ENTROPY STRESS BASED ON ORGAN AND MITOCHONDRIAL METABOLIC LOADING

A Thesis

by

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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 called work currency of the body, while the remainder is released as heat. Earlier literature introduced availability concepts from thermodynamics, related the specific irreversibility and entropy generation rate to metabolic efficiency, and energy release rate of each organ, and computed whole body specific entropy generation rate at any given age as a sum of entropy generation within four vital organs; Brain, Heart, Kidney, Liver and the rest of organs. The current work includes the effects of i) two additional organs: adipose tissue and skeletal muscles, for application to athletes, ii) proportions of nutrients oxidized which affects blood temperature and metabolic efficiencies, iii) converts the entropy stress from organ/cellular level to mitochondrial level, and iv) relates these parameters as biomarkers in biological aging process.

Based on 7 organ model, considering a male of 84 kg steady mass, the lifetime energy expenditure is estimated to be 2726.46 MJ/kg body mass, with contributions of 86.4, 825.8, 274.8, 131.4, 316.4, 661.1, 430.4 MJ to each unit body mass by Adipose Tissue, Brain, Heart, Kidney, Liver, Rest of Mass, Skeletal Muscle, while lifetime entropy generated 6051 kJ/(K kg body mass) with contributions of 191.7, 1832.7, 610, 291.7, 702.3, 1467.2, 955.2 kJ/K to each unit body mass. Based on mitochondrial volume and 5 organ model, the lifetime energy expenditure is estimated to be 15529.6 MJ/ cm^3 of mitochondrial volume of whole body, with contributions of 8250, 2435,

3040, 1805, 1.9E-05 MJ to each unit volume of mitochondria in organs, serving as biomarkers in the biological aging process of organs, while lifetime entropy generated is 34465 kJ/(K cm^3 of mitochondrial volume) with contributions of 18310, 5400, 6740, 4010.5, 4.3E-05 kJ/K respectively to each unit of mitochondrial volume. The organ entropy stress ranking based on unit volume of mitochondria within an organ {kJ/ (K cm^3 of mito of organ k) show brain being highest and liver lowest.

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Contributors

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The data analyzed for Section 4-Model, Methodology, and Procedure, and draft version of EXCEL based software were provided by Professor Annamalai. The analyses depicted in Section 4 were conducted in part by Professor Annamalai and his graduate students of the Department of Mechanical Engineering, Texas A&M University, and were published in 2008-2012. All other work and modifications conducted for the thesis were completed by the student independently.

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NOMENCLATURE

ATP	Adenosine Tri-Phosphate
AdT	Adiabatic Temperature
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
CV	Control Volume
DNA	Deoxyribonucleic Acid
ERR	Energy Release Rate
EU	European Union
F	Fat
G	Gibbs Free Energy
GCF	Growth Correction Factor
H	Heart
HV	Heating Value
HHV	Higher Heating Value

K	Kidney
KE	Kinetic Energy
L	Liver
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
ROS	Radical Oxygen Species
SM	Skeletal Muscles
SMR_K	Specific Metabolic Rate of organ k
T	Temperature
U	Internal Energy
V	Volume
vf_{Mito}	Volume Fraction of Mitochondria
W	Work
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
$\dot{m}_k$	Mass flow rate of nutrient n in organ k
$\dot{m}_{O2,n,k}(t)$	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
$\dot{q_{k,m}}$	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
$\Delta\bar{G}_C^o$	Gibbs Free Energy for Combustion
$\Delta\bar{G}_M^o$	Gibbs Free Energy for metabolism (with ATP production)
$\Delta\bar{G}_{ATP}^o$	Gibbs Free Energy

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
$v_{O2,n}$	Stoichiometric oxygen mass per unit mass of nutrient n
$\eta_{\mathrm{n,k}}$	Metabolic efficiency of nutrient n in organ k

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

Page

1. INTRODUCTION AND BACKGROUND

According to England [1] "when a group of atoms is driven by an external source of energy (like the sun or chemical fuel) and surrounded by a heat bath (like the ocean or atmosphere), it will often gradually restructure itself in order to dissipate increasingly more energy. This could mean that under certain conditions, matter inexorably acquires the key physical attribute associated with life" which invokes the Darwinian hypothesis. Every living organism is associated with some movements of the species which requires work (W); further the warmth of the organisms under which biological reactions proceed require energy to overcome heat loss (Q). Thus Q and W require constant energy consumption of a biological system (BS) to support essential life sustaining functions of various organs including the vital organ: brain (B), heart (H), kidney (K), liver (L), lungs (Lu), and the rest (R). This work is provided by cells through the production of Adenosine tri-phosphate (ATP) via the oxidation of nutrients/fuels for the body. The BS performs everyday activities such as exercising (walking, running, lifting weights, chewing and grinding food like a blender, etc. which are called external work, W_{ext}) and which are provided by conversion of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) within skeletal muscles. The body provides the required energy (Q+W) through oxidation of nutrients (n): carbohydrates (CH), fats (F), and proteins (P) produced after digestion of food. Typically the CH and F provide significant fraction of energy. The energy release rate $\dot{q}, (\frac{J}{s})$ and conversion to work rate $\dot{W}, (\frac{J}{s})$ and heat rate $\dot{Q}, (\frac{J}{s})$, (energy transfer due to temperature difference) must follow the first law (Conservation of energy) and second law (direction of energy transfer/chemical reaction,

irreversibility (I) and limited conversion of energy into work) of thermodynamics. While W is organized energy, Q is random energy and entropy S (J/K) is a term introduced in thermodynamics as measure of Q. The release of heat "Q" results in increase of the thermal energy; thus more the number of states in which molecules store energy (translational, rotational, vibrational and various quantum states) and more is the entropy. The specific entropy is a ratio of S to mass of system (m); thus s= S/m, {J/ (g K).

For a BS, the irreversibility is due to property gradients such as mass transfer due to concentration or mass fraction gradient (Y_k), heat transfer due to temperature (T, K) gradient, momentum transfer by velocity gradients (*V, m/s*), work transfer due to pressure (P, N/m^2) gradient and the direction of reaction (as well as mass transfer) due to chemical potential gradient (known as the Gibbs function, g_k, J/g). The Gibbs function is defined as g= h- Ts, J/g where h refers to energy content of the system and Ts refers to unavailable part of energy "h" for an isothermal system such as human body, plant leaves. Thus "g" is a measure of available part of energy "h" for conversion to work. More generally thermodynamics define stream (open system) availability as ψ= h- T_0s, J/g for any system where T_0, temperature of environment (e.g. T_0 =298 K on earth). The stream availability concepts is used for many engineering devices where interactions are with T of system >> environment at T_0 {e.g. steam turbine where temperature of steam T >> T_0}. Most of the life sustaining chemical reactions occur almost isothermally within BS where T_0 surrounding an organ is almost same as body temperature T_B and hence ψ= g when system control volume is elected within the body.

The BS can be considered as a bio-engine, which converts a part of chemical energy of nutrients into thermal energy through Q and remaining as work W in the form of production ATP (called work currency of BS) from ADP and Adenosine mono-phosphate (AMP). The "Q" causes heating effect resulting in rise of thermal energy (U) of BS while conversion to ATP is equivalent to work in thermodynamics. Thus the metabolic process involving ATP production is accompanied by entropy generation (σ, J/K), which can be quantified as a net metabolic or entropy stress being experienced by the BS. When a gas expands through a reversible adiabatic (where heat transfer Q=0) turbine delivering work (W_s) , the entropy leaving {$s_{e,rev}$, J/(g K)} is the same as entropy entering (s_i) if there is no frictional/irreversible process i.e. entropy generation, $\sigma_m = s_{e,rev}-s_i = 0$. However friction between fluid and turbine requires a part of work W_{rev} to be used to overcome friction between fluid and the blades which causes heating effect resulting in rise of exit temperature T_e (causing rise in thermal energy of gas leaving) which cause $s_e > s_i$ in the adiabatic turbine and hence $\sigma_m = s_{e,rev}-s_i > 0$ and less work W delivered since $W_{irrev} = W_{rev}$- frictional work. The difference {s_e - s_i} is called specific entropy generation, σ_m {J/ (g K)}. Similarly irreversibilities within BS (e.g. blood pumped through vessels to overcome friction, O_2 transported across alveoli in lungs into capillaries due to Δg_{O2} gradient, irreversible oxidative energy release due to $\Delta G = G_P - G_R$ of reactions involving R $\rightarrow$P where R could be glucose and oxygen and P could be CO_2 and H_2O cause entropy generation, σ which is affected by the following parameters:

1. Age (t)
2. Metabolic Efficiency (η_{Met})

3. Nutrient Composition (% CH, F, and P)
4. Activity Level of BS/Athletes

The second law of thermodynamics provides information on entropy generation (σ) and extent of irreversibility (I) through entropy balance (S, J/K for σ) and availability balance (Ψ. J for I). Note that I and σ are inter-related: $I = T_0 \sigma$. However, caution should be exercised on comparing a BS with heat engine, which uses a cyclic process to deliver work W while BS uses chemical process (converting one form of chemical energy stored within nutrient to another form of chemical energy stored within ATP). An analogy could be fuel cells. The conventional analysis considers the BS as an open system, with a constant exchange of heat, work, and mass between the system and its surroundings. Using BS as **homogeneous** system where there is uniform release of energy release for all organs, one can estimate energy released by BS every day and entropy generated by the BS every day {Figure 1}.

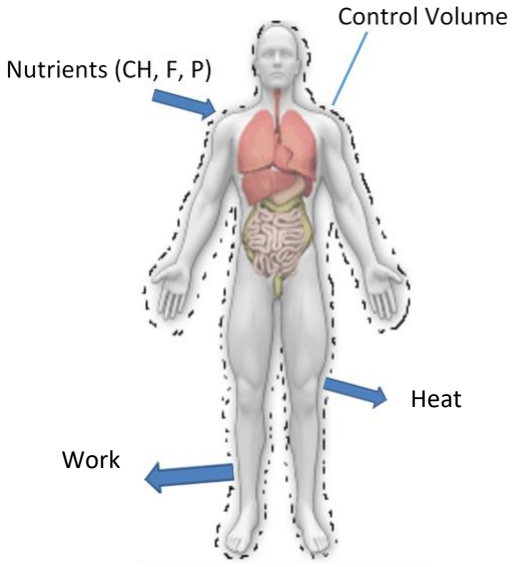

Figure 1: Homogeneous Approach Control Volume

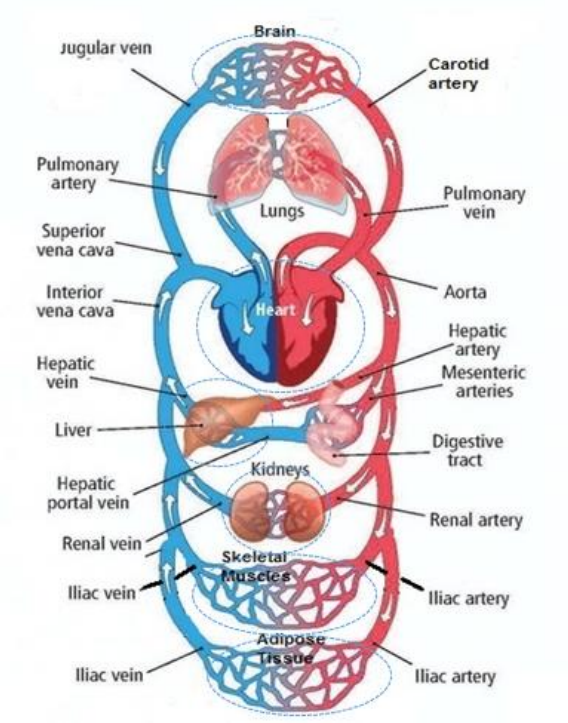

Figure 2: Heterogeneous Approach Control Volume

However BS is a heterogeneous system where there is varying contributions of organs to the total energy release rate of BS. Thus treating the BS as heterogeneous system consisting of various organs one can estimate energy released by BS as a sum of energy released by all organs within body and entropy generated by all organs within the isothermal BS {Figure 2}. Here the nutrients and oxygen from capillaries of organ k are transferred to cells via the interstitial fluid {Figure 3}.

Both approaches have been shown to give same results for whole body but with more information from heterogeneous approach [23, 35]. The heterogeneous approach presumes that metabolic rate per unit mass of organ is proportional to metabolic rate per unit mass of cells. The oxidation occurs within mitochondrion of the cell {Figure 6}, the ratio of mitochondrial volume to cell volume varies from organ to organ and hence specific metabolic rate of organ k varies from organ to organ. The current work will extend the entropy generation concept to mitochondrial level.

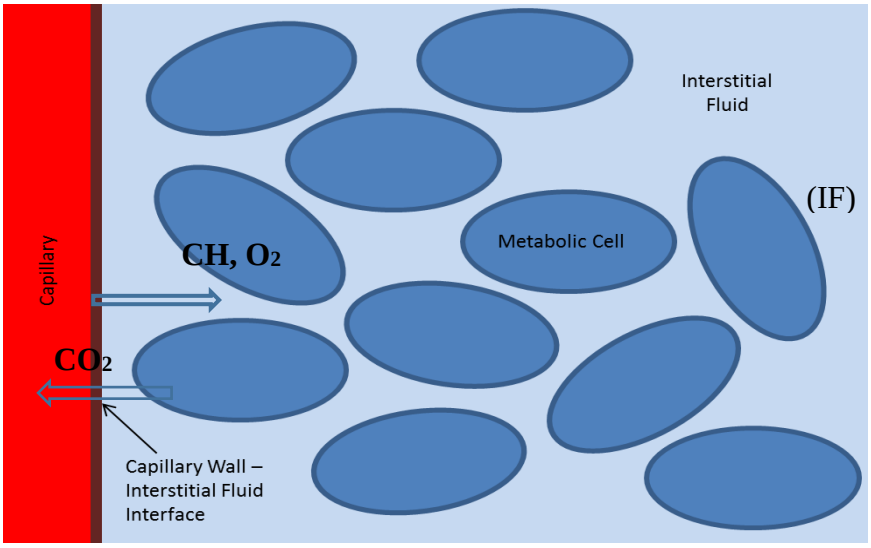

Figure 3: Illustration of Capillary of Organ k Supplying Oxygen to Tissue k Consisting of Metabolic Cells Suspended in Interstitial Fluid (IF). Cells Consume CH (1000 ppm in Blood) and O_2 (300 ppm in Blood) and Undergo Oxidation Releasing Energy.

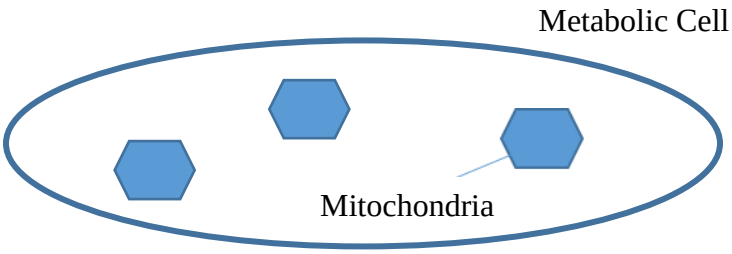

Figure 4: Illustration of Mitochondria Within Each Metabolic Cell

Further the work attempts to extend the work to athletes who operate under intense physical activities which alter energy release distribution (e.g. SM contribution significant energy release to BS) and compare them with normal BS.

Section 2 presents a literature review on first and second laws, availability analyses in thermodynamics and application to BS and previous work on entropy

generation in BS and relation to life span. Section 3 outlines overall goal, specific objectives of current research and tasks performed to achieve overall objectives. Section 4 deals with brief description of model, and methodology adopted in obtaining solutions. Section 5 presents results and discussion followed by Section 6 and Section 7 summarizing the results and future work. Appendixes A and B contain derivations on Allometric Laws based on Organ Mass (m_k) and relation of Entropy Generation to Organ Failure respectively.

2. LITERATURE REVIEW

Entropy generation occurs within the whole body (with control volume just interior of skin) due to internal and external irreversibilities {Figure 1}: The internal irreversibility includes: I) cells of organ k ($\sigma_{cl,m,\,k}$, J/ (K kg of organ k) where vast number of irreversible chemical reaction occurs, II) Interstitial fluid around cells where property gradients exist (O_2 , CO_2, glucose, temperature), III). Skeletal muscles where ATP is used to move muscle fibers against stationary muscles involving frictional process and heart muscles due to pumping action, IV) pressure losses in circulation system, V) frictional/duct losses in breathing in and out etc. The external irreversibility occurs due to the property gradients between the surface of body and surroundings. These gradients within the body and at the interface are however necessity to sustain life.

Based on second law of thermodynamics, the heat "Q" results in entropy generation at the cellular level. Thus, there is a perpetual outflow of energy and hence disposal of entropy generated in the form of heat to the environment. There is striking similarity between the field of combustion science which deal with oxidation at high temperature (order of 1200-1500°C, without use of catalysts) and the field of metabolism in BS where oxidation at low temperature (37°C) is aided by catalysts. One of the earliest work using second law for estimating the specific entropy generation over human life span (J /kg body mass K) was performed by Hershey and Wang [7].

$$\sigma_M(t)\left[\frac{J}{kg\ bodymass\ K}\right] = \int_{t_{birth}}^{t} \dot{\sigma}_M(t)dt \qquad (1)$$

Where t, age of human and $\dot{\sigma}_{M.}(t)$ specific entropy generation rate (W/kg body mass K) at given age t. Of all the entropy generation sources, the major contribution to whole body entropy generation comes from cells (i.e. internal irreversibility) where almost 2/3 is released as heat. All gradients disappear when a biological system dies and decays into its non-living elemental form. At this juncture, cumulative entropy generated by BS over life span reaches a maximum.

There are two approaches in analyzing the metabolism and entropy generation rate $\dot{\sigma}(t)$ of BS: I) Homogeneous II) Heterogeneous.

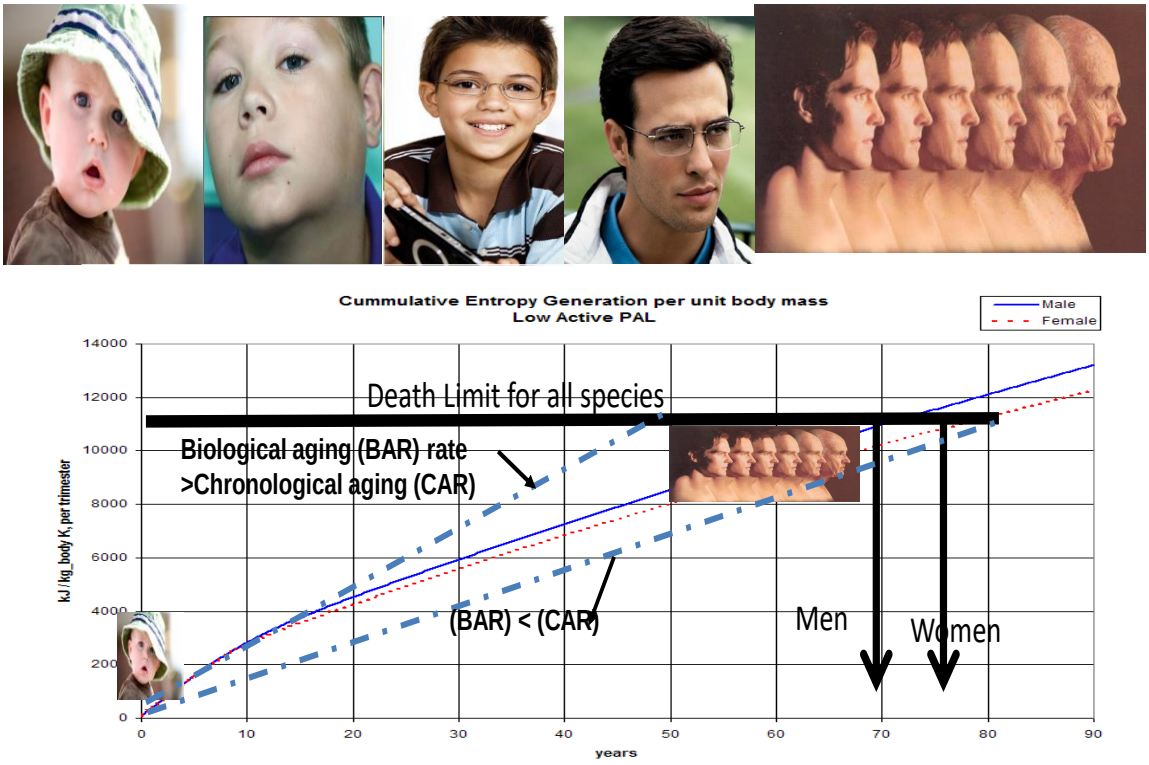

Figure 5: Entropy Generation vs Aging in Calendar Years (Chronological Aging, CA) With the Upper Limit of About 11,000 kJ per Kg Body Mass, Life Span of Man and Woman are 70 and 75 Years. With Higher $SERR_M$ (kJ/kg Body Mass; Uncontrolled Diet), the Biological Aging Rate > Compared to Chronological Aging Rate (CAR). Under Diet Control, Biological Aging Rate (BAR)< (CAR) [58].

2. 1 Homogeneous Approach

Life Span Hypotheses-Homogeneous System

The following theories can be applied to a homogeneous system

i) Energy: This theory is also known as the rate of living (ROL) theory, which assumes that the lifetime specific metabolism of a BS is constant at 839 MJ/kg. [2] This hypothesis can also be observed in BS with high specific metabolic rate (SMBR) having a shorter lifespan, whereas those with lower

SMBR have longer lifespan. If the ROL is applied to all BS, a study on rhesus monkeys fed 30% calorie restriction (CR) diet reported increased survival, however a significant increase in life span. [3] Therefore, nutrition restriction would have to play a role in longevity of BS.

ii) Radical Oxygen Species (ROS): This theory suggests that ROS in the form of O_2 is released as a bi-product of energy metabolism in the mitochondria during the phosphorylation processes, and utilized in the combustion process. The ROS released during the metabolic process can affect the BS in various processes, such as attacking cells, cause cell copy error, and cause damage to proteins, lipids, and DNA, eventually leading to cell death. [4] There is a difference in the ROS and the ROL models, as they are not positively correlated at times, for e.g. birds have high metabolic rates along with having a longer life span. [5]

iii) Entropy generation Hypotheses: The thermodynamics present the entropy balance equation for any engineering system as

$$\frac{dS}{dt} = \frac{\dot{Q}}{T_b} + \dot{m}_i s_i - \dot{m}_e s_e + \dot{\sigma} \qquad (2)$$

Where T_b for human body is taken as T_B, with control volume boundary inside skin surface. The term dS/dt represents the entropy accumulation rate within body, $\dot{m}_i s_i$ input entropy through mass intake {air, nutrients through mouth}, $\dot{m}_e s_e$ is entropy leaving through exhaust of waste products {CO_2, H_2O through nose}. The oxidative process/metabolism involves energy release $\{\dot{q}\}$ and a part of $\dot{q}$ is used in ATP

production{ called work, $\dot{W}$ in engineering} and remainder as heat $\dot{Q}$ (random energy); it is the "Q" which cause entropy generation {Eq. (2)} .

Hershey and Wang used homogeneous approach used IInd law for estimating the specific entropy generation over human life span{Eq. (1)}.

Where $\dot{\sigma}_{M.}(t)$ specific entropy generation rate (W/kg body mass K; note M for whole body mass) at given age t. In estimating, $\dot{\sigma}_{M.}(t)$ they assumed that all the energy released via oxidation cause entropy generation and the change of entropy due to advection {$\dot{m}_i s_i$ and $\dot{m}_e s_e$}. Their calculations indicated that a lifetime accumulation of specific entropy production was $\dot{\sigma}_{M,life}$=10,025 kJ/kg_K (2,395 kcal/kg_K) for human males and 10,678 kJ/kg_K (2,551 kcal/kg_K) for females including the advection term. The lifetime entropy production (or internal entropy) due to metabolic activity ($\dot{q}$) was found to be 10,280 kJ/kg K (2,456 kcal/kg K) and 11,105 kJ/kg_K (2,653 kcal/kg_K) for males and females respectively. 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, that is, once (δσ/dt, kJ/kg K) reaches zero.

Silva and Annamalai [6] used the homogenous approach in estimating energy released and entropy generated over whole life span, used the nutrients intake data provided by Silva [15] accounted for the ATP production, physical activity level and arrived at the specific entropy generation rate ($\dot{\sigma}_M(t)$) of whole body as a function of age. As in thermodynamics, the heat part of energy Q (=difference between ΔG and work) results in entropy generation. They estimated the average male and female lifespan to be

73.78 and 81.61 years respectively by assuming maximum entropy generation to be 11400 kJ/K per kg of body [6]. Changes in calorie intake also impacted entropy generation and overall lifespan, yielding a fractional increase in lifespan with fractional reduction in caloric intake. [6] They ignored composition effects in estimating irreversibility

$$\dot{W}_{opt} = \sum_n \dot{m}_{n,reacted} \left|\Delta G^0_{c,n}\right|, whole\ body, n = CH, F\ and\ P \quad (3)$$

Typically $\Delta G^0_{c,n}$ (typically <0 for exothermic reactions) and include the effects of composition. It is called optimum/maximum work in thermodynamics for the nutrient "n" in an isothermal organ. Silva and Annamalai found that the availability efficiency used in thermodynamics for an isothermal system is same as metabolic efficiency in biology. Thus, metabolic efficiency (η_{Met})

$$\eta_{Met,n} = \frac{W_{ATP,n}}{|\Delta G^0_{c,n}|} \quad (4)$$

Where the $\Delta G_{c,n}$ is maximum possible work of nutrient "n" in absence of irreversibility, and $\eta_{Met,n}$ is called availability efficiency in engineering. Assuming quasi-steady state during aging process, they dG/dt =0, the irreversibility rate of a system of interest is equal to sum of irreversibility of each macro-nutrient:

$$\dot{I} = \dot{W}_{opt} - \dot{W}_{ATP} = T_B \dot{\sigma} = \sum_n \dot{m}_{n,reacted} \left|\Delta G^0_{c,n}\right| * (1 - \eta_{Met,n}) \quad (5)$$

Where $\dot{m}_{n,reacted}$ could be less than $\dot{m}_{n,in}$ and unreacted Gibbs function of nutrients cancels out. Dividing by body mass m_B,

$$i\left(\frac{kJ}{kg\ body\ mass\ K}\right) = \frac{\dot{I}}{m_B} = T_B \dot{\sigma}_M = \sum_n \frac{\dot{m}_{n,reacted}}{m_B} |\Delta G^0_{c,n}| * (1 - \eta_{Met,n}) \quad (6)$$

The inclusion of metabolic efficiency in the entropy generation concept reveals that lower ATP production 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 [8]. Vasku et al they modified the analysis of Annamalai and Silva to include the effect of environment and included the effects of environment on entropy generation rate [9]. Note that $\Delta G_{c,n}^{0}$ is evaluated as though each species are pure at standard temperature and pressure $\Delta G_{c,n}^{0}$.

Silva and Annamalai used Eq. (6) , then data on i) Dietary Intake rate of nutrients $\dot{m}_{n,reacted}$ (t) from birth to death as a function of age (t) and assumption of T efficiency of digestion to be 100 % ii) g(J/kg) of nutrients CH, F and P ,and iii) body mass $m_B(t)$, then summed over all nutrients {Typical intakes: 1194 kilocalories per day: 70% from carbohydrate, 15%: from protein and less than 15% from fat. [11] Estimated specific entropy generation rate $\dot{\sigma}_M(t)$ (W/k kg body mass) as a function of age and computed cumulative $\sigma_{M,life}$ { kJ/K kg body) using Eq. (1).

Whole body analysis of allometric laws and studies are useful in estimating SREE and entropy generation of BS per g body mass; for e.g SREE a mouse which has similar physiological function as human is found to be is almost 7 times that of humans [3] and surface area to volume ratio is used to explain the scaling group [7]. However the

extent of contribution by each organ to whole body cease to exist at organ level for human and mouse.

2. 2 Heterogeneous Approach

Most studies on energy (metabolism) and entropy in biological systems dealt with the biological species as a whole, as though it is a homogeneous system. Recent works in this area tend towards a heterogeneous approach i.e. considering each organs individually and evaluating energy and entropy contributions from it. [12]

Even though the blood flow rate to various organs varies and hence energy release rate varies from organs to organs. But all organs are subjected to almost same temperature (T_B), uniform oxygen arterial pressure and almost same concentration of nutrients: CH, F and P in blood. In biology, the blood oxygen content of about 300 ppm (300 g per million g of blood) corresponds to O_2 content in blood surrounding an hypothetical alveoli containing gaseous mixture with p_{O2} =100 mm of Hg. [11] The glucose content is about 900 ppm {or 600—1400 mg of glucose per L of blood}.

Wang [7] adopted heterogeneous approach and showed the exponents in the whole body-allometric law can be derived by summing of the metabolic rates of vital organ BHKLR (5 organ approach); they later includes skeletal muscle (SM) and adipose tissue (AT, which is fatty tissue packed between organs); 7 organ approach) and improved the accuracy on prediction of whole body allometric law exponents. Annamalai and Silva used similar approach in estimating total body entropy generation rate as a sum of individual entropy generation rates of all organs: Thus,

$$\dot{\sigma}_M(t)\left[\frac{J}{s,kg\ bodymass\ K}\right] = \sum_k \dot{\sigma}_{m,k}(t)\frac{m_k(t)}{mB(t)} \quad (7)$$

Where k= B, H, K and L (vital organs) and R (residual organ).The $\dot{\sigma}_{m,k}(t)$ is evaluated as follows:

$$\dot{I}_k = T_B\dot{\sigma}_k = -\left\{\sum \dot{m}_{n,reacted}\,(1-\eta_n) * \Delta G^\circ{}_{c,n}\right\}_k \quad (8)$$

Since $|\ \Delta G^\circ{}_{c,n}\ | = |\ \Delta H^\circ{}_{c,n} - T_B\ \Delta S_{c,n}{}^\circ\ |$ and engineering literature shows that $|\ \Delta G^\circ{}_{c,n}\ | \approx C_g\ HHV_n$, where constant $C_g \approx 1.05$ and hence $\Delta G^0{}_{c,n}$ is approximately same as energy released by unit mass of fuel.

$$\dot{I}_k = T_B\dot{\sigma}_k \quad \approx \quad C_g\ \left\{\sum \dot{m}_{n,reacted}\,(1-\eta_n) * HHV_n\ \right\}_k \quad (9)$$

Thus, the term within summation $\sum \dot{m}_{n,reacted} * HHV_n$ represents energy released within organ k when all nutrients are oxidized; Eq. (9) can also be converted into rate form (Watts) when using rate of nutrient consumption.

$$\dot{I}_k = T_B\dot{\sigma}_k \quad \approx \quad C_g\ \left\{\sum \dot{m}_{n,reacted}\,(1-\eta_n) * HHV_n\ \right\}_k \quad (10)$$

When data for oxidation rates of various nutrients within an organ is not available, Eq. (10) allows us to use the allometric laws like equation (7) to estimate entropy generated.

$$\dot{I}_k = T_B\dot{\sigma}_k \quad \approx \quad \dot{q}_k - \dot{q}_k\ \ \eta_{Met,k} \quad (11)$$

Where $\dot{q}_k$ is energy released by all nutrients within organ k, $\eta_{met,k}$ is the average metabolic efficiency and $\dot{q}_k\ \ \eta_{met,k}$ energy used in ATP production by all nutrients.

When k= B, H, K and L (vital organs), they contribute only 3% of body mass but contribute almost 30-40% of whole body metabolic rate and hence whole body entropy

generation rate. [8] This approach facilitated the ranking of various vital organs in terms of their contribution σ_k (J/K of organ k over lifetime) to the lifetime entropy generation of whole body. The size of vital organs from smallest to largest: kidney 0.29 kg, Heart 0.31 kg, Brain : 1.33 kg and liver 1.39 kg; [12] the size of organs affect the metabolic rate in W/kg of organ mass since all the cells are not exposed same oxygen concentration and hence it affect allometric laws for each organ.[10] They also provided a normalized scaling group for determining the degree of irreversibility within each organ during whole life span. These studies revealed that heart has highest specific entropy generation while liver had the lowest and entropy stress at organ level.

Allometric Laws

The energy release rate at organ level relied on the allometric relations since proportions of nutrients oxidized are not known at organ level. Generally the allometric law is expressed as

$$Y = aX^b \tag{12}$$

Where Y, the parameter of interest (e.g. energy release rate via metabolism, heart beat rate, number of breathes per min, life span etc.) while X, could represent known parameter (e.g., body mass, organ mass, etc.), a and b are allometric constants. One of the most discussed metabolic allometric law in bioenergetics is the Kleiber's law, which states that the Resting Energy Expenditure (REE in Watts) is given in terms of body mass ($X=m_B$, kg) as [8]:

$$\dot{q}(Watts) = REE(W) = a * m_B^b \tag{13}$$

Dividing by body mass, the specific REE is given as,

$$\dot{q}_M = SREE\left(\frac{W}{kg}body\ mass\right) = \frac{a*m_B^b}{m_B} = a * m_B^{b-1} \quad (14)$$

Where a= 3.55, b= 0.75. Biologically, organs are a group of tissues which are self-contained and are specialized in performing a particular function. Physically, they vary in their masses (m_k) and dimensions and energy release rate ($SREE_k$) depending on the specialized function they perform.

Typically, the biology literature presents the allometric law for specific metabolic rate or specific of an organ/tissue in terms of overall body mass, $m_{B,i}$

$$\dot{q}_{k,m}\left(\frac{W}{kg\ of\ organ\ k}\right) = \ e_k\ m_B^{f_k} \quad (15)$$

Where e_k and f_k are "body mass" based allometric constants for organ k.

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

$$m_k(kg\ organ\ mass) = c_k\ m_B^{f_k} \quad (16)$$

Where c_k and d_k are allometric constants at organ level.

Further the previous work converted the "body mass" based allometric relation for each organ into "organ mass" based allometric relation [8]:

$$\text{SREEk} = \quad \dot{q}_{k,m}\left(\frac{W}{kg\ of\ organ\ k}\right) = \ \left(\frac{e_k}{c_k^{\left(\frac{fk}{dk}\right)}}\right) m_k^{\frac{f_k}{dk}+1} \quad (17)$$

Where $-1/3<\{f_k/d_k+1\}<1$ for most organs. An elementary overview for such low and high limits {items VII and VIII} is given by Miller [10].

Annamalai and Silva applied the 5 organ heterogeneous approach, used allometric laws and showed the following:

i) Organs can be ranked based on specific entropy generation of each organ; they are 135.4, 62.4, 55.5, 124.1, and 3.7 for H, B, L, K and R (MJ/kg of organ K) [8]. The heart seems to be most "stressed" and liver the least stressed.

ii) Whole body life time specific entropy generation (kJ/kg body K) is sum of entropy generation contributed by BHKLR to each unit body mass.

Whole Body Specific Entropy Generation Rate (W/kg Body Mass K)

One can use the allometric laws for masses of organs of 70 kg humans and estimate the energy release rate of BHKLR and total metabolic rate of whole body. The size of vital organs from smallest to largest are: kidney 0.29 kg, Heart 0.31 kg, Brain: 1.33 kg and liver 1.39 kg [15]. Even though the vital organs BHKL contribute only 3% of body mass, they contribute almost 30-40% of whole body metabolic rate {Figure 6}[6] and hence is expected to contribute significantly to the whole body entropy generation rate.

Following Annamalai and Silva the organ based specific entropy generation (σ_m (t) kJ at age t per kg of organ mass per K) is given as

$$\sigma_{k,m}(t)\left[\frac{J}{kg\ organ\ mass\ k}\right] = \int_{t_{birth}}^{t} \dot{\sigma}_{m,k}(t)dt\,, k = B, H, K, L\ (vital\ organs)\ and\ R \tag{28}$$

Letting t= t_{life}, $\sigma_{m,life}$ can be obtained. The organ based approach facilitated the ranking of various vital organs in terms of their entropy stress $\sigma_{k,m,life}$ {J organ k over lifetime /K). These studies revealed that heart has highest specific entropy generation while liver had the lowest.

The whole body specific entropy generation (σ_M, W from k per kg of body mass per K) as a function of age t is given as:

$$\sigma_M(t)\left[\frac{J}{kg\ body\ mass\ k}\right]$$

$$= \int_{t_{birth}}^{t} \sum_{k} \dot{\sigma}_{m,k}(t)\left(\frac{m_k(t)}{m_B(t)}\right) dt, k = B, H, K, L\ (vital\ organs) and\ R \quad (19)$$

Where $m_B(t)$ change of mass with age t.

The size of organs may affect the specific metabolic rate in W/kg of organ mass since all the cells within an organ are not exposed same oxygen concentration and hence it affect allometric laws for each organ [5] . However Elia and others assumed that $SREE_k$ is independent of body mass and hence organ mass [5].

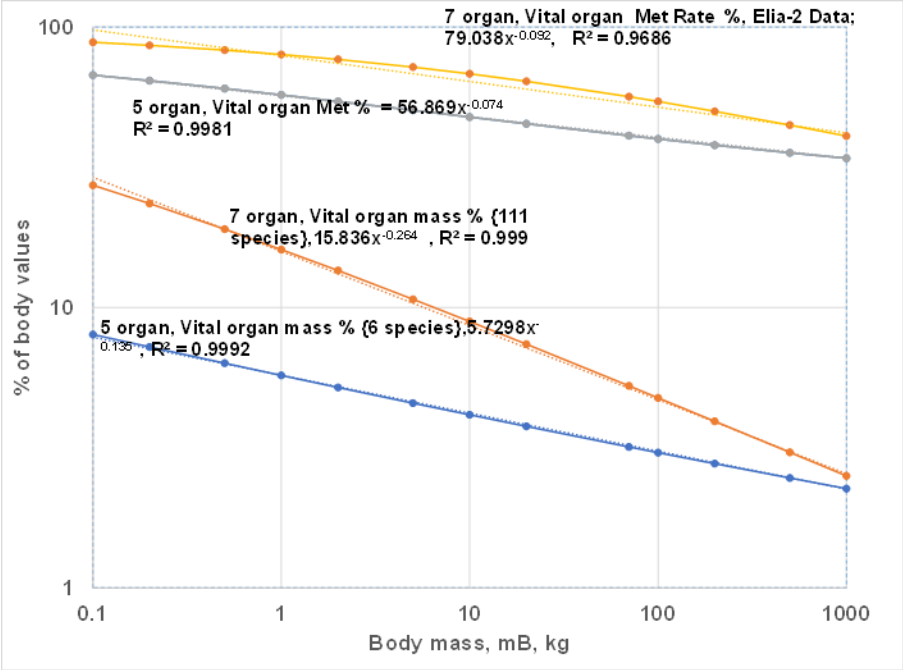

Figure 6: Correlation of % Vital Organ Mass and Contribution % by Vital Organs Towards Overall Metabolism Based on i) Wang Five Organ Data (6 species) with Body Mass Dependent Specific Organ Metabolic Rate, ii) Wang Seven Organ Data (111 Species for Organ Mass Allometry) with Body Mass Independent Elia's Specific Organ Metabolic Rate.

Note 1: For smaller species, the vital organs get "burnt out" within short period of life span! ATP production per kg body mass is also highest for smaller species compared to larger species and thus "ants" and children" are more active with muscular movements.

Mitochondria

The review reveals that more the energy release rate per unit mass or volume of organ (or per cell in the organ) more the specific entropy generation rate per unit mass or volume of organ (or per cell) and lower the metabolic efficiency , higher the amount of heat released and higher entropy generation rate. Both heat, Q (which raises temperature of blood and hence cells) and higher specific energy release rate $\dot{q}_{k,m}$ results

in more radical oxygen species (ROS) and more damage to DNA in each organ. The ROS plays a major role in the rate of telomere erosion [16].

The oxidation does not occur within cell but within mitochondria. So the above studies inherently presume that mitochondrial densities (Mito volume % in each cell) are same in all organs and as such 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 % vary from organ to organ [31]. Mitochondria are known to be the main source of radical oxygen species due to electron transfer process. The ROS within mitochondria is believed to be primary cause of mitochondrial DNA (mtDNA) damage in Alzheimer's disease patients [17].

Further there is variance in diet composition and hence metabolic efficiency compared to sedentary individuals. The SM accounting for 30% -50% of body mass converts chemical energy of nutrients into work (ATP) which results in muscle {where Myoglobin, M =16000 kg/kmol exists in muscle cells and heart cells which enhances O_2 transport to mitochondria} movements at an average efficiency of 25% with remainder appearing as Q which is lost via skin due to blood circulation [18]. Just like car requiring more power when accelerating (W per kg body mass), the humans require higher and higher O_2 delivery rate to deliver higher external power per kg during exercise. Eventually a maximum uptake is reached called V_{O2max} which is 34 mL of O_2 /min/kg body mass for untrained human vs 50 mL/min/kg for athletes. The calories from fat burnt is almost 50 % but fat burnt % decreases during later period of exercise. So the metabolic efficiency varies during exercise depending on proportion of F and CH. Thus,

the entropy stress analysis must include literature data on Mito volume %, estimate mitochondrial metabolic loading and the corresponding DNA damage to each organ.

2. 3 Athletes

The previous studies are applicable to average human. Athletes training for endurance sports, such as long distance runners rely largely on aerobic metabolism, resulting in more efficient oxygenation of skeletal muscle tissue. Athletes who are primarily focused on strength building and improving overall performance can achieve this by providing the body with necessary nutrients to build, repair and maintain lean body mass. CH are essential for optimum athletic performing, and they are depleted constantly due to extreme exercise, which provide a requirement of replenishing it throughout the day. Glycogen, which is the main form of energy storage in human beings is used as an energy source when performing hypertrophy training. Glycogen storage is directly proportional to the difference in consumption of CH, and the amount used during training and daily activities. For optimum performance, athletes are recommended to consume 2-3 grams of CH per pound body weight per day.

The SM are of extreme importance to athletes. Higher energy demands for athletes' causes' variance in diet compared to sedentary individuals. Higher metabolic efficiency implies lesser entropy generation at cell level. However, during exercise over short periods, the blood flow rate to SM increases almost 12.5 times that of blood flow at rest indicating increased entropy generation rate over period of exercise. In addition calories burnt during exercise period (520 ± 60 kcal over 45 min), the higher metabolic

rate is continued for next 14 hours. Under rest the 14 hours burned 964 Kcal while after exercise it burned 1154 k cal. i.e. 20 % increase in BMR [13].

Some metrics to consider when analyzing athlete entropy generation of athletes include the amount of oxygen intake during the physical activity is being performed, the myoglobin storage in muscles and heart, number of capillaries around muscle groups, and size of mitochondria in muscle cells. These metrics can vary drastically when comparing trained athletes to untrained individuals, and during exercise versus during rest.

2. 4 Nutrients

It is essential that the nutrition intake of the athlete is obtained in the correct ratio of macronutrients, consisting of mainly P, CH, and F, while providing sufficient micronutrients such as vitamins and minerals, and adequate fluid intake to support the body. The nutrition being provided to each athlete plays a vital role in calculating entropy generation. Thermodynamic properties of each organic food group are given below:

Table 1: Thermodynamic Properties of Fuels [15]

Fuel Type	Molecular Formula	MW (kg/k mol)	RQ	HHV_{O2} (MJ/kg of O_2) Note 1	HHV (MJ/ kg)	Metabolic Efficiency
Glucose (CH)	$C_6H_{12}O_6$	180	1	14.66	15.63	38.2
Fat (F)	$C_{16}H_{32}O_2$	256	0.7	13.63	39.12	32.2
Protein (P)	$C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$	118	0.8	13.99	28.893	10.4

Note 1: HHV_{O2}= HHV (KJ/kg nutrient)/st O_2 (kg O_2 per kg nutrient); note that HHVO2 of CH is slightly higher compared to fat and hence CH is preferred fuel when O2 is limited. However on unit volume basis in blood the fat has higher energy release per unit volume and preferred fuel when O2 and fat are available for long duration exercise; Whole body RQ = 0.80 and hence CH % = (mole) and CH % (mass). Most organs (L, SM, H) use fatty acids

The proportions of CH and F can be determined if one can determine the Respiratory Quotient (RQ) – which is a Ratio of CO_2 moles used and oxygen moles consumed for oxidation The ATP that is produced by each of these food groups also varies based on the oxygen requirement and food composition. About 40% of energy generated through metabolism of glucose and fats is used for formation of ATP, whereas the remainder is released as heat. [9] The energy released in protein synthesis is much lower than both glucose and fats need to be modified for athletes and we need to separate athletes based on the type of sport they participate in, type of diet, the categories being intensity level, potential of bodily collision and dynamic versus static sports.

The literature review revealed the following:

1. All previous work consider the entropy stress based on unit mass of organs or per cell if all organs have same number of cells per unit mass. However, the oxidation reactions are performed within mitochondrion of cells and the mitochondrion density (number of mitochondrion per unit volume of cell or volume ratio of mitochondria to cell volume) varies from organ to organ. Thus the entropy stress must be estimated per unit volume of mitochondria for each organ. The question is that do they follow same ranking as organ mass or cell based entropy stress?
2. Further there is no previous work relating the entropy stress of organs of athletes and comparison to a normal humans. For athletes AT and SM are important. Thus, instead of 5 organs, one must consider 7 organ approach for estimating entropy stress. The current work considers all above issues.
3. Aging is related to the damage of cell through DNA damage in each organ: does the cell damage follow the volume based specific metabolic loading of organ (W/cm^3 of organ k) or entropy stress (W/cm^3_K)? Does it follow the volume specific metabolic loading of mitochondria (W/ cm^3 of mitochondria)?

Thus, the current work attempts to answer a few of above.

2. 5 Biological Aging (BA) and Chronological Aging (CA)

The chronological aging (CA) is measured in terms of calendar years and most retirement planning are made on CA. One may be at age 50 but feels like age 80 while others may be at age 80 but feels like 50's. Thus Milevsky and his co-researchers recommend using biological aging provided by biomarkers in your life [52]. These

biomarkers could be energy release from unit mass of the body{$q_M(t)$} as a function of age (t) which follows Rubner's hypothesis and $\sigma_{M,life}$ which follows Siva and Annamalai hypothesis {Figure 6}; later work by Annamalai and Silva extended these biomarkers to organ level.

3. OVERALL GOAL, SPECIFIC OBJECTIVES AND TASKS

The overall goal of research related to biological systems (BS) is to transfer knowledge from the fields of thermodynamics and combustion science to the field of biology particularly in the following areas:

I. I-st and II-nd Laws and availability analyses in engineering system vs BS.

II. Adiabatic temperature (AdT) in combustion of fuels vs AdT of blood leaving various organs.

III. Chemical equilibrium between Hb {M= 680000 kg/kmol} and oxygen, production of Hb (O_2), Hb $(O_2)_2$, .Hb $(O_2)_4$.

IV. Transport of O_2 gas in mixture of gases within carbon cloud vs transport of dissolved O_2 in blood across capillaries.

V. Oxidation of single carbon particle vs oxidation of nutrients in cells and single cell temperature.

VI. Langmuir surface oxidation kinetics of carbon [54] vs Michaelis–Menten volumetric oxidation kinetics [55] within cells. Can the low temperature solutions (stable and unstable) lead to ATP oscillation and make the cells acquire the ability to move?

VII. Adoption of literature on energy release rate from oxygen deficient carbon cloud in engineering to specific metabolic/energy release rate ($SREE_k$) from organ k { k,= Brain, heart, kidney etc.}

VIII. Deduction of allometric Laws for organs and the whole body Kleiber's law using Combustion Science and Thermodynamics. [12]

A few the above tasks had been performed and more are in progress, theses have been produced and several articles have been published/under review [56, 6, 15, 35].

The specific objectives of current work are to i) extend the second law concept on entropy stress of organ by including two additional organs: skeletal muscles (SM) and adipose tissue (AT) so that analyses can be extended to athletes and ii) modify the model to estimate entropy stress at mitochondrial level. In order to achieve the specific objectives the following tasks were performed:

i) Collect existing literature on metabolism in SM and AT and extend the 5 organ (B-H-K-L-R where R: residual mass) model to 7 organ model by including the two additional organs: (AT) and (SM), and extend the 7 organ { AT-B-H-K-L-R-SM} analysis to athlete.

ii) Estimate the maximum possible temperature rise of blood (i.e. adiabatic and non-work conditions) in blood as it passes through an organ since it is indirectly related to entropy generation.

iii) Study the effects of proportions of nutrients being oxidized, (CH): (F): (P) which affect metabolic efficiencies and hence the amount of entropy generation in various organs.

iv) Provide ranking vital organs based on metabolic rate at mitochondrial level and compare with the ranking of organs based on whole organ

v) Study the effects of increased blood flow during exercise on metabolic rate, maximum possible exit temperature on each organ and entropy stress.

4. MODELING, METHODOLOGY AND PROCEDURE

The methodology to be followed in order to fulfill the mentioned objectives has been listed below:

1. Treat the body as 7 organ/compartments (AT-B-H-K-L-R-SM) and extend the 5 organ analysis of to 7 organs tissues (Skeletal muscle (SM) and adipose tissue (AT)) and residual mass (R).
2. Calculate the specific energy expenditure and entropy generation rate within organ k , $\dot{\sigma}_{m,k.}$ (W/kg of organ k)
3. Using allometric laws for Mitochondrial density, estimate Mito volume based specific entropy generation rate within organ k ($\dot{\sigma}_{v,k.}$ W/ cm^3 of Mito within organ k).
4. Obtain results on specific energy release rate and entropy generation rate and study the , effects of the Pure CH, pure F and a blend of nutrients (CH:F:P) (which affect the overall metabolic efficiency) on entropy generation rate.
5. Based on body growth data estimate lifetime energy expenditure and entropy generation of each organ k.
6. Rank the organs based on mitochondrial metabolic loading.

The current section provides a brief description of model and approach used in obtaining the results and discussion.

4. 1 Modification to Homogeneous Approach

More general approach on availability and irreversibility analyses are is given here including the composition effects in estimating stream availability and Gibbs function. Following Silva and Annamalai [6], the homogenous approach in estimating energy released and entropy generated over whole life span, is briefly outlined below. Consider the availability balance equation for an open system [7]

$$\frac{d(E_{CV}-T_0S)}{dt} = \sum_{n,Inlet} \dot{m}_{n,i}\psi_{n,i} - \sum_{n,exit} \dot{m}_{n,e}\psi_{n,e} - \dot{W} - \dot{I}, E = U + KE + PE = H - PV + KE + PE \qquad (20)$$

Where "n" represents the nutrients n (e.g., n= CH,F and P) U, internal energy, kinetic energy (KE) { e.g. running } and potential energy (PE) of body {e.g. climbing stairs} of body, stream availability (as per EU definition) of nutrient "n" , $\psi_n = h_{n,i} - T_0 s_{n,i}$ {e.g. availability in through intake of n= CH, F and P, food intake), $\psi_{n,e} = h_{n,e} - T_0 s_{n,e}$, availability exiting through waste products n = CO_2, H_2O etc. }, $\dot{W}$ work rate {i.e. $\dot{W} = \dot{W}_{\text{ATP (internal)}} + \dot{W}_{\text{exit}}$, where external work includes, PdV for breathing, lifting weights, climbing stairs etc.}, $\dot{I}$ irreversibility rate $= T_0 \dot{\sigma}$ {e.g. oxidation process resulting in energy release in the firm of heat Q}. Eq. (20) is applied to human body with control surface (CS) just inside skin and hence the CV is almost isothermal within whole body at T_B and hence $\psi_j = g_j$, Gibbs function (J/kg) of species j which include nutrients "n" , CO_2, O_2, H_2O and other species. One may compute "g_j" and hence with $T_i = T_e = T_B$, and ignoring KE and PE {e.g. resting}, E= U= H-PV, Eq. (20) is written as [7]

$$\frac{dG}{dt} = \sum_{n,Inlet} \dot{m}_{n,i} g_{n,i} - \sum_{n,exit} \dot{m}_{n,e} g_{n,e} - \dot{W_{ATP}} + P\frac{dV}{dt} - \dot{I} \quad (21)$$

Rate of Change of Gibbs Energy of body of BS = Gibbs Energy added through mass in (including chemical part; e.g. CH, F and P) - Gibbs Energy removed through mass exiting (including chemical part; e.g. CO_2, H_2O) - Gibbs Energy converted into ATP energy (energy currency of the body) + PdV work added through volume deformation/breathing in and out-Gibbs energy destroyed through irreversibility (mainly in the form of heat, Q). Where G= H-T_B S, g= h-T_{Bs}. During oxidation of nutrients CH and F, the chemical energy of CH and F is converted into another firm chemical energy of ATP while remainder is released as heat $\dot{Q}$ which causes entropy generation and hence finite $\dot{I}$. Selecting CV as isothermal body of BS and under quasi-steady state (QS) for short period,

$$\dot{m}_i = \dot{m}_e, \frac{dG}{dt} = 0 \quad (22)$$

Ignoring PdV/dt, setting $\dot{I}$ =0 in Eq. (21), one can show that total optimum work rate is equal to sum of optimum work of each macro-nutrient

$$\dot{W}_{opt,iso} = \sum_n \dot{m}_{n,reacted} \left|\Delta G_{c,n}\right|, whole\ body, n = CH, F\ and\ P;\ \Delta G_{c,n}\left(\frac{KJ}{kg\ of\ n}\right)$$

$$= G_{P,n} - G_{R,n}; \left|\Delta G_{c,n}\right| = G_{R,n} - G_{P,n} \quad (23)$$

Where $G_{P,n}$ Gibbs function of product species of nutrient oxidation {e.g. CO_2, H_2O from oxidation of n=CH}, $G_{R,n}$ Gibbs function of reactant species of nutrient oxidation {e.g. n=CH; other species including oxygen }, $\dot{W}_{opt}$ is the optimum work given in terms of

sum of Gibbs function change of all three nutrients. Typically $\Delta G_{c,n}$ (typically <0 for exothermic reactions). Silva and Annamalai found that the availability efficiency definition in thermodynamics for an isothermal system is same as metabolic efficiency in biology. Thus, metabolic efficiency (η_{Met})

$$\eta_{Met,n} = \frac{W\ in\ Thermo}{W_{opt,iso}\ in\ Thermo} = \frac{W_{ATP,n} in\ BS}{|\Delta G_{c,n}| in BS} \tag{24}$$

Where the $\Delta G_{c,n}$ is maximum possible work of nutrient "n" in absence of irreversibility, and $\eta_{Met,n}$ is called availability efficiency of nutrient in engineering. Using Eq. (24) in (21), and under quasi-steady state (QS) for short period, dG/dt=0, ignoring PdV/dt, one the irreversibility rate of a system of interest is equal to sum of irreversibility of each macro-nutrient:

$$\dot{I} = \dot{W}_{opt} - \dot{W}_{ATP} = T_B \dot{\sigma} = \sum_n m_{n,reacted} \left|\Delta G_{c,n}\right| * (1 - \eta_{Met,n}) \tag{25}$$

Where $\dot{m}_{n,reacted}$ could be less than $\dot{m}_{n,in}$ and unreacted Gibbs function of nutrients cancels out. Dividing by body mass m_B,

$$i(\frac{KJ}{kg\ body\ mass\ K}) = \frac{\dot{I}}{m_B} = T_B \dot{\sigma_M} = \sum_n \frac{\dot{m}_{n,reacted}}{m_B} \left|\Delta G_{c,n}\right| * (1 - \eta_{Met,n}) \tag{26}$$

The inclusion of metabolic efficiency in the entropy generation concept reveals that lower ATP production or lower amount of conversion to ATP should result in higher Q, and higher temperature rise around cells. The increased temperature rise (due to higher Q) can also cause increased ROS along with decreased ATP energy available

for repair and creation of new cells (including the damage cause by environmental factors, concussion in athletes), and accumulation of damaged cells causing rapid aging and reduced life span. This is consistent with hypothesis of Kirkwood [8]. Vasku et al [9] modified the analysis of Annamalai and Silva to include the effect of environment and included the effects of environment on entropy generation rate. Higher is η_{Met}, higher is the amount of ATP, and hence higher the capability to repair and re-create the cells, lower is irreversibility and lower is the conversion to heat which causes entropy generation. Physical meaning will be given later. As in thermodynamics, the heat part of energy Q_n {≈difference between $\Delta G_{c,n}$ and $W_{ATP,\,n}$ which is same for ideal mix of species in a plasma: $\dot{m}_{n,reacted}(t)|\Delta G_{c,n}|(1-\eta_{Met,n})$.

Composition of Species and Gibbs Function

$$G_{R,CH}\,\frac{KJ}{kg\ of\ CH} = g_{CH}(T_B, P, X_{CO2}) + v_{O2,CH}\,g_{O2}(T_B, P, X_{O2})$$

$$G_{P,CH}\,\frac{KJ}{kg\ of\ CH} = v_{CO2,CH}\,g_{CO2}(T_B, P, X_{CO2}) + v_{H2O,CH}\,g_{H2O}(T_B, P, X_{H2O})$$

Where $\nu_{O2,CH}$, $\nu_{CO2,CH}$ $\nu_{H2O,CH}$ stoichiometric mass of O_2, CO_2, H_2O per kg of CH; similarly one can estimate $G_{R,F}$, $G_{P,F}$ etc. The Gibbs function of CH on mole basis is given as (ideal gas model)

$$\bar{g}_{CH}(T_B, P, X_n) = \bar{g}^0_{CH}(T_B, P^0) + \bar{\nabla}_{CH}\,(P - P^0) + \bar{R}T_B \ln(X_{CH})$$

$$\approx \bar{g}^0_{CH}(T_B, P^0) + \bar{R}T ln(X_{CH}) \quad (27)$$

Where $\bar{g}_{CH}(T_B, P, X_n)\left(\frac{KJ}{kg\ CH}\right) = \frac{\bar{g}_{CH}(T_B,P,X_n)\left(\frac{KJ}{kmol\ CH}\right)}{M_{CH}\frac{kg}{kmol\ CH}}$

When T_B= 310 K, x_{CH}= 0.001{glucose: 1000 ppm, g per million g blood, assume $Y_{CH}=X_{CH}$} RT ln{X_{CH}} ≈ (-17800 kJ/kmole), which is just 2 % 0f $g^0_{f,\,CH}$ at 298 K, 1 bar = (-917,200) [10]

$$\bar{g}_{CH}(T_B, P, X_n) = \bar{g}^0_{CH}(T_B, P^0) \text{ or } g_{CH}(T_B, P, X_n) \approx g^0_{CH}(T_B, P^0) \quad (28)$$

(ideal gas model, XCH<0.001 for CH within 2% error)

$$\frac{\Delta G_{c,n}(T_B,P,X_k)}{R_n T_B} \approx \{\frac{\Delta G^o_{c,n}(T_B)}{R_n T_B} + \sum_k \ln(X^{\nu_k}_{k,e})\} \approx \frac{\Delta G^o_{c,n}(T)}{R_n T_B} \; since \; \frac{\Delta G^o_{c,n}(T_B)}{R_n T_B} \gg \sum_k \ln(X^{\nu_k}_{k,e}) \quad (29)$$

Where $X_{k,e}$: mole fraction of species leaving the system and ν_k, stoichiometric coefficient of species in the oxidation reaction. For non-ideal mixture X_k is replaced by activity a_k. [10, 7] The term $RT_B \sum_k \ln(X^{\nu_k}_{k,e})$ is called reaction quotient for ideal solution. The assumption that $\Delta G_{c,\,n} \approx \Delta G_{c,\,n}{}^0$ implies that "g" for each species is evaluated as though it is pure at standard temperature and pressure.

It has been shown before that $\Delta G^o_{c,n}(T_B) \approx C_g |\Delta H^o_{c,n} T_B|$ [35], where C_g ranges from 1 to 1.05 for many nutrients. Applying to organ k, and assuming C_g =1 {Eq. (29)}

$$\dot{I}_k = \dot{W}_{opt} - \dot{W}_{ATP} = T_B \dot{\sigma}_k = \sum_n m_{n,reacted,k} \left|\Delta G_{c,n}\right| * \left(1 - \eta_{Met,n}\right)_k = \dot{q}_k \left(1 - \eta_{Met,avg}\right)_k \quad (30)$$

Dividing by organ mass, m_k

$$i_k = \frac{I_k}{m_k}\left(\frac{\dot{W}atts}{kg\ organ\ k}\right) = \dot{W}_{opt} - \dot{W}_{ATP} = T_B \dot{\sigma_{k,m}} \approx \dot{q}_{k,m}\left(1 - \eta_{Met,avg}\right)_k \quad (31)$$

If mitochondrial volume per unit volume of cell is MiV, then

$$i_{k,v} = \left(\frac{Watts}{cm^3 mito\ k}\right) = T_B \dot{\sigma}_{k,V} \approx \frac{\dot{q}_{k,m}}{\rho_k} * \frac{1}{MiV}\left(1 - \eta_{Met,avg}\right)_k \quad (32)$$

Since MiV= Mito volume per cell*no of cells in 1 kg organ / {cell volume* no of cells per kg organ} = Mito volume in whole organ/organ volume.

4. 2 Maximum Possible Blood Temperature

The ROS production rate is function of body temperature T, oxygen concentration and activation energy and ROS production rate is extremely sensitive to temperature. A part of the energy released is converted into work (ATP) and part is released as heat Q; higher is Q, higher is temperature rise ΔT and higher is σ. Appendix A shows an approximate relation between ROS and temperature or σ. Thus it is of interest to estimate maximum possible blood temperature estimated under zero heat loss, called AdT. Based on combustion science, AdT is same as cell temperature within which oxidation occurs. When carbon particle burns in air temperature under diffusion control of O2 from air where oxygen concentration is 230000 ppm (g per million g air) to carbon, the particle temperature is same as AdT and AdT is of the order of 2000 K. However the cell oxidizes the nutrients using O_2 from capillaries where oxygen concentration is 300 ppm (g per million g of blood)) and the difference between AdT and body temperature is of the order 1 K. Using conservation of energy for blood entering an organ and leaving an organ, the maximum rise in blood temperature is given as: {Appendix A}

$$(T_{exot} - T_{in})_k = \frac{Y_{O2in} * OEF_k * HV_{O2} * \left(1 - \eta_{Met,k}\right)}{c_p}$$

$$= \frac{Energy\ released\ by\ nutrients\ oxidation\ per\ kg\ blood * (fraction\ into\ heat)}{heat\ capacity\ per\ kg\ blood} \quad (33)$$

Where Y_{O2in}, oxygen mass fraction in blood entering organ (about 300 ppm), OEF, oxygen extraction fraction, HV_{O2}, energy released per g of O2 consumed and Y_{O2in}*OEF*HV_{O2} is energy relased per g blood. If blood flow rate to organ k in mL/s=a_k m_B^{dk} [24], energy release rtae per g organ is $e_k\ m_B{}^{f_k}$ and organ mass is $c_k\ m_B{}^{d_k}$ then one can show {Appendix A} that the temperature diference between venous and arterial blood of each organ k is given

$$(T_{exot} - T_{in})_k$$

$$= \frac{Energy\ released\ as\ heat\ per\ kg\ organ\ in\ kg * (mass\ of\ organ\ in\ kg)}{\rho\left(\frac{kg}{mL}\right) * blood\ flow\ rate\ in \frac{mL}{s}}$$

$$* (Fraction\ as\ heat)\left(\frac{1}{heat\ capacity\ in \frac{J}{kg\ blood}}\right)$$

$$= \frac{e_k m_B^{f_{k^*}} c_k m_B^{d_k}}{\rho_{Bl} a_k m_B^{b_k}}\left(1 - \eta_{Met,k}\right)\left(\frac{1}{c_p}\right) = \frac{e_k c_k m_B^{f_k + d_k - b_k}(1-\eta_{Met,k})}{a_k\{c_p * \rho\}} \quad (34)$$

Where

$$Y_{O2in} * OEF * HV_{O2} energy\ released\ in\ J\ per\ kg\ blood = \frac{e_k m_B^{f_{k^*}} c_k m_B^{d_k}}{\rho_{Bl} a_k m_B^{b_k}} \quad (35)$$

Where $OEF = J_k m_B^{L_k}, J_k = \frac{c_k e_k}{h_k \rho_{bl} Y_{O2in} HV_{O2}}, L_k = f_k + d_k - i_k$

.

$$(T_{exit} - T_{in}),\ ^{o}C = N_k m_B^{Lk}, N_k = \frac{J_k Y_{O2in} HV_{O2}}{C_p} = \frac{c_k e_k}{h_k \rho_{bl} c_p} \tag{36}$$

Note that evaluation of OEF requires a knowledge of the oxygen mass fraction in blood and other allometric constant.

4. 3 Effects of Partial Opening of Capillaries at Rest, Opening of Capillaries During Exercise and Related Allometry

At rest, capillaries within a fraction of volume of organ ($f_{cap,op}$) are open {red in Figure 5} while remaining are closed {1-$f_{cap,op}$}. However, the capillaries within open region must supply "extra heat" to overcome the heat loss from closed region. Thus if Q_{op} is heat loss from open region of organ, then Q_{cl} heat loss from closed region must be

$$Q_{cl} = Q_{op} * \frac{1-f_{cap,op}}{f_{cap,op}} \tag{37}$$

when $f_{cap,op}$=1, Q_c= 0 as it should be;

$$Total\ heat\ loss = Q_{op} + Q_{cl} = Q_{op} + Q_{op} * \frac{\{1 - f_{cap,op}\}}{f_{cap,op}}$$

$$= Q_{op}\{1 + \frac{\{1 - f_{cap,op}\}}{f_{cap,op}} = Q_{op}\left\{\frac{1}{f_{cap,op}}\right\} = q_{cap,op} * \frac{1 - \eta_{Met}}{f_{cap,op}} \tag{38}$$

$$Total\ heat\ loss = Energy\ for\ work + heat\ loss\ from\ open +$$

$$heat\ loss\ from\ closed = q_{cap,op} f_{cap,op} + Q_{cl} = \left(q_{cap,op} * f_{cap,op}\right) + \{q_{cap,op} *$$

$$(1 - \eta_{Met}) * f_{cap,op}\} * \left\{\frac{1-f_{cap,op}}{f_{cap,op}}\right\} = q_{cap,op} f_{cap,op}[1 + (1 - \eta_{Met})\{\frac{(1-f_{cap,op})}{f_{cap,op}}\}] \tag{39}$$

when $f_{cap,op}$=1, then total met rate = $q_{cap,\,op}$, Note that $f_{cap,op}$ cannot be zero.

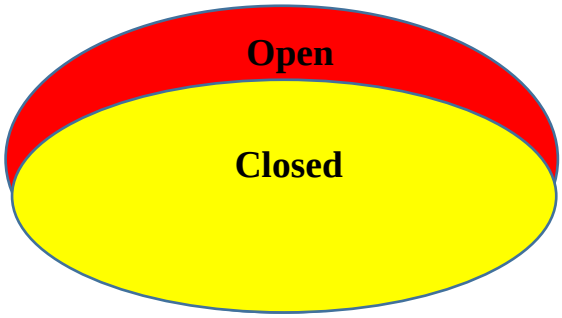

Figure 7: Red: Capillaries Open Region Yellow: Capillaries Closed Region, A+B, Total Organ Mass.

If specific heat loss from open region is $Q_{m,op}$ {W per kg organ mass), then heat loss from closed region $Q_{m,Cl}$ (W per kg organ mass) is set equal to $Q_{m,Cl}= Q_{m,op}*\{1-f_{cap,op}\}/f_{cap,op}$. Total heat loss from unit mass of organ is $Q_m= Q_{m,Op} + Q_{m,Cl} = \{Q_{m,Op}/f_{cap,op}, \}= \{q_m* (1-\eta_{Met}\}/f_{cap,op}, \}$ where q_m is metabolic rate per unit mass of organ.

$$\dot{q}_{m,k}\left(\frac{W}{kg\ of\ k}\right) = \dot{q}_{m,k,op} * f_{k,Op} \tag{40}$$

At rest

$$\dot{q}_{rest} = \dot{q}_{rest}\left(\frac{W}{kg\ of\ k}\right) = a_{k,rest} m_k (kg)^{b_k}$$

$$\dot{q}_{m,k,rest}\left(\frac{W}{kg\ of\ k}\right) = a_{k,rest}m_k(kg)^{b_k} = \dot{q}_{m,k,op} * f_{k,Op,rest} \quad (41)$$

$$\dot{Q}_{rest} = \dot{Q}_{Op} + \dot{Q}_{Cl,rest}$$

Assuming

$$\dot{Q}_{Cl,rest} = \dot{Q}_{Op} * \frac{1 - f_{k,Op}}{f_{k,Op}}$$

$$\dot{Q}_m = \dot{Q}_{Op,m} + \dot{Q}_{Cl,m} = \dot{Q}_{Op,m} + \dot{Q}_{Op,m} * \frac{1 - f_{k,Op}}{f_{k,Op}} = \frac{\dot{Q}_{Op,m}}{f_{k,Op}}$$

$$\dot{Q}_{Op,m} = \dot{q}_{m,k,op} * f_{k,Op} * (1 - \eta_{Met,k}) \quad (42)$$

Where $f_{k,op}$: fraction of mass open to blood flow and hence metabolism.

Then

$$\dot{Q}_{m,Op} = \dot{Q}_{m,k,Op}\left(\frac{W}{kg\ of\ k}\right) * (1 - \eta_{Met,k}) f_{k,op}$$

$$\dot{Q}_m = \frac{\dot{Q}_{Op,m}}{f_{k,Op}} = \dot{q_{m,k,op}} * (1 - \eta_{Met,k}) \quad (43)$$

Hence, metabolic rate in open region must be increased in open region must be equal to heat loss from unit mass of whole organ and ATP production in open region. Assuming that the closed region does not require ATP for cell death and repair in closed region,

ATP energy

$$\dot{W}_{ATP,m} = \dot{q}_{m,k,Op}\left(\frac{W}{kg\ of\ k}\right) * \eta_{Met,k} * f_{k,Op} \quad (44)$$

Total energy released

$$\dot{q}_{m,k} = \dot{Q}_m + \dot{W}_{ATP,m} = \dot{q}_{m,k,op} * \left(1 - \eta_{Met,k}\right) + \dot{q}_{m,k,Op} * \eta_{Met,k} * f_{k,Op} \quad (45)$$

$$\dot{q}_{m,k} = \dot{q}_{m,k,op}\{(1-\eta_{Met,k}) + \eta_{Met,k} * f_{k,Op}\}$$

$$\frac{\dot{q}_{m,k,op}}{\dot{q}_{m,k}} = \frac{1}{\{(1-\eta_{Met,k})+\eta_{Met,k}*f_{k,Op}\}} = \frac{1}{\{1-\eta_{Met,k}(1-f_{k,Op})\}} \quad (46)$$

$$\dot{q}_{m,k} = \frac{\dot{q}_{m,k}}{\{1-\eta_{Met,k}(1-f_{k,Op})\}} = \frac{e_k m_B^{f_k}}{\{1-\eta_{Met,k}(1-f_{k,Op})\}} = e'_k m_B^{f_k}, e'_k = \frac{e_k}{\{1-\eta_{Met,k}(1-f_{k,Op})\}}$$

(47)

If we assume $\eta_{MET,k}$=1/3 and $f_{k,Op}$=1/3,

$$\dot{q}_{m,k} = \frac{\dot{q}_{m,k}}{\{1-\left(\frac{1}{3}\right)\left(1-\frac{1}{3}\right)\}} = \frac{9}{7}\dot{q}_{m,k} = \frac{9}{7}e_{k,rest}m_B^{f_k} = e'_k m_B^{f_k}, e'_k = \frac{9}{7}e_{k,rest}$$

Substituting value of $\dot{q}_{m,k,op}$from {Eq. 47} in {Eq. 43},

$$\dot{Q}_m = \dot{q}_{m,k} * \left(1-\eta_{Met,k}\right) = \frac{\dot{q}_{m,k} * \left(1-\eta_{Met,k}\right)}{1-\eta_{Met,k}(1-f_{k,Op})}$$

$$\frac{\dot{Q}_m}{\dot{q}_{m,k}} = \frac{1-\eta_{Met,k}}{\{1-\eta_{Met,k}(1-f_{k,Op})\}} \quad (48)$$

When $f_{k,op}$=1, $\frac{\dot{q}_{m,k,op}}{\dot{q}_{m,k}} = 1$; when f_{kop}=0, $\frac{\dot{q}_{m,k,op}}{\dot{q}_{m,k}} = \frac{1}{\left(1-\eta_{Met,k}\right)}$

4. 4 Life Time Specific Energy Release of Organ

The lifetime energy release per unit mass of organ k is given as

$$q_{k,m,life}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right)$$

$$= \int_{t_{birth}}^{t_{st,1}} \dot{q}_{k,m}(t)dt + \int_{t_{st,1}}^{t_{st,2}} \dot{q}_{k,m}(t)dt + \int_{t_{st,2}}^{t_{life}} \dot{q}_{k,m}(t)dt\,, k$$

$$= B, H, K, L, AT, SM, R$$

(49)

Using Eq. (15) in Eq. (49), the life time metabolic energy release from organ k per unit mass of organ k is given as

$$q_{k,m,life}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right)$$

$$= \int_{t_{birth}}^{t_{st,1}} e_k m_B(t)^{f_k}\, dt + \int_{t_{st,1}}^{t_{st,2}} e_k m_B(t)^{f_k}\, dt + \int_{t_{st,2}}^{t_{life}} e_k m_B(t)^{f_k}\, dt, k =$$

$$B, H, K, L, AT, SM, R \quad (50)$$

If growth is ignored (m_B = constant}, the above yields

$$q_{k,m,life}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right) = m_B\{e_k(t_{life} - t_{birth})\}, k = B, H, K, L, AT, SM, R$$

Growth Correction Factor

The body mass, m_B for humans is not constant and grows with age (t, since conception) until reaching steady mass m_B, at t= $t_{st,1}$ remains almost constant until t= $t_{st,2}$ and then it decreases $t_{st,2}<t< t_{life}$. If the relation for m_B can be found from data given in [5] and is approximately given by

$$m_B(t) = \quad m_{B,st}\,(\frac{t}{t_{st}})^z \quad (51)$$

Where "t" is age from day of conception, t_{st} is age required from to achieve steady body mass and as such organ masses which are related to body mass remain constant after t_{st}. It is noted that Wang et al measured organ weights and found that the mass almost remains constant for most vital organs after 21 years. [23]

Then the values for "p" given are as follows:

Period I: for $t_{birth} < t < t_{st,1}$, z = 0.75 (mass increase period)

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)

Where Life Span is typically defined from birth to death; so $t_{life} = t_{death}-t_{birth}$ to achieve a stable/steady mass, $(t_{st,1}- t_{st,2})$ is constant mass period and $(t_{life} - t_{st,2})$ is period during which body mass starts decreasing. Letting $t^* = t/t_{death}$.

$$\frac{q_{k,m,life}}{(t_{death}-t_{birth})e_k m_{B,st}^{f_k}} = \frac{q_{k,m,life}}{t_{life}e_k m_{B,st}^{f_k}}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right)$$

$$= \frac{1}{t_{st,1}^{*pf_k}}\int_{t*birth}^{t*_{st,1}} t^{*zf_k}dt* + \frac{1}{t_{st,1}^{*pf_k}}\int_{t*_{st,1}}^{t*_{st,2}} t^{*zf_k}dt* + \int_{t*_{st,2}}^{1} t^{*zf_k}dt*$$

Where $t_{death}-t_{birth}= t_{life}$. More generally

$$\frac{q_{k,m,life}}{t_{life}e_k m_{B,st}^{f_k}}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right)$$

$$= \{\frac{t_{st,1}^*\left(1-\left\{\frac{t_{birth}^*}{t_{St,1}^*}\right\}^{g_k+1}\right)}{(g_k+1)} + \left(t_{st,1}^* - t_{st,1}^*\right) + \frac{t_{st,2}^*\left[\{\frac{1}{t_{st,2}^*}\}^{-g_k+1}-1\right]}{(-g_k+1)}\}$$

Where $g_k = z\ f_k$ for specific metabolic rate of organ k.

$$\frac{q_{k,m,life}}{t_{life}e_k m_B^{f_k}}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right) = \{\frac{t_{st,1}^*\left(1-\left\{\frac{t_{birth}^*}{t_{St,1}^*}\right\}^{zf_k+1}\right)}{(zf_k+1)} + \left(t_{st,2}^* - t_{st,1}^*\right) + \frac{t_{st,2}^*\left[\{\frac{1}{t_{st,2}^*}\}^{-|z|f_k+1}-1\right]}{(-|z|f_k+1)} \quad (52)$$

Ignoring period III,

$$\frac{q_{k,m,life}}{t_{life}e_k m_B^{f_k}}\left(\frac{KJ}{kg\ of\ organ\ mass\ k}\right) = F_q(t^*_{st,1}, t^*_{birth}, g_k) = \{\frac{t^*_{st,1}\left(1-\left\{\frac{t^*_{birth}}{t^*_{St,1}}\right\}^{g_k+1}\right)}{(g_k+1)} + \left(1-t^*_{st,1}\right)\}$$

(53)

When fk=0, g_k= 0. F_k=1

4. 5 Life Time Specific Entropy Generation of Organ (W/K kg of Organ Mass k}

Eq. (10) can be used to obtain heat part of energy release as $q_{k,m,life}(1-\eta)$ and hence entropy generation is given as $\sigma_{k,m,life} = \frac{q_{k,m,life}(1-\eta)}{T}$ and hence using in Eq. (53)

$$\frac{T\sigma_{k,m,life}\left(\frac{W}{K\ kg\ of\ organ\ k}\right)}{t_{life}e_k m^{f_k}_{B,st}(1-\eta_k)} = F\left(t^*_{st,1}, g_k, t^*_{birth}\right) = \{\frac{t^*_{st,1}\left(1-\left\{\frac{t^*_{birth}}{t^*_{St,1}}\right\}^{g_k+1}\right)}{(g_k+1)} + \left(1-t^*_{st,1}\right)\}$$

(54)

Table 1 row # 3 presents this result. It is noted that $\frac{T\sigma_{k,m,life}}{(1-\eta_k)} = q_{k,m,life}$ as gk →0 (constant organ size),

$$\frac{T\sigma_{k,m,life}}{t_{life}e_k m^{f_k}_{B,st}(1-\eta_k)} = F\left(t^*_{st,1}, g_k, t^*_{birth}\right) \rightarrow (1-t^*_{birth}) \approx 1\ since\ t^*_{birth} \approx 0$$

4. 6 Life Time Energy Contribution by Organ to Unit Mass of Body (W by k /Kg of Body)

The energy contributed by organ of mass m_k to each unit body mass (W by organ k per kg body mass) by multiplying $\dot{q}_{k,m}(t)$ by $m_k(t)/m_B(t)$ which is equal to $c_k\ m_B\ (t)^{dk-1}$.

Thus

$$\dot{q}_{k,M}[\frac{W\ by\ organ\ k}{kg\ body}] = c_k\ e_k\ m_B(t)^{(d_k+f_k-1)} \quad (55)$$

The energy released by all organs to each unit mass in the body (W by all organs /kg of body) is estimated by summing the results from item (v). Result is given in row #4.

$$q_{M,life}\left(\frac{KJ}{kg\ of\ body\ mass}\right)$$

$$= \int_{t_{birth}}^{t_{st,1}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt + \int_{t_{st,1}}^{t_{st,2}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt +$$

$$\int_{t_{st,2}}^{t_{life}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt\,, k = B, H, K, L, AT, SM, R \quad (56)$$

Then integrating with time, one obtains the result given in row #4. Note $g_k = p(f_k + d_k - 1)$ for spite time organ metabolic energy release contributed to each unit body mass.

4. 7 Life Time Entropy Contribution by Organ to Unit Mass of Body (W by k /K kg of Body)

The entropy generation contributed by organ k to each unit body mass (W by organ k per kg body mass per K) by multiplying $\dot{\sigma}_{k,m}(t)$ by $m_k(t)/m_B(t)$ or $c_k\, m_B(t)^{\,dk-1}$ and then integrating with time;

$$\frac{T\sigma_{k,M,life}}{t_{life}\,\dot{q}_{k,M,st}(1-\eta)}$$

$$= \int_{t_{birth}}^{t_{st,1}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt + \int_{t_{st,1}}^{t_{st,2}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt$$

$$+ \int_{t_{st,2}}^{t_{life}} e_k m_B(t)^{f_k} c_k m_B(t)^{d_k} dt\,, k = B, H, K, L, AT, SM, R$$

(57)

Note $g_k = p(f_k + d_k - 1)$ for specific life time organ entropy generation.

4. 8 Life Time Entropy Contribution by Organ to Whole Mass of Body (W by k /K)

The entropy generation contributed by organ k to whole body (W by organ k /K) by multiplying $\dot{\sigma}_{k,m}(t)$ by $m_k(t)$ or $c_k\, m_B\,(t)^{\,dk}$ and then integrating with time; Note g_k= p(f_k+d_k1) for specific life time organ entropy generation.

4. 9 Mass and Energy Contribution by Vital Organs Including SM, AT and R

Previously relations were presented for the % energy (energy release rate by all 5 vital organs BHKL/whole body energy release rate) and % mass (total mass of vital organs BHKL/whole body mass) contribution by BHKL. The 7 organ model include BHKL, SM, and AT. Using Eq. (53), one can estimate metabolic rate of each organ, then sum all "VITAL" organs, divide by whole body metabolic rate and obtain % contributed by vital organs:

$$Metabolic\ Rate\ contribution\ by\ VITAL\ organ, \%$$

$$= \frac{total\ VITAL\ organ\ Met.rate}{\dot{q}} * 100 = 100 * \frac{\sum_{B,H,K,L} c_k e_k m_B^{d_k+f_k-1}}{\sum_{AT,B,H,K,L,R,SM} c_k e_k m_B^{d_k+f_k-1}} \qquad (58)$$

When f_k=0 [6], the 7 organ model yields

$$Metabolic\ Rate\ Contributed\ by\ VITAL\ organ\ \%$$

$$= \frac{total\ VITAL\ organ\ Met.rate}{\dot{q}} * 100 = 100 * \frac{\sum_{B,H,K,L} c_k e_k m_B^{d_k-1}}{\sum_{AT,B,H,K,L,R,SM} c_k e_k m_B^{d_k-1}}$$

Where e_k, Elia's constants.

$$Mass\ contributed\ by\ VITAL\ organ, \% = \frac{Total\ VITAL\ organ\ mass}{m_B} * 100$$

$$= \frac{\sum_{B,H,K,L} c_k m_B^{d_k}}{m_B} * 100 = 100 * \sum_{AT,B,H,K,L,R,SM} c_k m_B^{d_k - 1}$$

(59)

Dividing Eq. (15) by (16)

$$Metabolic\ Rate\ per\ unit\ mass\ of\ VITAL\ organs = \frac{Watts}{kg\ vital\ organ\ mass}$$

$$= \frac{Total\ VITAL\ organ\ Met.rate}{Total\ VITAL\ organ\ mass} = \frac{\sum_{B,H,K,L} c_k e_k m_B^{d_k + f_k - 1}}{\sum_{AT,B,H,K,L,R,SM} c_k e_k m_B^{d_k - 1}} \quad (60)$$

When f_k=0 {Elia's results}

$$Metabolic\ Rate\ per\ unit\ mass\ of\ VITAL\ organs = \frac{Watts}{kg\ vital\ organ\ mass}$$

$$= \frac{\sum_{B,H,K,L} c_k e_k m_B^{d_k - 1}}{\sum_{AT,B,H,K,L,R,SM} c_k e_k m_B^{d_k - 1}} \quad (61)$$

These relations shows body mass dependent specific organ met rate; Elia on the other hand assumes Later et al studies [50] (assumed RM met rate is fixed at 0.462 W/kg of RM) metabolic rate of species ranging from 40 to 104 kg humans and did not find boy mass dependent organ met rate (assumed by Wang; however Wang assumed body mass dependent relation for RM) but they assumed residual met rate to be 0.462 W/kg and is constant for body mass from 40-105 kg and selected reference man of 73 kg for BHKL and 0.462* RM (RM : residual mas: body mass- BHKL mass). Therefore,

BHKL rates do not change since the mass is constant, even though RM mass is changing. To account for conflicting f_k changed from 0 to -1/3 in this study.

Table 2 provides non-dimensional results for lifetime specific entropy generation in terms of allometric coefficients, growth period, and steady period; once allometric constants are known the 2nd column is used to extract $\sigma_{k,m,life}$, $q_{k,m,life}$ etc. provided metabolic efficiency of diet moisture, body temperature and life period. Table presumes that metabolic efficiency does not vary with age (i.e. composition of diet mixture is fixed throughout life period).

4. 10 Specific Energy Release and Entropy Generation of Organs Based on Mitochondrial Volume

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

$$vf_{Mito} = p_k m_B^{q_k} \tag{62}$$

Oxidation occurs within mitochondria while glycolysis occurs within the cell but outside the mitochondria. Since oxidation produces significant amount of ATP, it is assumed that entropy generation is dominated by oxidation and hence for purpose of entropy generation at mitochondrial level, it is assumed that all the ATP is generated within mitochondria as shown in figure:

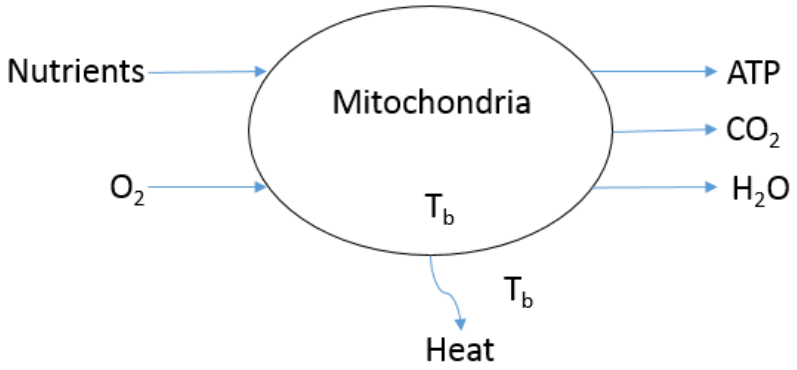

Figure 8: Schematic Diagram of the Thermodynamic System; a Large Number of Mitochondria Within Cell of Given Size Results in Increased Mitochondrial Volume (MiV) %

The organ volume is a sum of cell volume and interstitial fluid volume. Here the organ metabolic rate and entropy generation rate are converted to rates at mitochondrial level using allometric law for mitochondrial volume fraction

$$\dot{q}_{k,V,Mito}\left(\frac{W}{m^3 of\ Mito\ of\ organ\ k}\right)$$

$$= \dot{q}_{k,m}\left(\frac{W}{kg\ of\ organ\ k}\right)\rho_k\left(\frac{kg\ of\ organ\ k}{m^3 of\ organ\ k}\right)\frac{1}{vf_{cell,k}\left(\frac{m^3 of\ cells\ in\ k}{m^3 of\ organ\ in\ k}\right)}\frac{1}{vf_{Mito}\left(\frac{m^3 of\ Mito\ k}{m^3 of\ cell\ k}\right)}$$

$$= \frac{\rho_k e_k m_B^{f_k}}{vf_{cell} p_k m_B^{q_k}} = \left(\frac{\rho_k e_k}{vf_{cell} p_k}\right) m_B^{f_k - q_k} \qquad (63)$$

Where vf_{cell}, volume fraction of cells = n_k (π $d_{cell}^3/6$), n_k, number of cells per cm^3 of organ k, d_{cell} , cell diameter. Previous literature provided details on conversion of allometric laws from body mass m_B to organ mass k for various parameters of interest [5] {Appendix

A}. If cell density is equal to organ density, metabolic rate per unit mitochondrial volume is given as:

$$\dot{q}_{k,Mito\ vol}\left\{\frac{W}{m^3 Mito\ organ\ k}\right\} = r'_{new,k}\left(vf_{Mito,k}\right)^{t'_k}, r'_{k,new} = \frac{e_k \rho_k}{{p_k}^{t'_k} vf_{cell,k}},$$

$$t'_k = \frac{f_k - q_k}{q_k} = \frac{f_k}{q_k} - 1 \qquad (64)$$

If $(f_k/q_k)>1$, mito-volume based metabolic rate {W/cm^3 of Mito within k} will increase with increase in vf_{Mito} but rate of increase will be different for different organs depending on . Then one can estimate entropy stress at mitochondrial level using Eq. (63).

Table 2: Summary of Modeling Section [5]:

#	**Desired Variable**	**Non-Dimensional form of Desired Variable**	**GCF_k Right Side of Eq. (53);** Note 7	**Example-Heart , Wang 5 data $SERR_K$ body mass depend; $f_k=m_{Bst}$=84 kg, 75 yrs, $t_{st,1}$=24 yrs, RQ $_{mix}$=0.80, η_{met}=0.312, mH $_{std}$=0.006*84 $^{0.98}$=0.46 kg z=0.75; $t_{st2}=t_{life}$=75 yrs** { NOTE 2}
1	Life Time Specific metabolic energy release by organ k, $\frac{kJ}{kg\ of\ organ\ mass\ k}$	$\frac{q_{k,m,life}}{t_{life}\,\dot{q}_{k,m,st}}$ or $\frac{q_{k,m,life}}{t_{life}\,e_k m_{B,st}^{f_k}}$	g_k in Figure 12 = 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=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=60.8GJ/kg heart
2	Life Time Specific Entropy Generation of organ k, $\frac{kJ}{K\ kg\ of\ organ\ mass\ k}$	$\frac{T\sigma_{k,m,life}}{t_{life}\,\dot{q}_{k,m,st}(1-\eta)}$ or $\frac{T\sigma_{k,m,life}}{t_{life}\,e_k m_{B,st}^{f_k}(1-\eta_k)}$	g_k in Figure 12 = 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)

Table 2 Continued: Summary of Modeling Section [5]:

#	**Desired Variable**	**Non-Dimensional form of Desired Variable**	**GCF_k Right Side of Eq. (53);** Note 7	**Example-Heart , Wang 5 data $SERR_K$ body mass depend; $f_k=m_{Bst}$=84 kg, 75 yrs, $t_{st,1}$=24 yrs, RQ $_{mix}$=0.80, η_{met}=0.312, mH $_{std}$=0.006*84 $^{0.98}$=0.46 kg z=0.75; $t_{st2}=t_{life}$=75 yrs** { NOTE 2}
3	Life Time metabolic energy contribution by organ k to unit mass of body, $\frac{kJ\ by\ k}{kg\ of\ body\ mass}$	$\frac{q_{k,M,life}}{t_{life}\,\dot{q}_{k,M,st}}$ or $\frac{q_{k,m,life}}{t_{life}\,e_k m_{B,st}^{f_{k+d_k-1}}}$	g_k in Figure 12 = 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 $qH, M, Life, st = t_{life}\,\dot{q}_{k,M,st}$ =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	Life Time Entropy Generation contribution by organ k to unit mass of body, $\frac{kJ\ by\ k}{K\ kg\ of\ body\ mass}$	$\frac{T\sigma_{k,M,life}}{t_{life}\,\dot{q}_{k,M,st}(1-\eta)}$ or $\frac{T\sigma_{k,m,life}}{t_{life}\,e_k m_{B,st}^{f_{k+d_k-1}}(1-\eta_k)}$	g_k in Figure 12 = 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

Table 2 Continued: Summary of Modeling Section [5]:

#	**Desired Variable**	**Non-Dimensional form of Desired Variable**	**GCF_k Right Side of Eq. (53);** Note 7	**Example-Heart , Wang 5 data $SERR_K$ body mass depend; $f_k=m_{Bst}$=84 kg, 75 yrs, $t_{st,1}$=24 yrs, RQ $_{mix}$=0.80, η_{met}=0.312, mH $_{std}$=0.006*84 $^{0.98}$=0.46 kg z=0.75; $t_{st2}=t_{life}$=75 yrs** { NOTE 2}
5	Life Time metabolic energy contribution by organ k to whole body ($q_{k,life}$)	$\frac{q_{k,life}}{t_{life}\,\dot{q}_{k,m,st}}$ or $\frac{q_{k,m,life}}{t_{life}c_k e_k m_{B,st}^{f_{k+d_k}}}$	g_k in Figure 12 = $z(f_k+d_k)$	$gH= z(f_k+d_k)=0.75*(-0.12+0.98)= 0.645$ GCF=0.874, $q_{H,Life,\,st}$=0.33* 84= 27.72GJ st by heart to whole body $q_{H,Life,}$ =27.72 GJ*0.874=24.1 GJ by heart to whole body
6	Life Time Entropy Generation contribution by organ k to whole body	$\frac{T\sigma_{k,life}}{t_{life}\,\dot{q}_{k,st}(1-\eta)}$ or $\frac{T\sigma_{k,m,life}}{t_{life}\,c_k e_k m_{B,st}^{f_{k+d_k}}(1-\eta)}$	g_k in Figure 12 = $z(f_k+d_k)$	$\sigma_{H,Life,st}$= 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

Table 2 Continued: Summary of Modeling Section [5]:

#	**Desired Variable**	**Non-Dimensional form of Desired Variable**	**GCF_k Right Side of Eq. (53);** Note 7	**Example-Heart , Wang 5 data $SERR_K$ body mass depend; $f_k=m_{Bst}$=84 kg, 75 yrs, $t_{st,1}$=24 yrs, RQ $_{mix}$=0.80, η_{met}=0.312, mH $_{std}$=0.006*84 $^{0.98}$=0.46 kg z=0.75; $t_{st2}=t_{life}$=75 yrs** { NOTE 2}
7	Life Time Specific metabolic energy release per m^3 mito within organ k, $\frac{kJ}{m^3\ of\ Mito\ within\ organ\ k}$	$\frac{q_{k,V,Mito,life}}{t_{life}\,\dot{q}_{k,V,st,Mito}}$ or $\frac{q_{k,V,Mito,life}}{t_{life}\frac{\rho_k e_k}{v f_{cell} p_k} * m_{B,st}}$	f_k replaced by f_k-q_k	fH=; F=1.015, $\dot{q}$ H.m, $_{st}$=25.9 W/kg heart; $q_{H,m,Life}$=62170 MJ/kg heart

Note 1: The allometric coefficients presume no AT , no SM; coefficients are from ref [5]

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.

5. RESULTS AND DISCUSSION

The data input is presented first for quantitative evaluation of lifetime energy expenditure per unit body mass, entropy generated by all organs and their contributions to each unit body mass, lifetime energy expenditure per unit mito-volume, entropy generated by all organs and their contributions to each unit mito-volume, maximum possible temperature rise within each organ.

5. 1 Data Input

The quantitative evaluation of entropy generated in each organ require nutrient properties particularly for metabolic efficiencies, body mass change with age and allometric coefficients of organs to estimate specific energy release rate ($SERR_k$, W per kg organ k) and blood flow rates to estimate maximum blood temperature rise within an organ k

Nutrients

The food intake consists of CH, F and P. The CH is represented by glucose, the fatty acid molecule (F) is saturated fatty acid molecule with 12- 16 C atoms and is typically represented by Palmitic acid $\{C_{16}H_{32}O_{2.}\}$ while empirical formulae $C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$ [6] is used for proteins (P).

Table 3 lists the properties of nutrients. It is noted from Table 3 that i) HHV_{O2} , the heating value per kg of stoichiometric O_2 remains almost constant, ii) $\frac{|\overline{\Delta G}^\circ_c|}{|\overline{\Delta H}^\circ_c|}$ is roughly constant around 1 due to T $\overline{\Delta S}^\circ_c$ <<$\overline{\Delta H}^\circ_c$. Thus energy release rate given by $\dot{m}_{k,F}\overline{\Delta H}^\circ_c$ where $\dot{m}_{k,F}$ is the rate of fuel consumption (which includes mostly CH and F) and is almost same as $\dot{m}\overline{\Delta G}^\circ_c$. Allometry law yields energy release rate $\dot{q}_k = \dot{m}_{k,F}|\overline{\Delta H}^\circ_c| =$

$\dot{m}_{O2,k} HHV_{O2}$ in terms of body (m_B) or organ mass m_k. iii) For same amount of O_2 consumed (same energy released) fat emits less CO_2 compared to CH due to lower RQ for F compared to CH. iv) lesser amount of O_2 consumed per the same ATP produced for CH {energy required per ATP) compared to fat {e.g. Brain uses mostly CH}, iv) energy density of fat (MJ/kg) is higher for fat compared to CH and thus energy storage in the form of fat occupies lesser volume. Metabolic efficiency of 38 % for CH indicates that roughly 38 % of energy released, $\dot{q}_k$ is captured by ATP.

Table 3: Properties of Nutrients

Glucose (CH): $C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$, $\overline{\Delta \mathbf{H}}^\circ_c$ = - 2815 MJ/kmol, $\overline{\Delta \mathbf{G}}^\circ_c$ = -2895 MJ / k mol, $\overline{\Delta \mathbf{S}}^\circ_c$ = 0.262 MJ/kmole K

RQ= 6/6= 1.0

With ATP production/metabolism[25],

$C_6H_{12}O_6 + 6O_2$ +38 ADP +36 phosphates$\rightarrow$ $6CO_2 + 6H_2O$ + 38 ATP, $\Delta \overline{G}_M{}^o$ = - 1770 MJ/kmol (65)

1 kg glucose + 1.0656 kg O2 $\rightarrow$ 1.466 kg CO_2 + 0.6 kg H_2O

0.938 kg glucose + 1.0 kg O2 $\rightarrow$ 1.376 kg CO_2 + 0.563 kg H_2O

FAT (F): $C_{16}H_{32}O_2 + 23\ O_2 \rightarrow 16\ CO_2 + 16\ H_2O$, $\overline{\Delta \mathbf{H}}^\circ_c$ = - 10015 MJ/kmol , $\overline{\Delta \mathbf{G}}^\circ_c$= -9840 MJ / k mol, $\Delta S_c{}^0$ = -5.69 kJ/kmole K (assumed T= 37 C) (66)

RQ= 16/23=0.696

With ATP production,

$C_{16}H_{32}O_2 + 23\ O_2 + 106$ ADP + 106 phosphates $\rightarrow$16 CO_2 +16 H_2O +106 ATP, $\Delta \overline{G}_M{}^o$ = –6715 MJ / kmol

1 kg of Fat + 2.869 kg of oxygen$\rightarrow$ 2.751 kg of CO_2 + 1.118 kg of H_2O,

0.349 kg of Fat + 1 kg of oxygen$\rightarrow$ 0.959 kg of CO_2 + 0.389 kg of H_2O,

Table 3 continued: Properties of Nutrients

Nutrients	**M, kg/kmol**	**St. O2 kg/kg nutrient (mole per mole nutrient)**	**HHV MJ/kg (MJ/kmol)=|ΔH_c^o|**	**RQ** {note 9}	**HHVO2 MJ/kg of O_2** {Note 2}
Glucose (CH) $C_6H_{12}O_6$ {Note 3}	180	1.066 (6 mole O2/mole CH)	15.630 (2813 MJ/kmol)	1	14.665
Fat (F) $C_{16}H_{32}O_2$ {Note 3}	256	2.869 (23 moles O2/mole F)	39.125 (10015 kJ/kmol) {Note 7}	0.7	13.635
Protein (P) $C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$ {Note 1, Note 3}	118	2.07 (5.83 moles O2/mole P)	28.893	0.80 0.82	13.944
Mixture {Note 5} CH:F:P 55:30:15 (Mass %)	182	1.68	23.754		14.129

Table 3 Continued: Properties of Nutrients

Nutrients	$\overline{\Delta G}^{\circ}_{c}$ **MJ/kmol** {Note 1}	$\overline{\Delta G}^{\circ}_{M}$ **MJ/kmol** {Note1}	$\frac{\lvert\overline{\Delta G}^{\circ}_{M}\rvert}{\lvert\overline{\Delta H}^{\circ}_{c}\rvert}$	**K mol O2 consumed per kmol ATP** {Note 10}	**Metabolic efficiency (%)** { Note 8}
Glucose (CH) $C_6H_{12}O_6$ {Note 3}	-2895		1.03	0.158	38.2
Fat (F) $C_{16}H_{32}O_2$ {Note 3}	-9840, -9800 {Note 4}	-6715	0.98	0.217	32.2
Protein (P) $C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$ { Note 1, Note 3}	-2665		0.98		10.4
Mixture {Note 5} CH:F:P 55:30:15 (Mass %)	43198 94		0.999		31.32 {note 6}

Note 1: $\Delta G_c°$, estimated from stoichiometric equation assuming each component is pure. Protein $C_{30_{32}}H_{4816}N_{780}S_8$ Fe_4; normalized: $CH_{1.588}N_{0.257}O_{0.288}S_{0.00263}$ $Fe_{0.00132}$ [2]

Note 2: HHVO2=HHV (kJ/kg nutrient) /st O2 (kg O2 per kg nutrient); note that HHVO2 of CH is slightly higher compared to fat and hence CH is preferred fuel when O2 is limited. However on unit volume basis in blood the fat has higher energy release per unit volume and preferred fuel when O2 and fat are available for long duration exercise [13]; $|\overline{\Delta H}^{\circ}_{c}| = M$ **$|\Delta H_c°|$;**

For calculations of energy release, $HHVO_2$=average of glucose and fat = {14665+13635}/2= **14140 J/g** or 14140 kJ/kg or 20200 J/L of O2 (CST) consumed

Note 3: Formula assumed for CH, F and P are C6H12O6, C16H32O2, $C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$ respectively; CH is large polymer having 2 million g per g mole [2]

Not all the heating values (based on dry basis) are bomb calorimeter valued. Only 95.5 5 is release through metabolism. Thus η_{CH}= 0.955; η_F= 0.977 η_P= 0.775 [2] Human body has 72 % water. On wet basis the CH in food has heat value of 4200 J/g indicating that HHV wet= HHV dry *fraction of dry mass of CH in wet; since HHV wet for CH, F and P = 4200, 33400, 8400 J/g then fraction of dry mass typically mH2O = 0.72 and m dry = 0.28 ; dry mass fraction in wet food: CH = 0.23, Fat: 0.83, P= 0.38 typical daily consumption: CH: 45 %, Fat: 40 %, Protein: 15 % {wet basis}[2]. One must use wet HHV

Note 4: Oxidation of Fatty Acids [26]

Note 5: Mix of CH and Fat: RQ= 0.81 [13] which yield CH: mole %, CH % mass % when CH and F are oxidized.

Note 6: Metabolic efficiency of mixture is estiamted using energy % contributed by each componet in mixture

Note 7: Fat on mass basis {9.35 Cal/g} prvodes 2.5 time smore nergy compared to CH {3.74 Cal/g}

GLUCOSE

Note 8: The is ATP base; when ATP s supplied to muscles, and if glucosecis ful, net energy release in bicep = 0.25 indicatng that ; i.e delivered by biceps

Energy added per kmol ATP formed from ADP, kJ/kmol, 31 [25]

Note 9: RQ is at cellular level while RER is at bulk level through nose; during exercise CO2 is buffered; sometime RER > 1 due to CH oxidation and as well as during anaerobic digestion somewhere within an organ where CO2 is released without consuming oxygen {e.g. stomach}

Note 10: The O2 consumed is an indication of energy released which supplies both heat and ATP work

Mass (Weight) vs Age

Figure 9 plots mass of male and female vs age using mean mass data UK data [27] on different age groups. The curve fits for both male and female are also provided for periods I and II. Mass loss period III is ignored.

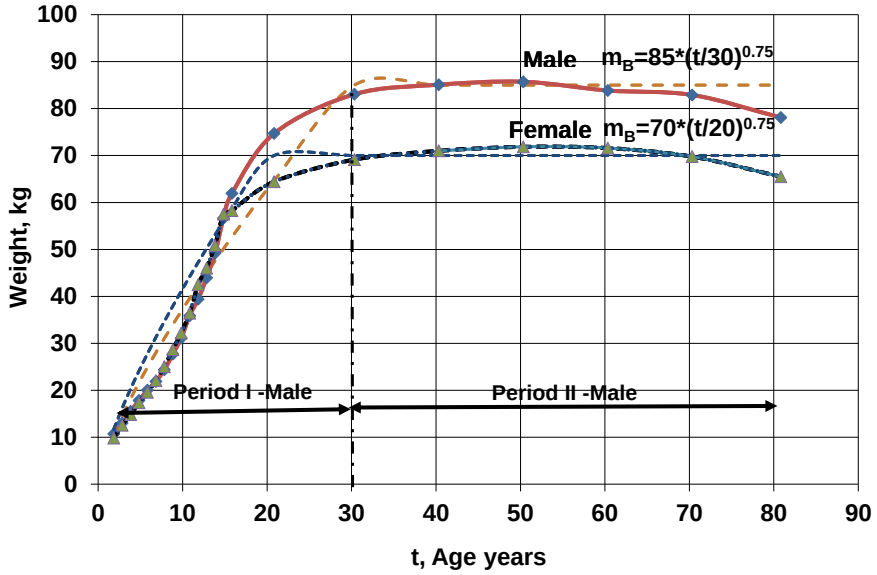

Figure 9: Mean Weight vs Age Based on UK Data 2002. Curve Fit for Male: $m_B= m_{B,st}*(t/t_{st})^p$, Male : m_{Bst}: 85 kg Male and 70 kg Female; t_{st}= 30 Years Male and 20 Years Female, Fit From Age 1 to 75 +Years [27]

Allometric Coefficients

Based on O_2 used by each organ k and blood flow rates to each organ, the energy released by organ k and are well documented and allometric relations are available. These relations are used to estimate specific energy release rate and entropy generation rate (W/kg K) and hence lifetime entropy generated (MJ/kg K) by each organ can be estimated. Here two types of allometric relations are presented I: Basic, II: Derived:

I) Basic Allometric Relations

The allometric constants obtained are as shown below: ($m_{B,st}$= 85 kg)The mass of organ, m_k, specific energy release rate of each organ k, $\dot{q}_{k,m}$ (W by k /kg of k) , blood flow rate to each organ ($\dot{V}_k$ t , mL to organ k /s), average Mitochondrial volume fraction ($vf_{k,Mito}$, cm^3 of Mito /cm^3 of cells within organ k) in terms of body mass (m_B, kg) etc.

A. Wang Five - Wang SMR_k (Five Organ Model)

Here the whole body is divided into 5 organs: B, H, K, L, RM. Table 4 lists the basic allometric constants. The specific metabolic rate of each organ k (SMR_k) is dependent on body mass and hence age [28]. 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 kg to 70 kg)}, Wang et al presented allometric relation for SMR_k and organ mass in terms of body mass as shown in Table 4. Larger mammals have lower SMR for organs compared to smaller mammals. Noticeable difference between the use of Elia's data based on 6 species which results in almost constant 11 W/kg for vital organs of smaller mammals (0.1kg) to 14 W/kg for larger mammals (1000 kg) but shows decreasing values from 51 W/kg (0.1 kg) to 8 W/kg for (1000 kg) with Wang's data.

B. Wang Seven - Elia-SMR_k (Seven Organ Model)

The whole body is divided into 7 organs: B,H,K,L, AT, which stores Triacylglycerols, $C_{55}H_{104}O_6$ which supply energy during starvation, SM and R (R7 organ model is different from R5 for Wang 5) with body mass independent SMR_k throughout growth [5] i.e. constant irrespective of size/mass of selected vital organ and rest of mass

R includes 8 sub-organs: adrenal, blood, gut, lung, skin, skeleton, spleen and thyroid The allometric constants for 7 organs were selected from Wang's 14 organ data: four higher metabolically active vital organs : BHKL and 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. Data was presented for allometric relation between organ masses and body masses for all 14(=4+2+8) organs. For current calculations, the organ masses of eight low active organs were computed for body mass ranging from 0.1 kg to 1000 kg, summed up and the sum is called as mass of residual organs (R7). The sum was plotted with body mass, allometric constants were then evaluated for the R7 and they are presented in Table 4 along with values for Wang-5-Wang SMRk.

II) Derived Allometric Relations

The body mass (m_B, kg) based allometric relations for SMR_k or $\dot{q}_{k,m}$ (W by k /kg of k), blood flow rate to each organ ($\dot{V}_k$, mL to organ k /s), average Mitochondrial volume fraction ($vf_{k,Mito}$, cm^3 of Mito /cm^3 of cells within organ k) can be re-derived in terms of organ mass (m_k, kg): $\dot{q}_{k,m}$ (W by k/kg of k). Further relations can be derived for oxygen extraction fraction (OEF_k,) {= oxygen used for energy release /oxygen supplied} in term of body mass (m_B, kg) or organ mass (m_k, kg), maximum temperature rise (T-T_B, °C) within an organ in terms of body mass (m_B, kg) or organ mass (m_k, kg) etc. Similarly $\dot{q}_{k,,V.Mito}$ (W by Mito /cm^3 of Mito within organ k) can be re-derived in terms of $vf_{k,Mito}$, Derivations for derived reaction are in Appendix A and the allometric coefficients are listed in Table 5.

Table 4: Basic Allometric Constants – Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data) [5]

$$Mitochondrial\ volumer\ fraction\ (MiV_f) = p_k m_B^{q_k} \quad (68)$$

Body mass growth with age: $m_B(t) = m_{B,st}\ (\frac{t}{t_{st}})^p$

Body mass: male m_{Bst} = 84 kg, t_{st} = 25 years; female m_{Bst} = 70 kg, t_{st} = 20 years {standard mass male 2002 UK data} [27] ; met rate: W;

Metabolic rate in W per kg of Vital organs BHKL=14.8 W per kg vital organs

Steady-state body mass of 70 kg ($m_{B,st}$; Reference man); t_{birth}= 10 months. t_{life}= 75 years.

Allometric Constants Wang 2000-7 Calder data rest mass (8 sub-organs – avg. Met rate) [29] Elia SMR_K

Organ	**Density (g/cc)**	**c_k, kg [23]**	**d_k**
	ρ	$m_k(kg)=c_k m_B(t)^{dk}$, m_B in kg	
Adipose Tissue	0.9	0.0753 (-)	1.19 (-)
Brain	1.036	0.1025 (0.011)	0.71 (0.76)
Heart	1.06	0.006 (0.006)	0.98 (0.98)
Kidney	1.05	0.0089 (0.007)	0.71 (0.85)
Liver	1.06	0.0491 (0.0330)	0.70 (0.87)
Residual Mass		0.3296 (0.939)	1.01 (1.01)
Skeletal Muscle	1.04	0.4683 (-)	0.99 (-)

Table 4 Continued: Basic Allometric Constants-Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data) [5]

Organ	**e_k (W/kg)**	**f_k (Note 7)**	**h_k**	**i_k**	**p_k**	**q_k**	**$\dot{q}_{k,m,st}$**
	$\dot{q}_{k,m,st}(t)(\frac{W}{kg\ of\ organ\ k})$ $=e_k m_B^{fk}$		$\dot{V}_{Bl,k}(\frac{mL\ to\ organ\ k}{s})$ $=h_k m_B(kg)^{ik}$		$(MiVf) = p_k\ m_B^{q_k}$		
Adipose Tissue	0.22	0.0	-	-	- (-)	- (-)	-
Brain	11.62 (21.62)	0.0 (-0.14)	0.101	0.704	0.0538 (0.0538)	-0.08 (-0.08)	0.0442
Heart	21.3 (43.113)	0.0 (-0.12)	0.224	0.714	0.4223 (0.4223)	-0.09 (-0.09)	0.146
Kidney	21.3 (33.414)	0.0 (-0.08)	0.603	0.774	0.38 (0.38)	-0.14 (-0.14)	0.108

Table 4 Continued: Basic Allometric Constants-Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data) [5]

Organ	e_k (W/kg)	f_k (Note 7)	h_k	i_k	p_k	q_k	$\dot{q}_{k,m,st}$
	$\dot{q}_{k,m,st}(t)(\frac{W}{kg\ of\ organ\ k})$ $=e_k m_B^{fk}$		$\dot{V}_{Bl,k}(\frac{mL\ to\ organ\ k}{s})$ $=h_k m_B(kg)^{ik}$		$(MiVf) = p_k\ m_B^{q_k}$		
Liver	9.7 (33.113)	0.0 (-0.27)	0.156	0.856	0.275 (0.275)	-0.13 (-0.13)	0.186
Residual Mass	0.58 (1.446)	0.0 (-0.17)	-	-	0.0816 (0.0816)	-0.09 (-0.09)	- (0.192)
Skeletal Muscle	0.63 (-)	0.0 (-)	0.769	0.737	- (-)	- (-)	

Fat Free mass = adipose tissue free mass= body mass - adipose mass [32]
Note 1: 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 O2/h or 0.453*14500=2.6 W or 2.6/7.56=0.33 W/kg corrected 0.165; SM: 0.492*0.63 kg; 3 L of o2/h=0.43 W/kg; 33] [31].
Note 2 and 3: Even though allometric constant is given for Residual mass, here it is calculated using relation:
Residual mass = Body mass- Sum of six organs (AT, BHKL, SM) for which allometric law is given.
Note 4: $c_p\left(\frac{J}{kgK}\right) * \rho\left(\frac{kg}{mL\ blood}\right) * \{T_{exit} - T_{in}\} = \frac{e_k c_k}{h_k} m_B^{(fk+dk-ik)}$
Note 5: mass and met rate relation coefficients for RM are given as ck=0.32961, dk=1.01 ek=3.588 f_k=-0.42; this leads to mass imbalance since total estimated mass did not add up to body mass; thus in current work the RM calculated as : Body mass- {mass of organs calculated using allometric laws of organs AT, BHKL, SM}.
Note 6: Hepatitic [34] for this case, "fk" are as follows:
f_k=0 for all organs; the e_k's (W/kg) are : 0.581, 11.622 , 21.307, 21.307, 9.685. 0.630, 0.581 W/kg of k, k=AT, B, H, K, L, SM, RM}
Note7: The values in Table 1 of Ref by Annamalai and Silva (2012) [35] are correctly shown here. The values in Table 1 if ref 1 listing 11.93 to 0.70 must be under heading W per kg organ mass.
Note 9: Liver mass scales as M_B 0.82; Aguttar mentions hepatocyte met rate scales as $m_B^{(-0.18)}$; If "N_m number of cells per unit mass, then hence specific met rate of liver scales as N_m* $m_B^{(-0.18)} \propto m_B^{-0.18}$ if N_m is constant. Metabolic rate of liver m_B 0.63 {Note 0.63≈0.64=0.82+(-0.18)=mass of liver : met rate per cell* no of cells=0.64 consistent with slice data}[36].
Organ mass relations from [29]
Note 10: Wang 7-Elia-Mod : 6 organ mass from Calder data [29] , 7th organ rest of mass-sum of 8 sub-organs and curve fitted with body mass; SMRK from Elia for AT,BHKL SM and SMRK for R from Wang.
Note 11: In the allometric constants for mitochondrial volume %, W, the mass of the body was erroneously entered in kg. instead of gms. However, if the MiV% calculated based on provided values, the above constants still falls within 95% confidence of exponents (q_k).

Table 5: Derived Allometric Relations-Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data)

$$\dot{q}_{k,m}(t), \frac{W\ of\ k}{kg\ of\ organ} = E_k m_k^{F_k}, E_k = \frac{e_k}{c_k^{\frac{fk}{dk}}} F_k = \frac{f_k}{d_k}$$

$$q'''_{k,m}(t), \frac{W}{cm^3\ of\ organ\ k} = q'''_{k,m}(t)\rho_k = e_k \rho_k m_B^{f_k}$$

$$\dot{q}_{k,V,Mito} \frac{W}{cm^3\ of Mito\ within\ organ\ k} = P_k m_B^{Q_k}, P_k = \frac{\rho_k e_k}{vf_{cell} p_k}\ , Q_k = f_k - q_k$$

$$\dot{q}_{k,m}(t), \frac{W\ of\ k}{kg\ of\ organ\ k} = B_k (Mivf_k)^{O_k}, B_k = \frac{e_k}{p_k^{\frac{fk}{qk}}}, O_k = \frac{f_k}{q_k}$$

$$\dot{V}_{Bl,k,V}(t), \frac{mL\ of\ blood}{s\ per\ kg\ of\ organ} = H_k m_B^{I_k}, I_k = i_k - d_k, H_k = \frac{h_k}{c_k}$$

Blood flow rate per unit mass of organ, $\dot{V}_{Bl,k,m}(t)$ (mL/s per kg of organ) =Blood flow per s to organ k/mass of organ k = $H_k\ m_B{}^{Ik}$, $Ik=i_k-1$, $H_K=h_k/c_k$, for blood flow mL/s per kg organ.

$$OEF = J_k m_B^{L_k}, J_k = \frac{c_k e_k}{h_k \rho_{bl} Y_{O2in} HV_{O2}}, L_k = f_k + d_k - i_k$$

Blood flow rate to organ k, $\dot{V}_{Bl,k}, \frac{mL\ to\ organ\ k}{s} = h_k m_B^{i_k}$

$$T_{exit} - T_{in},\ {}^oC = N_k m_B^{L_k}, N_k = \frac{J_k Y_{O2in} HV_{O2}}{c_p} = \frac{c_k e_k}{h_k \rho_{bl} c_p}, L_k = f_k + d_k - i_k$$

Density of organ, kg/mL =0.00106, volume fraction of cell (vf_{cell}) =0.0916

Table 5 Continued: Derived Allometric Relations-Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data)

Organ k	**E_k**	**F_k**	**H_k**	**I_k**	**B_k**	**O_k**
	$\dot{q}_{k,m}, \frac{W}{kg\ organ\ k} = E_k m_k^{F_k}$		$\dot{V}_{Bl,k,V}(t), \frac{mL\ of\ blood}{s\ per\ kg\ of\ organ} = H_k m_B^{I_k}$		$\dot{q}_{k,m}(t), \frac{W\ of\ k}{kg\ of\ organ\ k} = B_k(Mivf_k)^{O_k}$	
AT	0.22 (-)	0.0 (-)	- (-)	-1.19 (-)	0.22 (-)	0.0 (-)
Brain	11.62 (9.420)	0.0 (-0.184)	0.985 (9.182)	-0.006 (-0.056)	14.681 (18.143)	0.0 (1.75)
Heart	21.31 (23.043)	0.0 (-0.1224)	37.333 (37.333)	-0.266 (-0.266)	23.029 (42.012)	0.0 (1.333)
Kidney	21.3 (20.947)	0.0 (-0.0941)	65.753 (86.143)	0.064 (-0.076)	24.390 (35.411)	0.0 (0.571)
Liver	9.69 (11.488)	0.0 (-0.168)	- (-)	-0.994 (-1.01)	0.58 (15.15)	0.0 (-)
Residual	0.58 (1.432)	0.0 (-0.168)	- (-)	-0.994 (-1.01)	0.58 (15.15)	0.0 (-)
SM	0.63 (-)	0.0 (-)	1.643 (-)	-0.253 (-0.253)	0.789 (-)	0.0 (2.222)

Table 5 Continued: Derived Allometric Relations- Wang Seven Elia Mod (Values in Parentheses are for Five Organ Data)

Organ k	P_k	Q_k	J_k	L_k	N_k
	$\dot{q}_{k,V,Mito} \frac{W}{cm^3\ of Mito\ within\ organ\ k} = P_k m_B^{Q_k}$		$OEF = J_k m_B^{L_k}$		$= N_k m_B^{L_k}$
AT	- (-)	0.0 (-)	- (-)	1.19 (-)	- (-)
Brain	2.442 (4.544)	0.0 (1.75)	- (0.524)	0.006 (-0.084)	3.090 (0.617)
Heart	0.584 (1.181)	0.0 (1.333)	(0.257)	0.266 (0.146)	0.150 (0.303)
Kidney	0.642 (1.008)	0.0 (0.57)	- (0.0863)	-0.064 (-004)	0.0824 (0.102)
Liver	0.408 (1.393)	0.13 (2.077)	- (1.558)	-0.156 (-0.256)	0.799 (1.836)
Residual	- (-)	0.0 (-)	- (-)	0.994 (0.84)	- (-)
SM	0.0893 (-)	0.0 (2.22)	- (-)	0.253 (0.053)	0.100 (-)

*: upper data for these organs are for 5 organ and lower data for 7 organ

Note 1: Non-dimensional Entropy Stress of k = (Lifespan specific entropy generation in organ k)/ (lifetime entropy generation in Heart)

Note 2: round of error in organ mass

5. 2 Verification of Results for Five and Seven Organ Data

Vital Organ Mass % Using Wang-Five-Wang SMR_k

In order to make sure that the current work with modification and inclusion of mitochondrial density, the MS Excel based programs were develop. Results were generated for 5 organs and checked for vital organ mass % contribution to whole body [5]. Note that the allometric coefficients in Wang 5 data for SMRk and organ mass (m_k) in terms of body mass (m_B) are based on 6 species: rat, rabbit, cat, human-1, human-2 ranging in mass from 0.48 kg to 70 kg [30]) a. Further Wang-5-Wang SMRk depends on body mass. Here the "VITAL" organ include only BHKL. Wang 5 organ data yields:

$$\textit{\% contribution to mass by the vital organs (6 species data)} = 5.73\, m_B^{-0.135},\quad R^2 = 0.999 \quad (69)$$

Vital Organ Mass % Using Wang-Seven-Elia SMR_K

Wang 2000 [30] reports allometric correlations for the masses of organs which include, AT, BHKL, SM while the residual mass (R) includes 8 sub-organs: Adrenal, blood, gut, lung, skin, Skeleton, spleen and thyroid [30] for which allometric correlations for mass are given. They were combined and curve fitted to yield

$$\text{Residual mass in kg (R)} = 0.3254\, m_B^{\,0.9944}$$

The results for vital organ mass % yield: Wang 7 organ data based on 111 species

$$\%\ \text{contribution to mass by the vital organs (110 species data)} = 15.84\, m_B^{-0.264},\quad R^2 = 0.999 \quad (70)$$

The vital organ mass at % for 5 organ case decrease at lesser rate with increase in body mass compared to vital organ % for 7 organ case. {Based on 111 species allometry}

Vital Organ Metabolic Contribution to Whole Body Metabolic Rate

With Wang 5 and 7, the results were obtained for vital organ metabolic contribution to whole body metabolic rate:

%Contribution by Vital organ to body met rate= 56.87$m_B^{-0.074}$, Wang-5 organ

Which checks with previously published correlation with minor correction [35]. As a check, the allometric law for vital organ to body metabolic rate agrees closely with correlation reported elsewhere {56.6 $mB^{-0.07}$ [30]}. Elia's data on constant SMRk, 0.581, 11.622, 21.307, 21.307, 9.685. 0.630, 0.581 W/kg of k for 7 organs} which are independent of body mass. This data set will be called as Wang-5-Elia SMR_k.

%Contribution by Vital organ to body met rate= 79.038$m_B^{-0.092}$, Wang-7 organ-Elia SMR_k

Which is different from 5 organ relation due to change in allometric coefficients for 7 organs fitted from data on 111 species instead of 6 species. Net effect is vital organ metabolism % for 7 organ case is higher (53.5%) compared to 5 organ case 37.1% for 70 kg reference man. The % contribution to basal metabolic rate (BMR) by four vital organs differ with 5 organ and 7 organ data essentially due to Elia's constant SMR_k of organs .

Later Wang et al modified allometric coefficients for the 5 vital organ mass (m_k) in terms of body mass (m_B) considering 111 species but still used the coefficients for BHKLR based on SMR_k data of 6 species and recalculated the exponents in whole body allometric law. This data set will be called as Wang-5 mod.

BMR for Whole Body with Wang-Five and Wang-Seven

As a further check, the metabolic rates of al organs were summed up to determine the whole body metabolic rate for both 5 organ and 7 organ data and they were fitted against body mas: the fit yields

$$\dot{q}\,(Watts) = 3.040\, m_B^{0.7713},\ Wang\ 5 - SMR_k,\ R^2 = 0.9997 \qquad (71)$$

The body mass dependent SMR_k data (Wang-5) showing W/kg body mass is 5.1 W/kg for species of 0.1 kg body mass and is 0.63 W/kg for species of 1000 kg body mass;

$$\dot{q}\,(Watts) = 2.509\, m_B^{0.8421},\ Wang\ 5 - SMR_k,\ R^2 = 0.9987 \qquad (72)$$

The body mass **independent** SMR_k data (Wang-7) showing W/kg body mass is 3.6 W/kg for species of 0.1 kg body mass and is 0.84 W/g for species of 1000 kg.

Lifetime Contribution on Specific Energy and Entropy

In order to check current results values were first computed for 84 kg human {standard steady body mass of a male based on UK data}. The lifespan energy expenditure value of 2.73 GJ/kg , 2.76 , , k=AT,B,H,K,L,SM,RM and Wang 5 organ data) and entropy stress of whole body 6.04 MJ/ (K kg body mass) (Elia 2) and was and 6.11 (Wang 5 organ) obtained; the value agrees with the findings of Speakman

[37]. This also checks with previously published data of lifespan energy expenditure 2.83 GJ/kg {Wang 5 organ} and 6.3 MJ/kg K {5 organ data}.

5. 3 Average Vital Organ Metabolic Rate (W/kg of Vital Organ)

The average vital organ metabolic rate is defined as

$$Specific\ Vital\ organ\ met\ rate\ \left(SMR_{avg,vital}, \frac{W}{kg}\right)$$

$$= \frac{Vital\ met\ rate\ \% * \dot{q}}{Vital\ Organ\ Mass\ \% * m_B} = \frac{Vital\ met\ rate\% * (am_B^b)}{Vit\ Organ\ Mass\ \% * m_B} \quad (73)$$

$$SMR_{avg,vital}, \frac{W}{kg} = \frac{56.087 m_B^{-0.074} * 3.040 m_B^{0.7713}}{5.73 m_B^{-0.135} * m_B} = 19.97 m_B^{-0.168}, Wang\ 5 \quad (74)$$

It is seen from 5 organ data that as the person grows, the vital organ mass % decreases and as such these metabolically active tissues (heart, lungs, brain, liver, and kidneys) contributes less and less to resting metabolic rate with age. Thus $SMR_{avg,vital}$,W/kg decreases. When using Wang-7 –Elia SMR_k

$$SMR_{avg,vital}, \frac{W}{kg} = \frac{79.038 m_B^{-0.092} * 2.509 m_B^{0.8421}}{15.84 m_B^{-0.264} * m_B} = 12.52\ m_B^{0.0141}, Wang\ 7 - Elia\ SMR_k \quad (75)$$

With Elia's data, it is seen that the W/kg of vital organs is almost constant (11 to 14 W/kg with higher value for larger body mass, mass is varied from 0.1 to 1000 kg) across all species i.e. almost independent of growth of mass (Period I). For reference humans with m_B= 70 kg

$$\dot{q}_{BHKL,m}\left(\frac{W}{kg\ of\ BHKL}\right) = 13.2\frac{W}{kg}, 11.8\frac{W}{kg}, Wang - 5\ and\ Wang - 7: Elia\ SMR_k$$

Which is almost 12-13 times that of whole body specific metabolic rate.

5. 4 Maximum Possible Blood Temperature Rise

Using the relations presented in Section 4, the temperature rise of vital organs were computed for 84 kg human and maximum possible values were computed {adiabatic and metabolic efficiency =0) are tabulated in table 5. Except for brain data for Wang 7 Elia mod, the temperature rise is less than 0.5 C for a normal 84 kg human. The allometry on blood flow rate to brain indicates somehow low values resulting in high temperature rise. Note that actual rise in temperature is about 70 % of rise due to metabolic efficiencies of about 30 %. A concussion in brain cause metabolic efficiency to be about 15 % which will increase the venous blood temperature. ROS relations in combustion science show that they are strong functions of temperature and the concentrations of various fuel and oxygen radicals. Since metabolic intensity within mitochondria of brain is almost 3 times that of heart, the temperature rise in blood were estimated using relations presented in Eq. 101 (Appendix A) and results are presented for an 84 kg man. [57]

The following affects the temperature rise:

a) body mass which affects the blood flow rate and metabolic rates of organ
b) 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 [38] which requires skin blood flow rate of almost 1.9 L/min for1.8 m2 area person. Core to skin temperature difference is of the order of 5 C}.
c) nutrients oxidized and concussion in brain which affect metabolic efficiency

The temperature difference is tabulated in Table 6. Yablonskiy et al [39] estimated temperature rise as 0.3 C using the local metabolic rates and measured regional cerebral blood flow as 0.55 mL/{g mass of organ*min}. Table 6 yields temperature of venous blood as 0.7*0.58=0.42 ^{o}C.

Table 6: Selected Quantitative Results for Steady State (84 Kg Person) and Over Life Span for Five Organ (in Parenthesis) and Seven Organ Data; Metabolic Efficiency Set to Zero to Get Maximum Possible Values

Organ	**Max Temp Rise , C**	**Organ mass, kg steady**	**MiVf-steady (Note 3)**	**$\dot{q}_{k,m}$ (W/kg organ mass)-steady**	**Energy release rate/ volume W /cm^3 of Mito (Note 1)**
AT	-	14.620 (-)	-	0.22	-
Brain	3.174 (0.425)	2.382 (0.319)	0.0377 (0.0377)	11.62 (11.63)	3.481 (3.482)
Heart	0.486 (0.578)	0.461 (0.461)	0.283 (0.283)	21.13 (25.33)	0.870 (1.034)
Kidney	0.062 (0.099)	0.207 (0.303)	0.204 (0.204)	21.31 (23.44)	1.194 (1.314)

Table 6 Continued: Selected Quantitative Results for Steady State (84 Kg Person) and Over Life Span for Five Organ (in Parenthesis) and Seven Organ Data; Metabolic Efficiency Set to Zero to Get Maximum Possible Values

Organ	**Max Temp Rise , C**	**Organ mass, kg steady**	**MiVf-steady (Note 3)**	**$\dot{q}_{k,m}$ (W/kg organ mass)-steady**	**Energy release rate/ volume W /cm^3 of Mito (Note 1)**
Liver	0.400 (0.590)	1.092 (1.558)	0.155 (0.155)	9.69 (10.01)	0.725 (0.749)
Residual Mass	-	26.617 (82.45)	-	0.63 (0.68)	-
Skeletal Muscle	0.308 (-)	37.608 (-)	0.055 (0.0)	0.58 (0.58)	0.133 (-)
Sum		82.99 (85.09) (note 1)			

Table 6 Continued: Selected Quantitative Results for Steady State (84 Kg Person) and Over Life Span for Five Organ (in Parenthesis) and Seven Organ Data; Metabolic Efficiency Set to Zero to Get Maximum Possible Values

Organ	**Normalized Energy Release Rate W/ cm^3 of Mito in k/W per cm^3 of heart**	**$\dot{q}_k$ (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**
AT		3.216 (NA)	86.4 (NA)	191.8 (NA)	1.14 (-)
Brain	4.002 (3.368)	27.680 (3.71)	825.8 (113.5)	1832.8 (252.0)	60.32 (62.25)
Heart	1 (1)	9.829 (7.09)	274.8 (335.6)	609.9 (744.8)	110.6 (135.00)
Kidney	1.373 (1.271)	4.406 (7.09)	131.4 (208.2)	291.7 (462.1)	110.6 (123.79)
Liver	0.834 (0.724)	10.578 (15.60)	316.4 (480.4)	702.3 (1066.2)	50.30 (55.37)
Residual Mass	- (-)	15.438 (56.17)	430.4 (1620.6)	955.2 (3596.9)	3.01 (3673.4)
Skeletal Muscle	0.153 (-)	23.693 (56.17)	661.1 (NA)	1467.3 (NA)	3.27 (-)
Sum		94.8 (94.2)	2726.5 (2758.4)	6051.0 (6121.9)	

Note 1: assumed n=1.75E+08 cells/cm^3

Note 2: Average cell volume $V_{avg.\ cell}$ = 1000 μm^3 = 1*E-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: MIV_f is under estimated since it is body mass based and body mass is 84 kg

The interstitial fluid (IF) will be hotter near the venous end. The increased temperature of cells cause rapid increase in ROS since ROS production rate is proportional to $[O_2]\, e^{\{-E/(RT)\}}$, which is called Arrhenius law in combustion science where E, activation energy and $[O_2]$, oxygen concentration in mole/cm^3 assuming first order reaction. Recall that ROS damages the normal cells and hence faster the ROS rate, more the degree of damage to cells. When metabolic rate per kg organ is higher, the ROS production is also higher and higher cell temperature occurs when higher amount of heat (Q) (i.e. lower metabolic efficiency) needs to be transferred {e.g. protein oxidation).

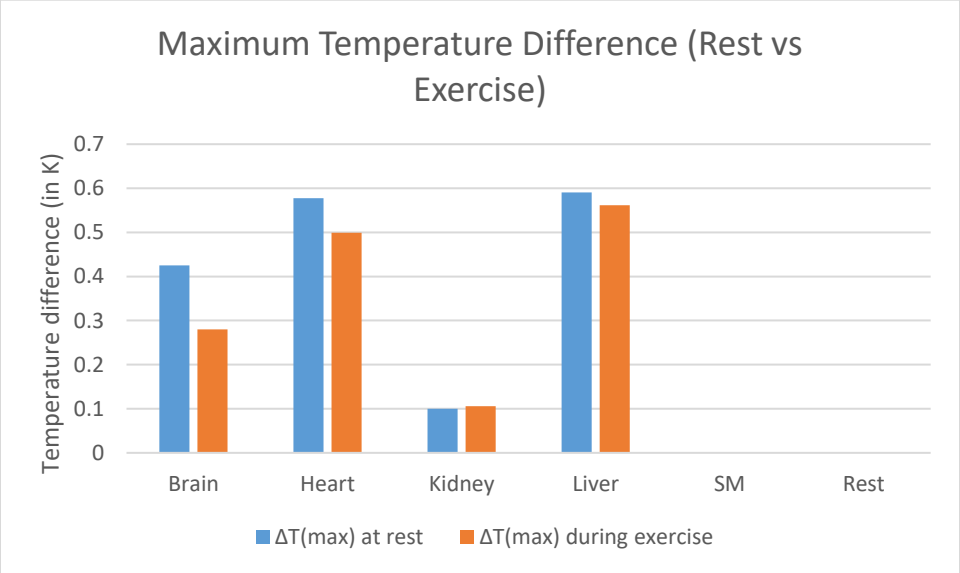

Figure 10: Maximum Temperature Difference (Rest vs Exercise)

Since there is increased blood flow, the current model which uses allometric constants presented for BMR where not all capillaries are open at rest and hence blood temperature decreases; preliminary data on temperature during exercise will be presented later after accounting for increase in open % capillaries.

5. 5 Average Respiratory Quotient (RQ) and Average Metabolic Efficiency

If mass % intake nutrients are known for CH:F:P, then for 55%:30%:15%.(mass%) which converts to 55.7, 21.3, 23.0 % on mole basis if M=180.12, 256.5, 119.3 kg/kmol and energy % 36:50:14 if heating values are 15573, 39110, 22790 J/g for CH, F and P. The molecular weight of mixture is 183 g/mol. The RQ for mixture is given as

$$RQ_{mix} = Mole\ fr.\ CH * RQ_{CH} + Mole\ fr._{F} * RQ_{F} + Mole\ fr.\ P * RQ_{P} \quad (76)$$

With RQ_{CH}=1, RQ_F=0.696, RQ_P=0.801 (N and S in protein un-oxidized) and RQ=0.82 for 55:30:15 (mass %) mixture with all proteins oxidized.

The mass fractions of nutrient; CH, F and P recommended by Scheett et al [40], is assumed to be CH: F: P = 55:30:15 (AMDR/RI) [41] {energy % 36:50:14}; converting on mole basis, one can obtain respiratory Quotient (ratio of moles of CO_2 to O_2) of 0.83 under basal condition. Converting on energy basis, this ratio of nutrients yields an overall mixture metabolic efficiency of 31.3% [6] assuming all proteins are oxidized. Neglecting proteins, η_{Met} = 0.35.

5. 6 Results Based on Whole Organ

Nutrients and Metabolic Efficiency

Silva et al studied the effects of diet composition on life span entropy generation using recommended AMDR/RI fir birth to death; the CH average is about 55%, Fat : 18-30 % (except baby< 6 months old) and Protein: 12-22 % (except baby< 6 months old). Typically urea excretion is used to estimate the g of P oxidized with assumption that each g of N released as urea 6.25 g of P oxidized [30]. Since protein is mostly used for repairing/replacing muscle fibers, only a part of protein intake is oxidized. Typically 10-12 % of REE is from protein oxidation and rest of 88-90 % is from CH and Fat for whole body. Since HHV_{O2} is roughly constant, the energy release rate provides information on O_2 consumed. Hence O_2 used must be 88-90 % by CH and F and about 10-12 % is from P. Hence dominant contribution to REE is from F and CH. [13]

Recall from Eq.(24) that the composition of diet affects the overall metabolic efficiency and hence entropy generated. The effects of nutrients are reflected in this model of entropy calculations through the metabolic efficiency at parameter (η_n). If % energy contributed by CH, F and P = 36.1:49.5:14.4 (energy %) for 55:30:15 (mass %) diet, then metabolic efficiency (energy weighted) = 0.361* 38.2+ 0.495*32.2+0.144*0.104 = 0.31.

The metabolic efficiency varies from organs to organs depending on % fat oxidized since fat has lower metabolic efficiency (32.2 %) compared to CH (38.2%). Some animals like grizzly bears depend mostly on fat [42].

When allometric laws are used at organ level, the information available is only for energy release rate and % oxidized for CH, F and P are typically unknown. Hence

allometric laws are used for energy release rate. However recent literature reports the nutrients consumption by different mouse organs as: Brain : CH 100 % (% based on energy delivered, met eff = 38.2%), Heart : CH:F: 30 %:70 %; SM: 37 %: 63 %; AT: 31%:61% [24]. Corresponding mass % are: CH for B 100 %. CH:F for H 52:0.48, SM 0.60:0.40, AT 53:47. Thus, if metabolic efficiencies are used for each component, then $\eta_{Met,\,B}$= 0.38, $\eta_{Met,\,H}$= 0.34; $\eta_{Met,\,AT}$= 0.34, $\eta_{Met,\,SM}$= 0.34 similarly RQ_B= 1.0, RQ_H= 0.78, RQ_{AT}= 10.79, RQ_{SM}= 0.80. Thus it is seen that metabolic efficiencies for most organs are 0.34 with brain being an exception with $\eta_{Met,\,B}$= 0.38.

A few references cite that almost 1/3 of energy needs is met by triacylglycerol's in diet. Particularly heart and liver release about 80% of energy from the oxidation of fatty acids [14]. Thus parametric studies are conducted for metabolic efficiencies of 0.31, 0.32 (pure fat), 0.35 and 0.38 (pure CH) in estimating organ stresses.

A) Pure CH

Figure 11 presents present entropy stress graph for pure CH and pure F for 84 kg male person {steady mass UK data}. It is seen that the pure CH has lowest lifetime entropy generation as less Q liberated.

B) Mixture of CH and F

Figure 11 presents the effect of mixtures of CH and F {energy fractions; 55 %, 45 %} on organ stress assuming all organs have same proportions of energy release for 84 kg person.

Reduced metabolic efficiency results in higher amount of heat Q along with higher temperature rise of venous blood [6] and hence higher entropy generation.

C) Mixture CH, F and P

Figure 11 presents the effect of mixtures of CH, F and P {energy fractions; 55%:30%:15%} on organ stress. As P has lower metabolic efficiency than CH and P, the lifetime entropy generation of this diet is the highest.

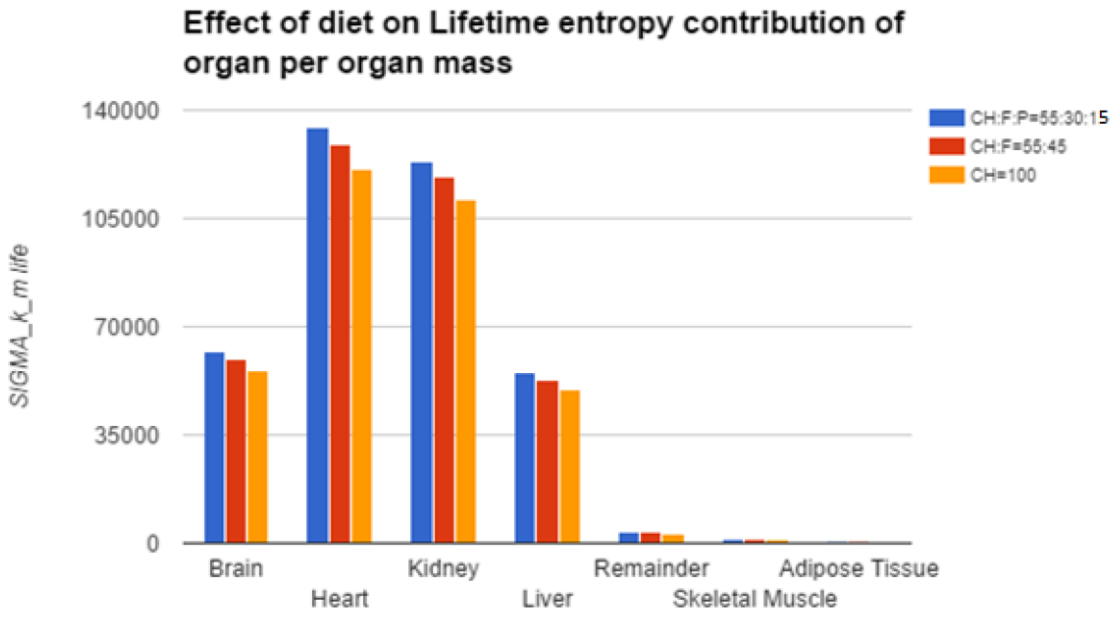

Figure 11: Lifespan Entropy Stress of Organ MJ/K Per Kg Organ Mass for Seven Organ Data, CH:F:P= 55:30:15, RQ= 0.82, Metabolic Efficiency = 0.382 for Pure CH, 0.312 for CH:F:P = 55:30:15, Metabolic Efficiency= 0.3184. Entropy Stress is Lower with Pure CH Since Less Q is Liberated

It can be inferred from Figure 11 that the lower metabolic efficiency of 55:30:15 diet compared to pure CH results in the highest Q, entropy generation rate (or ROS rate), and lifetime entropy generation at given life span. When compared to Figure 5 where pure glucose is consumed over life time with high metabolic efficiency (η_{Met} = 0.38) and hence high ATP production accompanied by lesser heat release ($\dot{Q}$) and hence lesser cell temperature rise and lesser entropy generation rate per gram of tissue, the low metabolic efficiency of this mixture (η_{Met} =0.313) and hence entropy generated is higher compared to pure glucose.

Life Time Entropy Stress

Recall that body mass is a function of age and metabolic rate increases with increase in body mass and reaches a stead value when body mass reached steady value. Eq. (53) presents a relation growth correction factor F to metabolic rate under constant body mass. Figure shows the results for growth correction factor, F which is function of age at which one reaches steady weight; GCF=1 if mass of body remains constant (p=0) irrespective of age which is unrealistic.

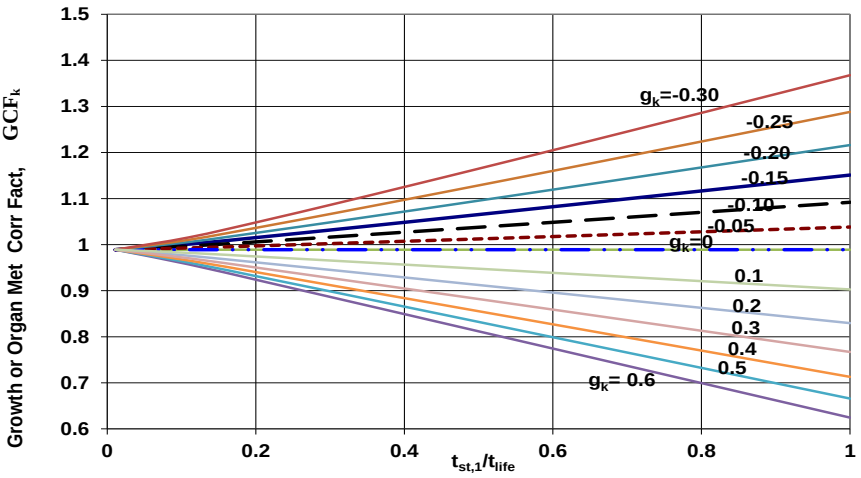

Figure 12: Effect of Body Mass Growth. Growth Correction Factor GCF_k. For Period I, $m_B(t) = m_{B,st}\,(\frac{t}{t_{st}})^z$ and Period II, $m_B(t) = m_{B,st}$ a, z=0.g_k=0

Note 1: For life time specific organ energy release or entropy generated: $g_k = z\,f_k$ specific organ allometry (non-isometric, $f_k \neq 0$) 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 SMRK {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, $m_B(t) = m_{B,st}\,(\frac{t}{t_{st}})^z$ and period II, $m_B(t) = m_{B,st}$ a, z=0.g_k=0.

Note 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 $f_k=0$.

Note 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}.

Note 4: $gk=z\{f_k-q_k\}$ for lifetime energy release and lifetime entropy contribution by organ k per cm^3 of mitochondria.

The value of $f_k = 0$ in Figure 10 implies that the specific metabolic rate of each organ (SMR_k, W/kg of k) remains constant and hence specific entropy generation rate ($\propto$ heat part of organ metabolism) irrespective of organ size {Elia's results}, body mass and age. Thus energy release rate per cell is invariant if number of cells of type k per unit mass of

organ k remains fixed from birth to death. The growth correction factor is unity. f_k=0 for all organs. For the cases considered with z= 0.75, t_{st}= 24 yrs, t_{life} = 75 years and the range of values for f_k {-0.08 to -0.468} , d_k { 0.76 to 1.19} and q_k { -0.14 to 0}, GCF varied from 0.87nto 1.12. In order to get a first estimate on life span parameters of interest, one may assume GCF =1 as a first approximation.

Effects of Adipose Tissue and Skeletal Muscles on Whole Body Entropy Generation Rate

Normal Human: For a normal human, the inclusion of AT and SM of normal human has negligible effects on over all energy release or entropy generation of whole body over lifetime; the mass of SM is almost 50-55 % of adipose or fat free mass [20]. The column 8 Table 6 lists the REE_k of each organ k and the total value of REE (= ΣREE_k,) is calculated to be 94 W for 84 kg body mass or 1.12 W per kg body mass under steady body mass conditions. This is in agreement with the Resting Energy Expenditure (REE) per unit mass value of 1.2 W/kg body mass obtained from literature [7]. The mass of organ k are tabulated in Column 3. The lifespan metabolic energy contribution by each organ k to each kg body mass (MJ by organ k to unit body mass), entropy contribution by each organ k to unit mass of body (kJ/K by organ k to unit body mass), and specific life span entropy generation rate by each organ k (kJ/K from k per unit organ mass) are shown in columns 9, 10 and 11 of Table 6. The last column shows the heart normalized entropy stress of organs. Inclusion of AT and SM did not affect whole body values significantly since they are low metabolically active organs.

Athletes: Both AT and SM may play major role for athletes if total exercise period forms significant % of life span since exercise increases metabolic rate by almost 300 % . Further there is an average increase of 20 % in BMR or next 14 hrs.

Five Organs vs Seven Organ Models

Wang's Five Organ Model: include BHKL and R along with body mass dependent SMT_k. The Wang 7- Elia Mod includes 7 organs AT BHKL R SM. The allometric coefficients are given in Table 4. The bar graphs in Figure 13 presents the life time specific entropy generated by each organ (MJ/K kg of organ k) for both Wang-5 and Wang 7 models. Figure 15 shows heart normalized entropy tress {entropy stress of organ k/entropy stress of heart}. The heart is the most entropy stressed organ while AT and SM are least stressed. **Figure 14** shows the contribution of the life time entropy generated by all organs to each unit body mass. Note that contribution of heart is much lesser compared to that of SM since mass of SM is very large compared to heart.

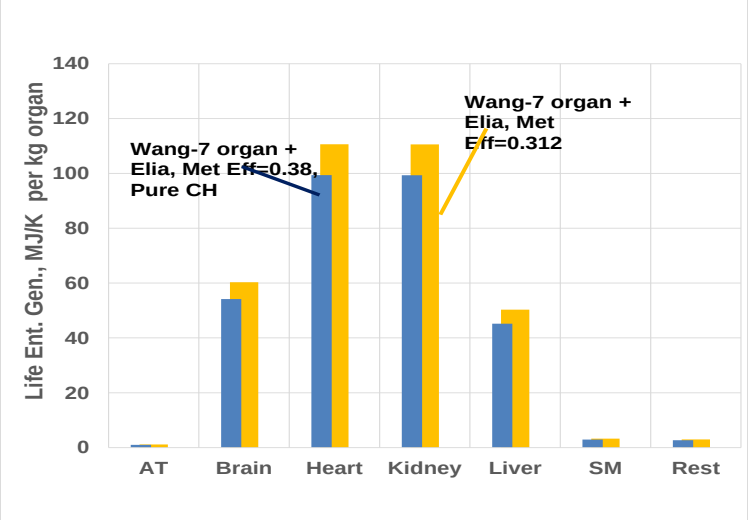

Figure 13: Lifespan Entropy of Organs in MJ/K Per Kg of Organ k

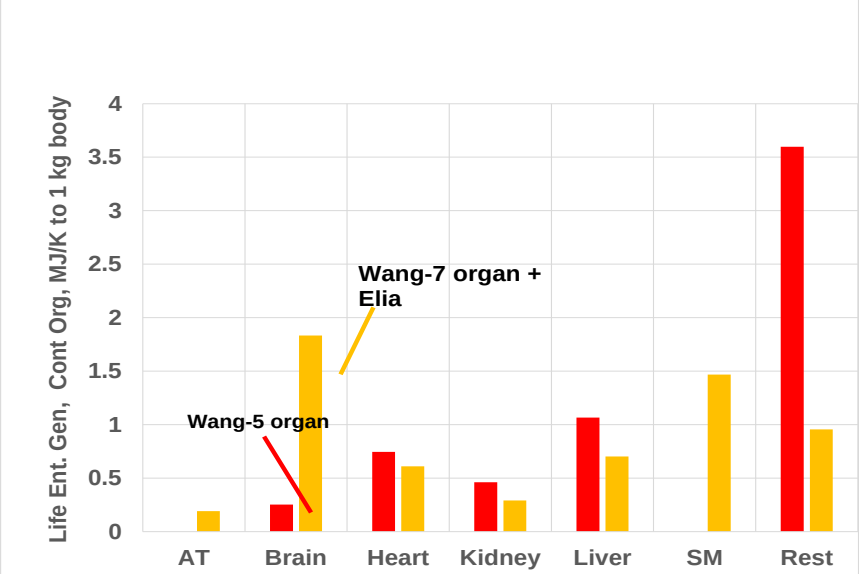

Figure 14: Entropy Stress – Heart Normalized Under Steady Body Mass: Five Organ vs Seven Organ ; Seven Organ Shows Almost Equal Stress Due to Assumption of Equal SMR_k for Heart and Kidney CH:F:P= 55:30:15, RQ= 0.82, Metabolic Efficiency = 0.312,m_{st}= 84 Kg Human

Note 1: total mass is not equal to the specified body mass of 84 kg due to use of allometry for the residual mass.

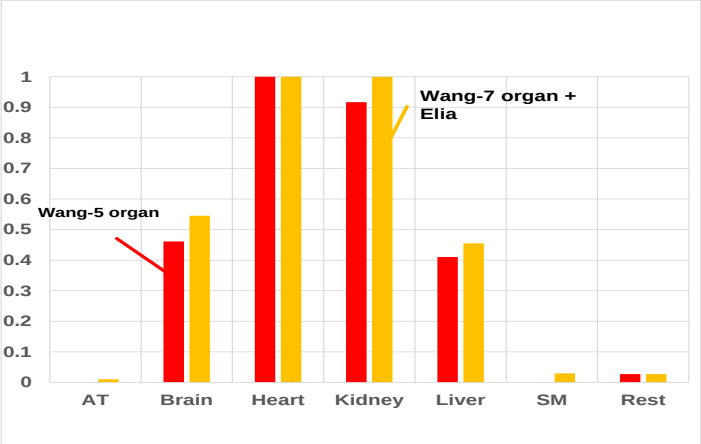

Figure 15: Lifespan Entropy Contribution by Organs MJ/K to 1 Kg Body Mass or kJ/K to 1 Kg Body Mass. The Seven Organ Data Has High Brain Mass (2.4 kg) vs Brain Mass of 0.32 Kg for Five Organ Data. Thus Results Seem Revised; CH:F:P= 55:30:15, RQ= 0.82, Metabolic Efficiency = 0.312, m_{st}= 84 Kg. Most Stressed Organ for Both Five and Seven Organ Data, CH:F:P= 55:30:15, RQ= 0.82, Metabolic Efficiency = 0.312, 84 kg

Thus cells with higher metabolic rate per unit mass (e.g. heart) leads to faster aging of organs since they contribute more heat (J/kg of organ k which is proportional to temperature rise. Vital organs account for 4-6 % body mass but account for metabolic rate 15-40 times that of equivalent SM and 5-100 times that of equivalent AT [27] indicating that vital organs age much faster compared to other organs.

5. 7 Results Based on Mitochondrial Volume

In order to compare the organ metabolic loading vs mitochondrial metabolic rate, data on mitochondrion volume fraction (MiV) was collected for various organs. The MiV is defined as ratio of volume of mitochondrion to volume of cell volume. Typically higher is MiV, higher is metabolic rate per cell. The MiV% in each cell [31] and specific metabolic rate of various organs are determined through the allometric

relations in terms of body mass. Column #4 and #5 tabulates the MiV% and $\dot{q}''_{k,V}$ respectively using allometric constants.

SMR_k Variation with Mitochondria Volume

Typically metabolism is modeled using Michaelis 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 remain constant in most organs. It is the basis of Krogh cylinder model used for metabolism of several organs [15].

Typical density of organ is of the order of 1 kg/L and as such the rate per L is approximately same rate per kg of organ. A plot on the mitochondrial volume fraction (column #4) vs SMR (energy release rate per unit mass of all organs) is shown in Figure 16 for both Wang 5 and Wang-7-Elia (mod) data. Note that Elia's SMR_k is body mass independent but depends on type of organ, its enzyme and mitochondrial volume fraction.

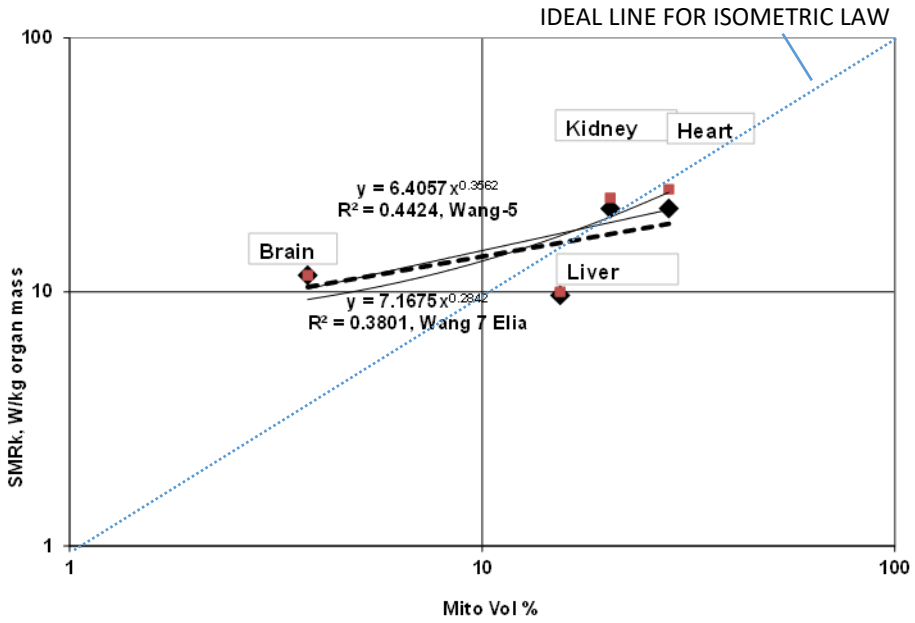

Figure 16: Relation Between Mitochondrial Volume % (MiV*100) and Specific Metabolic Release Rate for Humans-84 Kg Person; Simplified Analysis and Kinetics Controlled Metabolic Rate Indicates Linear Dependency of SMR_k on Mitochondrial Volume %.

If SMR increases in proportion to mito vol % then slope =1; but slope <1; thus metabolic rate per unit volume decreases with increase in mito vol% as shown in Figure 16. It is seen that higher the mitochondrial volume % in organ higher the specific metabolic rate organ (W per kg of organ), however not in direct proportion, possibly due to organ dependent enzyme activities. A least square straight line fit for vital organs only yields the slope as 0.284 for Wang 7 Elia (mod) and 0.352 with Wang 5, although both

indicating positive slopes. Liver seems to deviate the most from the straight line fit for both Wang-5 and Wang-7 Elia (mod) data.

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

In order to investigate i) whether $SMR_{k,Mito\ vol}$ is same for all organs, ii) why the deviation occurs for liver, and iii) whether re-activities of mitochondrion expressed in W/cm^3 of Mito same for all organs and iv) to estimate the degree of damage to DNA within mitochondria (based on $SMR_{k,Mito\ vol}$, the metabolic rate per unit volume of mitochondria within an organ k is required. Hence, allometric laws given for SMR_k and MiV fraction given in terms of body mass are converted into allometric law of SMR_k in terms of MiV fraction. Appendix A shows the derivation:

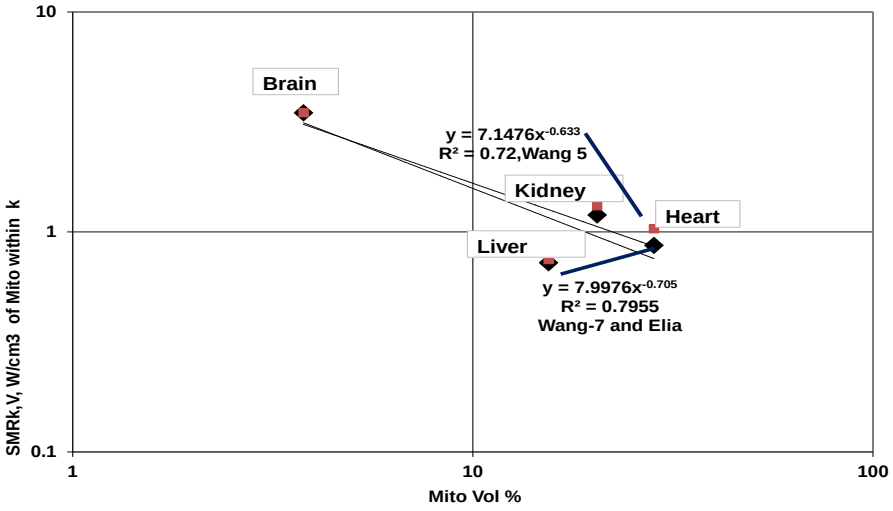

Figure 17: $SMR_{k,V,Mito}$, vs Mitochondrial Volume %. It Decreases with Increased Mitochondrial Volume % Possibly Due to Diffusion Limitations.

Recall the following equation from Section 4

$$i_{k,V} = \frac{Watts}{cm^3 mito\ k} = T_B \dot{\sigma}_{k,V} \approx \frac{\dot{q}_{k,m}}{\rho_k} \frac{1}{MiV_k} (1 - \eta_{Met,avg})_k$$

Since average MiV_k for whole organ = Cell Mito volume fraction *{cell volume per kg organ} /ρ_k ≈ Cell Mito volume fraction if IF volume in 1 kg mass<<<{cell volume per kg organ}

$$SMR_k \left(\frac{W}{kg\ of\ k}\right) = \dot{q_{k,m}} = B_k (Miv_{k,Mito})^{O_k}, where\ B_k = \frac{e_k}{{p_k}^{F_k}}, O_k = \frac{f_k}{q_k}$$

(73)

$$SMR_k \left(\frac{W}{kg\ of\ k}\right) = SMR_{k,V,Mito} \left(\frac{W}{cm^3 of\ Mito\ in\ k}\right) * vf_{k,Mito} \left(\frac{cm^3 of\ Mito\ in\ k}{cm^3 of\ cells\ within\ k}\right) *$$

$$n_k \left(\frac{no.of\ cells\ within\ organ\ k}{cm^3 of\ k}\right) * \frac{1}{\rho_k} \left(\frac{cm^3 of\ k}{g\ of\ k}\right) \quad (75)$$

Solving for $SMR_{k,V,Mito}$

$$SMR_{k,V,Mito} \left(\frac{W}{cm^3 of\ Mito\ in\ k}\right) = \frac{\rho_k * SMR_k}{vf_{k,Mito} * n_k} \quad (76)$$

Using allometry for SMR_k in terms of Mito Volume fraction (Eq. 76)

$$SMR_{k,V,Mito} \left(\frac{W}{cm^3 of\ Mito\ in\ k}\right) = \frac{\rho_k}{n_k} B_k (vf_{k,Mito})^{O_k - 1} \quad (77)$$

The mitochondrial volume % BHKL organs are obtained as 3.8, 28.3, 20.4, and 15.5 % with highest % for heart and lowest for brain. Whether one use 7 organ or 5 organ data, the mito-volume % are same since it is a function of body mass only. Assuming n_k= 1.75x108 cells/cm^3, and density given in Table 5 for vital organs $SMR_{k,V,Mito}$ were obtained and plotted as shown in Figure 16, which plots $SMR_{k,V,Mito}$ vs Mitochondrial volume % based on Eq. (80). While the plots in Figure 16 show that SMRK increases

with the mitochondrial volume % in organ, the plots in Figure 17 show that $SMR_{K,v,Mito}$ shows decreasing rate with increase in MiV %. The power law fit yields the slope as -0.633 for Wang 5 data, and -0.705 for Wang-7 data:

$$SMR_k\left(\frac{W}{kg\ of\ k}\right) \propto {vf_{k,Mito}}^{-0.633+1} \propto {vf_{k,Mito}}^{0.367}, Wang-5\ data$$

$$SMR_k\left(\frac{W}{kg\ of\ k}\right) \propto {vf_{k,Mito}}^{-0.705+1} \propto {vf_{k,Mito}}^{0.295}, Wang-7\ and\ Elia\ data$$

The slopes in the fits indicates that either the $SMR_{K,v}$ is not kinetic controlled or enzyme reactivity's are different for different organs. If one compares these results to carbon combustion in engineering literature, diffusion control is a strong possibility particularly when mitochondrial volume is increased. As MiV % increased, consumption rate of O2 increases (Watts) which require faster diffusion rate from capillaries to the cells.

From Figure 17, it as shown that liver has large deviation from the fit. It has been shown in earlier literature that SMR_k is low due to problems with oxygen accessibility [4] since capillary 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 [7]; 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 with increasing size of organ [15]. To summarize, the SMR is not only affected by mitochondrion volume %, but also by transport rate of O_2 and oxygen accessibility to all cells. It is also affected by enzyme reactivity within mitochondrion of cell [51].

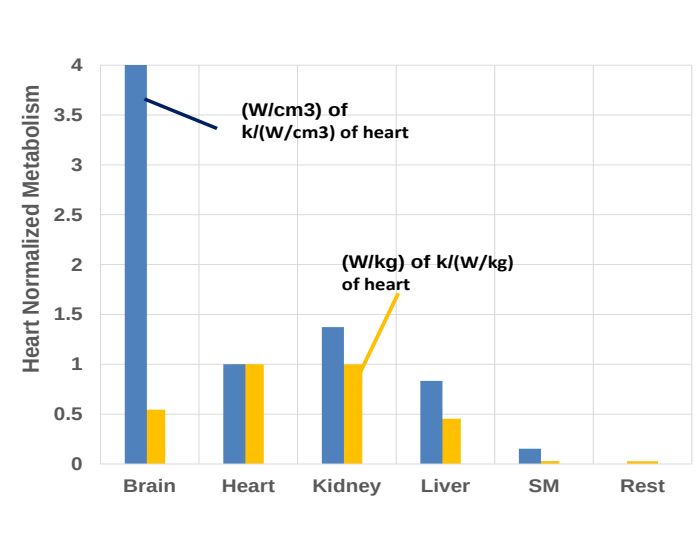

Figure 18: Vital Organ Stress Based on Whole Organ and Based on Mitochondrial Stress of Each Organ (W/cm^3 of Mito) , 84 Kg Person

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

$$\frac{\dot{q}'''_{Mito,k}(t)}{\dot{q}'''_{Mito,H}(t)} = \frac{\rho_k}{\rho_H}\frac{e_k p_H}{p_k}\, m_B{}^{q_H - q_k}, \quad relative\ MtDNA dmage$$

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

In other words, the energy release rate per unit volume of organ is not directly related to MiV as seen in Figure 16.

F_k varies from 0.57 to 2.08, however so does relative enzyme reactivity within a cell. While the heart contains highest MiV, and highest energy release rate per organ volume, the highest energy release per MiV occurs in brain. When entropy stress concept is used, the entropy stress based on MiV (W/K cm^3 of Mito) is different compared to entropy stress based on organ mass.

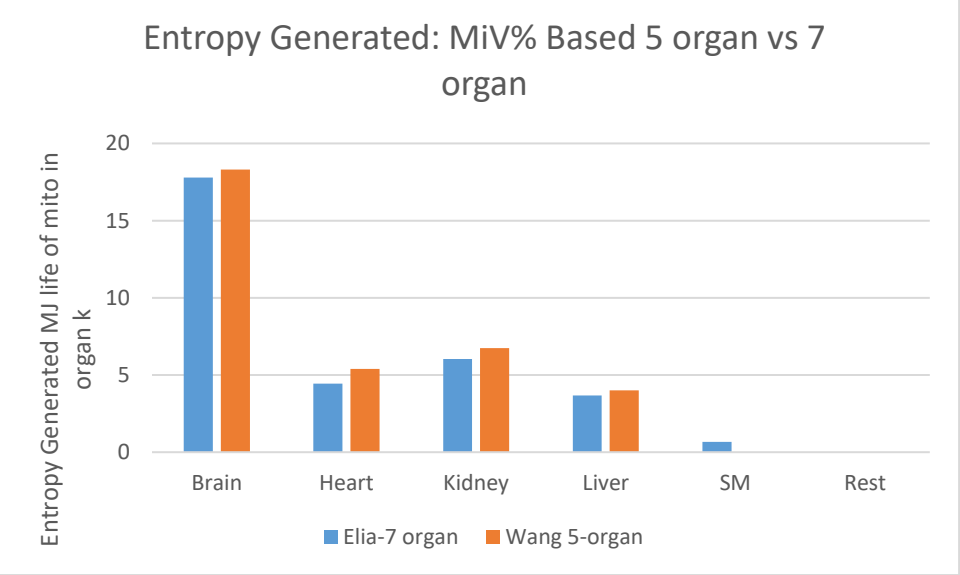

Figure 19: Entropy Generated: MiV% Based on Five Organ vs Seven Organ Models

Athletes and Effects of Partial Opening of Capillaries

(Modeling equations provided in Section 4.2)

Almost 25 % of capillaries are open at rest; thus not all cells are serviced at rest. Under exercise, most capillaries open up increasing the metabolic rate of organ. Dividing organ into open and closed regions, there is energy release from open region in ATP production (W) and heat (Q) in open region; however there is heat loss from closed regions in addition to open region. Hence metabolic rate in open region must be such that it is equal to a sum of heat loss and ATP production in open region.

It was assumed that the closed region does not require ATP for death and repair of cells in closed region. If blood flow rate through open regime remains the same whether capillaries are closed or not, the O2 dependent Krogh model will reveal same metabolic rate per unit volume. However increased amount per unit volume is required to overcome heat loss from cells of closed region which require more transfer rate of O2 at rest {where only 25 % is open} which can be achieved by increasing blood flow rate slightly through open capillaries to deliver more oxygen . In other words ratio of blood flow rates during rest and exercise may not be proportional to fraction of capillaries open!

Figure 20 shows the effects on average specific metabolic rate and specific heat loss rate, while Figure 21 shows the effects on average specific metabolic rate and ATP production rate.

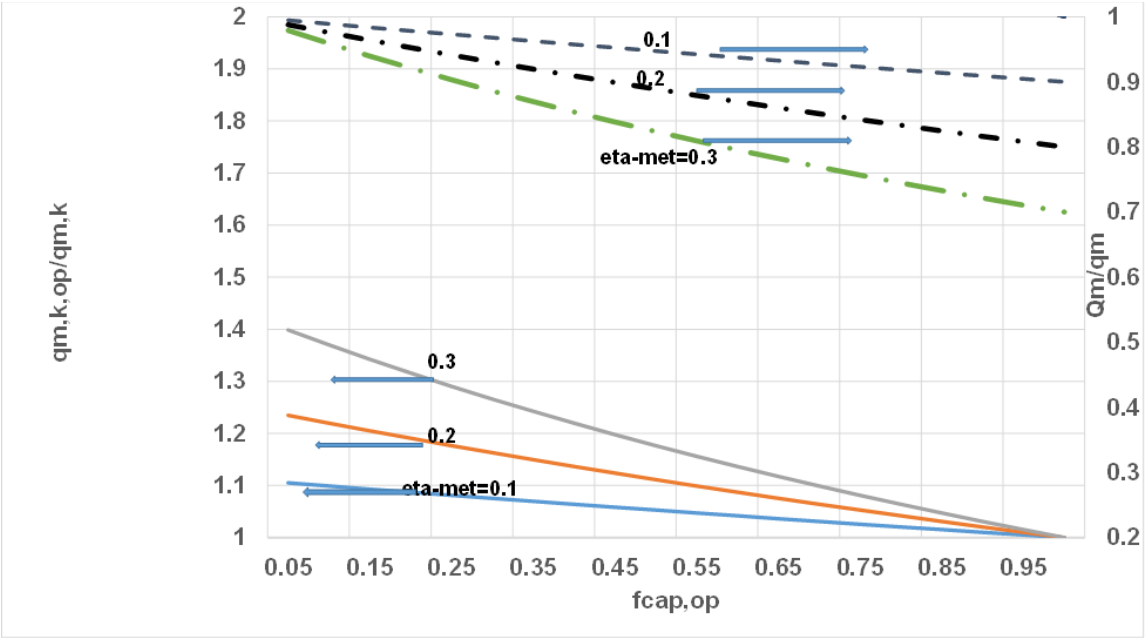

Figure 20: Effects on Dimensionless Average Specific Metabolic Rate and Specific Heat Loss Rate

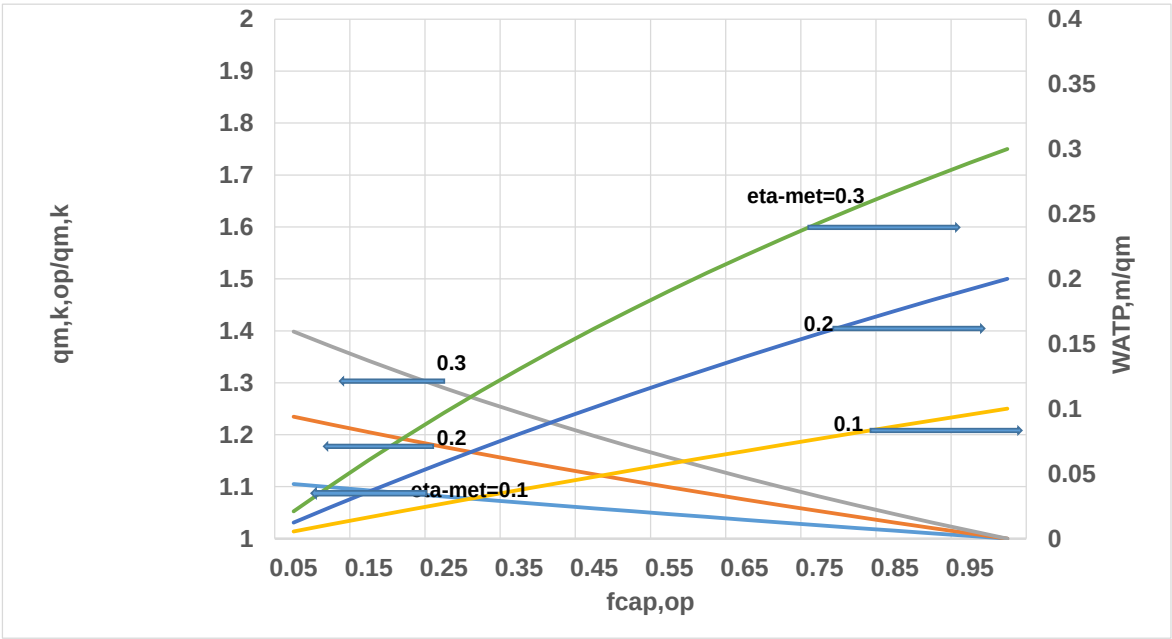

Figure 21: Effects on Dimensionless Average Specific Metabolic Rate and ATP Production Rate

5. 8 Significance, Application to Medical Field and Biological Aging

How could these results be used in the Medical Field? A procedure is given below for monitoring the biomarkers {q_M (t){ kJ or Calories of energy release per kg mass of body} vs age (t) , σ_M (t) { kJ /(K per kg mass of body)} vs age (t). If not a medical questionnaire may be prepared, which is useful in estimating the BA rather than CA. Here step by step procedure is provided (numbers in parenthesis{ } for a human of 84 kg ($m_{B,\,st}$) with 5 organ model)

1. Assume as though the person has constant body mass or steady mass {84 kg}. Estimate k-th organ mass using allometric relation $m_k = c_k\ m_{B,st}{}^{d_k}$ and known c_k,and d_k (Table 4) ; {thus for heart, k=H, $m_{H,st}$= 0.48 kg)
2. Estimate metabolic rate per unit mass of organ k during steady body mass period

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

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

$$\dot{q}_{k,m,st} = \dot{q}_{k,m,st} * t_{life} \text{ where } t_{life} \text{ in } s = 75\ yrs * 3.15 * x10^7\ \frac{s}{yr} = 2.37x10^9\ s$$

$$q_{k,m,st,life} = 25.3\ \frac{W}{kg\ heart} * 2.37x10^9\ s * \frac{1\ GJ}{10^9\ J} = \frac{60\ GJ}{kg\ heart}$$

4. If $SERR_k$ and metabolic efficiency within that organ are constant over whole life, then amount of steady heat rate,

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

5. Multiplying t_{life} { $= 2.37 \text{x} 10^9$ s over 75 years} one get GJ of heat per kg of heart over life span as

$$Q_{k,m,st,life} = 17.5 \frac{\text{W}}{\text{kg heart}} * 2.37 \text{x} 10^9 \text{ s} * \frac{1 \text{ GJ}}{10^9 \text{ J}} = \frac{41.5 \text{ GJ}}{\text{kg heart}}$$

6. Estimate entropy generation rate from organ k as

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

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

7. Multiplying t_{life} { $= 2.37 \text{x} 10^9$ s over 75 years} one get entropy generation by unit mass of organ H in KJ of heat per kg of heart per K as

$$\sigma_{H,m,st} = \dot{\sigma}_{H,m,st} * t_{life}$$

$$= 0.0565 \frac{W}{kg \; heart \; K} * 2.37 * 10^9 s * \frac{1MJ}{10^6 J} or \frac{41.5 \; GJ}{310K \; kg \; heart}$$

$$* \frac{1000 \; MJ}{GJ} = \frac{134MJ}{kg \; heart \; K}$$

Now repeat procedure for contribution by each organ to unit mass of body over life span

8. Estimate the contribution rate by the heart 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,

$\dot{q}_{k,M,st} = \frac{25.3W * 0.48 \; kg \; heat}{84 \; kg} = 0.145 \; W$ contribution 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

$\dot{q}_{k,M,st,life} = 0.145 \frac{W}{kg\ body\ mass} * 2.37 * 10^9 s * \frac{1GJ}{10^9 J} = 0.35GJ$ by heart over life span to unit body mass.

Heat part of above is

$\dot{q}_{H,M,st,life} = 0.35 \frac{GJ}{kg\ body\ mass} * (1 - 0.31) = 0.24GJ$ of heat by heart over life span to unit body mass.

Life time entropy generation can be given as

$$\dot{\sigma}_{\mathrm{H,m,st}} = \frac{0.24\ \mathrm{GJ}}{\mathrm{kg\ body\ mass} * 310\ \mathrm{K}} \frac{10^3 \mathrm{MJ}}{\mathrm{GJ}} = 0.78 \frac{\mathrm{MJ}}{\mathrm{kg\ body\ mass\ K}}$$

9. 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. But for Wang 5 Wang SERRK model, the $SERR_k$ changes with age since body mass does not remains constant from birth to death and as such growth correction factors (GCF) are necessary. However 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 growth correction factor (GCF) are necessary when contribution to unit body mass is required for both Elia and Wang 5 Wang $SERR_k$ model. Thus use charts.

6. CONCLUSIONS AND FUTURE WORK

The inclusion of entropy generation for adipose tissue and skeletal muscle has minimal effect on whole body entropy generation rate. Increased % of glucose diet seems to increase life span while increased protein % shortens life span. The increased mitochondrial density within the cell seems to increase the specific energy release rate per unit volume of organ (SER_V); but the increase rate of SER_V is not necessarily in proportion to increase in MiV. Based on metabolic loading per unit volume of mitochondria, the ranking differs from ranking based on organ or cell level. Brain has the highest loading at mitochondrial level and liver has the lowest loading amongst all vital organs. Particularly athletes with constant concussions may be subject to more brain anomalies near the end of their lifetimes

1. Results for the entropy generation for adipose tissue and skeletal muscle are included. It has only minimal effect of total specific entropy generation.
2. Results for the effect of composition of diet (CH:F:P %) on lifetime specific entropy contribution of each organ to total entropy generation of whole body are given. The increased % of glucose in diet decreases lifetime entropy generation through improved metabolic efficiency and hence life span is increased.
3. In general the increased volume % of mitochondria within cell seems to increase the specific energy release rate per unit volume of organ. However, the degree of increase in metabolic rate of each organ is not in proportion to increase in vol % . While heart has the highest energy release rate per unit volume of heart, the brain has the highest energy release rate per unit volume of mitochondria.

4. The ATP or higher metabolic efficiency was shown to slow the process of aging [19] which seems to suggest the ability of ATP to restore/repair the damaged cell or create new cells with full functional characteristics. While ATP is the “c The ATP or higher metabolic efficiency was shown to slow the process of aging [19] which seems to suggest the ability of ATP to restore/repair the damaged cell or create new cells with full functional characteristics. While ATP is the “creator” of cell” (synthesis) supplying energy to make the cell through oxidation, it also serves as the “destroyer” (decomposition) of cells through generation of ROS.
5. In authors opinion and recent size dependent cloud combustion engineering analogy to vital organs of various sizes which explains negative exponent of SMR of organs , the metabolic rate per kg of vital organ must increase for smaller species and hence 5 organ SMR is close to engineering results.
6. Presented possible biomarkers for estimating biological aging of species using either specific energy release rate from vital organs and/or entropy generation rate vs chronological years aging whether the upper limit is reached rapidly or slowly.
7. Derive allometric laws for athletes, taking into consideration exercise period and changes in food intake.
8. Model assumes oxygen is available for complete metabolism and biogenesis, however oxygen deficit metabolism may cause changes to model. Studying effects of oxygen deficit metabolism should also be considered in future models, as it has been linked to the creation of cancer cells.

9. Study the effects of concussion for athletes in more detail, and relate it to the entropy stress model.

REFERENCES

1. Pinker S. *The Second Law of Thermodynamics, Life History: Why Things Fall Apart. The Wall Street Journal*. Dec. 31, 2016 - Jan. 1, 2017 | C1.

2. Balmer R. *Modern Engineering Thermodynamics.* Academic Press, Burlington, MA, USA. 2011. Doi: 10.1016/B978-0-12-374996-3.00017-8.

3. Wang Z, Zhang J, Ying Z, Heymsfield S. *Organ-Tissue Level Model of Resting Energy Expenditure Across Mammals: New Insights into Kleiber's law*. ISRN Zoology 2012. 673050.

4. Singer D. *Size Relationship of Metabolic Rate: Oxygen Availability as the "Missing Link" Between Structure and Function*. Thermochimica Acta. July 2006. Doi: 10.1016/j.tca.

5. Elia M, Kinney JM, Tucker HN. *Energy metabolism: tissue determinants and cellular corollaries.* New York, NY: Raven Press, Ltd, 1992:61-79.

6. Silva CA, Annamalai K. *Entropy generation and human aging: lifespan entropy effect of diet composition and caloric restriction diets*. J. Thermodynamics. 2009. 18673. Doi: 10.1155/2009/186723.

7. Annamalai K, Puri I, Jog M. *Advanced Thermodynamics Engineering. 2nd ed. Chapter 14, pp.1096*. Boca Raton, FL, USA: CRC Press; 2011. ISBN 9781439805725 – CAT# K10287.

8. Kirkwood TBL. *Understanding the Odd Science of Aging*. Cell. Vol. 120, Feb. 25, 2005. 437-447. Doi: 10.1016/j.cell.2005.01.027.

9. Bienertova-Vasku J, Zlamal F, Necesanek I, Konecny D, Vasku A. *Calculating Stress: From Entropy to a Thermodynamic Concept of Health and Disease*. PloS ONE. 2016.11(1): e0146667. Doi:10.1371/journal.pone.0146667.

10. Atkins P, De Paula J. *Physical Chemistry (Chapter 4)*. Ninth Edition. Oxford University Press. 2010. Oxford, UK. ISBN-13: 9780199599592.

11. Conolly J, Romano T, Patruno M. *Effects of dieting and exercise on resting metabolic rate and implications for weight management.* Family Practice. 1999; 16 (2):196-201. Doi: 10.1093/fampra/16.2.196.

12. Wang Z, Ying Z, Bosy-Westphal, Zhang J, Heller M, Later W. *Evaluation of Specific Metabolic Rates of Major Organs and Tissues: Comparison between Nonobese and Obese Women. Intgrative Physiology.* Obesity. 2012. 20, 95-100. Doi: 10.1038/oby.2011.256.

13. Shulman G, Peterson K. *Metabolism, Chapter 58. Medical Physiology: A cellular and Molecular Approach*. Philadelphia, PA. 2012. Elsevier Saunders. ISBN: 978-1-4377-1753-2.

14. Kummitha C, Kalhan S, Saidel G, Lai N. *Relating tissue/organ energy expenditure to metabolic fluxes in mouse and human: experimental data integrated with mathematical modeling.* Physiol Rep, 2 (9). 2014. e12159, doi: 10.14814/phy2.12159.

15. Miller J. *Oxygen Deficient Metabolism in Organs: A link to Combustion Science.* Master of Science Thesis, Mechanical Engineering, Texas A&M University. Dec 2014.

16. Serra V, Zglinicki T, Lorenz M, Saretzki G. *Extracellular Superoxide Dismutase Is a Major Antioxidant in Human Fibroblasts and Slows Telomere Shortening.* The Journal of Biological Chemistry, Vol. 278, No. 9. February 28, 2003. pp. 6824 –6830.

17. Gemma C, Vila J, Bachstetter A, Bickford P. *Oxidative Stress and the Aging Brain: From Theory to Prevention*. Riddle DR, editor. Brain Aging: Models, Methods, and Mechanisms. Boca Raton (FL): CRC Press/Taylor & Francis; 2007. Chapter 15.

18. Segal Steven. *Exercise Physiology and Sports Science (Chapter 60) Medical Physiology: A cellular and Molecular Approach.* 2012. ISBN: 978-1-4377-1753-2.

19. Dewey F, Rosenthal D, Murphy Jr D. Froelicher V, Ashley E. *Does Size Matter? Clinical Applications of Scaling Cardiac Size and Function for Body Size. Division of Cardiovascular Medicine and the Division of Pediatric Cardiology*.StanfordUniversity2008.Doi: 10.1161/circulationaha.107.736785.

20. Firbes G. *Human Body and Composition: Growth, aging, Nutrition and Activity*. Springer Verlag, NY. 1987. Doi: 10.1007/978-1-4612-4654-1.

21. Shen W, Wang Z, Punyanita M, Lei J, Sinav A, Kral J, Imielinska C, Ross R, Heymsfield S. *Adipose Tissue Quantification by Imaging Methods: A Proposed Classification*. Obesity Research. 2003; 11(1):5-16.

22. Knab AM, Shanely RA, Corbin KD, Jin F, Sha W, Nieman DC. *A 45-minute vigorous exercise bout increases metabolic rate for 14 hours.* Med Sci Sports Exerc. 2011. 43(9):1643-8. doi: 10.1249/MSS.0b013e3182118891.

23. Wang Z, Ying Z, Bosy-Westphal A, Zhang J, Schautz B, Later W. *Specific metabolic rates of major organs and tissues across adulthood: evaluation by mechanistic model of resting energy expenditure.* The American Journal of Clinical Nutrition. 2010; 92(6):1369-1377. doi:10.3945/ajcn.2010.29885.

24. Lindstedt SL, Schaeffer J. *Use of allometry in predicting anatomical and physiological parameters of mammals*. Laboratory Animals. 2002. 36, 1–19.

25. Lodish H, Berk A, Zipursky SL, Matsudaira P, Baltimore D, Darnell J. *Molecular Cell Biology. 4th edition.* New York: W. H. Freeman. 2000.ISBN-10: 0-7167-3136-3.

26. Lehninger AL, Nelson DL, Cox MM. *Principle's of Biochemistry 2nd ed. Chapter 16: Oxidation of Fatty Acids*. J. Chem. Educ. 1993. 70(8). Doi: 10.1021/ed070pA223.1.

27. Department of Health, England. Health Survey for England 2002. National Archives(2007).(Access: http://www.dh.gov.uk/en/Publicationsandstatistics/PublishedSurvey/HealthSurveyForEngland/Healthsurveyresults/DH_4001334)

28. Hershey D, Wang HH. *A New Age-Scale for Humans.* Lexington Books. New York, USA, 1980.

29. Calder WA III. *Size, Function, NS Life History*. Dover: New York, NY, USA, 1996.

30. Wang Z, Heshka S, Gallaghar D, Boozer C, Kotler DP, Heymsfield SB. *Resting energy expenditure-fat-free mass relationship: new insight provided by body composition modeling.* American Journal of Physiology – Endocrinology and Metabolism. Sep 2000. Vol. 279 no. 3, E539-E545.

31. Else PL, Hulbert AJ. *Mammals: an allometric study of metabolism at tissue and mitochondrial level.* The American Physciological Society. 1985. R415-R421.

32. Gallagher D, Belmonte D, Deurenberg, Wang Z, Krasnow N, Pi-Sunyer FX. *Organ-tissue mass measurement allows modeling of REE and metabolically active tissue mass.* American Journal of Physiology – Endrocrinology and Metabolism. Aug 1988. Vol. 275 no. 2, E249-E258.

33. Davies M. *On Body Size and Tissue Respiration.* Journal of Cellular and Comparative Physiology. Volume 57, Issue 3, Feb 2005.

34. Later W, Bosy-Westphal A, Hitze B, Kossel E, Gluer CC, Heller M. *No evidence of mass dependency of specific organ metabolic rate in healthy humans*. Am J Clin Nutr. October 2008. Vol. 88 no.4 1004-1009.

35. Silva C, Annamalai K. *Entropy Stress and Scaling of Vital Organs over Life Span Based on Allometric Laws.* Journal of Entropy. 2012, 14, 2550-2577.

36. Agutter PS, Wheatley DN. *Metabolic Scaling: Consensus or Controversy?* Theoretical Biology and Medical Modeling. Nov 2004. Doi: 10.1186/1742-4682-1-13.

37. Speakman JR. *Body size, energy metabolism and lifespan – A Review*. J. Exp. Biol. 2005, 208, 1717-1730.

38. Gisolfi CV, Wenger BC. *Temperature Resulation During Exercise: Old Concepts, New Ideas.* Exercise & Sport Sciences Reviews. January 1984. Volume 12-Issue 1-pp 399-416.

39. Yablonskiy DA, Ackerman JJH, Raichle ME. *Coupling between changes in human brain temperature and oxidative metabolism during prolonged visual stimulation.* Proceedings of the National Academy of Sciences of the United States of America. 2000;97(13):7603-7608.

40. Scheett TP, Stoppani J, McGuigan MR. *Nutrition for Strength/Power Athletes*. NSCA Sports Nutrition Education Program. 2012. (Can be accessed at: https://www.kinkaid.org/uploaded/Athletics/Falcon-Fitness/NSCA_-_SNP_Strength-Power_Athletes-slides.pdf)

41. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholestrol, Protein and Amino Acids*. Food and Nutrition Board. Institute of Medicine of the National Academies. The National Academic Press, Washington, D.C. 2002. (Can be accessed at: https://www.nap.edu/read/10490/chapter/1)

42. Nelson RA, Edgar Folk G Jr, Pfeiffer EW, Craighead JJ, Jonkel CJ. *Behaviour, Biochemistry, and Hibernation in Black, Grizzly, and Polar Bears.* Int. Conf. Bear Res. And Manage. 1983. 5:284-290.

43. Lindstedt SL. *Allometry: Body Size Constraints in Animal Design.* National Research Council (US). Drinking Water and Health, Volume 8: Pharmacokinetics in Risk Assessment. Washington, DC. National Academies Press (US). 1987.

44. Little JP, Safdar A, Bishop D, Tarnopolsky MA, Gibala MJ. *An acute bout of high-intensity interval training increases the nuclear abundance of PGC and activates mitochondrial biogenesis in human skeletal muscle.* Am J Physiol Regul Integr Comp Physiol. Jun 2011. 300(6):R1303-10. Doi: 10.1152/ajpregu.00538.2010.

45. D'Antona G, Ragni M, Cardile A, Tedesco L, Dossena M, Bruttini F, Caliaro F. *Branched-Chain Amino Acid Supplementation Promotes Survival and Supports Cardiac and Skeletal Muscle Mitochondrial Biogenesis in Middle-Aged Mice.* Cell Metabolism. 2010. doi: 10.1016/j.cmet.2010.08.016.

46. Okabe K, Inada N, Gota C, Harada Y, Funatsu T, Uchiyama S. *Intracellular temperature mapping with a fluorescence lifetime imaging microscopy*. Nat Commun. 2012. 3:705. doi: 10.1038/ncomms1714.

47. Cornish-Bowden A. *Metabolic efficiency: Is it a useful concept?* Biochemical Society Transactions. Jan 1983. doi: 10.1042/bst0110044.

48. Vasudevan DM, Sreekumari S, Vaidyanathan K. *Textbook of Biochemistry for Medical Students, 6th edition.* Jaypee Brothers Medical Publishers (P) Ltd. 2011. ISBN: 978-93-5025-016-7.

49. Boron WF, Boulpaep EL. *Medical Physiology (3rd Edition).* Elsevier, Philadelphia, PA. May 2016. ISBN-13: 978-1455743773.

50. Later W, Bosy-Westphal A, Hitze B, Kossel E, Gluer C-C, Heller M, Muller MJ. *No evidence of mass dependency of specific organ metabolic rate in healthy humans.* Am J Clin Nutr. October 2008. Vol. 88 no. 4 1004-1009.

51. Annamalai, K and Miller, J. *A Link Between O_2 Deficient Metabolism In Organs And Group Combustion In Engineering*. 10th U. S. National Combustion Meeting, April 23-26, 2017, College Park, Maryland.

52. Milo R and Phillips R. *Cell Biology by the Numbers*. Garland Science, Taylor and Francis Group. July 2015. ISBN – 978-0-8153-4163-5.

53. Huaxiong H, Milevsky MA, Salisbury TS. *Retirement Spending and Biological Age.* SSRN Electronic Journal. February 16, 2017 Doi: 10.2139/ssrn.2918055.

54. Annamalai, K and Ryan, W. *Interactive processes in gasification and combustion-II. Isolated carbon, coal and porous char particles.* Process in Energy and Combustion Science. December 1993. 19(5):383-446.

55. Johnson, KA and Goody RS. *The Original Michaelis Constant: Translation of the 1913 Michaelis Menten Paper.* Biochemistry. 2011. 50 (39), pp 8264-8269. Doi: 10.1021/bi201284u.

56. Silva, C and Annamalai, K. *Entropy Generation and Human Aging: Lifespan Entropy and Effect of Physical Activity Level.* Journal of Entropy. June 2008. 10,100-123; doi: 10.3390/entropy-e10020100.

57. Hall ED, Andrus PK, Oostveen JA, Fleck TJ, Gurney ME. *Relationship of Oxygen Radical-Induced Lipid Peroxidative Damage to Disease Onset and Progression in a Transgenic Model of familial ALS.* Journal of Neuroscience Research Volume 53 Issue 1. 1 July 1998. Pages 66-77.

58. Anderson RM, Bitterman KJ, Wood JG, Medvedik O, Sinclair DA. *Nicotinamide and PNC1 govern lifespan extension by calorie restriction in Saccharomyces cerevisiae*. Journal of Nature. 2003. 423:181-185

APPENDIX A

CONVERSION OF ALLOMETRIC LAWS BASED ON MASS OF BODY IN TERMS OF MASS ORGAN K

Previous literature provided details on conversion of allometric laws from body mass m_B to organ mass k for various parameters of interest [35] If parameter is specific metabolic rate (SMR) from body mass to mass of organ k. The body mass based allometric

laws for $\dot{q}_{k,m}(t)$ and m_k are given as

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

Where allometric law for organ mass is

$$m_k\ (\text{kg organ mass}) = c_k\ m_B{}^{d_k}$$

Where c_k and d_k being constants for organ k. The elimination of m_B between (1) and (2) leads to allometric law based on organ mass [**Annamalai and Silva, 2012]**

$$\dot{q}_{k,m}(t)\left(\frac{W}{\text{kg of organ k}}\right) = \left\{\frac{e_k}{c_k^{\frac{f_k}{d_k}}}\right\} m_k^{\left(\frac{f_k}{d_k}\right)}$$

More generally, if two allometric laws for Y_1 and Y_2 are based on X_{com} (X common to both) then the allometric law for Y_1 can be converted on Y_2 basis; consider

$$Y_1 = r_1\ X_{com}{}^{t_1}$$

$$Y_2 = r_2\ X_{com}{}^{t_2}$$

Then eliminating X_{com},

$$X_{com} = \left(\frac{Y_2}{r_2}\right)^{1/t_2} \text{ and hence } Y_1 = r_1\left(\frac{Y_2}{r_2}\right)^{t_1/t_2} = \left(\frac{r_1}{r_2^{t_1/t_2}}\right) Y_2^{(t_1/t_2)}$$

$$Y_1 = r_{new}\ Y_2{}^{t_{new}}$$

Thus, relation and allometric coefficients for Y_2 based on Y_2 are

where $r_{new} = \left(\frac{r_1}{r_2^{t_1/t_2}} \right)$, $t_{new} = \frac{t_1}{t_2}$

Consider the following allometric relation for MiV %

$$\mathbf{MiV_k\ (mitochrialvolume\%in\ organ\ k) = p_k\ m_B^{\ q_k}}$$

With $Y_1 = q_{k,m}$, $Y_2 = MiV$, $X_{com} = m_B$, $r_1 = e_k$, $t_1 = f_k$. $r_2 = p_k$, $t_2 = q_k$, the allometric law based on Y_2 is given as

$$Y_1 = \dot{q}_{k,m} = r_{new} \left(MiV\right)^{t_{new}}, \quad r_{new} = \frac{e_k}{p_k^{t_1/t_2}}, \; t_{new} = \frac{f_k}{q_k}$$

$$\dot{q}'''_{Mito,k}(t) \left(\frac{W}{cm^3 \ of \ mito \ within \ \ organ \ k} \right) = \frac{\dot{q}'''_{k,m}(t)\ \rho_k}{Mito\ volume\ within\ organ\ k\ per\ unit\ vol\ of\ \ forgan\ k} = \frac{\dot{q}'''_{k,m}(t)\ \rho_k}{MiV\ \ fraction * n}$$

where n = number of cells per unit volume of organ k

$$\dot{q}'''_{Mito,k}(t) = \frac{e_k\ \rho_k\ m_B^{\ f_k}}{n_k(cells/cm3\ of\ organ\ k) * V_{cell,k}(cm^3\ per\ cell)\ MiV\ \ fraction} = \frac{e_k\ \rho_k\ m_B^{\ f_k}}{n_k\ V_{cell,k}\left(p_k\ m_B^{\ q_k}/100\right)}$$

APPENDIX B

CAPILLARY BLOOD TEMPERATURE RISE (ΔT), OXYGEN EXTRACTION FRACTION (OEF) AND CELL TEMPERATURE

Temperature heterogeneity exists within cells due to oxidation and several biochemical reactions. Here following combustion science relations for mitochondrial temperature are presented as long continuum approximations are valid. Small differences in temperature can alter the biochemistry of reactions and cell growth and multiplications.

According to Okabe et al, "It is noteworthy that the energy of glucose metabolism in cells is equivalent to a temperature increase of at least 2 °C within an entire cell, because of the following reasons: the total free energy released by the oxidation of glucose (glucose +6O2right arrow6CO2+6H2O) is 2870 kJ mol−1; the specific heat capacity of the cell can be estimated to be 4.184 J (gK)−1 (similar to water); the intracellular glucose concentration is kept to at least 3–5 mM, when the culture medium includes 25 mM glucose (that is, in the present condition)." [46] Average temperature difference was estimated to be 0.96 C between nucleus and cytoplasm. Assumed to be same as blood leaving the organs. The maximum possible temperature of blood leaving organ is given under adiabatic condition (Q=0). The metabolic is proportional to $e^{-E/RT}$ based on oxidation kinetics. The BMR is typically proportional to body mass (3/4) at given T_{body}. If T increases

$$\frac{BMR}{BMR_{normal}} = \frac{M_B * \left(\frac{3}{4}\right) * e^{-\frac{E}{RT}}}{M^{\frac{3}{4}} * e^{-\frac{E}{RT_{normal}}}}$$

BMR/BMR_{normal}= . (M_B(3/4) * $e^{-E/RT}$)/{ M^3/4) * exp (- E/RTnornal).

The T changes depending upon size of organ, type of nutrients oxidized. Thus metabolic rate increases locally for each organ.

The CH is large molecule M = 2 million g/gmole while single mono C_6H_{12} O_6 Apply energy conservation equation in mass format. Let inlet temperature of blood to be T_{in}. If $Y_{O2,in}$ is in ppm (g per million g of blood) of O2 supplied and if oxygen extraction fraction is

OEF, then $YO_{2,exit}$= $YO_{2,in}$ (1-OEF)

Energy released per g of blood supplied = Y_{O2in}* OEF* HV_{O2}

Each g of O2 consumed is aproximately equal to each g of glucose oxidized.

Energy release per g of O2 supplied = OEF* HV_{O2} ≈ Energy gained by products = c_p*ν_{Prod}*(Texit- Tin)

Where ν_{Prod} = mass of products per g of O2 supplied and products of mass 3333 g is are doinared by plasma (νP) .Thus under adiabatic conditions (no heat loss) , and accounting for metabolic efficiency

$$Y_{O2in,k} * OEF_k * HV_{O2} * \left(1-\eta_{M,k}\right) = 1 * cp(T_{exit,k} - T_{in})$$

$$(T_{exit,k} - T_{in}) = \frac{Y_{O2in,k} * OEF_k * HV_{O2} * \left(1-\eta_{M,k}\right)}{c_p}$$

$$(T_{exit,k} - T_{in}) = \frac{O2used\ \ per\ \ g\ organ\ k * organ\ mass\ served\ per\ g\ \ blood\ blood * HV_{O2} * fraction\ converted\ \text{into}\ Heat\ in\ organ\ k}{heat\ \ capacity\ \ per\ \ g\ \ blood}$$

With specific organ metabolic rate (W/kg of k) = $e_k\ m_B^{\ f_k}$, blood flow rate to organ k (mL/s per kg orgna k) = $h_k\ m_B^{\ i_k}$, organ mass $m_k = c_k\ m_B^{\ d_k}$ = The OEF in terms of blood flow rate, and allometric laws for orhan can be given as follows:

$$\text{OEF}_k = \frac{O2\ used,k}{O2\,\text{sup}lied\ to\ k} = \frac{\dot{q}_{k,m}}{\dot{V}_{bl,m,k}\left(\frac{\text{mL/s}}{kg\ organ\ k}\right)\rho bl\left(\frac{kg}{mL\ blood}\right)Y_{O2in,k}\ HV_{O2}\left(\frac{J}{kg\ O2}\right)} = \frac{e_k\ m_B^{\ f_k} * m_k}{h_k\ m_B^{\ i_k} * \rho_{bl}\ Y_{O2in,k}\ HV_{O2}} = \frac{c_k e_k\ m_B^{\ f_k+d_k-i_k}}{h_k\ \rho_{bl}\ Y_{O2in,k}\ HV_{O2}}$$

$$\text{OEF}_k = J_k\ m_B^{\ L_k},\ J_k = \left(\frac{c_k e_k}{h_k\ \rho_{bl}\ Y_{O2in}\ HV_{O2}}\right),\quad \text{L}_k = f_k + d_k - i_k$$

Once metbolic rate per kg organ mass is known, with $Y_{O2,in}$ = 300x10^{-6} per g of blood , OEF=0.25 (for Liver), c_p= 3.8 j/kg C, HHV_{O2}= 14200 J/g , the maximum temperatureris is 0.28 C; the OEF for heart is 0.5 and hence the maximum temperatureris is 0.56 C. The adiabatc temperature rise is extremely low compared engineering sstems which use air (nitrogen to oxygen mass ratio = 3.45) for combustion due to high inerts to oxygen ratio in blood {=1-900x10^{-6} glucose- 300x10^{-6} -900x10^{-6} oxygen }/300x10^{-6}≈ 3330}. Glucose levels: 60-140 mg/DL of blood.

$$(T_{exit} - T_{in}) = \frac{Y_{O2in} * OEF * HV_{O2}}{c_p} = \frac{Y_{O2in} * HV_{O2}}{c_p} * \text{J}_k\ m_B^{\ B_k}$$

$$(T_{exit} - T_{in}) = \frac{Y_{O2in} * OEF * HV_{O2}}{c_p} = \text{N}_k\ m_B^{\ L_k},\quad \text{N}_k = \frac{\text{J}_k\ Y_{O2in} HV_{O2}}{c_p} = \left(\frac{c_k e_k}{h_k\ \rho_{bl}\ c_p}\right)$$

Accounting for meabolic eficiency:

$$(T_{exit} - T_{in}) = \Delta T = \frac{Y_{O2in} * OEF * HV_{O2}\left(1-\eta_M\right)}{c_p} = \text{N}_k\ m_B^{\ L_k},\quad \text{N}_k = \frac{\text{J}_k\ Y_{O2in} HV_{O2}\left(1-\eta_M\right)}{c_p} = \left(\frac{c_k e_k}{h_k\ \rho_{bl}\ c_p}\right)$$

OEF and η_M varies from organ to organ. Consider organ k:

$$(T_{exit} - T_{in})_k = \Delta T_k = \frac{Energy\ relased\ as\ heat\ per\ \ g\ \ blood\ \ in\ organ\ k}{heat\ \ capacity\ \ per\ \ g\ \ blood}$$

If $\dot{Q}_{k,m}$ is specfic energy released as heat in W/g of k , then $\dot{Q}_{k,m}\ m_k$ is energy released as heat for whole organ k and $\frac{\dot{Q}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}}$ is energy relased asheat per g blood flow to organ k.

Thus,

$$\frac{\dot{Q}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}} = Y_{O2in} * OEF * HV_{O2}\left(1-\eta_M\right) = \Delta T_{\mathrm{k}}\ c_p$$

Where ρ, kg per mL of blood, cp specific heat in J/kg K= 3800 J/kg K

$Y= h_k\ m_B^{ik}$, m_B: body mass , Y blood flow rate.

Table 7: Blood Flow Rate Allometric Constants for Vital Organs

Organ	Units, Y	h_k	i_k	R^2
Adrenal	ml/s	0.016	0.753	0.982
Brain*	ml/s	0.101	0.704	0.999
Heart	ml/s	0.224	0.714	0.991
Renal	ml/s	0.603	0.774	0.999
Liver (hepatic)	ml/s	0.156	0.856	0.987
Liver (splanchnic)	ml/s	0.648	0.764	0.994
Lung	ml/s	0.107	0.889	0.907
Muscle	ml/s	0.769	0.737	0.984
Skeleton	ml/s	0.525	0.632	0.971
Skin	ml/s	0.255	0.741	0.995

Maximum Possible Blood Temperature

The ROS production rate is function of body temperature T, oxygen concentration and activation energy and ROS production rate is extremely sensitive to temperature.

If there is no heat loss from skin, each circulation raises blood temperature by 0.28 C. Yablonskiy et al [39] estimated temp rise as 0.3 C using the local metabolic

rates. During fever, the body wants to kill bacteria by raising blood temperature. The body does it by reducing skin circulation which reduces heat loss. Thus ever starts say by 0.1 C for first circulation which requires about 1 min {=5 L bold/ (5 L/min) = 1 min); in 15 minutes your fever is 15*0.1= 1.5 and hence 38.5 C! After bacteria is killed, it restores skin circulation and hence go back to normal temperature.

Using conservation of energy for blood entering an organ and leaving an organ, the maximum Rise in blood temperature is given as:

$$(T_{exit} - T_{in}) = \frac{Y_{O2in} * OEF * HV_{O2}}{c_p} = \frac{Energy\ released\ \ per\ \ g\ \ blood}{heat\ \ capacity\ \ per\ \ g\ \ blood}$$

Where YO2in , oxygen mass fraction in blood entering organ (about 300 ppm), OEF, oxygen extraction fraction, and HV_{O2}, energy released per g of O consumed. Further

$$(T_{exit} - T_{in}) = \frac{Energy\ released\ \ per\ kg\ \ organ(W/kg)}{heat\ capacity\ in J\ \ per\ kg\ blood} \frac{mass\ of\ \ organ\ in\ kg}{\rho\ (kg/mL) * blood\ \ flow\ rate\ in\ mL/s} = \frac{e_k\ m_B{}^{f_k} * c_k\ m_B{}^{d_k}}{a_k\ m_B{}^{b_k}\{c_p * \rho\}} = \frac{e_k c_k\ m_B{}^{f_k + d_k - b_k}}{a_k\{c_p * \rho\}}$$

APPENDIX C

ENTROPY GENERATION-ORGAN FAILURE - LIFE SPAN

In lay man's language, the entropy generation is a measure of how things can go wrong irreversibly.[1] Why entropy generation is relate ti organ failure and life span? Here we provide simply physical explanation. Typically, the exhaust temperature (T_{2s}) is cooler than inlet temperature (T_1) due to work delivery. Where T_{2s} is exit temperature when there is no friction and turbine is adiabatic. However there is always friction between gas and blade materials which cause heating effect result in temperature $T_2 > T_{2s}$. Thus gas leaving the turbine is "extra" hotter { $T_2 - T_{2s}$) and higher energy content in exhaust implies higher entropy $s_2 > s_1$; the difference is called entropy generation $\sigma_{12} = s_2 - s_1$. As entropy is generated it is flushed out through exit stream. After few years, the material degrades due to contact friction and σ_{12} keep increasing and hence a measure of σ_{12} is measure of degradation of material. Similarly in the organ there is constant degradation within cells due to irreversible oxidation reaction (also called as electron transfer process) and some electrons are "lost" and get attached to other species creating radical oxygen species (ROS) which cause damage to normal DNA. Hence the cells starts loosing functional capability and face death. However the cells constantly divide and repair i.e. cell regeneration. Further depending organ, but each cell's life cycle is different. If "$n_{cell,m}$" is the number density cells per unit mass of organ, $n_{cell,m}$ keeps decreasing as oxidation keeps continuing during aging process. For some organs they could also be released within days/weeks and some never. Thus, cellular turnover I is a part of the aging process, divide less efficiently, and eventually number of cells dying is more than number replaced. When energy release occurs, a part of energy is directly captured by ADP and it produces ATP without causing temperature rise (equivalent to work, W) in thermodynamics which do not cause entropy generation). The remaining energy is released as heat (Q) which causes entropy generation, σ. More the Q, more the σ; as the name implies this Q is necessary to keep body warm at normal temperature T_B and overcome heat loss . It varies from organ depending on proportions of CH, F and P oxidized. Considering organ k, the heat Q_k results in temperature rise ΔT_k for organ k. It is well known in combustion science that temperature rise causes increased reaction rate or increased production of ROS.

$$\frac{d[ROS]_k}{dt} = A\exp\left(-\frac{E}{RT_k}\right) = A\exp\left\{-\frac{E}{R\left(T_B+\Delta T_k\right)}\right\}$$

Since $\Delta T_k/T_B << 1$

$$\frac{d[ROS]_k}{dt} = A\exp\left\{-\frac{E}{R\left(T_B+\Delta T_k\right)}\right\} = A\exp\left\{-\frac{E}{RT_B}\right\}\exp\left\{\frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right\} \approx A\left\{1+\frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right\}\exp\left\{-\frac{E}{RT_B}\right\}, \frac{E}{RT_B}\frac{\Delta T_k}{T_B} << 1$$

Recall that

$$\frac{\dot{Q}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}} = Y_{O2in} * OEF * HV_{O2}\left(1-\eta_M\right) = \Delta T_{\mathrm{k}}\ c_p$$

$$\frac{d[ROS]_k}{dt} = A\exp\left\{-\frac{E}{R\left(T_B+\Delta T_k\right)}\right\} \approx A\left\{1+\frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right\}\exp\left\{-\frac{E}{RT_B}\right\} = A\left\{1+\frac{E}{RT_B}\frac{\dot{Q}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}c_p\ T_B}\right\}\exp\left\{-\frac{E}{RT_B}\right\}$$

Since $\frac{\dot{Q}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}T_B} = \frac{\dot{\sigma}_{k,m}\ m_k}{\dot{m}_{Bl,\mathrm{k}}}$ and letting $\dot{m}_{Bl,\mathrm{m,k}}\ \frac{g\ of\ \ blood\ \mathrm{int}o\ k}{s\ g\ of\ \ k} = \frac{\dot{m}_{Bl,\mathrm{k}}}{m_k}$

$$\frac{d[ROS]_k}{dt} \approx A\left\{1+\frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right\}\exp\left\{-\frac{E}{RT_B}\right\} = A\left\{1+\frac{E}{RT_B}\frac{\dot{\sigma}_{k,m}}{\dot{m}_{Bl,m,k}c_p}\right\}\exp\left\{-\frac{E}{RT_B}\right\}$$

If each ROS attaches to one DNA of each cell, number of cells per unit volume of organ k becomes under dysfunction becomes

$$-\frac{d[\mathrm{n}_{\mathrm{cell,k}}]}{dt},\ \frac{cells\ under\ \ disfunction}{cm^3\ s} = \frac{d[ROS]_k}{dt} \approx A\left\{1+\frac{E}{RT_B}\frac{\Delta T_k}{T_B}\right\}\exp\left\{-\frac{E}{RT_B}\right\} = A\left\{1+\frac{E}{RT_B}\left(\frac{\sigma_{k,bl}}{c_p}\right)\right\}\exp\left\{-\frac{E}{RT_B}\right\}$$

where $\sigma_{k,bl}$, $entropy\ gneration\ per\ unit\ \ blood\ \ flow\ to\ organ\ k$, $\frac{J\ \ of\ \ k}{K-g\ \ blood\ \ to\ k} = \frac{\dot{\sigma}_{k,m}}{\dot{m}_{Bl,m,k}}$

Higher entropy generation, $\sigma_{k,bl}$ higher the rate of cell death (implying dysfunctional) . About 10 % of bone cells die every year. i.e

$-\frac{d[N_{bone\ \mathrm{cell}}]}{dt} = \frac{0.10 * N_{cell,bone}}{year}$ while for skin cells

$-\frac{d[N_{Stomach\ \mathrm{cell}}]}{dt} = \frac{0.20 * N_{Stomachcells}}{day}$, N= n* Volume of organ

Why ATP for Palmitic Acid Changes?

Consider Glucose oxidation

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O, \Delta {G_C}^o = -2895\frac{kJ}{mole}$$

$$C_6H_{12}O_6 + 6O_2 + 38ADP + 38P_i \rightarrow 6CO_2 + 6H_2O + 38ATP + heat, \Delta {G_M}^o = -1790\frac{kJ}{mole}$$

Since $\Delta {G_M}^o$ is less nagative dyue to 30 ATP moles of ATP production gain per ATP = {2895-1790}/38 = 29.1 kJ per mole of ATP i.e

$$ADP + P_i \rightarrow ATP + H_2, \quad \Delta G^o = -29.1\frac{kJ}{mole}$$

Now we consider oxidation of Palmitic acid

$$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O \qquad \Delta {G_C}^o = -2338\frac{kcal}{mole} = -9.78 * \frac{10^6 kJ}{kmole}$$

The Gibbs Free Energy associated with the oxidation of Palmitic acid is ΔG^o = -9.78 x 10^6 kJ/kmol [28]. With ATP production

$$C_{15}H_{31}COOH + 23O_2 + 106ADP + 106P_i \rightarrow 16CO_2 + 16H_2O + 106ATP + heat$$

The Gibbs Free Energy associated with the oxidation of Palmitic acid is ΔG^o = -9.78 x 10^6 kJ/kmol [28]. With ATP production

$$C_{15}H_{31}COOH + 23O_2 + 106ADP + 106P_i \rightarrow 16CO_2 + 16H_2O + 106ATP + heat$$

Thus, the ATP in palmitic acid reaction gained 106*29.1 = 3085 kJ/mol or 3.085x10^6 kJ/kmol of palmitic acid. The resultant Gibbs Free Energy of the balanced chemical reaction including ATP in the products side yields $\Delta G_{M,\,fat}$ = -6.695 x 10^6 kJ/kmol for palmitic acid. Accordingly the metabolic efficiency should be

$$\eta_{Met,F} = \frac{3085}{9780} = \ 31.5\%$$

The final oxidation reactions with 129 ATP molecules included is shown below:

$$C_{16}H_{32}O_2 + 23O_2 + 129\ ADP \ + 129\ Pi \ \rightarrow 16CO_2 + 16H_2O + 129\ ATP \quad \Delta G^o = -1436.4\frac{kcal}{mole}$$

$$= -6.01 * \frac{10^6 kJ}{kmole}$$

$$\eta_{II} = \frac{Net\ Work_{Out}}{Q_{in}}$$

$$\eta_{II,\ F} = (1 - \frac{1436.4}{2338}) = 38.5\% \quad (F\ Metabolic\ Efficiency)$$

Traditional Method [26]:

Palmitic acid has 16 Carbons; the beta oxidation yields 8 acetyl-coA,7 NADH and 7FADH2

$$C_{16}H_{32}O_2 \rightarrow 8\ acetyl\ coA, +7\ NADH + 7\ FADH2$$

Which consumes 2 ATP.

The 8 AcetylCoA --->24 NADH+8FADH2+8ATP (Kreb's cycle)

We have 24+7 =31 NADH, 7+8=15 FADH2, and 8ATP

1 NADH yields 3 ATPs; 1 FADH2 gives 2 ATPs

So far we have: (7+24) NADH *3 ATP per NADH+(7+8) FADH2 *2 ATP per FADH2 + 8= 93+30+8= 131

2 ATPs are used to activate palmitate to palmitoyl coA==>net ATP=131-2 =129

Net = 131-2= 129

See [47]:

ATP + H2O= ADP + Pi $\Delta G0' = -30.5$kJ/mol of ATP

129 ATP + 129 H2O= 129 ADP + 129 Pi $\Delta G0' = -3935$ kJ/mol (30.5*129)

Palmitic acid + 23 O2 $\rightarrow$16CO2 + 16H2O' = -9780kJ/mol

Therefore, metabolic efficiency = 3935/9780 = 40 %

Then, ΔG_M with ATP production = 9780-3935 =5845 kJ/mol (30.5*129)

When one uses ΔG (which include concentration effects)

ATP + H2O .= ADP + Pi $\Delta G0' = -30.5$kJ/mol of ATP

$$\hat{g}_k\{T,[]\} = \bar{g}^0(T) + \bar{R}T\ \ln\left([k]\right), ideal\ sol$$

$$\Delta G = \bar{g}_{ADP}{}^0(T) + \bar{R}T\ \ln\left([ADP]\right) + \bar{g}_{Pi}{}^0(T) + \bar{R}T\ \ln\left([Pi]\right) -$$
$$\bar{g}_{ATP}{}^0(T) - \bar{R}T\ \ln\left([ATP]\right) - \bar{g}_{H2O}{}^0(T) - \bar{R}T\ \ln\left([H2O]\right)$$
$$= \Delta G^0(T) + \bar{R}T\ \ln\left\{\frac{[ADP][Pi]}{[ATP][H2O]}\right\}$$

If ATP/ADP = 0.1, then with concentration effects

$$\Delta G = \Delta G^0(T) + \bar{R}T\ \ln\left\{\frac{0.1[Pi]}{[H2O]}\right\}$$

<u>New Method/Concept</u>: [48]

The C_{16} yields 8 acetyl coA, 7 NADH and 7 FADH2 as before

The 8 acetyl generates $\rightarrow$ 24 NADH + 8FADH2+ 8 ATP as before

We have 24+7 =31 NADH, 15 FADH2, 8ATP;

Yield from NADH is 2.5 ATP instead of 3 ATP in the traditional way, each FADH2 yields 1.5 ATP instead of 2 ATP in traditional way (since this use two extra enzymes)

So we have 31*2.5+ 15*1.5+8 = 77.5+ 22.5+ 8 = 108

Activation = -2; ATP_{NET} = 108-2= 106 ATP

η_{MET}=30.5* 109=3325/ 9840=33.8

This also agrees with ATP sated for palmitic acid [49]. Some sources use larger ATP production of 129 ATP = {(8-1)*17+12-2} equivalents per palmitate. ATP changes in number due to requirement of two possible additional enzymes for beta-oxidation of unsaturated fatty acids.