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Optimizing our patient's entropy production as therapy?

Hypotheses originating from the physics of physiology

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Abstract

Physical laws dictate that energy is preserved; yet energy gradients irreversibly dissipate, thus producing entropy. As living complex non-equilibrium systems, humans must produce entropy continuously over time to create healthy internal emergent order. Entropy production is measured by heat production divided by temperature. Several hypotheses are presented. First, human entropy production is due to both metabolism and consciousness, dissipating energy and information gradients. Second, the physical drive for maximal entropy production is responsible for spontaneous formation of fractal multi-scale self-similar structures in time and space, ubiquitous and essential for health. Third, the evolutionary drive for enhanced function and adaptability selects states with both robust basal and maximal entropy production (i.e. the capacity to augment it when required). Last, targeted focus on optimizing our patients' entropy production will improve health and clinical outcomes. These hypotheses have implications for understanding health, metabolism and consciousness, and offer novel clinical treatment strategies.

Keywords: Maximum Entropy Production Principle; Fractal Structures; Complex Non-equilibrium Systems; Monitoring of Scale-invariant Variation, Thermodynamics

Introduction

Physicians are naturally physicists at heart, seeking to understand why their patients are ill, so as to improve their care. Our patients (and indeed all of life) are governed by the physics of non-equilibrium thermodynamics (i.e. systems of flow). Essential for our health continuously over time is our ability to constantly burn oxygen into carbon dioxide, which serves to continuously be dissipating a chemical energy gradient, and thus be continuously producing entropy. Illness is characterized by reduction in entropy production (both basal and maximal), and death by its cessation. Entropy production is defined physically by our heat production (due to both metabolism and consciousness) divided by our body temperature (i.e. $S=Q/T$). Understanding the clinical importance of entropy production requires that we explore the thermodynamic physics of physiology.

In this article, these concepts are reviewed, discussed and hypotheses presented, believing they may offer novel and helpful insights regarding understanding and treatment of our patients, and merit further investigation. Nature's pursuit of optimal entropy production is hypothesized to lead to spontaneous ordered structures that define health, where physical and evolutionary forces together shape human entropy production. The origins and health of physiologic fractal structures as well as systemic properties such as healing and consciousness are discussed along with therapeutic implications. Experiments required to disprove these hypotheses are suggested. The aim is to stimulate critical appraisal and improved understanding of the physics of physiology in order to better care for our patients.

Introduction to Entropy

A brief review of the scientific concept of entropy is essential to begin. Thermodynamic Laws inform us that energy is always conserved (First Law), yet its quality degrades (as energy quality connotes its ability to perform work), as nature will seek to spread out or eliminate energy gradients (Second Law).^(1, 2) This loss of energy's ability to perform work is measured as entropy. Change in entropy of a system is universally positive; that is, loss of energy's ability to do work is irreversible, and provides directionality to time, always moving forward. Thus, entropy is produced. Microscopically, entropy production is probabilistic: for example, a system will pursue states with greater accessible microstates (i.e. microscopic configurations) that

reflect more spreading out of gradients, resulting in greater entropy overall. If energy gradients exist, entropy production spontaneously occurs in order to irreversibly break down the gradient, as “nature abhors a gradient”.(3) If this were the end of the story, we would observe that nature would simply degrade into maximally dispersed energy gradients (i.e. an orderless soup). However in striking contrast, nature and life are characterized by the continuous creation of remarkable ordered complex systems that are far from thermodynamic equilibrium. In fact, it is precisely by continuously producing entropy (i.e. degrading energy gradients) that life spontaneously creates its internal order.

Entropy production and life

All of us are living systems that must continuously import free energy (i.e. O₂, glucose, H₂O, food), continuously export waste (i.e. CO₂, urine, stool), necessarily continuously producing entropy to our environment, until we don't, signifying the end of our life. As originally highlighted by Edwin Schrödinger (1887–1961) in 1944,(4) life derives “order from order” from generation to generation (i.e. he postulated the necessity of a genetic code), and “order from disorder” (i.e. creating internal order only if accompanied by a greater release of entropy or disorder to the environment). As any thermodynamic body, our entropy production is equal to heat production (Q) divided by temperature (T). Studying entropy production in multiple living systems, Ichiro Aoki has noted that all living creatures go through a process of initial rising entropy production, then stability, followed by a period of slow decline, then a period of deterioration to zero, synonymous with death.(5, 6) This graphical representation of sigmoidal shaped initial rise in entropy production, followed by a gently falling plateau period, followed by loss during aging and death is precisely similar to the observed pattern of VO₂max levels during growth, middle age, illness and dying.(7-9) Indeed given the association between entropy production and heat production and metabolism, it suggests the origins of organ and cellular metabolic function may be fundamentally related to entropy production.

Maximum Entropy Production

Derived from atmospheric and multidisciplinary science, increasing evidence suggests that complex non-equilibrium systems, characterized by continuous energy dissipation (and thus entropy production) will adopt stable states involving maximal entropy production (given system

constraints) such that the energy dissipation and entropy production will not only occur spontaneously, it will do so in the most efficient way possible. This Maximum Entropy Production Principle (MEPP) suggests that energy flow will naturally find the path that optimally dissipates the energy gradient, bound by the system's constraints, and will even lead to a system developing internal ordered structures, provided those structures enhance the energy flow. Although the MEPP has been questioned due to an apparent lack of clearly defined conditions required,(10-15) its application is supported in all complex non-equilibrium systems which clearly display "emergence".(16, 17) MEPP has demonstrated effectiveness in the solution of a broad variety of problems,(16, 18-21) and yet here, our focus is improved understanding of our patients and their care. To that end, we return to physiology, metabolism and structures associated with health.

Entropy production and the Origin of Metabolism and Complex Structures

A complex non-equilibrium system will adopt an internal state of greater complexity (i.e. complex order) if the state is associated with greater energy flow, which enables greater energy gradient dissipation, and thus greater entropy production; that is, ordered structures form to enhance energy flows. Examples are replete in nature, from Bénard cells (spontaneous convective flow in liquid layers) to spontaneous formation of a whirlpool that enhances the flow down the drain of a bathtub, to tornados, hurricanes and more. This physical force selects paths of system change to select states that enhance energy flow. Metabolism, the burning of oxygen to carbon dioxide is precisely the principal means aerobic cells and organisms produce entropy. Indeed, reduction of oxygen provides for "close to the largest possible transfer of energy for each electron transfer reaction", and this steep thermodynamic gradient of oxygen is believed critical to the development of multicellular complexity.(22) Furthermore, if a cooperative collective of multiple cells is capable of greater entropy production, then nature's physical drive to enhance entropy production may help drive the spontaneous leap from single to multi-cellular organisms. Analogously, the growth of cities has been enabled by the capacity to allow for greater energy flow into the city, and clearance of waste from it. Supporting this principle, Chiasson has observed a remarkable pattern of increasing energy flow normalized by system size (measure in ergs per sec per gram) universally in inanimate and then animate non-equilibrium systems since the origin of the universe; in fact, energy flow density so closely correlates with system

complexity, that is represents a reasonable measure of complexity itself.(23) Thus, according to MEPP, the origin of the complexity of oxygen burning metabolism has arisen from the dynamics of living systems adjusting themselves to lead to maximum entropy production.(24)

In addition to metabolic function, physiologic structures form spontaneously driven by MEPP. For example, the ubiquitous presence of fractal structures (i.e. those which demonstrate multi-scale self-similarity) are hypothesized to originate because they optimize entropy production. Everywhere in nature, including anatomy and physiology, fractal physical structures spontaneously form, demonstrating their defining bounded multi-scale self-similarity, that is similar characteristic patterns (e.g. branching, waves) over many scales of magnitude within the bounds of the system. Spatially, fractal structures (e.g. trees, mountains, coastlines, river deltas, lightning, tornados, whirlpools) appear ubiquitously demonstrating bounded, measurable, multi-scale self-similarity. Anatomically, alterations in these structures are associated with systemic change, known as illness in patients (e.g. altered tracheobronchial tree structure in asthma,(25, 26) altered vasculature in stroke,(27, 28) and altered CNS fractal dimensions in brain pathology(29)). Temporally, nature is also replete with complex time-series, which display power-law dynamics, again with bounded multi-scale self-similarity. These characteristics are found with heart rate variability (HRV) and respiratory rate variability (RRV), and whose complexity characteristics are preserved in health, and reduced with illness, stress and ageing.(30-53) Applying MEPP to understand the origin of fractal heart and respiratory rate dynamics, we previously hypothesized that the fractal structure of HRV and RRV develops as a self-organizing emergent event, spontaneously occurring and continuously enabling the system to optimize its entropy production.(54) Thus, nature's drive to optimize entropy production is hypothesized to explain why fractal structures are ubiquitous and spontaneously self-organizing. For example, fractal geometry of coastlines serve as an attractor, with coastlines universally and naturally converging to a fractal shape, as irregular coastlines help dampen sea waves.(55)All of this applies to the origin of complex structures observed in physical (i.e. mountain ranges, coastlines), geological (i.e. Richter's Law) systems as well as biologic systems in space (e.g. fractal vascular trees) and time (e.g. HRV, RRV). However biological systems have also been driven by a separate and complementary force, namely evolution.

Impact of Evolution

If the drive to dissipate energy gradients leads to complex dissipative structures that are a natural physical phenomenon ubiquitous in nature from whirlpools to hurricanes to trees to cities, then what impact does evolution separately have in the biological world, where selection based on survival and reproductive potential has played a central role over millennia? It would seem that these two forces, namely physical and evolutionary, would lead to independent yet related impact. It is hypothesized that while nature's physical efforts serve to augment entropy production, complexity and function, evolution selects for an additional feature, namely adaptability or ability to tolerate increased workload, measurable by the capacity to augment entropy production if and when required. Both function and adaptability, measured by basal and maximal entropy production, are thus hypothesized to be a useful means to measure health. Basal entropy production is necessary for function, maintenance and repair (i.e. healing), whereas capacity to augment entropy production and augment work output would be required for adaptability, capacity to augment workload, to evade or respond to threats, either physical or illness related. Illness is hypothesized to be characterized by reduction in either resting and/or maximal oxygen consumption; however, if the reduction in maximal consumption is profound, then a compensatory elevation in resting energy expenditure may appear as a response, for example with COPD(56) or sepsis(57). Human entropy production is most readily estimated by oxygen consumption, reflecting metabolism and heat production, assuming stable temperature. Thus, overall health, reflecting both function and adaptability, is hypothesized to be related to either the ratio or difference between maximal oxygen consumption and resting energy expenditure. Supporting both resting and maximal entropy production ensures both function and adaptability are optimized, both important to overall health. While this exploration on non-equilibrium thermodynamics may seem already too complex, it does not end with metabolic thermodynamic entropy production; informational entropy production must also be considered.

Informational Entropy Production

Greater than any other living creature, we have developed a remarkably complex central nervous system that performs an additional and vital form of entropy production. The study of entropy has long since been performed in both information science and thermodynamics.(58) Formally

linking the two, Landauer's principle states that any loss of information must be accompanied by entropy production in the environment,(59) now confirmed experimentally.(60-63) As the most cognitively advanced living creature, it is hypothesized that humans do not only produce entropy thermodynamically metabolically but also through information loss through our consciousness. To clarify, "loss of information" through consciousness connotes both a synthesis of data into meaning and storage with memory. Akin to diminishing the resolution of a photograph without losing its meaning, information loss is synonymous with entropy production, and is irreversible; and no process can result in a net gain of information over time.(64) When one translates an array of information or data into a shorter description indicating meaning or understanding, that synthesis of information connotes some loss of information, as the meanings or symbols we use to simplify the world never truly reflect all the detail of the real image.

As a thought experiment relevant to all of us, let us imagine the origins of consciousness in an unborn child approaching and then experiencing birth. Initial sensory information would be vast and largely uncorrelated, yet through repeated experiences, recurring patterns are detected, and meaning ascribed, as consciousness grows. Just considering visible sensory information, imagine the information initially exposed to a newborn infant's eye and its evolution over time; initially incomprehensible and uncorrelated, this vast array of visual sensory information is slowly reduced into meaning and memory as consciousness forms, remarkably and spontaneously in every single child. In a spontaneous emergent phenomenon, information is integrated and understood as shapes and symbols (e.g. faces, words) that effectively synthesize and reduce information into manageable quantities. The loss of uncorrelated information and gain of memories, classifications, theories, names, etc is hypothesized to represent human informational entropy production; thus, the emergence and the growth of consciousness is thus again a byproduct of nature's drive for maximal entropy production. While one imagines consciousness as a driver of creating information, its origins are derived from nature's aim to synthesize information and in so doing produce entropy. To summarize, dependent upon yet distinct from metabolism, the spontaneous emergence of human consciousness requires the processing, synthesis and storage of information, reflecting the ubiquitous phenomenon of nature's pursuit of entropy production.

Evaluation and Implications

The hypotheses that fractal structures form to augment entropy production, that health is characterized by elevated baseline and maximal entropy production, and that human entropy production includes informational processing all merit rigorous evaluation. The association between complex fractal structures and flow may be evaluated by evaluating both in broadly disparate systems, analysing the growth in flow as well as complexity of physical model of energy flow (e.g. whirlpools, hurricanes), as well as explored with computational models. The hypothesis that health is characterized by both elevated baseline and capacity to augment entropy production may be tested by measuring resting and maximal heat production of a wide variety of humans. In addition, of greatest interest to clinicians, these hypotheses may be evaluated by their potential to improve patient care.

Therapeutic Implications

The clinically relevant hypothesis to evaluate is that targeted focus on optimizing our patient's entropy production, both at rest and maximally, will improve their health and clinical outcomes. As entropy production is measurable as heat production divided by temperature, and assuming temperature remains relatively constant, and heat production varies greatly with physical activity (which drives metabolism), entropy production over time is thus closely linked to metabolism over time. Heat production reaches maximal values at near peak exercise (i.e. VO_2max) maintainable for very short intervals; yet over longer periods, heat production is predominantly secondary to resting energy expenditure (REE).(65) Pursuing a strategy of optimizing resting and capacity for maximal entropy production is concordant with existing data and care. Athletes have both elevated resting energy expenditure, and the highest levels of maximal oxygen consumption, which can be enhanced with interval exercise training.(66) If oxygen consumption (and entropy production) is markedly reduced, efforts to augment it should be instituted, by restoring what limiting factor exists (e.g. limitation in cardiac output, oxygen content, perfusion or cellular consumption). In patients, ensuring adequate oxygen delivery and ventilation, renal, hepatic and intestinal waste removal, and early ambulation after critical illness and surgery, all represent foundational therapies that support metabolism and entropy production. If entropy production is required for our patients to generate internal order (and generating internal order

might also be described as healing), then the body's ability to heal itself, in addition to the emergent appearance of fractal order occurring during embryogenesis, may simply reflect nature's physical drive for maximizing entropy production.

Given entropy production is heat production divided by temperature, therapeutic alteration in temperature offers an avenue to test these hypotheses, and to better understand physiologic temperature alteration. Hyperthermia or fever may be beneficial if it enhances entropy production or the potential for recovery (i.e. pathways leading back to recovery). Fever might thus be viewed as a means to overcome a potential barrier in order to stimulate the creation of such pathways, otherwise unavailable. As fever enhances metabolic rate and oxygen consumption(60, 67-69) as well as immune function, (70, 71) fever is hypothesized to be useful if it augments metabolism and heat production to a greater proportional extent than the rise in temperature, such that entropy production is increased; thus suppressing fever in routine infection may be harmful.(72, 73) However, in critically ill patients with markedly elevated basal entropy production (i.e. elevated REE), fever is unlikely to further augment metabolism, and thus may not be beneficial, even harmful.(74) If temperature increases without a greater proportional rise in heat production, overall entropy production is reduced. Analogously, cooling patients may help maintain or enhance entropy production, delivered locally or systemically, if the cooling does not further reduce metabolism and heat production. Certainly, hypothermia is beneficial when energy supplies are deficient, such as after cardiac arrest,(75) or for cryopreservation of tissues and embryos, when one wishes to decrease metabolism. In addition, cooling is helpful to avoid local temperature elevation after joint arthroplasty.(76) Thus, monitoring entropy production may offer a means to guide when hyperthermia or cooling are helpful and when they are not. In summary, temperature alteration is hypothesized to be therapeutic if it augments resting and maximal entropy production.

Given the association of fractal structures to optimal entropy production, then monitoring multi-scale self-similar fractal structures may assist with monitoring of systemic properties helpful to forewarn and/or guide decision making, and second, restoring fractal structures pose a means to augment basal and maximal entropy production. Health is associated with fractal fluctuations of heart and respiratory rate, and illness and aging are associated with loss of fractal variation.(77-80) Loss of fractal anatomy (e.g. emphysema, atherosclerosis) impairs internal organ specific

dissipation of energy gradients. Continuous monitoring of scale-invariant variation to detect when it is altered may offer a means of detecting the early onset of illness, or help to guide decision-making.(45, 50, 81, 82) In addition, restoring scale-invariant life-support offers value in improving oxygen delivery; for example, improvement in jugular venous oxygen saturation is observed during rewarming from bypass with biologically variable pulsatile (vs. apulsatile or conventional pulsatile) cardiopulmonary bypass,(83, 84) and biologically variable ventilation improves arterial oxygenation(85, 86). Thus, monitoring and/or restoring fractal physiology to help make clinical decisions, and/or to directly enhance entropy production may both prove therapeutic.

Last, the therapeutic implications of restoring or enhancing information processing and storage as a vital form of informational entropy production merits brief discussion. Clearly, restoring basal entropy production (i.e. basal consciousness) is a key component to critical care medicine. Avoiding or using light sedation in critically ill patients is part of standard care,(87-89) as deep sedation is harmful. A focus on restoring functional consciousness would complement existing guidelines. The question of the potential benefit of enhancing both basal and maximal information processing is worthy of further exploration; are brief periods of intense efforts to utilize information processing and memory therapeutic? The impact of this approach in clinical psychology is beyond the scope of this initial discussion.

Conclusions

All living systems produce entropy to survive; after a period of growth in entropy production, we lose it slowly during aging or abruptly during illness, and its cessation signifies the end of life. Helping our patients to optimize their entropy production at rest and maximally may assist with health and healing. Physiological and clinical research is required to critically appraise these hypotheses, with the hope that new understanding leads to improved patient care.

Declarations

Ethics Approval and consent to participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

Andrew JE Seely is the Founder and Chief Science Officer for Therapeutic Monitoring Systems, a company created to help commercialize waveform-based variability-derived clinical decision support software tools at the bedside, in order to improve care. He holds several patents related to utilizing variability monitoring to improve care.

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Author's Contributions

Dr. Andrew Seely is the sole author of this paper.

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Figure 1: Complex adaptive dissipative cognitive system

Table 1: Key concepts

Entropy Production	<ul style="list-style-type: none"> Entropy is a measure of quality of energy (i.e. its ability to perform work). While energy is conserved, energy gradients are universally and irreversibly dispersed, producing entropy (i.e. loss of energy quality). Complex non-equilibrium systems that are continuously breaking down energy gradients seek to augment their entropy production (i.e. MEPP). Entropy production equals heat production (Q) divided by temperature (T); however human heat production is largely determined by metabolism, and is greatly impacted by temperature (e.g. fever drives increased metabolism). In all living structures, an initial growth in entropy production is observed, followed by a plateau, then a fall, and its cessation occurs with death.
Physical structures	<ul style="list-style-type: none"> Fractal structures in nature (i.e. bounded multiscale self-similarity) form spontaneously in order to optimize entropy production. Fractal anatomic (i.e. tree-like) and temporal (e.g. heart rate variability) structures found in human physiology are essential for optimal systemic entropy production.
Impact of Evolution	<ul style="list-style-type: none"> The evolutionary drive for enhanced function and adaptability is hypothesized to select states with both robust basal entropy production and the capacity to augment it when required.
Informational Entropy Production	<ul style="list-style-type: none"> Humans also produce entropy through the synthesis and storage of information into meaning and memory within the central nervous system. The origin of consciousness may reflect nature's drive to produce entropy.
Health	<ul style="list-style-type: none"> Overall human health, reflecting both function and adaptability, is hypothesized to be related to elevated both resting and maximal entropy production, estimable by the basal resting energy expenditure and maximal oxygen consumption.
Illness	<ul style="list-style-type: none"> Breakdown of fractal structures in space (i.e. vascular networks, tracheobronchial tree) or time (i.e. heart rate variability) occurs with illness. Illness and aging are associated with either a decrease in basal or maximal entropy production, or both.
Therapeutic Implications	<ul style="list-style-type: none"> Optimizing our patient's entropy production, both at rest and maximally, will improve their health and clinical outcomes, including both metabolism and consciousness. Monitoring loss of fractal variability to predict clinical outcomes may be useful to assist clinical decision-making. Restoring fractal physiology through biologically variable life support may be useful to enhance entropy production. Therapeutic temperature alteration may be guided by monitoring the impact on heat production divided by temperature; hyperthermia or cooling may be beneficial if they enhance entropy production.

Figures

Figure 1

Complex adaptive dissipative cognitive system