.65	−2895	-	1.03	0.158	38.2
Fat (F), $C_{16}H_{32}O_2$	256	2.869 (23 moles O_2/mol F)	39.125 (10,015 MJ/kmol)	0.7	13.60	−9840, −9800	−6715	0.98	0.217	32.2
Protein(P), $C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$	119	1.53 (5.70 moles O_2/mole empirical P)	22.79 (2712 MJ/kmol)	0.80 0.82	14.87	−2665	-	0.98	-	10.4
Mixture, CH:F:P, 55:30:15 (Mass %)	182	1.68 (9.56 moles O_2 per mole mix with empirical P)	23.75 (4328 MJ/kmol)	0.82	14.146	4,319,894	-	0.999	-	31.23

Note 1: These are energy ratios. Typically P/O ratio = 2.5–3.0 for NAD linked substrate and 1.5–2.0 for succinates [31].

Table 3. Basic Allometric Constants-Wang-7 Elia (Wang-5 models in parenthesis except as indicated). $\dot{q}_{k,\,m}\left(\frac{W}{\text{kg of organ k}}\right) = e_k\, m_B^{f_k}$, m_k (kg organ mass) $= c_k\, {m_B}^{d_k}$, $\dot{V}_{Bl,k}\left(\frac{\text{mL to organ k}}{s}\right) = h_k\, m_B(kg)^{\,i_k}$, $vf_{Mito} = p_k\, {m_B}^{q_k}$. For $\dot{q}_{k,m,st}$ for 85 kg human; p_k q_k values from Else, P L and Hulbert A J for mammals ranging from 18–2067 g. Fat Free mass = adipose tissue free mass = body mass − adipose mass [32].

Organ	Density g/cc	c_k, kg [33]	d_k	e_k W/kg	f_k	h_k (Note 4)	i_k (Note 4)	p_k (Note 3)	q_k (Note 3)	$\dot{q}_{k,m,st}\left(\frac{W}{\text{kg of k}}\right)$
-	ρ_k	$m_k(kg) = c_k m_B(t)^{d_k}$, m_B in kg		$\dot{q}_{k,m}(t)\left(\frac{W}{\text{kg of organ k}}\right) = e_k\, {m_B}^{f_k}$		$\dot{V}_{Bl,k}\left(\frac{\text{mL to organ k}}{s}\right) = h_k\, m_B(kg)^{\,i_k}$		$(MiVf) = p_k\, {m_B}^{q_k}$		-
Adipose Tisue-7 organ [20]	0.9–0.92 [20]	0.0753 (-)	1.19 (-)	0.22	0.0	-	-	- (-)	- (-)	-
Brain	1.036 [20]	0.1025 (0.011)	0.71 (0.76)	11.62 (21.62)	0.0 (−0.14) −0.07 [34]	0.101	0.704	0.0538 (0.0538) [25]	0.00 (0.00) [25]	0.0442
Heart (1.06) [20]	1.06	0.006 (0.006)	0.98 (0.98)	21.3 (43.113)	0.0 (−0.12)	0.224	0.714	0.282 [34] (0.227)	−0.044 [34] (−0.09)	0.146
Kidney (1.05) [20]	1.05	0.0089 (0.007)	0.71 (0.85)	21.3 (33.414)	0.0 (−0.08)	0.603	0.774	0.562 [35] (0.144)	−0.056 [35] (−0.14)	0.108
Liver (1.06) [20]	1.06	0.0491 (0.0330)	0.70 (0.87)	9.7 (33.113)	0.0 (−0.27) −0.24 [25]	0.156	0.856	0.18 [36] (0.112)	−0.09 [36] (−0.13)	0.186
Residual Mass (RM)-Wang 2000-7 organ mass-Elia-Mod (SMRK for AT, BHKL SM and R with Wang)	-	0.3296 (0.939)	1.01 (1.01)	0.58 (1.446)	0.0 (−0.17)	-	-	- (-)	- (-)	(0.192)
Skeletal Muscle [20,25]	1.04	0.4683 (-)	0.99 (-)	0.63 (-)	0.0 (-)	0.769 (0.769)	0.737 (0.737)	0.0438 (0.0438) [25]	−0.09 (−0.09) [25]	-

Note 1: Elia values are: BHLK, SM, AT, RM: 11.62, 21.3, 9.7, 21.3, 0.63, 0.22, 0.58 W/kg [20]. Adipose Tissue; 21% body mass ref male (70 kg); 33% in ref female; wt: 12% of body wt; m_B = 63 kg, adipose: 63 × 0.12 = 7.56 kg; 0.453 L of O_2/h or 0.453 × 14,500 = 2.6 W or 2.6/7.56 = 0.33 W/kg corrected 0.165; SM: 0.492 × 0.63 kg; 3 L of O_2/h = 0.43 W/kg [25,37]. Note 2: the allometric constants for mitochondrial volume fraction were selected from [34–36] for heart, liver and kidney respectively, for BS mass ranging from 0.02 kg to 250 kg. For kidney, the kidney cells are assumed to follow same allometric relation as reported for modular TAL. However for brain mitochondrial volume fraction for BS with wide ranging mass are not available. Hence Else and Hulbert data were selected for MiV generated for mass ranging from 0.02 to 2 kg. Since exponent for q_k is zero (Brain), indicating body mass is independent of MiVf, due to which it can be applied to BS with higher mass. Note 3: Values in (. . .) parentheses are based on Else Hubert [25] data for MiVf allometry for mammals in mass range 0.018 kg mouse to 2.067 kg rabbit. Else and Hulbert data indicate body mass independent MiVf of cells within brain and hence assumed valid for humans of 84 kg. Reference [27], for Hepatocytes of 0.020 kg mice to 200 kg horse, 26 for Cardiocytes of 0.003 kg shrew to 920 kg cattle and 28 for renal medullary cells of 0.011 kg bats to 400 kg horse. Note 4: Here constants remain same for Wang-5 or Wang-7.

Table 4. Derived Allometric Relations-Wang 7 Elia Mod (Values in parentheses are for 5 organ data). $n_k = 1.75 \times 10^8$ cells/cm^3 (assumed), vf_{cell} = cell volume/organ volume = $(n_k\ \pi\ {d_{cell}}^3/6)$.

Organ k	E_k	F_k	H_k	I_k	B_k	O_k	P_k	Q_k	J_k	L_k	N_k
-	$\dot{q}_{k,m}$, $\frac{W}{kg\ organ\ k} = E_k\ {m_k}^{F_k}$ $E_k = \left(\frac{e_k}{\frac{f_k}{d_k}}\right)$, $F_k = \left(\frac{f_k}{d_k}\right)$	Note 1, Note 2	$\dot{V}_{Bl,k,m}$, $\frac{mL\ of\ blood}{s\ kg\ organ\ k} = H_k {m_B}^{Ik}$, $H_k = h_k/c_k$ $I_k = i_k - d_k$,	Note 1	$\dot{q}_{k,m}(t)\left(W\ of \frac{k}{kg} organ\ k\right) = B_k(Mivf_k)^{O_k}$, $B_k = \frac{e_k}{\frac{f_k}{q_k}}$, $O_k = \frac{e_k}{\frac{f_k}{q_k}}, q_k \neq C$, $B_k = \frac{e_k}{\frac{p_k}{f_k}}, O_k = f_k, q_k = 0$		$\dot{q}_{k,v,Mito}\left(\frac{W}{cm^3\ of\ Mito\ organ\ k}\right) = P_k {m_B}^{Q_k}$, $P_k = \frac{\rho_k e_k}{vf_{cell} p_k}$, $Q_k = f_k - q_k$ Note 1		$OEF = J_k\ {m_B}^{L_k}$ $J_k = \left(\frac{c_k e_k}{h_k\ \rho_{bl}\ Y_{O2in}\ HV_{O2}}\right)$, $L_k = f_k + d_k - i_k$	Note 1	$(T_{exit} - T_{in})$, °C $= N_k\ {m_B}^{L_k}$ $N_k = \frac{J_k Y_{O_2 in} HV_{O_2}}{c_p}$ or $N_k = \left(\frac{c_k e_k}{h_k\ \rho_{bl}\ c_p}\right)$ Note 1
AT	0.22 (-)	0.0 (-)	- (-)	−1.19 (-)	0.22 (-)	0.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)
Brain	11.62 (9.42)	0.0 (−0.184)	0.985 (9.182)	−0.006 (−0.056)	11.62 (14.36)	0.0 (−1400) Note 2	2.44 (4.544)	0.0 (−0.14)	2.623 (0.524)	0.006 (−0.084)	3.090 (0.617)
Heart	21.31 (23.04)	0.0 (−0.122)	37.333 (37.333)	−0.266 (−0.266)	22.53 (39.16)	0.0 (2.72)	0.874 (1.769)	0.044 (−0.076)	0.127 (0.257)	0.266 (0.146)	0.150 (0.303)
Kidney	21.3 (20.95)	0.0 (−0.094)	65.753 (86.143)	0.064 (−0.076)	21.99 (32.95)	0.0 (1.43)	0.434 (0.681)	0.056 (−0.024)	0.07 (0.086)	−0.064 (−0.004)	0.0824 (0.102)
Liver	9.69 (11.49)	0.0 (−0.310)	3.177 (4.727)	0.156 (−0.014)	11.31 (24.32)	0.0 (3.00)	0.623 (2.128)	0.09 (−0.18)	0.678 (1.558)	−0.156 (−0.256)	0.799 (1.836)
Residual	0.58 (1.43)	0.0 (−0.168)	- (-)	−0.994 (−1.01)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)	- (-)
SM	0.63 (-)	0.0 (-)	1.643 (-)	−0.253 (-)	0.84 (-)	0.0 (-)	- (-)	- (-)	- (-)	- (-)	- (-)

Note: 1: c_k, d_k, e_k and f_k for AT and SM are not defined for 5 organ model. Note 2: When allometric laws are given say for m_k and $\dot{q}_{k,m}$ in terms of body mass, m_B, then on conversion to organ mass-based allometry; $F_k \to \infty$ when $d_k \to 0$; but still $\dot{q}_{k,m}$ will tend to correct limit. For this case, one may set d_k to a, low value say 10^{-4} in getting appropriate numbers. Similar approaches are adopted for other parameters.

5.4. Maximum Possible Blood Temperature

Sacher et al. assumed that life span is a function of 4 variables: body mass (m_B) and temperature (T_B), specific metabolic rate of body and brain mass [36]. Since metabolic rate is related to m_B, and body temperature (T_B) is affected by the blood temperature, life span relation could be reduced to two variables: brain and body mass [37] if T_B is constant. Since brain mass is related to body mass [19,30], then life span may be further reduced to a single variable of either body mass or metabolic rate. It is noted that these expressions for life span do not seem to account for varying body mass with age or growth correction factor (GCF) while Annamalai and Silva [8] accounted for GCF and as well as the effect of metabolic efficiency (which indirectly affects body temperature by affecting "Q" and hence Sacher's relation showing effect of body temperature). Whichever organ's venous blood temperature is high, it faces more oxidative damage. Using the relations presented in Section 4 and derived allometric constants listed in Table 4, the maximum temperature rise of vital organs were computed for 84 kg human ($m_{B,st}$, metabolic efficiency = 0) and they are tabulated in Table 5. Except for brain data for Wang 7-Elia model, the temperature rise in almost all organs is less than 0.5 °C. Even though brain constitutes only 2–3% body mass, it consumes 20–25% of body's total oxygen or total energy release indicating high specific energy release rate (W/kg brain mass) of body. Brain temperature in humans is normally 0.5–1 °C warmer compared to temperature around spinal cord of body [38]. Note that actual rise in temperature is about 70% of maximum possible rise when metabolic efficiency of about 30%. A concussion in brain causes metabolic efficiency to be about 15% (estimated from ATP data of [30] which shows ATP decreasing from 2320 nmol/g to 1095 nmol/g wet within 4 days after concussion) and according to current analysis the increased heat part of energy release will cause increased brain temperature with brain injury (i.e., due to reduced metabolic efficiency) is confirmed with data of increase in brain temperature by 1–2 °C [38,39]. Further change in temperature by more than 1 °C affects neurological functions of rat °C with metabolic rate increasing by 7% per °C rise in temperature. ROS relations in combustion science show that the ROS production rates are exponential functions of temperature (Equation (24)) and proportional to the concentrations of fuel and oxygen thus the decreased metabolic efficiency results in more ROS damage. The following affects the temperature rise:

1. body mass, which affects the blood flow rate and metabolic rates of an organ
2. blood flow rates and OEF during resting period exercise (during exercise the metabolic rate may increase to 480 W, almost 6 times that of normal resting metabolic rate which requires skin blood flow rate of almost 1.9 L/min for 1.8 m^2 area person. Core to skin temperature difference is of the order of 5 °C with skin temperature around 30–31 °C) [40]
3. metabolic efficiency
4. nutrients oxidized and concussion in brain which affect metabolic efficiency

Table 5. Selected Quantitative Results for Steady state (84 kg person) and over Life Span for 5 organ (in parenthesis) and 7 organ data with metabolic efficiency = 0.31; however for blood temperature, metabolic efficiency set to zero to get maximum possible values.

Organ	Max Temp Rise, C	Organ Mass, kg Steady	MiVf-steady (Note 3)	$\dot{q}_{k,m,st}$ (W/kg Organ Mass)-Steady	$\dot{q}_{k,V,Mito,st}$ W/cm^3 of Mito (Note 1)	Normalized Energy Release Rate W/cm^3 of Mito in k/W per cm^3 of Heart-Steady	$\dot{q}_k$ (W by k)	$q_{k,M,\ life}$ MJ to One kg Body)	$\sigma_{k,M,\ life}$ (kJ/K) to One kg Body Mass	$\sigma_{k,m,\ life}$ MJ/K per kg Organ Mass	Heart Normalized Entropy Stress during Lifetime (Note 1)
AT	-	14.620 (-)	-	0.22	-		3.216 (NA)	86.4 (NA)	191.8 (NA)	1.14 (-)	1.0% (-)
Brain	3.174 (0.425)	2.382 (0.319)	0.0538 (0.0377)	11.62 (11.63)	2.44 (2.44)	2.3 (1.93)	27.680 (3.71)	825.8 (113.5)	1832.8 (252.0)	60.32 (62.25)	54.5% (46.1%)
Heart	0.486 (0.578)	0.461 (0.461)	0.232 (0.283)	21.31 (25.33)	1.06 (1.26)	1 (1)	9.829 (7.09)	274.8 (335.6)	609.9 (744.8)	110.6 (135.00)	100% (100%)
Kidney	0.062 (0.099)	0.207 (0.303)	0.439 (0.204)	21.31 (23.44)	0.556 (0.612)	0.524 (.485)	4.406 (7.09)	131.4 (208.2)	291.7 (462.1)	110.6 (123.79)	100% (91.7%)
Liver	0.400 (0.590)	1.092 (1.558)	0.121 (0.155)	9.69 (10.01)	0.928 (0.959)	0.873 (0.76)	10.578 (15.60)	316.4 (480.4)	702.3 (1066.2)	50.30 (55.37)	45.5% (41.0%)
Residual Mass	-	26.617 (82.45)	-	0.63 (0.68)	-	- (-)	15.438 (56.17)	430.4 (1620.6)	955.2 (3596.9)	3.01 (3673.4)	2.7% (2.7%)
SM	0.308 (-)	37.608 (-)	0.055 (0.0)	0.58 (0.58)	- (-)	0.455 (0.455)	23.693 (56.17)	661.1 (NA)	1467.3 (NA)	3.27 (-)	3% (-)
Sum	-	**82.99 (85.09) (Note 1)**	-	-	-	-	**94.8 (94.2)**	**2726.5 (2758.4)**	**6051.0 (6121.9)**	-	-

Note 1: assumed n = 1.75 × 10^8 cells/cm^3. Note 2: Average cell volume $V_{avg,cell}$ = 1000 μm^3 = 10^{-9} cm^3, ΔT for blood around heart ($T_{out} - T_{in}$) through blood = 0.58 C; ΔT for Mito of heart in C. Note 3: MiVf is under estimated since it is body mass-based and body mass is 84 kg.

5.5. Results Based on Organ

Values for cumulative entropy generation ($\sigma_{k,ife}$, MJ/K per kg of k) for each organ over life span were generated for both Wang-5 and Wang-7 models.

5.5.1. Metabolic Efficiency

In estimating the overall metabolic efficiency of all organs, the % energy released by each nutrient is used. With assumption of 55:30:15, CH:F:P (mass %), the energy release % is computed as 36.1%, 49.5% and 14.4% via CH, F and P [9] and hence $\eta_{Met} = 0.361 \times 38.2 + 0.495 \times 32.2 + 0.144 \times 0.104 = 0.31$. Salin et al. [41] reports that there is variation of P/O ratio within an individual and amongst individuals due to diet, temperature and environmental factors. The current work presumes that it is affected only by diet, i.e., composition % of CH:F:P metabolized.

5.5.2. Growth Correction Factor (GCF)

With increase in body mass, the organ masses change along with SMRk (Wang-5 model) where f_k is non-zero (Equation (10)); the exponent is typically negative and varies depending on size of an organ (theoretical rationale given in Miller [15]) and $f_k = 0$ when Elia model is used. Recall that body mass is a function of age and metabolic rate increases with increase in body mass and reaches a steady value when body mass reaches a steady value. Equation (18) presents a relation for the growth correction factor GCF. A chart has been constructed for GCF vs. non-dimensional age with g_k (= f_k z) as parameter. Figure 4 shows the results for growth correction factor, GCF; GCF = 1 if mass of body remains constant (z = 0) irrespective of age or when $f_k = 0$ (Elia Constant).

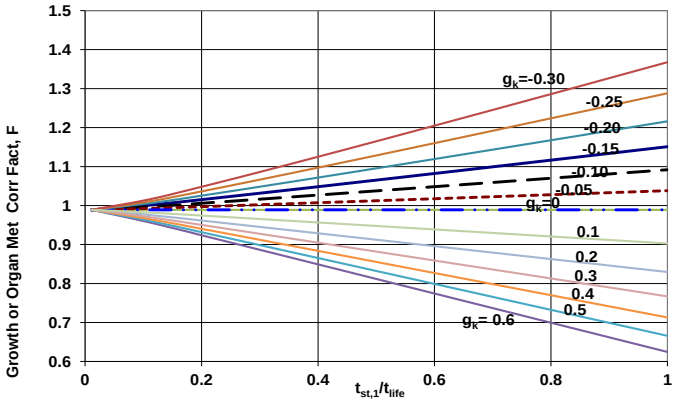

Figure 4. Effect of Body mass growth on growth correction factor GCF_k. For period I (see Figure 2), $m_B(t) = m_{B,st}\ (t/t_{st})^z$ and period II, $m_B(t) = m_{B,st}$ a, z = 0, g_k = 0; (1) For lifetime specific organ energy release or entropy generated: $g_k = z\ f_k$ specific organ allometry (non-isometric, $f_k = 0$) on the "F" factor. $g_k = z\ f_k$; z > 0 indicates body mass growth and z < 0 indicates decrease in body mass (period II); $f_k = 0$ for constant SMR_K (e.g., Elia data); Wang-5 data indicates $0 < f_k < -0.27$; in authors' opinion $0 < f_k < -1/3$. Thus, mostly $g_k < 0$ during body mass growth period and $g_k > 0$ during body mass decrease period for most organs since $f_k < 0$. For period I, $m_B(t) = m_{B,st}\ (t/t_{st})^z$ and period II, $m_B(t) = m_{B,st}$ a, z = 0, g_k = 0.; (2) $g_k = z\ (f_k + d_k - 1)$ in chart for lifetime energy release and lifetime entropy contribution by organ k to each unit mass of body; $g_k = d_k - 1$ in case $f_k = 0$; (3) $g_k = z\ (f_k + d_k)$ for lifetime energy release and lifetime entropy contribution by organ k to whole body; $g_k = d_k$ in case f_k = 0 (Elia constants); (4) $g_k = z\ (f_k - q_k)$ for lifetime energy release and lifetime entropy contribution by organ k per cm^3 of Mito.

Last Column in Table 1 illustrates the procedure with an example for estimating lifetime entropy generation for the human heart.

5.5.3. Effects of Diet Composition

Figure 5 shows the results for organ entropy stress for the Wang-7 model as a function of various nutrient % metabolized in organs. The allometry-based EXCEL program for 7 organs was checked by summing up lifetime entropy contribution by each organ to unit body mass and the allometry-based sum was estimated to be 6050 kJ/(K kg body mass), which is slightly less than the estimated value by Silva and Annamalai (Figure 1) with use of dietary intake recommended by Food and Nutrition board. It can be inferred from Figure 5 that the lower metabolic efficiency of 55:30:15 diet (η_{Met} = 0.31) compared to pure CH (η_{Met} = 0.38) results in the higher values for Q, entropy generation rate (or ROS rate), and higher lifetime entropy generation for prescribed life span. Almost pure glucose (>90%) is used in brain with high ATP production rate accompanied by lesser heat release $(\dot{Q})$ and hence lesser cell temperature rise and lesser entropy generation rate per kg of tissue. The ATP or higher metabolic efficiency was shown to slow the process of aging [38], which seems to suggest the ability of ATP to restore/repair the damaged cell or create new cells with full functional characteristics. Increased ATP production or increased metabolic efficiency [35] (i.e., reduced entropy generation rate, slower BAR Figure 1) when flies are subjected to near Infra-red light and life span increased from 3 weeks (controls) life span increased 11–12 weeks; further activities increased. Edman, et al. [36] has shown that lifespan improves with a low-protein diet since low protein concentration implies higher CH and improving metabolic efficiency.

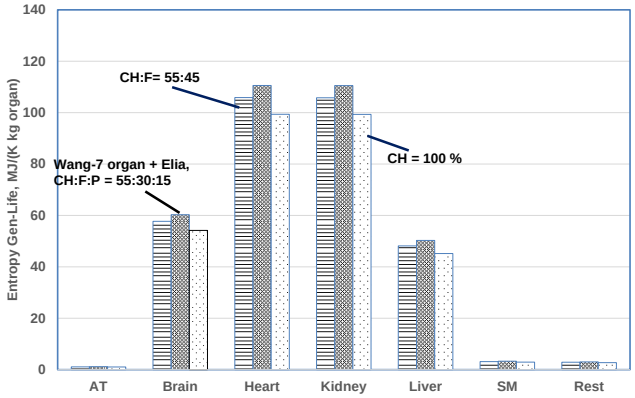

Figure 5. Lifespan Entropy Stress of organ MJ/K per kg organ mass—Wang-7 organ (1) CH:F:P = 55:30:15 Mass % (35:47:18, Heat %), RQ = 0.82, Met Eff = 0.312; (2) CH:F = 55:45 Mass % (33:67, Heat %), RQ = 0.79, Met Eff = 0.34; (3) CH = 100 Mass % (100% Heat %), RQ = 1.0, Met Eff = 0.38; Entropy stress is lower with pure CH since less Q is liberated; all organs are assumed to have same Met Eff.

Higher metabolic efficiency (η_M) represents better use of nutrients in maintaining the healthy state of organs within BS. Further in support of the current hypothesis, pigeons were found to live ten times longer (35 years) than rats (4 years) [42], even though both species have the same mass and hence similar metabolic rates. It is noted that the effects of nutrients on aging and life span are studied strictly from the point of view calories released and metabolic efficiency. Typically, glucose concentration is 1000 ppm (or g per million g of blood in engineering terminology) while oxygen is only 300 ppm indicating rich nutrient:oxygen mixture. However the presence of increased % of glucose in blood stream affects the filter system (kidneys) and its effects on entropy stress of kidney and other organ functions are not studied. While the oxygen extraction fraction (OEF) is only 0.10–0.15 for healthy kidneys (0.5% of body mass), the diabetes requires additional metabolic input (more O_2 consumption resulting in more ROS) in order to perform more filtration of solute [43] thus accelerating the entropy production rate or aging for kidneys and these factors are not included in the model.

5.5.4. Effects of 5 Organ vs. 7 Organ Models

Figure 6 shows a comparison of heart normalized entropy stress for the two models: Wang-5 and Wang-7 organ Model with selected diet (CH:F:P = 55:30:15). The Wang-5 include BHKL-R5 along with body mass-dependent SMR_k while the Wang-7 Model includes 7 organs AT-BHKL-R7-SM with Elia's body mass independent SMR_k. Note that Wang-7 with Elia data shows almost same entropy stress as Wang-5 model.

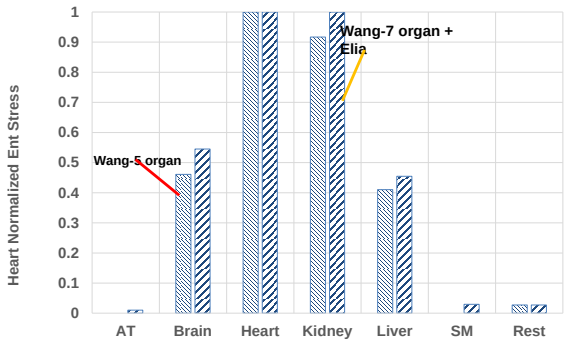

Figure 6. Comparison between Wang-5 and Wang-7 Models for heart normalized Entropy stress. The 7 organ data had high brain mass (2.4 kg) vs. brain mass of 0.32 kg for 5 organ data. CH:F:P = 55:30:15, RQ = 0.82, Met Eff = 0.31, m_{st} = 84 kg. Lifetime specific entropy generation for heart is 135 MJ (K kg heart) for Wang-5 and 110.62 MJ/(K kg heart) for Wang-7 essentially due to similar constant metabolic rate for Elia mode for both Kidney and heart. The heart is the most entropy stressed organ for Wang-5 and both heart and kidney are most stressed for Wang-7 model while AT and SM are least stressed. Thus, cells with higher metabolic rate per unit mass (e.g., heart) leads to faster biological aging of organs. Vital organs account for 4–6% body mass but account for metabolic rate 15–40 times that of SM and 5–100 times that of AT [44] indicating that vital organs age much faster compared to other organs.

5.6. Results Based on Mitochondria

5.6.1. SMR_k (W/kg Organ k) Variation with Mito Volume

Typically, metabolism is modeled using Michaelis and Menten (MM) kinetics, which are analogous to Langmuir Hinshelwood (LH) kinetics on carbon combustion except for the difference that MM is based on volume of reacting system while LH is based on surface kinetics. If temperature of body is fixed, the kinetics controlled rate in W/cm^3 of Mitochondria is a function of temperature and hence it is typically assumed that the consumption rate of O_2 per unit volume of organ remains constant in most organs as presumed in Krogh cylinder model for metabolism. However the oxidation occurs in mitochondrion of the cell and as such the O_2 consumption rate per unit volume of Mitochondrion is constant and higher the MiV fraction within the cell, higher is the SMR_k. Thus, a plot on the SMR_k (energy release rate per unit mass of organ) vs. mitochondrial volume % is presented in Figure 7 for both Wang-5 and Wang-7 models. Brain has the lowest Mito volume % (5.4%) while heart has the highest Mito volume % (15.5%). It is seen that higher the mitochondrial volume % in organ, higher the specific metabolic rate organ (W per kg of organ). If SMR_k (W/kg organ k) is proportional to $(MiV\%)^n$, then least square straight line fit for vital organs yields the slopes as $n = 0.83$ (i.e., $n < 1$) with Wang-5 and 0.67 for Wang7-Elia but both indicates positive slopes. Note that Elia's SMR_k used in Wang-7 model is body mass independent but depends on type of organ, its enzyme and mitochondrial volume fraction. It is apparent from both models that SMR_k does not increase in direct proportion to MiV fraction probably due to organ-dependent enzyme activities and/or oxygen transport rate limitation [14,15], i.e., slopes are less than 1. As MiV % increased consumption rate of O_2 increases (Watts) which require faster diffusion rate from capillaries to the cells. If one compares these results to

carbon combustion in engineering literature, diffusion control is a strong possibility particularly when mitochondrial volume is increased.

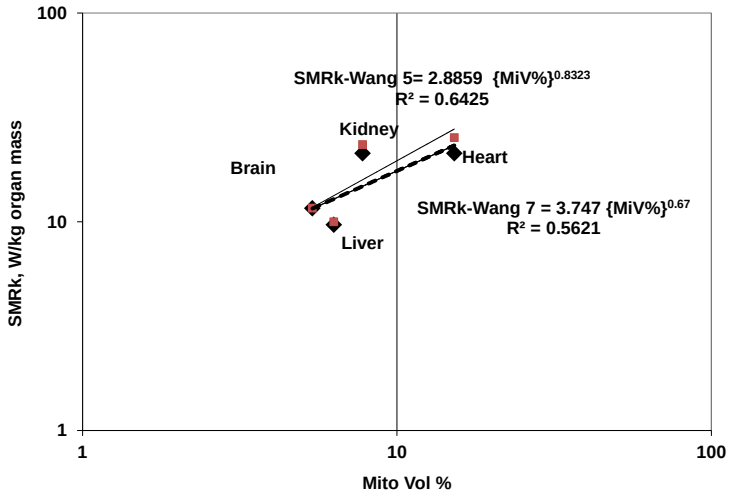

Figure 7. Relation between mitochondrial volume % (MiV $*$ 100) and specific metabolic release rate (W/kg) for humans-84 kg person; simplified analysis and kinetics controlled metabolic rate indicates linear dependency of SMR_k on Mitochondrial volume %. SMRk (W/kg organ k) is proportional to (MiV %)^n with n = 0.83 for Wang-5 and 0.67 for Wang-7. Note $n < 1$.

5.6.2. $SMR_{k,V,Mito}$ (W/cm^3 of Mito) Variation with Mito Volume

In order to investigate whether $SMR_{k,V,Mito}$ (W/cm^3) is same for all organs, and to ascertain the degree of damage to DNA within mitochondria, which is proportional to metabolic loading, $SMR_{k,V,Mito}$ quantitative estimation of $SMR_{k,V,Mito}$ is required for all organs. If mitochondrial volume fraction, $MiVf_k$, number of cells per unit volume (n_k), and density of organ k are known, then one can convert SMR_k to $SMR_{k,V,Mito}$ (Watts/cm^3 of Mito of k). Whether one use 7 organ or 5 organ data, the Mito volume % are same since it is a function of body mass only. While the plots in Figure 7 show that SMR_k increases with the mitochondrial volume % in organ, the plots in Figure 8 shows that $SMR_{K,v,Mito}$ decreases with increase in MiV %. Since SMR_k in Figure 7 are proportional to (MiVf)^n where $n < 1$ and since $SMR_{k,V,Mito} \frac{W}{cm^3 \text{ of Mito in k}}$ is proportional to (MiVf)^n/MiVf $\propto$ (MiVf)$^{n-1,}$ then ($n - 1$) < 0 (See Figure 7); then $n - 1 = -0.17$ for Wang 5 and -0.33 for Wang-7 while power law fit in Figure 8 indicates the corresponding slopes as -0.153 and -0.315.The R^2 is very low since SMR_k was divided by mitochondrial volume and uncertainty in Mito volume % is magnified.

It has been shown in earlier literature that SMR_k is low particularly for large organs due to problems with oxygen accessibility [22], since capillaries must service a large number of cells in a large organ. In engineering literature detailed models called group combustion have been developed on the effect of oxygen deficiency on specific energy release rate (W/kg) vs. radius of spherical fuel clouds [12]; increasing size or mass of cloud (which is similar to increasing size of organ in biology) results in reduced energy release rate per unit mass of cloud. When this theory is extended to organs it shows decreasing SMR_k with increasing size of organ [14,15]. To summarize, the SMR_k is not only affected by mitochondrion volume %, and enzyme reactivity within mitochondrion of cell but also by transport rate of O_2 and oxygen accessibility to all cells.

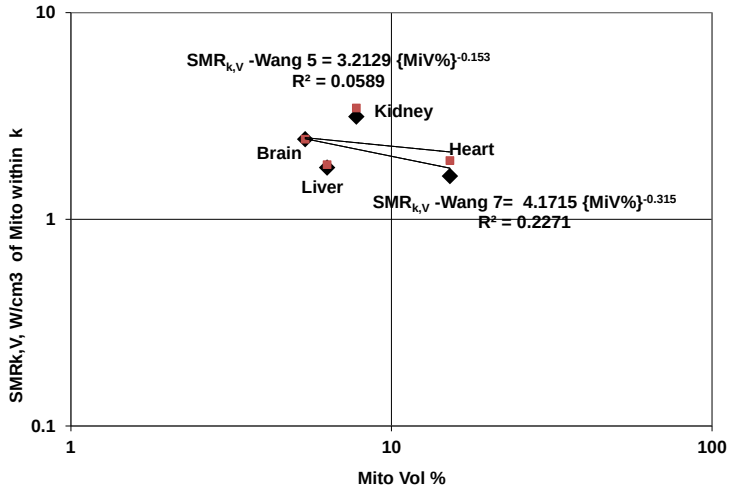

Figure 8. The Volume-based Specific Metabolic Rate of Organ k (W/cm^3 of Mito) vs. Mito volume %. It decreases with increased mitochondrion volume %, possibly due to diffusion limitations. $SMR_{k,V}$ (W/cm^3 of Mito) is approximately proportional to $(MiVf)^{n-1}$ (See Figure 7); then $n-1=-0.17$ for Wang 5 and -0.33 for Wang-7 while Figure indicates corresponding slopes as -0.153 and -0.315.The R^2 is very low since SMRK was divided by mitochondrial volume and uncertainty in Mito volume % is magnified.

In order to ascertain the degree of damage to organ k relative to heart, the heart normalized metabolic intensity of mitochondrial intensity ratio (MIR) is defined as

$$\mathrm{MIR} = \frac{\dot{q}'''_{\mathrm{Mito,k}}(t)}{\dot{q}'''_{\mathrm{Mito,H}}(t)} = \frac{\rho_k}{\rho_H}\frac{e_k p_H}{p_k} m_B{}^{Q_H - Q_k},\ \text{relative Mito} - \text{DNA damage}$$

which assumes that all organs have same number density of cells and same cell size ($V_{cell,k} = V_{cell,H}$). Figure 9 shows the results. The net energy release rate per mitochondrial volume of the organs differ due to the difference in mitochondrial volume density (MiV) for each organ.

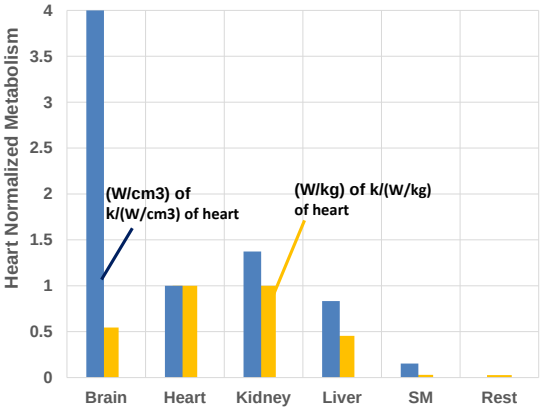

Figure 9. Comparison of Heart normalized Metabolic Stress based on unit organ mass (W/kg) and unit Mitochondrial volume (W/cm^3 of Mito), 84 kg person; 1.26 W/cm^3 of Mito (or 1260 W/kg of Mito) in heart, and 25.3 W/kg of heart. Wang7-Elia Model.

From Figure 10 it can be inferred that life span entropy generated per unit volume of mitochondrion is highest in the brain, followed by the heart, liver, and kidney. This result is vital for football athletes, who are subject to multiple concussions to the brain, which further reduce the

metabolic efficiency of the organ [30,38], thereby increasing blood temperature and hence entropy generation i.e., brain is biologically aging faster for the athlete with repeated concussion. Once again, it is important to note that the ranking of the organs based on entropy generation changes when the analysis is based on MiV %. As the mitochondria is considered the engine of the cell, this model is more accurate to quantify organ failure as compared to whole organ model.

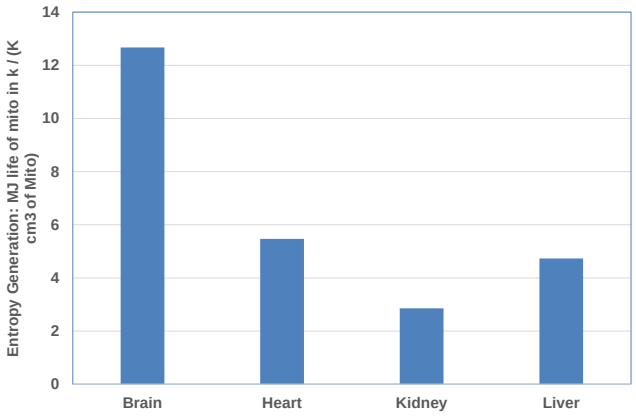

Figure 10. Lifespan Entropy Loading in Mitochondria given in MJ life of Mito in k/(K cm^3 of Mito); Wang7-Elia Model.

5.6.3. $SMR_{k,V,Mito}$ Variation of Organs with Body Mass

The Figures 7–9 present results for $SMR_{k,V,Mito}$ of 84 kg human. Using Equation (19) and data in Table 3 for vital organs, $SMR_{k,V,Mito}$ can be obtained as function of body mass. Table 3 indicates that $(f_k - q_k) < 0$ indicating increased $SMR_{k,V,Mito}$ for brain and liver of smaller species compared to humans and vice versa, and $(f_k - q_k) \approx 0$ for kidney and heart, indicating almost constant $SMR_{k,V,Mito}$ irrespective of body mass of BS.

6. Suggested Procedure for Estimation of Biological Aging

How these results could be used in the Medical Field in estimating metabolism-based biological aging rate (BAR)? Based on energy release rate per unit mass, there are two possible methodology for determining the biological aging rate (BAR) and entropy generation rate:

Method I: Organ Allometry Method: The determination of BAR_k of vital organ k (W/kg organ k) and the total BAR_M of organs per kg body mass (W/kg body mass) vs. age require non-intrusive measurements of oxygen consumption rate of each organ and mass of each organ. In absence of non-intrusive measurements, the body mass ($m_B(t)$) vs. age(t) and the allometric laws for each organ in terms of body mass outlined here can be used to estimate metabolic rate of each organ (t) (W per kg organ mass) and the whole body $\dot{q}_M(t)$ (W per kg mass of body), vs. age may be used as biomarkers. With assumption of constant metabolic efficiency, $\dot{\sigma}_M(t)$ (W/(K per kg mass of organ)) and $\dot{\sigma}_M(t)$ (W/(K per kg mass of body)) vs. age(t) can also be determined.

Method II: Overall Body Calorimetry Method: Overall specific "Calories" release rate $\dot{q}_M(t)$ and entropy generation rate, $\dot{\sigma}_M(t)$ vs. age can be estimated from measured body mass and wet nasal gas analyses assuming dominant nutrients metabolized are CH and fat.

Steps in Organ Allometry (Method-I, heterogeneous): The procedure is given below for monitoring the biomarkers: $\dot{q}_{k,m}(t)$ and $\dot{\sigma}_{k,m}(t)$ (W/ (K kg body mass)} and $\sigma_M(t)$ (kJ/ (K kg body mass)) vs. age(t). Here step by step procedure is given with an example for heart of a human with steady mass of 84 kg ($m_{B,st}$).

A. Energy Release Rates

1. First assume as though the person has constant body mass or steady mass (for e.g., the UK data reveals $m_{B,st}$ = 84 kg). Estimate kth organ mass using allometric relation and known c_k, and d_k (Table 3); thus for heart, k = H, $m_{H,st}$ = 0.48 kg when $m_{B,st}$ = 84 kg.
2. Estimate specific energy release rate ($SERR_k$) or specific metabolic rate (SMR_k) (W/kg organ k) during steady body mass period with known e_k and f_k given by allometric law:

$$\dot{q}_{k,m,st}\left(\frac{W}{\text{kg organ k}}\right) = e_k {m_{B,st}}^{f_k}, \dot{q}_{H,m,st} = 25.3\frac{W}{\text{kg heart}}, \ (k = H)$$

3. Multiplying t_{life} one get GJ per kg of heart over life span

$$\dot{q}_{k,m,st} = \dot{q}_{k,m,st} t_{life} \text{ where } t_{life} \text{ in s} = 75 \text{ years} \times 3.15 \times 10^7 \frac{\text{s}}{\text{year}} = 2.37 \times 10^9 \text{s}$$

$$q_{H,m,st,life} = 25.3\frac{W}{\text{kg heart}} \times 2.37 \times 10^9 \text{s} \times \frac{1 \text{ GJ}}{10^9 \text{ J}} = \frac{60 \text{ J}}{\text{kg heart}}$$

See last column in Table 4. Similarly estimate $\dot{q}_{k,m,st}$ and $q_{k,m,st,life}$ for all organs.

4. Estimate the contribution rate by each organ to unit mass of body:

$$\dot{q}_{k,M,st}\frac{\text{W by k}}{\text{kg body}} = \frac{\dot{q}_{k,m,st} m_{k,st}}{m_{B,st}}$$

So with k = H, the contribution rate by heart to unit body mass is estimated as

$$\dot{q}_{k,M,st} = \frac{25.3 \text{ W} \times 0.48 \text{ kg heart}}{84 \text{ kg}} = 0.145 \text{ W}$$

$$\dot{q}_{k,M,st} = \frac{25.3 \text{ W} \times \ 0.48 \text{ kg heart}}{84 \text{ kg}} = 0.145 \text{ W contriution rate by heart to unit mass of body}$$

Multiplying t_{life} one get GJ contributed by heart over life span to each unit body mass

$$q_{H,M,st} = \frac{0.145 \frac{\text{W by heart}}{\text{kg body mass}} \times 2.37 \times 10^9 \text{ s}}{\frac{10^9 \text{ s}}{\text{GJ}}} = 0.35\frac{\text{GJ by heart}}{\text{kg body}}$$

Similarly estimate $\dot{q}_{k,M,st}$ and $q_{k,M,st,life}$ for all organs.

5. Add contributions by all organs to each unit body mass under steady period and check the total with estimate from Kleiber's law. In Method A, the biomarkers which determine BAR are empirical organ allometric coefficients, steady mass and the metabolic rate (First law, heterogeneous) which determines the slope of biological aging curve in Figure 1.

B. Entropy Generation Rates

6. Assuming constant average metabolic efficiency (η_{Met}) for all organs, estimate heat part of $SERR_k$

$$\dot{Q}_{k,m,st} = \dot{q}_{k,m,st}(1 - \eta_{Met}), \dot{Q}_{H,m,st} = 25.3\frac{W}{\text{kg heart}}(1 - 0.31)$$
$$= 17.5\frac{W}{\text{kg heart}} \text{ with } \eta_{Met} = 0.31$$

and estimate corresponding entropy generation rate from organ k as

$$\dot{\sigma}_{k,m,st} = \frac{\dot{Q}_{k,m,st}}{T_B},\ T_B \text{ in K} = 310 \text{ K and for heart}$$

$$\dot{\sigma}_{H,m,st} = \frac{17.5}{310} = 0.0565 \frac{W}{\text{kg heart K}}$$

7. Multiplying t_{life} ($= 2.37 \times 10^9$ s over 75 years) one get GJ of heat per kg of heart over life span as

$$Q_{k,m,st,life} = \dot{q}_{k,m,st}(1 - \eta_{Met}),\quad Q_{H,m,st,life} = 17.5 \frac{W}{\text{kg heart}} \times 2.37 \times 10^9 \text{ s} \times \frac{1 \text{ GJ}}{10^9 \text{ J}} = \frac{41.5 \text{ GJ}}{\text{kg heart}}$$

and corresponding

$$\sigma_{H,m,st} = \dot{\sigma}_{H,m,st}\ t_{life} = \frac{41.5 \text{ GJ}}{310 \text{ K kg heart}} \times \frac{1000 \text{ MJ}}{\text{G J}} = \frac{134 \text{ MJ}}{\text{kg heart K}}$$

8. Following part A, the contribution by each organ to unit body mass are given below:

$$\dot{Q}_{k,M,st} = \frac{\dot{q}_{k,m,st}\,(1 - \eta_{Met})\,m_k}{m_{B,st}},\quad \dot{Q}_{H,M,st} = 0.1 \frac{\text{W by heart}}{\text{kg body}},\ Q_{H,M,st,life} = 0.24 \frac{\text{GJ by heart}}{\text{kg body}}$$

$$\sigma_{H,m,st,life} = 0.78 \frac{\text{MJ by heart}}{\text{K kg body mass}}$$

9. Add entropy contributions by all organs to each unit body mass under steady period to determine lifetime entropy generation per unit body mass. In Method B, the biomarkers which determine BAR are empirical organ allometric coefficients, steady mass, entropy generation rate (second law, heterogeneous)which determines the slope of biological aging curve in Figure 1.
10. If Elia's model is used where specific organ metabolic rate does not change with body mass (e.g., from birth to death), all the numbers in rate form per unit mass of organ will not change or growth correction factor = 1 for all rate form based on unit mass of organ. However, for Wang-5, the SMR_k change with age since body mass does not remains constant from birth to death and as such GCF are necessary. Further organ mass changes with age (due to change with body mass with age) and hence their contribution to unit body mass will change even for Elia model; as such estimates for GCF are necessary when contribution to unit body mass is required for both Elia and Wang-5 models. Thus, one must use charts presented in Figure 4. When period of standard mass is short compared to life span, GCF $\approx$ 1.0.

Method II: Overall Body Calorimetry (Second Law, Homogeneous)

In Method II, the biomarkers that determine BAR are body mass, breathing rate and nasal exhaust analyses, which determine the whole body specific energy release rate ($SERR_M$) and metabolic efficiency as function of age in determining the biological aging curve in Figure 1. In addition, one may use empirical organ allometry and sum over all organs to estimate SMR_M and check with measured SMR_M.

1. Monitor the patient's breathing rate $\dot{V}_{Breathe}$ (L/s), mass of body ($m_B(t)$) and CO_2, O_2 and H_2O % in nasal exhaust gases vs. age.

2. If metabolism is dominated by CH (nutrient 1) and F (nutrient 2), then using nasal exhaust analysis, get RQ using Figure 11 [45]:

$$\mathrm{RQ} = \left(\frac{\mathrm{X_{CO_{2,e}}} (\mathrm{N_2/O_2})_\mathrm{i}}{\mathrm{X_{N_{2,e}}} - \mathrm{X_{O_{2,e}}} (\mathrm{N_2/O_2})_\mathrm{i}} \right)$$

where X_k, mole (or volume) fraction of gaseous species k in dry exhaust.

3. Determine heat fraction contributed by CH and fat. Since RQ of blended nutrient mixture is given as

$$\mathrm{RQ} = \ \mathrm{HF_1}\ \mathrm{RQ_1} + \ (1 - \mathrm{HF_1}\ )\mathrm{RQ_2}$$

where HF_1, ratio of energy released by nutrient 1 (CH) to energy released by the blend (mixture of CH and fat). Then for $RQ_1 \neq RQ_2$, the above equation yields heat fraction faction of CH, (nutr 1) and fat (nutr 2)

$$\mathrm{HF_1} = \frac{(\ \mathrm{RQ} - \ \mathrm{RQ_2})}{\{\ \mathrm{RQ_1} - \mathrm{RQ_2}\}}, \ \ \mathrm{RQ_2} \neq \mathrm{RQ_1}$$

$$\mathrm{HF_2} = \frac{(\ \mathrm{RQ} - \ \mathrm{RQ_1})}{\{\ \mathrm{RQ_1} - \mathrm{RQ_2}\}}, \ \ \mathrm{RQ_2} \neq \mathrm{RQ_1}$$

where HF_2 represent the ratio of energy released by metabolism of fat (i.e., "Calories" released by fat) to total energy released by blend. RQ_1 for glucose = 1, RQ_2 for fat is 0.7. The mole fraction of CH in nutrient mixture can also be estimated if needed.

$$\mathrm{X_{CH}} = \mathrm{Mole\,Fr\,CH} \ = \ \frac{(23\ \mathrm{RQ} \ - 16)}{(17\ \mathrm{RQ} - 10)} \tag{25}$$

Knowing molecular weights, mass fraction of CH can be determined.

4. Estimate oxygen extraction fraction (OEF) from inspired air:

$$\mathrm{OEF} = 1 - \frac{\mathrm{X_{O_{2,e}}}}{\mathrm{X_{N_{2,e}}}} (\mathrm{N_2/O_2})_\mathrm{i},$$

5. Estimate the overall metabolic efficiency of the body vs. age:

$$\eta_{\mathrm{Met}} = \frac{\{\text{Mole Fr CH } \eta_{\mathrm{Met,CH}}\ \Delta G_{\mathrm{CH}} + (1 - \text{Mole Fr CH}) \eta_{\mathrm{Met,F}} \Delta G_\mathrm{F}\}}{\{\text{Mole Fr CH } \Delta G_{\mathrm{CH}} + (1 - \text{Mole Fr CH}) \Delta G_\mathrm{F}\}}$$
$$\eta_{\mathrm{Met}} \approx \ \mathrm{HF_1} * \eta_{\mathrm{Met,CH}} \ + (1 - \mathrm{HF_2}) \eta_{\mathrm{Met,F}} \tag{26}$$

Figure 12 shows variation of metabolic efficiency and glucose mass % metabolized with RQ if it is assumed that dominant energy release occurs via metabolism of a mixture of CH and F. If RQ increases with age, the more glucose metabolized and less fat metabolized indicating accumulation of "fat" mass if "fat" consumption is known.

6. Using nasal exhaust analysis, get oxygen extraction fraction (OEF), determine specific metabolic rate (SMR_M)

$$\mathrm{SMR_M} = \frac{\mathrm{SMtR}\ \{\mathrm{Watts}\}}{\mathrm{m_B}\{\mathrm{kg}\}} = \frac{\dot{\mathrm{V}}_{\mathrm{Breathe}} \left(\frac{\mathrm{L}}{\mathrm{s}} \right) \rho_{\mathrm{air}} \left(\frac{\mathrm{kg}}{\mathrm{L}} \right) * 0.23 * \mathrm{OEF} * \mathrm{HV_{O_2}} \left(\frac{\mathrm{J}}{\mathrm{kg\ O_2}} \right)}{\mathrm{m_B}}$$

where oxygen mass fraction in air is assumed to be 0.23. Further specific entropy generation rate vs. age is given as

$$\dot{\sigma}_\mathrm{M}(\mathrm{t}) \left(\frac{\mathrm{kW}}{\mathrm{K\ kg}} \right) = \frac{\mathrm{SMR_M}(\mathrm{t})(1 - \eta_{\mathrm{Met}}(\mathrm{t}))}{\mathrm{T_B}\{\mathrm{K}\}}, \tag{27}$$

As such BAR cane be compared with CAR as shown in Figure 1. Equation (27) accounts for variation of metabolic rate and metabolic efficiency with age while the results reported in Figures 9 and 10 are based on constant metabolic efficiency.

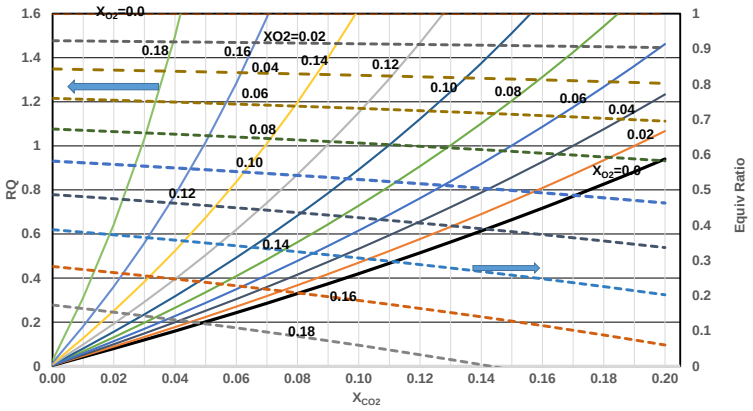

Figure 11. Determination of RQ (primary Y axis) and Oxygen Extraction Fraction (OEF, secondary Y (same as equivalence ratio) using nasal dry exhaust gas analysis. Valid for any C–H–O fuel under complete combustion (products CO_2, H_2O, O_2 and N_2) or metabolism of nutrients. Solid lines: RQ vs. X_{CO2} with oxygen mole fraction as a parameter; dashed lines: OEF vs. X_{CO2} with oxygen mole fraction as a parameter. As CO_2 % in exhaust increase, it implies increasing production of CO_2 or RQ for given O_2 %. At given CO_2 %, increase in O_2 % in exhaust implies decreasing amount of O_2 consumed or increasing RQ. The equivalence ratio for lean mixtures in engineering (O_2 required to completely burn given amount of fuel/O_2 supplied for same amount of fuel) is same as ratio of oxygen used for metabolism to oxygen supplied or oxygen extraction fraction in biology. The lean and rich mixture concept for fuel: air mixtures in engineering system does not apply to typical rich mixtures of nutrients (CH and F) and oxygen in blood stream (Figure adopted from [45]).

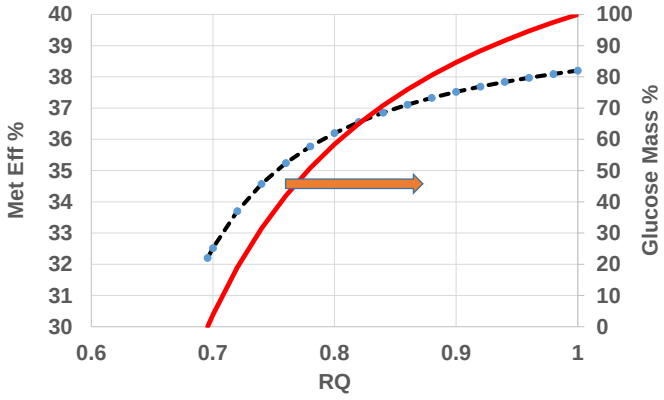

Figure 12. Variation of Metabolic Efficiency and glucose mass % metabolized for a mixture of CH and F vs. RQ. CH: Glucose, F: Fat. Solid Line: Met Eff vs. RQ. Dashed Line: glucose mass % metabolized vs. RQ.

For e.g., if measured CO_2, H_2O and O_2 % are 3.6, 6.2 and 15.6 [16], then using atom balance, RQ = 0.85, OEF = 0.21, η_{Met} = 0.352, CH % (mole): 80%; CH % (mass): 74%; rest is fat. η_{Met} = 0.37; If breathing rate is 360 LPH, then metabolic rate is 83 W and one can check whether the SMR of 83 W is close to value based on Kleiber's law.

Note on Biological Aging and Lean Body Mass (LBM)

An average male has 76–82% of LBM while female has 69–75%.The LBM % decreases with age [46]. It is LBM which results metabolism. Thus when fat % is increased, the decreased mass of LBM must increase its specific metabolic rate so that heat loss from fat is compensated and fat mass can be maintained at body temperature. Hence the previous numbers under methods I and II must be divided by fraction of LBM in the body in order to estimate BAR. Hence biological aging rate is accelerated when LBM % decreases. Thus an additional measurement during office visit could be LBM %. Recently CDC reported that people of age 65 and older must exercise at least 2.5 h of exercise per week and it improves lean body mass % and mitochondrial functions [47]. Further exercise results in increasing open % of capillaries, serves more number cells and increasing blood flow under same pressure difference across the organs; it results in more ATP per unit volume of organ with more ability to repair and create new cells.

7. Summary and Conclusions

1. While Rubner's relies on 1st law analysis for estimating the aging rate (irrespective of metabolic efficiency), the current work uses 2nd law analysis for estimating entropy generation per unit mass of organ and per unit volume of mitochondria, which can be used as one of the biomarkers for predicting the biological aging rate.
2. The inclusion of entropy generation for adipose tissue and skeletal muscle has minimal effect on whole body specific entropy generation rate.
3. Increased % of glucose diet seems to increase life span while increased protein % shortens life span due to low metabolic efficiency of proteins.
4. The increase in SMR_V (per unit volume of organ) is less than proportional to increase in mitochondrial density (Mitochondrial volume %, MiV) within the cell.
5. The heart is the most stressed organ whether one adopts 5- or 7-organ model for resting humans when organ-based entropy stress model is used.
6. Ranking of entropy stress based on unit volume of mitochondria differs from entropy stress ranking based on unit mass of organ. At a mitochondrial level, the brain has the highest stress and liver has the lowest loading among all vital organs. Particularly athletes with constant concussions may be subject to more brain anomalies near the end of their lifetimes due to low metabolic efficiency with concussion.
7. While ATP produced via oxidation of nutrients supplies energy for repair and replacement of cells (synthesis) through oxidation, such an oxidation path also serves as the "destroyer" (decomposition) of cells through generation of ROS and hence involves delicate balance.
8. With currently available diagnostic tools for measurements of nasal exhaust gas composition, respiration rate and body mass vs. age, the whole body specific energy release and entropy generation (which accounts for whole body average metabolic efficiency) methodologies can be used to provide one of the biomarkers for tracking biological aging.

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Author Contributions: Kalyan Annamalai conceived most of the basic concepts, formulated the governing equations, obtained the solutions for several parameters of interest, developed the Excel-based programs for use in obtaining quantitative data, prepared the rebuttal to three reviewers and finally revised the paper with supporting data from literature. Arnab Nanda collected literature and ran the various parametric cases as part of manuscript and wrote the initial draft of paper.

Conflicts of Interest: The authors declare no conflict of interest.

Symbols and Acronyms

ATP	Adenosine Tri-Phosphate
AT	Adipose Tissue
B	Brain
BA	Biological Aging
BAR	Biological Aging Rate
BS	Biological Systems
C	Specific Heat Capacity
CA	Chronological Aging
CAR	Chronological Aging Rate
CH	Carbohydrates
CR	Calorie Restriction
CV	Control Volume
DNA	Deoxyribonucleic Acid
ERR	Energy Release Rate
EU	European Union
F	Fat
FNB	Food and Nutrition Board
GCF	Growth Correction Factor
H	Heart
HV	Heating Value
HHV	Higher Heating Value
K	Kidney
KE	Kinetic Energy
L	Liver
LBM	Lean Body Mass
LH	Langmuir Hinshelwood
MiV	Mitochondrial Volume Density
MM	Michaelis Menten
OEF	Oxygen Extraction Factor
p	Pressure
P	Protein
PE	Potential Energy
R	Rest of Organs
ROL	Rate of Living theory
ROS	Radical Oxygen Species
SM	Skeletal Muscles
U	Internal Energy
V	Volume
vf_{Mito}	Volume Fraction of Mitochondria
W	Work

Nomenclature

h	Enthalpy, kJ/kg
I	Irreversibility, kJ
$\dot{I}$	Irreversibility rate, kJ/s
M	Mass, kg
m_B	Body Mass
m_k	Mass of organ, k
$\dot{m}_n$	Mass flow rate of nutrient n in organ k
$\dot{m}_{O_2,n,k}$	Consumption rate of oxygen by nutrient n in organ k
Q	Heat, kJ
$\dot{Q}$	Heat transfer rate due to metabolic heat release $\dot{q}_k$ at organ k, kJ/s
$\dot{q}_{k,n}$	Specific metabolic energy release rate from organ k per unit mass of organ k
$\dot{q}_{k,M}$	Energy release rate of organ k contributed to the unit mass of body
S	Entropy, kJ/K
s	Specific Entropy, kJ/kg K
T_B	Body temperature, K
t	Time or age
t_{st}	Time to reach steady weight
U	Internal Energy
W_K	Work delivered by metabolism at organ k
ΔG_c°	Gibbs Free Energy for Combustion
ΔG_M°	Gibbs Free Energy for metabolism (with ATP production)

Greek Symbols

η	Metabolic efficiency
σ	Entropy generation, kJ/K
$\sigma_{M,k}$	Entropy contribution to unit mass of body by whole organ k
$\dot{\sigma}_M$	Entropy generation rate per unit body mass (W/kg of body mass K)
$\dot{\sigma}_{m,k}$	Specific entropy generation rate of organ k (W/K-kg of k)
ψ	Stream availability, kJ/kg
$\nu_{O2,n}$	Stoichiometric oxygen mass per unit mass of nutrient n
$\eta_{n,k}$	Metabolic efficiency of nutrient n in organ k

General Notes

A bar (-) on top of any property indicates its specific property per kmole of substance
A dot (.) on top of any property indicates its time rate of change

Appendix A. Nasal Gas Analyses

The readers are referred to more general derivations provided in [45] involving any C–H–O nutrients/fuels. Here derivations are provided for specific nutrients: glucose (CH) and fat (F). Consider a mixture of x moles of carbohydrate (CH) represented by $C_6H_{12}O_6$ and $(1 - x)$ moles of fat represented by $C_{16}H_{32}O_2$. When this mixture undergoes stoichiometric oxidation,

$$x\,C_6H_{12}O_6 + (1-x)\,C_6H_{32}O_6 + (23-17x)\,O_2 \rightarrow (16-10x)\,CO_2 + (16-10x)\,H_2O \quad \text{(A1)}$$

The RQ factor along with "x" for a fuel can be determined from known CO_2 % and O_2 % in nasal exhaust gas. The general methodology is to formulate the following reaction equation. Assuming complete combustion, using atom conservation for CH: F fuel mixture;

$$x\,C_6H_{12}O_6 + (1-x)\,C_{16}H_{32}O_2 + a\,O_2 + b\,N_2 \rightarrow c\,CO_2 + d\,H_2O + e\,O_2 + f\,N_2 \quad \text{(A2)}$$

Equation (A2) shows that there are 7 unknowns for C–H–O fuel: x, a, b, c, d, e, and f. Thus 7 equations are needed to determine the unknowns. Four equations are obtained using atom balance of C, H, O, and N. The three additional equations are generated as follows. (1) b/a in dry air = 79/21 = 3.76; (2) dry CO_2 mole fraction in products, $X_{CO2} = c/N_{dry}$ where $N_{dry} = c + e + f$; and (3) dry O_2 mole fraction in products, $X_{O2} = e/N_{dry}$. Thus

all 7 unknowns can be solved including "x". In addition A: F ratio (= (b + a)), RQ (= (16 – 10x)/(23 − 17x)), and, equivalence ratio, φ (= O_2 used or required in combustion/O_2 supplied, same as oxygen extraction fraction, OEF for lean mixture or φ < 1). Derivations are skipped (See [39] for more details and any general C–H–O fuel). Charts are presented in the main body for limited parameters.

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