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Research Article

Energy wise Regulation to Regularized Self-Vitality System – 2 Regularium

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Abstract

The whole organism is energy concerned, and the energy economy mode prevails from basic cell regulation to higher systems regularized along with environmental setup. Energy and resources are basic and expressed everywhere. Concerning energy, as external interactions magnify, the whole human body may be viewed as a jumbo compo of physiological cues and environmental signals acting at different sites with complex cellular, neural or humoral controls and interacting functional nodes. The classical neural and endocrinal frame often becomes insufficient to understand it. Though disorders around the metabolic syndrome now prevail medical literature, energy related disorders are far more complex and need a better understanding from the whole person organism level.

Maintenance of homeostasis starts with organ systems with their set reflexive responses in reactive mode. Over the central reflexively reactive mechanisms, particularly with saliency and its linkage mechanisms and frugal liver provisions, self-vitality systems have evolved. Activities are generally meant for being energetic productive. The organism level needs to gain advantage of both basic energetic efficiency as well as the capacity for energetic production. To reduce erratic energy costs by placing the right job at the right time, regularized patterns have to be formed to match the environment to direct a certain physiological process to take place at a specific time of the day or night. Through set patterns consciously or subconsciously in various states and levels, the set regularium of each individual could function to conserve energy or being energetic productive as life requires. As a whole coordinating myriads of scenarios for self enhancement in living, the person then functions in adaptivity and useful patterns to suit the best survival and achieve snug-fit states positively. Poorly set self-vitality systems lead to pathologies. The self-vitality system concerning energy which is basic from cells to physiological processes and up to organismic level has a much wider context, and the paper is put in smaller succinct paragraphs in pertinent areas to describe the whole, and pathologies are only briefly described.

Keywords: Brain-liver dyad; Basic energetic efficiency; Energy related disorders; Energetic productive living; Regulation and regularium; Snug and fit

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Introduction

The body is endowed at birth with biological robustness [1]. During development, matching mechanisms from the core are subsequently followed by well-coordinated mechanisms [2] to suit itself in the surrounding environment depending on sufficient energy supply and well-kept reserves. For the body to live with all the many activities yet seemingly with little restrain, the individual organism coordinates energy intake and usage while frugally uses energy and resources. While the organ systems have their set reflexive responses in reactive mode, there are bigger integrated body systems which have evolved for self-vitality over environments recurring with repeated similarities. Then such higher systems regularized along with environments put up set autonomized responses in catering for these repetitive situations through life with less energy restrains and furnishing surplus resourcefulness. Poorly set self-vitality systems lead to pathologies [3]. The whole organism is energy concerned, and the understanding of energy problems and metabolic diseases needs a better understanding from the whole person organism level [4].

Energy Regulation Inherent for Life

Bioenergetics refers to the processes by which life transfers energy from a source to an organism starting from the cell. Energy fuels and regulates the body internal functions. Life may be viewed as an autonomized makeup that gains organization and energy in the world of entropic disorganization Evolution in whatever context refers to the continuous changes in the structure, state, function, behaviour, and pertinent attributes of a system with time [5]. The energy system can be regarded as a complex adaptive system. The sources of energy available promote evolutionary biological complexity associated with concomitant increase in organismic capacity for energetic production. For energy economy of the organism, energetic efficiency and the capacity for energetic production are two attributes with particular evolutionary significance [6]. Regulatory mechanisms maintain these throughputs. In highly developed organisms, the established system complexity may progress for more energetic production even at the expense of energetic efficiency, even with more "energy waste". Regularized life formations maintain necessary set patterns.

Fundamentals

Catabolic or anabolic events provide the source of energy at cellular level with Adenosine Triphosphate (ATP). Human metabolism runs on one kind of energy, chemical energy, to support living and essential functions like heartbeat, metabolism, respiration, water and body temperature homeostasis, and body repair. The harsher the environment, the more energy is needed to maintain integrality. Beyond immediate body needs, energy is converted into storage as glycogen or fat as endurance fuels. Energy-conservation pathway could have been the major force which powered and directed the early evolution of the cell [7]. Evolving for organismic energy-wise operations, the energy systems with inner interactions to in-out responses to the environment would change over time, as it may include energy consumption (aggregate and structure), improvements in energy efficiency, reductions in the cost of energy, and changes in the driving forces and energy-related regulation. While cellular functions empower physiological processes and physiological functions feed cells [8], regulatory mechanisms important for energy balance exist in all levels.

Inherent Regulation

Energy provision: Being life's energy reservoir [9] since the dawn of life [10,11], ATP energy is released by hydrolysis into adenosine diphosphate/ monophosphate (ADP/AMP) and phosphate/pyrophosphate, respectively to fuel cellular processes. As being bound by hundreds of protein structures, ATP participates in the signalling of key bioprocesses [12] through protein phosphorylation reaction. The regulatory role of ATP is demonstrated as a transmitter in intercellular purinergic signalling [13], and as a hydrotrope regulating cellular compartmentalization [14].

AMP activated protein kinase (AMPK) pathway and target of rapamycin (TOR) pathway are well conserved since ancient eukaryotes [15] and pre-eukaryotic era [16]. They evolved to sense and co-ordinate metabolic activities in the cytosol with those in the mitochondria and plastids by being the major control points of energy signalling [17].

Chemical energy sources is extracted from nutrients for utilization by cells for cellular functions driving biological processes. Fuel molecules derived from digestive degradation of macronutrients, (carbohy-drates, lipids, and proteins) become smaller molecules to be absorbed. In aerobic respiration, all fuel molecules converge to a central cycler of metabolism, the tricarboxylic acid (TCA) cycle where their acetyl group of acetyl-CoA would be completely oxidized to CO_2 with concomitant reduction of electron transporting coenzymes (reduced nicotinamide adenine dinucleotide, NADH, and reduced flavin adenine dinucleotide, $FADH_2$). The NADH serves as a central hydride donor to ATP synthesis through mitochondrial oxidative phosphorylation (OXPHOS), along with the generation of reactive oxygen species (ROS) [18]. TCA cycle in glycolysis gains ATP and NADH, while the end product in the cytoplasm as pyruvate enter the mitochondria [19] for further metabolism.

Mitochondria from its ancient bacterial origin [20,21] endowed human cells with the powerhouse for energy as well as enabling flexible physiological responses to new environments through symbiotic evolution [22]. The acquisition of the mitochondria fundamentally enabled expansion of energy availability per gene that support more genetic regulatory complexity facilitating the evolution of morphological complexity [23,24].

Energy regulated all over: NADH oxidation process in the cell occurs primarily via mitochondrial metabolism. NAD+ reduction is required to maintain energy balance and the redox state of a cell. The rates of oxidation and reduction of NAD and NADH must be continuously balanced within the cell to maintain the pathways of anabolism and catabolism.

Feedback mechanisms in metabolic pathways regulate energy metabolism by sensing changes in metabolic intermediates or end products and modulating enzyme activity to maintain homeostasis. Oxoglutarate dehydrogenase (OGD) complex, a highly regulated enzyme in TCA cycle, converts α-ketoglutarate (αKG) to succinyl CoA with NADH generation, but both end products inhibit the reaction. OGD can be viewed as a redox sensor in the mitochondria, and evolutionary conserved reaction of OGD degradation is believed as required for metabolic adaptation [25]. Increased NADH/NAD+ ratio is associated with increased ROS production and inhibited OGD activity, as removed ROS can restore OGD activity [26]. Mitochondrial NAD+ levels, in contrast to its cytosolic pool, can be well maintained more stably [27], possibly maintaining cell survival even in stressed cells with OXPHOS better preserved [28].

Feedback of NADH into metabolism determines the rate of catabolism and energy production through changing the αKG/citrate ratio [26]. Besides, in the nucleus, NAD+ also has significant signalling roles in controlling and regulating metabolic pathways, altering sirtuin 1 (SIRT1) activity [29,30], a key regulator of hepatic glucose and lipid metabolism [31], and modifier of gene expression through histone deacetylation. Aging has been shown to promote the decline of nuclear and mitochondrial NAD+ levels [32]. NAD+ can serve as a protein modifying agent, with a direct consequence to a cellular protein activity [33]. A structural analogue to NAD+, with significantly lesser amounts, is NADP+ and its reduced form NADPH essential for detoxification of oxidative stress [34,35].

High levels of ATP and citrate inhibit phosphofructokinase, a key enzyme in glycolysis, thereby slowing down glucose catabolism when energy levels are sufficient. Conversely, low levels of ATP and high levels of ADP stimulate phosphofructokinase activity, promoting glycolytic flux to generate more ATP. AMPK as a cellular energy sensor is a key signaling pathways integrating peripheral and central metabolic signals and mediates control of metabolic homeostasis [36,37]. AMPK senses fuel availability in providing regulation of carbohydrate and lipid metabolism, mitochondrial and lysosomal homeostasis, and DNA repair [38]. AMPK also regulates autophagy and mitophagy [39,40]. AMPK affects feeding, glucose control and insulin sensitivity, regulating glucose uptake, fatty acid oxidation, mitochondrial oxidative capacity and insulin sensitivity [41]. It promotes energy production and conservation. Conversely, the mTOR signalling pathway, activated by nutrients and growth factors, promotes anabolic processes such as protein synthesis and cell growth when energy and nutrient availability are sufficient. The mTOR and SIRTs, as nutrient-sensing pathways, respond to changes in fuel molecule levels to regulate key metabolic processes such as protein synthesis, autophagy, and mitochondrial function in response to nutrient availability, energy status, and cellular stress.

The Regulated Whole as A Neuro-Metabolic Complex

Cell-Organismic regulatory needs: Different cell types require and use different fuels [42]. The transformation of the chemical energy of fuel molecules into useful energy is strictly regulated, and several factors control the use of glucose, fatty acids, and amino acids by the different cells. Red blood cells are devoid of mitochondria and therefore can rely only on glucose for ATP synthesis. The blood-brain barrier prevents the access of lipids to brain cells, which rely solely on glucose as fuel molecules, or ketones from the liver as substitute. Besides, the type of food substrate that is oxidized would change according to the physiological situation of the cell, such as the fed or fasting states. Hormones may also switch key enzyme activities and different signals dictate how cells adapt to each situation.

Local-global mix: While each level of cells, tissues and organs try to secure their share of energy and resources for their functional needs, each of them in different body locations contributes to influence as well as puts up certain controls mutually for viability of the whole. Some may be more relevant for the specific location. As an example, cholecystokinin (CCK) that stimulate gall bladder contraction, is released from intestinal "I" cells in response to feeds and stimulate the digestion of fat and protein. Its receptors are expressed in the central nervous system [43]. CCK and its variants are found in the thyroid C cells, adrenal medulla, bronchial mucosa, and spermatogenic cells [44]. The specific affinity of membrane receptors on target cells determines the action of CCK [45]. Similar discovery and characterization of gastrointestinal tract hormones has led many to regard the foregut as an endocrine organ. Now there are a lot more of gut hormones found.

Yet local controls also influence the whole. Discovery of the adipose tissue-derived hormone leptin [46] has transformed understanding of white adipose tissue from functioning as a simple energy storage depot to re-understanding it as an active endocrine organ. There are controls positioned at each site from each level but there can be controls from remote sites. Thus in bone, bone-derived factors regulate for its local bone metabolism and metabolic functions as needed, while additionally, even seemingly remotely, these factors can regulate global energy homeostasis by altering insulin sensitivity, feeding behaviour, and adipocyte commitment [47]. Similarly, in kidney which functions mainly for excretion, erythropoietin is produced by the peritubular cells to stimulate red blood cell production according to blood oxygen levels [48]. Concerning energy, whereon physiological cues and environmental signals act at different sites with complex controls, the whole may be viewed as a jumbo compo of functional nodes interacting with each other through cellular, neural or humoral signals.

A neuro-metabolic complex: Classically the hormones and neural regulation are well established for viewing the whole. As the top of a neuro-metabolic complex [49], the human brain, in comparison to other species, exhibits one of the highest energy demands relative to body metabolism [50]. Even a number of adipose secretory factors interact with neural circuits through the brain to regulate numerous processes in adipose tissues for lipid storage and non-shivering thermogenesis towards whole-body energy homeostasis [51].

Then, the hypothalamus is understood as the main regulation station [52-55], while autonomic system is the regulator arm. Sympathetic nervous systems controls catabolism on glucose and lipids, while parasympathetic nervous system contributes to anabolism and promotes glycogen storage in the liver [56]. In controlling the endocrine system, the hypothalamus acts through both the parvocellular neurosecretory projections as well as through the autonomic nervous system. The neural pathways, particularly the hypothalamic nuclei and autonomic nervous system, are pivotal in modulating the bilateral metabolic interplay between the cerebral and hepatic compartments [57].

Energy economy in organisms is organismic: Cellular signalling pathways, nutrients and environmental stimuli [58], enzyme regulation, catalytic activity, substrate availability and hormone integration all affect one another. The jumbo compo of controls may need much more to be really understood. Energy and resources are basic and expressed everywhere. As each functional part of the jumbo compo evolves in specific or dedicated functions, and when an organism expands in adaptiveness to multiple environmental variables, division of labour emerges as the only viable evolutionary strategy [59]. As external interactions magnify, necessary signals become sophisticated, internal interactive drives lead to development of comparable sophistications, even entangled through transport circulation and channels.

In the thrust to find some key explanations through the complicated mess of interrelated reactions and pathways, many axes came up for a more consolidated interpretation, including the liver-adipose axis [60], the brain-liver axis [61], gut-liver axis [62], and other different axes like gut-brain axis [63], gut-organ axis [64], heart-gut axis [65], gut-muscle [66], gut-bone axis [67], and kidney-gut axis [68], referring to their bidirectional relationship. The complicated entanglements as a whole have by no means been better depicted. Putting forward the multiple interactions of the metabolic complex, the sites, receptors, reactions and interreactions, pathways and regulations are all adding up more and more to the complexity.

Amongst the myriads of cellular, metabolic and physiological events, hormones and the brain with neurohumoral mechanisms mediate various interactions and regulations, Yet for energy concerns, the body's cells express everywhere as they interface with the environment to live. Energy metabolism in fact are organismic. Really, inter-organ and inter-tissue communication maintain homeostasis and adaptation [69]. Organs and tissues communicate under healthy and pathologic conditions by secreting proteins, lipids, metabolites, and small noncoding RNAs, whereby most tissues can communicate with local and distant tissues/organs in an autocrine/paracrine/endocrine manner [70]. The brain and the body, together with organization of cells, tissues and organs, evolved through an organismic level facing the environment. Though disorders around the metabolic syndrome now prevail medical literature, the physiology and pathophysiology of energy related disorders are far more complex. The person viewed from the whole through life coordinating myriads of scenarios for self enhancement would be a better frame for health management when energy efficiency provides adaptivity and useful patterns to suit the best survival and achieve snug-fit states positively [71] (Figure 1).

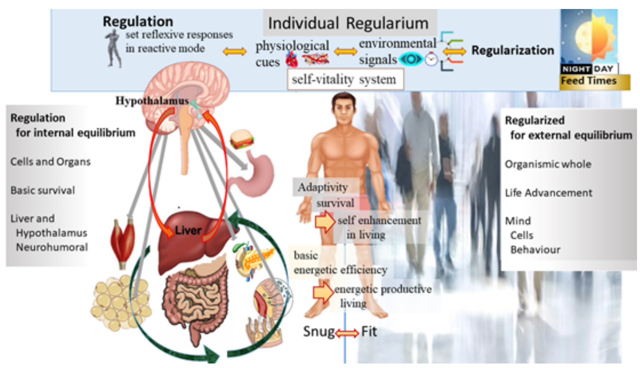

Figure 1: Regulation vs regularium.

Regularized Forward Advancement for Self Vitality

The evolutionalized sophisticated human body has become energetic productive, putting up actions and endeavours for living. Internally, mechanisms for regulation prevail, even as feedbacks in metabolism, as physiological regulation at the metabolic sites, and up to higher regulation centers. Life however is inherently unpredictable and cannot be regulated. Simply habits cannot suffice every living mode. To face and overcome unexpectedness, individuals tend to mode their living by regularizing it, through whatever understanding, feelings and believes pertaining to their life as useful.

Regulatory processes prevail and influence energy redistribution. Adaptively, regularization for a pattern of life make a consistent order for operations so that stability save energy. The multi-determined energy balance under environmental, physiological and learned influences may drive the system to energy conservatory or to energetic productive propensities [6]. Through set patterns consciously or subconsciously in various states and levels, the set regularium of each individual could function to conserve energy or being energetic productive as life requires. Regulation depend on equilibrium between different processes thus allowing these stably functioning in the body. Regularium from different body parts being coupled together in evolution of life forms synergizes actions in promoting energy surplus, developing advantageously as one co-organized control for the body to balance between actualization efforts and resources, ideally being snug and fit [71] when energy efficiency prevails.

Snug and Fit

Between adaptability and snug capacity: Not only energy homeostasis that matters, for energy is used also for individual advancement. Adaptability to fit is bestowed from genetic endowment [72]. Generally, adaptability is a manifestation of the body reacting in relation to an external environment, mainly specific environments.

"Snug" embodies a capacity to assume body stability in the environment, this capacity conducive to suiting easily in relation to different environments. The body is endowed with mechanisms for a snug entirety with equilibrial responses as well as well-coordinated mechanisms for integrality [71].

With "survival of the fittest" concept, the topic of "fitness" has become popular in biology, sociology, and various fields including even medicine, with fitness theories. Following these theories, people are driven to adapt to the environments including work and society, and as a result, currently everyone by himself or by peers is being pushed to face various stresses. Darwin must have felt misquoted as his concept became often too handy to lump everything that matters to the ability to fit. It was not meant for being the only concept for organisms to live.

"Snug" is an important concept that has been overlooked [71]. In a fuller perspective, the body is striving to meet many objectives and would be more or less tuned to the environment with internal and external processes, which varies to a degree for how the individual acts fit to the environment and stays snug to the core itself. The ability of the core to stay snug, like the ability to adapt, actually exists in every type of creature. Fit to survive; snug to live. The core actively or passively resets itself in various levels of snug states whereby the external drive for advance are supported and sufficient to cope with both the internal and external environment for fluctuations and interferences.

Achieving stability: Life is filled with examples of stability and change, even in chemical bonds and thermodynamics. Systems in equilibrium are balanced and stable. Stability generally enables change by a secure and consistent base, and the provision of resources for a better realization of the change. As homeostasis ushered by Claude Bernard in 1849 and Walter Bradford Cannon in 1926 noted often insufficient to explain the whole of internal changes, various equilibrium responses are added on including heterostasis [73] (a multistage distribution of balance), allostasis [74] (a predictive regulation to dynamic balance), hormesis [75] (dose-dependent: low dose stimulation adaptive but high-dose damaging), and others [76]. These various adaptive mechanisms in fact can be viewed as different levels of adaptability while regulating host neuroendocrine balance. Fit to the environment and snug to the core − this is a principle that is traversing all medicine.

Fit to survive and snug to live, Energy efficiency: Essentially, the body must rely on a stable core to maintain the entirety including energy and reserves to support the individual's stability in moving forward in different domains and terrains. Since childhood, the body has to move and change its form to adapt to the external environment, but the body will always return to its righted self, starting from the primitive reflexes and further from matured well-coordinated habitual patterns. The ability to body snug stems from the strong inertia as matching mechanisms from the core to the surroundings [77]. Setting the body in its basal position through righting, restitution and remodelling [71], the body core continues in snug formation while its somatic actuator axis (體本) match the surrounding environment during growing up so that that the whole person return to the snug stable frame. When the body maintains a stable position, more activities can be carried out, and, with more success in coping life events, more consolidated would this poise with readiness be, thus fitting in snug. Self-regulation of integrality that can be remodelled is a functional mechanism to achieve "snug".

This is energy efficiency, demonstrated when coping situations greatly reduce the effort and energy reserves required. Energy efficiency refers to systems that provide the same level of output or benefit with less energy consumption [78]. The most basic body strategy to manage and maintain itself well and snug is to start with well-functioning units that work for providing basic support and contingent readiness. From these emergent strength arises from performances that are repeatedly successful with consequent affirmative self-registered directives modes.

Activities under energy considerations: The body has emergent patterns resulting from the dynamics within. The body core endows the person with body anticipatory and reactive mechanisms, enhancing effectiveness and efficiency. Consolidated, the energetic productive body minimizes wastage for disparate overt actions spread diversely.

Thus energetic productive activities start with inherent energy conservation. During activities, movements are continually and automatically optimized energy wise [79-81] to serve for burning the least energy possible. Energy efficiency is a prevailing need [82] and well set and established.

Physical activity and exercise exert profound effects on energy metabolism. Physical activity can improve muscle strength and boost up endurance through increasing mitochondrial volume and adaptations [83-85]. Depending on the muscle mass involved and the intensity of the activity, the energy expenditure in activities varies. Activation of a whole cascade of sophisticated and complex neurohormonal responses guarantee proper fuel supply to muscular performance [86]. For this, body states are set various, the regularium is related to energy reserves.

Activities are generally meant for being energetic productive for life. However, engaging oneself in diverse activities in many directions is magnifying energy consumption. Streamlining life's activities in individuals is not achieved easily. But this necessary tact to reduce energy wastage is in fact evolved in human beings. Regulatory mechanisms are certainly in place; but the disparate body parts in action could form regularized couples. It is illustrated in a brain-liver dyad.

Brain Liver Dyad, In Energetic Productive with Control

Life with different environments impose limitations and demands over the body to internally regulate feasibly for a better being externally. Emergent patterns evolved from coupled organ functions make up a regularium during advancement: the brain serves to cater for myriads of activities while the liver supports for energy by provisions. In parallel with brain size evolution with more neurons, the liver evolved [87, 88] in increasing complexity and increasing dominance and size.

While body metabolism is strong with countless chemical processes on-going continuously to allow life and normal functioning, environmental demands can often topple the body energy provisions. For gaining advantage of both energetic efficiency and the capacity for energetic production at the organism level, the brain work in saliency and the body is poised in energy efficiency while the liver makes provisions frugally.

The brain in energy efficiency control: saliency

Saliency is a mechanism by which organisms survive with their limited perceptual and cognitive resources. In the interest of keeping things simple or for minimizing energy's sake, a subset of the available data becomes the highlight or the region of interest, to work out well in the multivarious scenarios.

The human brain is powered though evolution to optimize fast transmodal integration of neural activity across brain regions to support complex functions with rapid associative computational processing even for cultural and social intelligence [89]. Larger brain networks were discovered: the midcingulo-insular Salience Network (SN), the lateral-frontoparietal Central Executive Network (CEN) and the medial-frontoparietal Default Mode Network (DMN). The SN constantly monitors the external world and directs resolutions to other brain networks to react to new environmental information and stimuli. The SN mediates switching between the DMN and CEN [90,91] as the DMN shows coherent activation during resting states awake with spontaneous attention while the CEN shows activation during cognitively and emotionally challenging activities [92]. The dynamics to switch is a means to proceed in line with salience and cognitive demand.

For salience, the most valued portion of external data for individual action/memory/reactional focus is captured and assigned to the deeper brain and body as being pertinent. Vision with its distinctiveness and preciseness is by far the most dominant sensor. Over the complexity of the visual world, through an attentional mechanism over surroundings, the region on which the eyes focus first reflects the degree of importance of that angle highlighted in the human visual system. Salience and relevance yield distinct neural signals. Salience is reflected in the initial registration of the target, and relevance is reflected in the elevated brain activity following the cue [93]. Thus the properties of the stimulus itself, how the stimulus fits with its context, and the internal cognitive state of the observer can increase salience. The focus would differ during free viewing without a specified task and during intended movements which shift images to become the primary focus.

Salience allows changes in their environment be quickly detected, though noise with irrelevant features may distract and disturb saliency maps. Evolutionarily in animals, salience is tied with detection of harmful or predatory dangers even during non-attentive non-heedful wandering without conscious attention. The bottom-up stimulus-driven negative emotional salience response [94] is modulated to reach the SN [95]. Any ongoing behaviour stops and attention is reoriented to the threatening environmental cues, also with an associated increase in parasympathetic arousal [96-99]. Salience is also a response to positive stimuli when being tied with vigilant detection of prey for meal or of partners for courtship during attentive search.

Besides affecting attention and choice, salience directs the individual's action and behaviour. Choosing a course of daily-life actions requires an accurate assessment of the associated risks and potential rewards. Adaptive environmental response is the redirection of attention to salient events, particularly with novelty, motivational or emotional value, or behavioural relevance [100]. Salient information detected, the SN redirects attentional resources and autonomic processes to generate adaptive cognitive and homeostatic responses [101,102]. As a major afferent cortical hub for perceiving viscero-autonomic feedback [102], the SN provides for conscious integration of autonomic feedback and responses with internal goals and environmental demands through its role in autonomic processing [103-106]. As the SN switches between the DMN and CEN, cognitively demanding tasks will lead to increased activity in the SN and CEN and decreased activity in the DMN [101], thus more executively oriented. The activated CEN supports working memory, executive function, and cognitive control processes. The recruitment of the cortico-striatal-thalamic loop circuits that contribute to the SN, could be central to mechanisms of cognitive control [107]. Along its neighbouring cingulo-opercular task-control network, a sustained vigilance or "tonic alertness" [108] is *poised* up in a behavioural or cognitive set. Thus the SN supports each moment in life in complex social environments.

Brain and body in energy efficient preparedness: Poise

In energy efficiency, the body itself is evolved. What is salient between the person and environment is mainly for mental dispositions of interactions. For the body in ordinary accustomed scenes and moments, the habitual poise composed from repetitive patterned positioning as the "tonic alertness" is used to optimize performance at the least energy cost.

The poise externally as the stance would establish a pattern of recognizable posture and practice while holding, moving and acting with force and stability [109]. Proprioception and vision go together [110] and set the Visual-Tactile system over the motion control [111]. Age-long posture control is also mediated by vision and proprioception [112]. The poise is a stable posture set unconsciously after being repeatedly shaped and molded through dynamically correcting the position in the moments and situations of life. The poise so built up is the setup of body operational modes set for accustomed moments, for recurrent contexts, and as such can best stand up to future similar situations. Stably in semi-equilibrium between widely divergent impulses, the poise holds a readiness in supporting the body for carrying out, coping or handling issues. The body may then put up normative responses promptly with external processes or tackling behaviours by simply fine-tuning over that habitualized set. Thus trained Olympic gymnasts remain so poised whatever mentally and physically challenging the event may be. Muscles are tuned up and endomysial myo-fascia net strung with repetitive use to align with set points for spatiotemporal orientation that is cost saving over long-term repetitive adaptation.

Internally the body similarly develops certain tendencies as the homeostatic mode [71], through its poised body state, a propensity in readiness that is continually reorganized for certain dispositional saliency. The body state is the setup poised for stabilizing the body and for reacting to the environment [2,71]. The body can go fitting over repetitive circumstances by changing just a small extent so that return to the poised neutral snug position can be ready and fast. A good poise formation helps to live effectively and efficiently between dichotomous needs of body energy conservation and expensive output to fit surroundings. Constantly remodelled to allow flexibility, the response modes over repetitive situations would tune relevant body parts in working out the habitual resource allocation, mental preparation, required form changes and internal coordination mechanisms in coping similar situations. A good poise in stabilized efficient readiness thus maximizes energy efficiency [109].

The poise externally and internally as a regularium reacts in preparedness and avoids off-matching and extraneous movements and mental strain that mean unnecessary energy outspread costs. In aging, many internal changes could lead to changes in poise and body state through the years [113].

The Mental-Visual-Tactile Grasp for energy efficiency

Since actual life in a variable environment is volatile and unpredictable, unceasing tasks may pose incalculable requirements for energy and resources. To reduce uncertainties and erratic energy costs, operational systems are evolved to place the right action for the right job at the right time, a grasp of the end. Notably, energy after volitional initiation of a task would often set up an internal drive, which cannot be simply halted until the end target is reached. The end point may be a grasp of a reachable object or a mental grasp of the situation. Not able to grasp the end point in time may lead to a diversified outspread of reaching and attending to link up in a futile attempt to reach the endpoint – an increase in mental or actuational efforts and energy.

The formalized interactive visual-tactile system can adjust with input-output error tracking [110,114,115]. With salience, the interpretative elements of the visual-tactile coordinative infrastructure are linked with power of association [116]. The interpretive processes of the brain extract visual information which can be inherently ambiguous against simultaneous contextual information. For interpretation, previous and ongoing scenes and reaction patterns are gathered to form the upcoming mental picture of scenarios from lifetime scenes and worldviews. The brain for a cost-effective performance would use its heuristic system to make inferences from previous scenes and moments, projecting from situational similarities for effective coping and management of uncertainties like predator considerations in the old days and social contexts nowadays. The visual system would map the surroundings for the moment, while scenarios guide its fast adjusting and accommodative search throughout the environment with alert sharp eyes. In general, an automatic habitual gaze is critical to efficiently identify objects with value. This habitual choice is not simply related to salience as driven by learned values of physical features of objects. There is an additional drive by motivational salience salience based on facilitated “re-learning” of values that were forgotten after long-term retention [117]. The way in which decision variables are processed differs in the valuation network and in the cortico-basal ganglia-thalamic circuitry [118]. Uncertainty as risk and ambiguity are dissociated under neural dynamics during value-based decision making [119]. Both risk and ambiguity processing seem to be related with cognitive control, conflict monitoring, and increased cognitive demand [120].

Action is meant for an outcome, and outcomes may be associated with rewards or risks or other positive/negative values. Other brain regions that control eye movements also play important role in higher cognitive functions. The midbrain superior colliculus traditionally understood to help animals reflexively orient themselves toward important locations in space and directing the eyes and head toward a bright flash of light, also plays a role in complex cognitive tasks for visual categorical decisions [121]. Time to relay and energy returns is much facilitated by the mental-visual-tactile coordinative infrastructure and the salience network with the body poised in manoeuvrable readiness.

The liver in controlled support

To be well-coordinated for self advancement with mind-directed adjustments over situations, energy from metabolism have to be read. The liver may be viewed as a neuro-hormonal-organic complex for a metabolic control center besides being a metabolic store. Though the brain and body through salience and linkage mechanisms work out the best for energy efficiency in fitting the environment, ever-readiness is expensive while frugality saves energy. The liver support these in a controlled manner [122]. Thus the brain-liver dyad provide the balance and control of energy stability for supporting activity and against stress by keeping the body fuller in reserve or surplus, replenishing body turnover in energy metabolism.

The liver reacts sensitively to the body energy state. To face unsteady energy fluctuations, particularly so in animal life with uncertainty of food resources and unceasing need for activity, the body would frugally use or not use the ready stores. Liver signalling mechanisms starts with switching cellular energy processing from anabolic to catabolic states by AMPK. AMPK is activated by liver kinase B1 and this activation is regulated by nutrients and by the cellular energy state in response to a change in the cellular AMP/ATP ratio in physiological processes and pathological stresses [123]. Thus, whether liver is geared to synthesize or utilize fuel metabolites is tightly regulated according to needs and surpluses.

The liver precisely regulate glucose and lipid metabolism in healthy individuals [124]. Innervations at the portal vein, as a strategic-site sensor after GI absorption, provides metabolic sensing including osmolality [125], glucose [126] and FA levels [127]. Here, decreased portal glucose concentrations immediately can trigger increased food intake [128] particularly its initiation [129]. It detects free FA levels, affecting feeding behaviour [130] and is crucial for directing fat deposition and regulating plasma metabolite levels [131]. The afferent sensory neurons also detect nutritional and absorptive hormones like incretins (that affect insulin release), GI hormones like somatostatin and leptin [132,133] and cholecystokinin (CCK), which is released in the duodenum in response to food intake.

The liver zonation allows a distribution of complementary metabolic functions in hepatocytes along a portocentral axis. The liver performs essential functions involved with anabolic and catabolic metabolism, nutrient processing and storage, detoxification, immunity, bile and protein secretion, and other processes simultaneously with energy-efficiency through this unique anatomic-functional zonal architecture [134]. The hepatocytes at different specific position along this lobular portocentral axis, though morphologically similar, would yet accomplish very different metabolic roles according to their positions. Metabolic zonation optimizes the liver for quick adaptive functioning to exogenous nutritional challenges and endogenous metabolic demands. The liver not only functions to supply essential nutrients to the brain but also serves crucially for detoxifying. Against brain senescence, the liver helps clearing detrimental cerebral proteins [135]. Liver dysfunction correlates with cognitive decline and Alzheimer's disease [136,137]. The liver would be the earliest affected organ when amyloid pathologically sets in.

There are plenty of signalling molecules originating from the liver. Hepatocytes secrete more than 560 types of hepatokines, regulating metabolic and inflammatory diseases locally and remotely [138]. When challenged with long-term starvation or overnutrition, the liver may secrete hepatokines to influence energy homeostasis [70], and impaired hepatic insulin-sensitizing substance production may produce liver steatosis [139]. Hepatokines, metabolites and afferent sensory nerves transmit metabolic stimuli from the liver to the brain, while the brain after integrating peripheral cues influence the metabolism of the liver for macronutrients [57].

While the liver produces various humoral substances as endocrine moderators [140,141], its interplay with nervous system, particularly with the hypothalamic nuclei and autonomic nervous system, modulates metabolic functions [57]. The gut-liver-brain complex involves endocrine, humoral, metabolic, and immune interactions [142,143]. The liver works with the brain and GI tract together to cater for different needs and inputs for metabolic balances. Through the brain's own metabolic sensors peripherally, and the associated hypothalamic neural mechanisms, glucose metabolism is controlled [144]. Operationally, the brain and GI tract may act in opposition to the liver [145]. This allows the GI-liver-brain energy network to act as a mutual-balancing circuit [129]. To keep the body fuller in reserve or surplus, the liver reacts sensitively to food uptake while interacting with the gut that fills itself from time to time through hunger and satiety [146]. The liver also regulates metabolism in other organs and cells by liver-brain signals. During fasting, the liver senses glycogen deficiency and through its afferent hepatic vagus nerve, lipolytic signals switch the energy source from carbohydrates to triglycerides to maintain energy homeostasis [147]. As the brain needs glucose as the fuel, pre- and postprandial mechanisms around the liver keep blood glucose levels constant. In general, through vagal afferent signalling, the liver-brain axis exerts anabolic effects on glucose metabolism [148]. Excessive lipid accumulation induced by the increased expression of PPARγ in the liver is also signalled through the nerve to the brain to induce sympathetic activity and increased energy expenditure as a homeostatic mechanism of energy metabolism [149].

As regulation of activities is through the brain, the liver supports regulation of metabolites in the regularium to meet the expanding possibilities of activities and associated metabolic needs with cost-effectiveness and frugality in usage: for the brain, saliency, for operation, the poise for energy efficiency, for the liver, frugality for support.

Energy Wise Self Vitality

The individual may have much more needs and causes to behave and actualize himself in multi-various endeavours in his perceived and conceived world in the environment. The precarious match between energy provision and endeavour-performance would indeed be delicate. Placing the right job at the right time cannot be done sufficiently well, and regularized patterns have to be formed to match those around the person. Over these reflexively reactive mechanisms with saliency and its linkage mechanisms and frugal liver provisions, self-vitality systems have evolved. The meaning of self-vitality systems has been illustrated in neuro-circulatory perfusion [3]. Maintenance of homeostasis starts with organ systems with their set reflexive responses in reactive mode. Without psychological adjustments, an individual would presumably not develop well-coordinated patterns enough to adapt through life with many environmental uncertainties. The neuro-circulatory perfusion self-vitality system, which evolved with energy efficiency for recurring similar situations, offers the individual well-patterned emotive or motive responses to various situations, wherewith remodeling in time from anticipating, actuating, and adjusting allows a pattern-transforming ability for circulatory shifts needed to cater for endeavour-performance preparedness. Then conscious control from above would be facilitated to manoeuvre over these motive or emotive patterns to achieve snug-fit self-actualization without much undue costs for adjustments and perturbations.

Concerning energy overall to the individual, the basic energy regulation in cellular and physiological level supports the general functioning. Over basic reflexively regulated mechanisms, well-coordinated mechanisms are not manifest since energy is too basic in diverse needs and usage. The self-vitality system with regularized pattern formation above the hardcore adaptations allow better control over this basically significant resource. Patterns are achieved through simulation of environmental patterns, or doctrines and theories for a discretion of the body regularium to decipher how nature should be, or, maintenance of a body regularium as perceived being cost-effective. Coupled with the regulatory commands of the hardcore organs, forming patterns for self-vitality allow conscious control be facilitated with the body being energy efficient. Discretion for energy related activities are better maneuvered, depending on good acquisitional strategies matching energetic productive living against basic energy efficiency.

Circadian rhythms to match environments

Diurnal rhythms in gene expression as circadian rhythm occur in almost all animal tissues related to daily cycles of activity including eating, sleeping, and fasting. Circadian clocks maintain subconscious periodicity in internal cycles of behaviour, physiology, and metabolism, to enable organisms for anticipatory integration of metabolic systems that optimize energy acquisition and utilization across the light-dark cycle. Circadian clock enhances energetic efficiency through temporal separation of anabolic and catabolic reactions [150]. Organisms have to keep track of time. Placing the right job at the right time, the biological circadian clock is a mechanism that directs a certain physiological process to take place at a specific time of the day or night. This fundamental adaptation mechanism is coordinated by the brain at a general level, but each organ or tissue is also being specifically timed. Light and dark as Zeitgebers have the biggest influence on circadian rhythms, but food intake, stress, physical activity, social environment, and temperature also affect them. These external cues tune the clock on physical, mental, and behavioural changes. The core loop is assisted by accessory loops and the combination provide more levels of regulation to stabilize molecular oscillations of the clock and increase system robustness. The diurnal rhythms in >80% of protein-coding genes constitutes a conserved regulatory mechanism that integrates whole body biochemical functions over many cell types [151].

The central master clock in the hypothalamic suprachiasmatic nucleus directed by light commands peripheral biological clocks located in organs and glands throughout the body. Yet the liver clock is intrinsic at tissue-level autonomy and particularly strong to set its own pace [152,153]. Entrained by feeding-fasting rhythms [154], the liver clock drives specific metabolic processes, particularly the cyclic expression of master regulators and rate-limiting enzymes of key hepatic metabolic outputs [155]. The liver as gateway from the gut into the rest of the body is strategic as nutrients, hormones and other signalling factors from the gut pass through it before reaching wider circulation. Matched to external cues, the whole pacemaker system allows anticipation and preparation in metabolism and activity for environmental changes so as to behave appropriately with right intensity at the right time of day and event.

Doctrines, theories, and principles

While habits tend to be difficult to change, they are "entrained" by doctrinal settings. Doctrines, theories and principles are concepts and beliefs, which in many people are useful for a certain quality of life. Cognitive dissonance theory [156] describes how individuals experience psychological tension when their behaviour contradicts their thoughts and beliefs. Consistency in behaviour is something humans tends to strive for [157]. There are a whole range of less formal belief systems that people set themselves up.

Eating beliefs are prevalent. People from different cultures possess various beliefs on food. Beliefs include food functions, medicinal values, and impacts on human bodies. Culture particularly offers certain food beliefs, which were handed down from generation to generation. In a culture are customary beliefs, food rules and laws, religions, and social groupings. The socially shared taken-for-granted practices and representations about food are often fixed in individuals and routinely practiced.

Similarly, sleep beliefs affect sleep patterns. People with insomnia are less realistic than good sleepers about the amount of sleep they require. Patients with insomnia disorders have unreasonable sleep beliefs, and the sleep structure is different from that of the normal control group [158].

Maintenance of a body regularium as perceived being cost-effective

Personal values are "broad desirable goals that motivate people's actions and serve as guiding principles in their lives". These may be shaped by social norms, cultural practices, and religious influences and felt as inherently valuable. While one's capacity for autonomy is usually viewed as arising from one's cognitive capacities [159], one's poise in disposition may be a significant component of the capacity for autonomy [160]. Also, as a dynamic state of balance between stability and stability, the poise is made up in regularium from concepts about composure and movement and readiness in behaviour, even balancing over challenges and preparedness for action plans. In energy efficiency, the poise holds a readiness in supporting the body for carrying out, coping or handling issues.

While the brain serves to cater for myriads of activities, it would certainly drain and exhaust energy to face variable environments with multi-various actions and endeavours. Formed scenarios facilitate their execution, overcoming pertinent variations in activity. Situation awareness includes salience, mental grasp, vision, poised physiological responses, and perceptive scenarios. Coupled with scenarios, the brain can hold a plan in focus for long enough duration to complete it. In daytime assertive operation mode, anticipation mechanisms try to guarantees that events are fully utilized and not missed.

Problems and Diseases

Burdens on Regulation

Physiological and socioeconomic factors interact to contribute to undernutrition and overt nutrition with consequent energy imbalance [161-163]. Problems in energy metabolism are well described, from general physical wasting and malnutrition and deficiencies to obesity and metabolic syndrome.

The association of undernutrition and overt nutrition and climate change would require physiological adjustments [164]. Facing changes in physical activity, diet variations, and environments with varying temperatures and humidity levels, the organismic adaptive ability is necessary to maintain metabolic homeostasis [165,166]. Thermogenic stressors compounded with obesogenic environments demand more adjustments [167,168]. Obesity, undernutrition, and climate change co-occur in time and place, interact with each other to produce complex sequelae, and share common underlying societal drivers [169].

Dysregulatory Outcome

Chronic energy deficit can lead to health issues and exacerbate those already compromising the individual. Body size, energy metabolism has been related to health and lifespan, even starting with neuropediatric diseases [170]. Dysfunctional energy metabolism (formation, utilization, storage, signaling, and regulation) contributes to disease conditions, even cancer, immune dysfunctions, neuro-immune diseases, behavioural disturbances, cardiovascular, neurological disorders and metabolic alterations.

Energy-related pathways overlap with each other, while the body's energy needs must be fulfilled over whatever fluctuations. Metabolic adaptation among various organs and their communication extend from situations of calorie restriction, variation in temperature and responses to exercise or high physical activity [4]. Depression was found related to body temperature alterations, as higher self-reported and wearable sensor-assessed body temperatures in the day were associated with greater depression symptom severity [171].

Excess weight initiates metabolic changes with subsequent chronic disorders, including diabetes, cardiovascular diseases, cancer, and aging [172-177]. Bone which sizably takes up postprandial glucose and fatty acid that fuel specific metabolic pathways of osteoblast differentiation and endochondral ossification, would be subjected to impaired bone homeostasis, osteoporosis and a higher fracture risk in metabolic disturbances related to obesity and diabetes [178,179].

Regulatory and Environmental Deviations

Obesity may arise from the complex interaction of obesogenic environment and the epigenome [180]. Only few specific genes can be consistently identified as causative for obesity [181,182]. Epigenetic changes are adaptive. Obesogenic exposure during pregnancy increases the risk for the child to develop long-term obesity and diabetes. Notably, human milk feeding has a protective role against obesity for the child [183,184].

Multiple factors, including environmental, genetic, and epigenetic mechanisms influence the complex networks of distributed neural circuits that integrate multiple hedonic and homeostatic cues. Feeding behaviour is controlled by two closely interrelated systems: food intake and reward. Homeostatic feeding starts with nutritional information from the gastrointestinal tract and liver are transmitted through the vagus nerve to the brain; information include those from hormones, such as Peptide YY (PYY), cholecystokinin (CCK), and ghrelin, secreted by gastrointestinal endocrine cells, signalling medullary solitary nucleus and the hypothalamus, to reduce homeostatic feeding [185,186]. On the other hand, in the reward system, the nutritional information from the gastrointestinal tract and liver is transmitted to the hypothalamus and the reward system as well, as the right vagal sensory neurons mediate preference for nutritive foods [187] and the right nodose ganglion sustain self-stimulation behaviour, conditioned flavour preference, and dopamine release from the substantia nigra [188]. Motivation to consume palatable foods even with subjective loss of control over one's eating behavior is a feature of hedonic hunger [189].

Epigenetic modifications are controlled by metabolites that interact with transcription factors or histone/DNA modifications. Disturbances in the regulation of gene expression or epigenetic modifications by cell metabolism can contribute to various diseases [190].

Environmental Distraction and Regularium Distorted

Food brands and products are developed to create sweet and salty snacks with vibrant colors, often precisely calibrated industrial recipe for temptation, as eye-catching indulgence hit on salience with flashy colours. In fact, salience and reward systems are concomitantly valued [191]. And salience while advantageous can lead to biases and misperceptions.

Hedonic appetite is aroused by fatty, sugary, artificially enhanced foods. In particular, sucrose increases the levels of dopamine in the nucleus accumbens, independent of sweet taste sensing [192], probably via the portal vein-liver-brain stem axis rather than systemic glucose levels and significantly affecting the reward system [193-195].

As sleep and circadian rhythms affect regulation of metabolic processes, digression of feeding patterns is associated with obesity [196]. When rhythms of feeding behavior are altered, strong feedback is sent to the peripheral molecular clocks such that varying degrees of phase shift can cause the systemic misalignment of metabolic processes [197].

The timing of food intake is a powerful environmental cue and meal timing and dietary composition rewire the circadian clock and systemic metabolism [198-200]. Dietary habits of individuals are influenced by their social circles, with family dynamics, peer influences, and community settings. Sleep is a metabolic master switch, and regulation of the sleep–wake cycle is the most powerful means for the circadian clock to exert metabolic control over the entire body [201]. Unhelpful beliefs about sleep are well documented in depression [202- 204].

Multiple stressors need be considered. Biological rhythmicity are impaired by nocturnal activities and irregular food intake, now too common. Early disruption of rhythms in life can lead to cognitive and behavioral defects later in development. Aging also promote cognitive decline by dampening clock function [205]. Dysbalance or disruption of the circadian clock has adverse metabolic and cardiovascular consequences. And contribute to pathologies, including endocrine disruption, cancer and health problems [206- 210].

The configured rhythms are not set, but adaptive to new life scenarios. The phasic temporal structure of the oscillators may be re-configured, synchronized to recurring cues after some transition time, and consolidated. Energy and activity thereby can be re-matched by adjustment between usage and storage and phase-matched by anticipatory patterned food-activity cycles.

Conclusive Remarks

The body's energy producing and storing processes are modulated by factors including genetic composition, lifestyle choices, hormones, metabolites, and environmental fluctuations. Epigenetic modifications are related to metabolites, nutrient-dense foods, non-discretionary and meal times, and digression of sleep patterns.

Sleep and feeding are good regulators of the circadian rhythm. The liver clock is particularly set by gastrointestinal influx of nutrients. Synchronization of the liver and central clock is important for health.

While doctrines and principles build up the individual's regularium for energy productive living, the loss of these frameworks would make the person lose energy to live properly. Similarly, the amount of energy is releasable during restful state or good poise. Loss of beloved living modes cause depression.

To reduce uncertainties whereby erratic energy costs are reduced, operational systems are needed to place the right action for the right job at the right time. These include promoting poise and symmetry, exercise to increase reserves, training for matching capabilities, good patterns for work, sleep and eating, and shaping the attitudes to snug-fit. Simply patterns set by the body adaptively regularized for the environment is basic to good body functions, and energy in snug. Better snug, more fit.

For the individual, there is the need of energy which supports stability, over which, change can be facilitated. Metabolic functioning and energy utilization are not the same throughout the year as it changes along the seasons and climates. It is not the same throughout one's life, and follows a pattern before final death. The life of a person follows all life forms – from growth, transformation, maturation and finally settling down in end-stage. At the stage of growth and development, the biological robustness endowed at birth offers a lot of energy for changes. Later transformation involves molding of body and its patterns along time frames of living in environments as well as apoptosis as regulated cell deaths. In later maturation stages, energy efficiency is the main stay while energy excess can be used for energetic productive living with the installed energy wise regularized patterns and storage facilities. The balance between energetic productive living and basic energy efficiency is often difficult at this age and may lead to storage-usage mismatch and discrepancies. When aged, the better the settled regularium in terms of energy wise patterns, the better the body sustains life, and the brain facilitated for sake of operations.

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