Article

Fractal Structure and Entropy Production within the Central Nervous System

Andrew J. E. Seely [1,2,*], Kimberley D. Newman [1] and Christophe L. Herry [1]

[1] Ottawa Hospital Research Institute, 501 Smyth Road Box 708, Ottawa, ON K1H 8L6, Canada;
E-Mails: knewman@ohri.ca (K.D.N.); cherry@ohri.ca (C.L.H.)

[2] Divisions of Thoracic Surgery & Critical Care Medicine, University of Ottawa, 501 Smyth Road,
Box 708, Ottawa Hospital-General Campus, Ottawa, ON K1H 8L6, Canada

* Author to whom correspondence should be addressed; E-Mail: aseely@ohri.ca;
Tel.: +1-613-737-8899 (ext. 74032); Fax: +1-613-737-8668.

Abstract: Our goal is to explore the relationship between two traditionally unrelated concepts, fractal structure and entropy production, evaluating both within the central nervous system (CNS). Fractals are temporal or spatial structures with self-similarity across scales of measurement; whereas entropy production represents the necessary exportation of entropy to our environment that comes with metabolism and life. Fractals may be measured by their fractal dimension; and human entropy production may be estimated by oxygen and glucose metabolism. In this paper, we observe fractal structures ubiquitously present in the CNS, and explore a hypothetical and unexplored link between fractal structure and entropy production, as measured by oxygen and glucose metabolism. Rapid increase in both fractal structures and metabolism occur with childhood and adolescent growth, followed by slow decrease during aging. Concomitant increases and decreases in fractal structure and metabolism occur with cancer *vs.* Alzheimer's and multiple sclerosis, respectively. In addition to fractals being related to entropy production, we hypothesize that the emergence of fractal structures spontaneously occurs because a fractal is more efficient at dissipating energy gradients, thus maximizing entropy production. Experimental evaluation and further understanding of limitations and necessary conditions are indicated to address broad scientific and clinical implications of this work.

1. Introduction

The central nervous system (CNS) is arguably the most complex, remarkable, seemingly impenetrable, not to mention endearing and personal complex system in Nature. The emergent properties of the CNS such as consciousness, memory, coordinated movement, and homeostasis, are as remarkable as the self-organized manner in which they are formed during embryogenesis and childhood. Thus, the CNS is fertile ground to explore concepts regarding the origin of self-organized structure and function in complex systems.

Before we begin, we would like to emphasize that this is not an expert review of the CNS, nor of its associated illnesses. The articles cited in this paper represent a smattering of a much broader literature, developed by experts whom have dedicated their lives to the study of the CNS (or to the study of fractals or entropy). Indeed the ideas herein are presented humbly in particular to those scientists, to stimulate innovative ideas and research that leads to improved care. However, there is also a case to be made that the ideas presented not only apply to the CNS, but to other complex systems found in nature. Here we focus on the fractal structures and the consumption of high quality energy (and entropy production) within the CNS, a quintessentially complex system. Yet as both fractal structure and entropy production are ubiquitously present in complex systems demonstrating emergence, the hypothesized link between the two has broader reaching implications, indeed beyond biology. Regardless, it is hoped that the discussion is at the least thought provoking and enjoyable.

What is a fractal? We use the word fractal to indicate the presence of self-similarity and scale-invariance, namely that internal structures repeat themselves over multiple levels of magnification or scales of measurement. While fractals are formally defined as mathematical constructs, fractal-like structure is observed in countless domains in nature. This includes temporal fractals (e.g., earthquakes, solar flares, heart and respiratory rate variability) and spatial fractals (e.g., coastlines, mountain ranges, clouds, river deltas, vascular beds, neuronal networks), whom all demonstrate similar patterns of structure (*i.e.*, self-similarity) across multiple orders of magnitude of time and space (*i.e.*, scale-invariance) within the limits and conditions of the system. This scaling or fractal structure provides a more stable, more "error tolerant" structure [1]. As the same pattern of fluctuation or branching "runs through" a fractal, the whole structure may be characterized mathematically by a single number or dimension. Fractal temporal structure may be characterized by a straight-line plot of on a log-log graph of amplitude of variation *vs.* frequency of its occurrence, and the slope of the line is the fractal dimension. A fractal has a non-integer dimension; for example, a coastline is a fractal, and its length depends on the size of ruler used to measure it; the shorter, more precise a ruler you use to measure its length, the longer it is. The fractal dimension of a coastline is a non-integer, lying between 1 (straight line) and 2 (surface). The fractal dimension thus provides a measure of complexity of a spatial object, in that a larger fractal dimension indicates more irregularity over smaller length scales (*i.e.*, magnification), and thus more complexity. In addition, methods have been developed to measure the fractal characteristics of time-series. For example, Detrended Fluctuation Analysis [2] Power Law analysis [3] and the Hurst exponent [4] provide

quantitative measurement of the fractal properties of a time–series. Heart and respiratory rate variability, the tracheobronchial tree, non-coding DNA sequences, and gait all provide clinical examples of spatial or temporal structures with long-range fractal correlations [5–8]. Fractal temporal structures are not only present, they differ in illness states; for example, the Hurst exponent (or rather the spectrum of Hurst exponents if the time-series is multi-fractal) of a gait time-series can distinguish between young, elderly and patients with Parkinson's, and correlate with severity with patients with Huntington's Disease [4]. As we shall see, fractal structures are ubiquitously present in association with the CNS.

What is entropy? Entropy is quite possibly the most important poorly understood concept in physiology. Invoked by Rudolph Clausius (1822–1888) to help characterize and quantify the concept of *quality of energy*, or the ability for energy to do work (as not all energy is created equal) and then developed by Ludwig Boltzmann (1844–1906) and Willard Gibbs (1839–1903), who characterized entropy as a measure of disorder, related to the number of microstates that are accessible to a system. Claude Shannon (1916–2001) pioneered the mathematical field of information theory and invoked the word entropy to describe the informational content contained in a message. William Thompson (1824–1907), and more recently Atkins [9] and Lambert [10], have popularized the concept of entropy as the process of energy dispersal at a given average temperature (*i.e.*, spreading out or elimination of energy gradients). While not immune from controversy, this approach appears to be complementary to other ways of describing entropy, and aids in teaching thermodynamics. With this approach, greater entropy (multiplied by temperature) is equal to greater energy dispersal, or greater spreading out of energy. This is distinct yet complimentary to other characterizations of entropy as greater disorder, more accessible microstates (*i.e.*, microscopic configurations) for a given macrostate (*i.e.*, system state), or as a measure of information. Entropy comes alive with the Second Law of Thermodynamics. Also having many formulations, the Second Law states that entropy change of a system and its surroundings is always positive. Relating to entropy as energy dispersal, "nature abhors a gradient" [11], or in other words, energy spontaneously will disperse if not hindered from doing so, thus producing entropy. This spontaneous entropy production is irreversible, creating a one-way arrow of time, indeed unique in physics.

Why focus on entropy production within the CNS? First, entropy production is essential for any biologic order. As highlighted by Edwin Schrödinger (1887–1961) in 1944 [12], given the Second Law, the only way life (*i.e.*, the beautiful order we see around us in nature) may exist, is if it is accompanied by release of entropy to the environment; indeed the "disorder" or entropy released to the environment must be greater than the "order" (*i.e.*, negative entropy) created internally for life to exist. The CNS is a quintessential complex system; it creates remarkable internal order, and thus must produce entropy in enormous quantities, which it does by consuming high quality energy releasing lower quality energy (through the process of oxygen metabolism and glycolysis). As all complex systems display emergence, our focus on entropy production enables a broader discussion that goes beyond the CNS. Last, our focus on entropy production is affected by our ability to measure it; studying entropy production of animals, humans and aquatic systems, Aoki notes that we cannot measure entropy content of living things, but we can study their entropy production [13]. Thus, entropy production is our focus.

Given this background, the aim of this paper is to explore and discuss the relationship between fractal structures and entropy production within the CNS. In Section 2, we explore spatial fractal structures that make up physical organization in the CNS, and evaluate changes in fractal network structure associated with aging and disease. In the third section, we briefly mention temporal fractals associated with the CNS and CNS illness (*i.e.*, electroencephalography), but note that the literature in this domain is much broader and merits a wider review than is possible here. In Section 4, we explore entropy production as it pertains to the CNS. We highlight oxygen consumption and glucose uptake as two accessible measures of entropy production, and evaluate the change in these measures again in association with aging and illness. Following this review and analysis regarding fractal structures and metabolism in the CNS, we will seek to link these ideas in a discussion (Section 5), followed by brief conclusions (Section 6).

The link between fractal structure and entropy production is a continuance of a prior exploration of the physiologic dimensions of variability of biologic measures such as heart and respiratory rate [14]. Electroencephalography (EEG), the *de facto* multi-dimensional time-series associated with the CNS, has been extensively studied with respect to its scale invariant properties [15–17]. Heart rate variability (HRV) and respiratory rate variability (RRV), similarly demonstrate fractal properties, which are mutually independent of one another [18–20]. Indeed, the origin for these naturally occurring fractal time-series within biology, geology, climatology, we believe, are similarly related to the origin of naturally occurring fractal spatial structures everywhere in nature. We have previously hypothesized that biologic variability contains (at least) two dimensions, namely overall degree of variation, and its complex scale-invariant fractal-like properties. We believe that overall degree of variation reflects adaptability of the system, and postulate it is proportional to the ratio of the maximal work possible (W_{max}) divided by resting work output (W_{rest}), *i.e.*, W_{max}/W_{rest}. Second, we believe that the fractal structure of variability develops as a self-organizing event, spontaneously occurring to enable system level optimal and stable entropy production [14]. Focusing on this second hypothesis, for this discussion, we will focus on the fractal spatial properties and their potential relationship to entropy production, within the CNS.

2. CNS Fractal Spatial Structure

The CNS physical structure is characterized by fractal neuronal and vascular anatomy. As fractal structures demonstrate self-similarity in shape over a range of spatial scales, fractal measures provide an estimate of structural complexity. The concept of the mammalian brain as a fractal structure was presented by Hofman in 1991 who provided a strong case in favor of the fractal geometry of the human cortex based on the surface-to-volume relations [21]. Studies on the human cortex, external cortex surface and the interface between human white and grey matter confirm their fractal dimensions [22–25]. Fractal measures have been used as measures of complexity in dendritic arborization of spinal cord neurons [26] and in the characterization of the complexity of grey matter and white matter structures of the brain [27–29].

There are several methods for computing the fractal dimension of objects including caliper methods [30,31], box-counting algorithms [30,32], dilation methods [33], and spatial frequency analysis [25]; however, for structural analysis of the CNS, the most prevalent method appears to be box-counting algorithms used on magnetic resonance imaging (MRI) of the brain. The traditional

box-counting method functions by repeatedly covering the fractal image with different-sized boxes and then evaluating the number of boxes needed to cover the fractal completely, resulting in a logarithmic function whose slope is the fractal dimension (FD) [30]. This 2D box-counting method was later modified including the implementation of HarFA software for fractal and harmonic analysis of 2D digitized images and modification of the box-counting mechanism, choice of box sizes and single slope analysis [34]. Based on the two dimensional (2D) box-counting method, a three-dimensional (3D) box-counting method was developed which incorporates a shape descriptor representing interior structure and combines interior structure with surface and general structure simultaneously providing a more comprehensive characterization of brain structures [28,29]. Because fractal objects in nature possess a limited range over which they exhibit fractal properties, fractal dimension is computed using data points on the linear portions of the box-count-box-size curve, where these data points demonstrate scale invariance.

Several studies have demonstrated that fractal measures are complementary to traditional measures of brain structure based on cortical thickness, grey matter volume [35] and voxel-based morphometry [36]. Furthermore, neuronal differentiation and synapse formation have been shown to occur in time and space with fractal dimension [37]. A more recent study has demonstrated a robust estimation of fractal measures for characterizing the structural complexity of the human brain including the pial surface, cortical ribbon volume, white matter volume and grey matter/white matter boundary [38]. What "added value" these techniques offer remains under investigation, usually in association with clinical problems.

2.1. Aging

Fractal studies on the development and aging of the human brain have shown increasing cortical complexity in early fetal life [39,40], and throughout childhood into adulthood [41] with decreasing complexity later in life [28,42,43]. In fact in 2001, Blanton and colleagues demonstrated that the complexity of the cortex folding characterized by fractal dimension increases with normal brain development over the first two decades of life in normal children [41]. In relation to cognitive changes and age, a study on the association of fractal dimension and white matter of the brain revealed that subjects with greater white matter complexity have greater than expected fluid abilities than predicted by their childhood intelligence and less cognitive decline between the ages of 11 and 68 years of age [44]. A study on the quantitative evaluation of age-related white matter microstructural changes on MRI multifractal analysis revealed a significant increase in both heterogeneity of the frontal lobes and executive dysfunction scores in healthy elderly subjects compared to young healthy subjects, suggesting that microstructural changes in the white matter preferentially occur in the frontal region with normal aging, and that these changes are associated with executive cognitive decline related to subcortical dysfunction [43].

2.2. Epilepsy

Epilepsy is a disorder characterized by paroxysmal brain dysfunction due to excessive neuronal discharge, and usually associated with some alteration of consciousness. Studies of interictal MRI scans by Cook and Free demonstrated reduced fractal dimensions in approximately half the patients

with frontal lobe epilepsy [24] and abnormal fractal dimensions in half patients with cryptogenic epilepsy [23], respectively.

2.3. Multiple Sclerosis

Multiple Sclerosis is a chronic inflammatory neurodegenerative disease caused by the destruction of myelin surrounding the neurons in the CNS. Compared to normal healthy subjects, patients with MS have been shown to have a significant decrease in white matter fractal dimension in both sections with MS lesions and sections with normal appearing white matter [45]. Conversely, one study of the fractal dimension of grey matter has shown that MS patients have a significant increase in grey matter fractal dimension compared to controls and such differences were apparent even in patients with first attacks of MS and patients with relapsing-remitting MS [46]. The difference in the structural changes in the white matter *vs.* grey matter suggests that different pathological processes are taking place. Moreover, these studies suggest that fractal dimensions might be a useful marker of diffuse damage even in its early stages.

The increase in grey matter fractal dimension seen in MS could be related to an increase in grey matter abnormalities, which has also been reported in grey matter fractal dimension analysis in schizophrenia [47]. In this study, schizophrenic patients had significantly larger fractal dimensions compared to healthy control subjects for whole brain volume and right hemisphere indicating differences in structural anomalies of the cortical folding.

2.4. Alzheimer's

Alzheimer's disease is a degenerative brain disease associated with dementia and is marked histologically by the degeneration of neurons in the cerebral cortex and the presence of neurofibrillary tangles and plaques containing beta-amyloid. Fractal studies of MRI in patients with Alzheimer's disease have revealed decreased fractal dimensions compared to control subjects for the anterior tip of the temporal lobe, the mammillary bodies, the superior colliculus, the most posterior edge of the corpus callosum, the inferior colliculus, and mid thalamus [42]. A subsequent study demonstrated that fractal dimension of the cortical ribbon in mild Alzheimer's patients was significantly different from that of the control subjects [48]. Of the brains used in this study it was found that atrophic changes that occur on the pial surface may either increase or decrease complexity—where changes in the pial surface that decrease folding decrease complexity and a changes that increase sulcal length increase complexity. The cortical ribbon was used to overcome the conflicting effects of the pial surface by inclusion of cortical thickness changes and structural changes at the grey/white matter junction. Overall these studies demonstrate the potential clinical application of cortical fractal dimensions as markers for structural changes that occur with Alzheimer's disease.

2.5. Stroke

A stroke is caused by an interruption of blood flow to the brain due to a rupture or blockage of a blood vessel and which results in the death and damage of neurons in the brain. In the case of stroke, research has shown that white matter complexity decreases following stroke [49]. More specifically, white matter complexity was lower in the stroke-affected hemisphere where greater residual

complexity was associated with improved motor function of the upper extremity in patients with left-subcortical lesions and right-cortical lesions with a more robust association in patients with lesions in the right hemisphere. Thus, fractal dimension assessment of brain white matter structural complexity may serve as a sensitive measure of brain white matter reorganization following a stroke.

2.6. Cancer

Cancer is the result of genetically-induced cell dysregulation based on cancer-associated mutations. Fractal studies on images of malignant tissues have revealed an increase in fractal dimension in malignant *v.s* normal tissue and an increase in fractal dimension/complexity with tumor grade in many different forms of cancer including brain [50,51], breast [52,53], cervical [52,54] and hepatocellular carcinomas [55]. These studies demonstrate the clinical potential of fractal analysis in the diagnosis and grading of malignant tumors. However, research on fractal dimension and vascular patterns in cancerous tumors have shown varied results. For instance, fractal studies on the microvasculature of grade II and grade III gliomas have demonstrated an increase in fractal dimension with tumor grade [50,51]. Furthermore, studies of hepatocelluar carcinomas have shown an increase in the fractal dimension of vasculature structures in malignant tissue compared to normal tissue, where the vessels of primary tumors showed greater fractal dimension when compared with hepatic metastases [55]. Conversely, fractal studies have also demonstrated that the microvasculature in normal pituitary tissue is more complex than in benign pituitary adenomas [56] and correlates with earlier findings demonstrating reduced microvascular complexity in malignant PRL producing carcinomas *vs.* benign pituitary adenomas [57]. Hence, it may be that some pituitary tumors may progress via a non-angiogenic pathway, which has also been demonstrated in a subclass of primary non-small cell lung cancers and glioblastomas which progress without neo-vascularisation and are more clinically aggressive than angiogenic tumors [58–61]. Overall, the variation in fractal dimension of cancer cells/tumor structure and vasculature is reflective of the complex nature of cancer and is determined by a multitude of factors including the origin of the tumor and the microenvironment. However, more importantly these studies demonstrate the clinical value of fractal dimension and complexity in the characterization and diagnosis of cancer.

3. CNS Temporal Fractal Structure

As previously mentioned, the CNS also exhibits temporal fractal structures, as measured by EEG, which measures electrical activity along the scalp, measuring voltage fluctuations from current flows within the neurons of the brain. While a comprehensive discussion of the fractal-like properties of EEG, and their alteration in illness states is beyond the scope of this paper, here we simply highlight several findings demonstrating that change in fractal dimension is associated with a switch from healthy to pathological state or an increased severity of illness. For example, the fractal dimension (FD) of resting EEG recordings of Alzheimer's patients was found to be lower than that of control subjects [62]. Ahmadlou *et al.* reported similar findings showing a high discrimination rate of Alzheimer's patients based on a global FD average over all loci in the β EEG sub-band [63]. Gomez *et al.* found that the FD of magnetoencephalography (MEG) recordings of 20 Alzheimer's patients were statistically significantly lower in 71 out of 148 channels than in 21 elderly controls [64]. In contrast, epilepsy is

associated with increased fractal dimension of the EEG. Bullmore *et al.* demonstrated in epileptic patients that FD rapidly increased across several SEEG channels at ictal onset and that the severity of the seizures was related to the increase in FD [65]. Others used alternate fractal properties to detect epileptic seizures [66]. Brain complexity was shown to globally increase with age using correlation dimension on resting EEG data, with a big jump during maturation (7–25 years old) and a slower growth up to 60 years old [67]. Finally, linking heart rate dynamics to CNS injury, He *et al.* reported on 327 patients with right or left-sided stroke that the FD of heart rate variability (HRV) is related to the risk of death after stroke, showing that the lower the FD, the greater the risk of death [68]. While greater exploration is undoubtedly necessary, these observations support a link between spatial and temporal fracture structure, highlight how alterations in temporal fractal structures occur in association with illness, and last, how there may be a pattern of increase, followed by decrease in EEG fractal dimension over the span of a human life.

4. CNS Entropy Production

Entropy is a concept originally from physics whereas metabolism is born of chemistry and physiology, yet both are essential to life. Metabolism is defined as the sum of the physical and chemical processes in an organism necessary for the maintenance of life. Entropy production is defined as the dissipation of energy gradients within an organism and to its environment, and is also necessary for the maintenance of life. The fundamental thermodynamic relation states that entropy production (multiplied by temperature) equals the sum of change in internal energy (through chemical reactions) and work. As both work and chemical reactions lead to heat, the heat production of a biologic system is proportional to its entropy production. Heat production occurs from chemical energy release, during the breakdown of macromolecules to create high-energy compounds (e.g., adenosine triphosphate) either through oxygen metabolism (oxygen consumption, carbon dioxide and waste production) or to a lesser extent, glycolysis (glucose converted to pyruvate); nonetheless, both are present in the CNS. We inhale oxygen, which is transported to tissue mitochondria, where metabolism contributes to the breakdown of macromolecules (carbohydrates, lipids, proteins) to liberate high quality chemical energy that drive work, all leading to heat dissipation, and entropy production [13]. Without oxygen consumption and glycolysis, we cannot produce heat, release entropy to the environment, cannot maintain homeostatic order, and we perish in a matter of minutes.

This relationship is further supported by studies demonstrating that the respiration (oxygen consumption and carbon dioxide production) in aquatic communities is closely related to entropy production, albeit they are measured in different units [13]. Thus, returning to the discussion of the CNS, we assert that CNS entropy production may be estimated by the burning of oxygen to carbon dioxide (measured for whole body as VO_2), or glucose metabolism (measured in individual organs using fluoro-2-deoxyglucose (FDG)-PET imaging). While further study is needed to understand the limitations of using oxygen and glucose metabolism as proxy measures for entropy production, we nonetheless will begin to explore the relationship between these measures and aging and illness.

The brain has the most abundant energy metabolism in the human body. Although it accounts for only 2% of total body weight, the brain requires approximately 20% of the total oxygen supplied by the respiratory system and 25% of the total body glucose in the resting awake state [69,70]. In fact, glucose is now recognized as the predominant energy substrate for the brain under physiological

conditions [71] and in the resting awake state cerebral glucose metabolism is considered a reliable index of neural activity [72]. As a result of its marked energy consumption, the brain is vulnerable to impaired glucose metabolism and indeed both hypoglycemia and hyperglycemia have been shown to affect the CNS and more specifically cognitive function [73–76].

4.1. Aging

The study of entropy production over the course of a human life has been studied by Ichiro Aoki [77–79]. Aoki calculates entropy production related to dissipation of energy and mass to the environment, and finds the entropy change due to mass exchange to be negligible (~2%), leaving the bulk of entropy production relating to heat loss due to radiation and evaporation of water. Measurement of metabolic entropy production (equal to heat production due to metabolism divided by temperature) per unit surface area was then found to be equal to total entropy production of the human body per unit surface area [77]. Multiplying by surface area, Aoki and others have tracked the change in human entropy production over a lifespan, finding a rapid rise from birth to age 16–18, with a slow drop-off afterwards [77]. It is noteworthy that this rise (in childhood and adolescence) and fall (after early adulthood) in entropy production occurs in conjunction with rise and fall in VO_2max tracked over a similar timeframe, used in sports medicine to evaluate overall level of cardiopulmonary fitness [80]. Moreover, studies have shown glucose metabolism, as measured by [^{18}F] fluoro-2-deoxyglucose (FDG)-PET, declines with age with significant decreases detected in the frontal and temporal lobes with normal healthy aging [72,81,82]. These findings on glucose metabolism are consistent with studies on fractal structure changes in the brain with aging which indicate that white matter microstructural changes occur predominantly in the frontal lobes with normal aging [43].

4.2. Epilepsy

In epilepsy focal interictal hypometabolism has been found to correlate with seizure foci; however it is unknown whether the hypometabolism is the result of the effects of repeated seizures, a pathological process or an initial insult [83]. Moreover, hypometabolism is less likely in children with new onset of seizures and it is hypothesized that synaptic mechanisms rather than neuronal loss may contribute to the hypometabolism [83,84]. FDG-PET studies revealed that glucose hypometabolism is a sensitive marker for locating the epileptogenic region in patients with temporal lobe epilepsy; however, the temporal hypometabolism was not related to the severity of the hippocampal damage [85]. Hence, hypometabolism indicates areas of malfunction but may not reflect the degree of altered fractal structures occurring in the brain associated with epilepsy.

4.3. Multiple Sclerosis

In MS, hypometabolism is widespread including the cerebral cortex, subcortical nuclei, supratentorial white matter and infratentorial structures with the most dramatic reductions occurring in the superior mesial frontal cortex, superior dorsolateral frontal cortex, mesial occipital cortex, lateral occipital cortex, deep parietal white matter and pons [86,87]. In fact the severity of cerebral hypometabolism was found to be related to the number of relapses and suggests that the measurement of cerebral hypometabolism in MS has the potential to be a clinical marker for monitoring disease

progression [88]. Moreover, reduced thalamic and cerebellar glucose metabolism was negatively correlated with total lesion volume [89]. Conversely, research has revealed regions of increased cerebral glucose metabolism in MS patients in both the parietal and frontal cortex, suggesting a cortical compensatory mechanism and regional cortical reorganization as these areas of higher metabolism were close to cortical areas of hypometabolism [89]. Like the MS fractal studies which demonstrate a decrease in white matter fractal dimension [45] and an increase grey matter fractal dimension [46], the metabolic studies are reflective of these results with concomitant increases and decreases in glucose metabolism, suggesting again a link between fractal structure and metabolism.

4.4. Alzheimer's

In Alzheimer's disease, cerebral glucose hypometabolism is an invariant pathophysiological feature and its occurrence precedes cognitive symptoms and pathological changes for years or even decades [90–94]. Alzheimer's patients demonstrate reduced regional glucose metabolism in the posterior cingulate cortex and parieto-temporal lobe in the early stages spreading to the prefrontal cortex with disease progression [95–97]. This research correlates with fractal studies on Alzheimer's patients demonstrating reduced fractal structures in the brain including regions of the temporal lobe [42] and suggests a possible link between glucose metabolism, fractal dimension and pathogenesis in Alzheimer's disease.

4.5. Stroke

Stroke produces an area of focal damage and distant areas of reduced blood flow and metabolism known as diachisis. In fact, contralateral cerebellar hypometabolism is a well established remote functional effect of cerebral damage, where the value of cerebellar metabolic asymmetry has a positive correlation with neurological status and the size of the infarction [98,99]. Remote metabolic depression is the result of suppressed synaptic activity due to a direct or transneural disconnection and the mapping of these areas allows for identification of disrupted networks as a consequence of stroke. In a case study of a patient with stroke in the left cerebral hemisphere, hypometabolism in the contralateral cerebellum and as well as hypometabolism of the primary insult in the left cerebral hemisphere was demonstrated 20 years post-stroke [100]. Cases of ipsilateral cortical hypometabolism have also been reported suggesting widespread neural effects of focal brain lesions [98]. Early studies demonstrated a significant association between reduced ipsilateral cortical metabolism and the occurrence of aphasia or neglect following subcortical stroke [101,102]. Furthermore, studies have demonstrated that subcortical stroke produces global cerebral hypometabolism which has a negative correlation with cognitive function and clinical status of the patient [103]. Overall the loss of complexity and fractal dimension in the brain following stroke correlates with these metabolic studies, demonstrating a concomitant reduction in fractal dimension and cerebral metabolism as a consequence of stroke.

4.6. Cancer

Most cancers including gliomas, CNS lymphomas and pituitary lesions are hypermetabolic with a high rate of glycolysis quantifiable by ^{18}F-FDG PET [104–109]. In fact ^{18}F-FDG has been the choice tracer for oncologic PET imaging despite its high uptake in normal grey matter [110,111]. ^{18}F-FDG

studies reveal a positive correlation between glucose metabolism and degree of malignancy in primary cerebral tumors [112–114] and CNS lymphomas [104,105]. Moreover, studies have demonstrated a negative correlation between tumor hypermetabolism and prognosis/survival [104,105,114–116]. Other principal challengers of ^{18}F-FDG include radiolabeled nucleosides (e.g., deoxy-^{18}F-fluorothymidine) which assess cellular proliferation and positron labeled amino acid analogs including ^{11}C-methionine and ^{18}F-fluorethyl-L-tyrosine, which participate in the increased protein metabolism of glioma cells and provide information on cellular proliferation [111,117]. Advantages of such tracers include lower background activity in normal brain tissue and improved detection of low-grade tumors [111,118–120]. In relation to fractal dimension, the hypermetabolism of cancer cells corresponds to the increase in fractal dimension in malignant tissue and with tumor grade in many different forms of cancer including brain [50,51], breast [52,53], cervical [52,54] and hepatocellular carcinomas [55]; and also corresponds to the increase in fractal dimension of tumor vasculature as seen in gliomas [50,51] and hepatocelluar carcinomas [55].

5. Discussion

Based on research within the CNS, we observe that increased fractal dimension in spatial structure is associated with increased entropy production, as measured by metabolism (see Table 1 for a summary). In brief, fractal dimension within the CNS increases with childhood and adolescence, and then decreases in association with age, [44] which parallels the rise and fall in entropy production over the same time frames [77] as well as the decrease in glucose metabolism with age [72,81,82]. Moreover, fractal studies have demonstrated a decrease in fractal dimension of the CNS with illness (*i.e.*, Alzheimer's [42], epilepsy [23,24], MS [45], stroke [49]) which correlates with metabolic studies demonstrating a decline in glucose metabolism with illness [83,85,88,90–97,101–103]. Conversely, there are diseases which demonstrate an increase in fractal dimension including cancer [50–55] and grey matter structural changes in MS [46]. Of significance, these diseases which demonstrate an increase in fractal dimension also demonstrate an increase in glucose metabolism. Overall these findings suggest a possible link between fractal structure and metabolism, and in general, support the association between network structure and function.

The association between network structure and function is by no means new, and has been recently reviewed by Suki, focusing on the emergence of life, genetic function, cells, and consciousness [121]. Suki proposes that phase transitions in structure enable phase transitions in function. Suki suggests that as network structure goes from sparsely connected to highly connected, there is a step-like, sigmoidal phase transition with a period of rapid increase in function, with a small change in network structure. Others, such as Maynard Smith and Szathmary [122,123], Macklem [124,125] have also highlighted the importance of transitions or phase transitions during evolution and the emergence of life, respectively. Here we highlight the role of fractals within the discussion of networks, function and phase transitions, noting that fractals are ubiquitously associated with phase transitions that involve dissipation of energy gradients.

Why do fractal structures and entropy production occur spontaneously in nature, during embryogenesis or plant growth, or adventuring beyond biology, during formation of river deltas, coastlines, mountain ranges, clouds, and so much more? The answer may have to do with the principle of maximum entropy production (MEP). The second law states that energy gradients will spontaneously

disperse leading to an overall increase in entropy (*i.e.*, law of increasing entropy); however, the MEP principle advances this theory in a subtle, yet critical fashion: energy dissipation will not only occur spontaneously but also will do so in the *most efficient way possible*. Heat flow will take the path of least resistance. Water on the top of a hill will naturally find the most efficient way to get from the top to the bottom. As articulated by Swenson, a "system will select the path or assembly of paths out of otherwise available paths that minimizes the [energy] potential or maximizes the entropy at the fastest rate given the constraints" [126]. However, as with water flowing down a hill, there is inherent stochasticity and chaotic dynamics. Thus, as with the second law, the MEP principle predicts probabilities, not certainties. Dewar has articulated a derivation of the MEP principle, expanding on work done by Edwin T Jaynes (1922–1998) regarding Shannon entropy [127]. As mentioned by Dewar, the MEP principle predicts reproducible (*i.e.*, the most probable) behaviour under the systems constraints [128]. The MEP principle has been applied widely, in particular in relation to atmospheric science, ocean circulation, ecology, the study of turbulence, and photosynthesis [129]. Dewar has shown that maximizing entropy production unifies multiple plant optimization theories that explain plant and ecosystem functioning [130] and the MEP principle may offer a general objective function for biological systems [131]. We have hypothesized that the spontaneous self-organization of fractal structures in time and space (e.g., lightning, coastlines, embryogenesis) occurs principally because those structures optimize their ability to dissipate energy gradients and thus produce entropy [14]. If this is true, self-organizing fractals and entropy production are not only ubiquitous but inextricably bound to each other.

Table 1. Changes in CNS Fractal Dimension and Entropy with Disease and Aging. <u>Abbreviations</u>: ⇓ decreased; ⇑ increased; ⇔ is associated with/related to; FD fractal dimension (SEE REFERENCES).

Pathology	Fractal Dimension (FD)	Entropy
Aging	⇑ FD of the cortex early in fetal life and childhood into adulthood [39–41]	⇑ human entropy production from birth to age 18 [77] ⇓ human entropy production after early adulthood [77]
	⇓ FD of the cortex and white matter in late adulthood [28,42,43]	⇑ and ⇓ entropy production correlates with ⇑and ⇓ in VO$_2$max in childhood and early adulthood, respectively [80] ⇓ entropy production—decreased glucose metabolism in frontal and temporal lobes with normal healthy aging [72,81,82]
Epilepsy	⇓ FD of white matter in half the patients with frontal lobe epilepsy [24] Abnormal FD of the cortex in half the patients with cryptogenic epilepsy [23]	⇓ entropy production –interictal glucose hypometabolism correlates with epileptogenic region [83,85]

Table 1. *Cont.*

Pathology	Fractal Dimension (FD)	Entropy
Multiple Sclerosis	⇓ FD of white matter containing MS lesions and normal appearing white matter [45]	⇓ entropy production—glucose hypometabolism of the cerebral cortex, subcortical nuclei, supratentorial white matter, infratentorial structures, superior mesial frontal cortex, superior dorsolateral frontal cortex, mesial occipital cortex, lateral occipital cortex, deep parietal white matter and pons [86,87]
		Degree of cerebral hypometabolism ⇔ number of relapses [88]
		Thalamic and cerebellar glucose hypometabolism ⇔ total lesion volume [89]
	⇑ FD of grey matter [46]	⇑ entropy production—increased cerebral glucose metabolism in the parietal and frontal cortex located close to areas of hypometabolism [89]
Alzheimer's	⇓ FD of anterior tip of the temporal lobe, mammillary bodies, superior colliculus, posterior edge of the corpus callosum, inferior colliculus and midthalamus [42]	⇓ entropy production—cerebral glucose hypometabolism including the posterior cingulate cortex, parieto-temporal lobe and prefrontal cortex [90–97]
	FD of cortical ribbon significantly different from control subjects [48]	
Stroke	⇓ FD of white matter in stroke-affected hemisphere [49]	⇓ entropy production—contralateral cerebellar hypometabolism [98–100], hypometabolism of primary insult [100], ipsilateral cortical hypometabolim [98,101,102], global cerebral hypometabolism [103]
		Contralateral cerebellar hypometabolism ⇔ size of infarction [98,99]
		Ipsilateral cortical hypometabolism ⇔ occurrence of aphasia/neglect [101,102]
		Global cerebral hypometabolism ⇔ cognitive function and clinical status [103]
Cancer	⇑ FD of tumor microvasculature of gliomas [50,51]	⇑ entropy production—glucose hypermetabolism in gliomas, CNS lymphomas and pituitary lesions [104–109]
	FD of tumor microvasculature of gliomas ⇔ tumor grade [50,51]	Glucose hypermetabolism ⇔ degree of malignancy in primary cerebral tumors [112–114] and CNS lymphomas [104,105]
	⇓ FD of tumor microvasculature of benign pituitary adenomas [56] and malignant PRL producing carcinomas [57]	Tumor hypermetabolism ⇔ prognosis/survival [104,105,114–116]

There would be numerous ways to test the hypothetical link between self-organizing fractal structure and entropy production within the CNS. During embryogenesis, are there metabolic, energy, and/or chemical gradients that accompany the formation of fractal structures? If one experimentally

eliminates those gradients, is there a resultant alteration of fractal structure? In physical structures such as fluids, does the appearance of a self-organized fractal whirlpool increase the rate at which water is drained from a bathtub? Does the elimination of the whirlpool reduce the rate at which water is draining? There would be multiple means to test these hypotheses. The application of entropy production to turbulence, a chaotic fractal structure associated with diffusivity and dissipation, would merit investigation, and is beyond the scope of this paper.

There is yet a further avenue for exploration that has not been yet addressed nor could be fully developed in this paper. As discussed above, Aoki has calculated the entropy production due to mass and energy dissipation in humans, and found that increases occur in the first two decades of life, with slow decline thereafter [77]. However Anokhin demonstrated that EEG fractal dimension continues to increase up to age 60 or so [67]. Is it possible that the CNS is performing another means to produce entropy other than mass and energy dispersal? What flows through the CNS almost as continuously as oxygen? Information! Information as energy and mass is not a new idea. According to Duncan and Semura [132,133], the Second Law may be formulated in terms of increase in entropy being equivalent to a loss of information (*i.e.*, classical information). This work again builds on that of E.T. Jaynes [134,135]. Here, loss of information paradoxically means gaining insight through synthesizing and summarizing, reducing the total amount of communication needed to convey the information. In other words, the extraordinarily important means by which the CNS may be producing entropy, long after fractal vascular networks and brain growth have been optimized during growth and development, is by reducing information, by doing what the CNS loves to do, synthesizing, organizing, classifying, all reducing information. Indeed, this paper might be considered an act of entropy production. Indeed, one might consider that all papers that distil literature into guidelines or summaries, or find truth in new equations, are acts of entropy production through loss of required information to convey the underlying message. Thus, it may be that tracking entropy production over a human life requires the calculation of entropy production due to the dissipation of mass and energy, as well as entropy production due to the loss of information. The controversy regarding whether entropy is equivalent to energy dispersal or to information [136] might be resolved by noting that they are independent. In other words, change in entropy $= \Delta S = \Delta S(\text{mass}) + \Delta S(\text{energy}) + \Delta S(\text{information})$. Clearly, the discussion of loss of information as an entropy producing function of the CNS or in general requires a much broader investigation. Nonetheless, the mention of informational entropy helps complete this exploratory discussion and merits further scrutiny.

Numerous other questions remain unanswered. What are the necessary conditions for maximum entropy production to lead to spontaneous formation of fractal structures? While non-linearity, potential for cascade behavior, and some element of randomness appear necessary, what else is necessary? As mentioned, the understanding of transition from laminar to turbulent flow may help shed light on this question. The importance of a stable high-quality energy supply is critical to energy dissipation and entropy production in general. Of fundamental importance to clinical science, how might the understanding regarding the association between fractals and entropy production improve care? What leads to the peak and then decreased entropy production during aging? If informational entropy production is included, when does the peak over one's life occur? Does exercise preserve cardiovascular and pulmonary fractal structures, and thus helps preserve maximal oxygen metabolism? As reviewed above within the CNS, cancer appears to be associated with both augmented entropy

production and fractal dimension, leading to harm to the host system, often due to overconsumption of energy substrate [50–55,104–109,112–116]. There is evidence that reducing glucose intake may help reduce progression of cancer, but is not a widely practiced [137–139]. Perhaps most importantly, what determines the level of fractal dimension and entropy production within tissue? Health is associated with a characteristic level, whereas cancer and illness may represent increased or decreased levels, respectively. Innumerable potential clinical applications remain to be discovered, elucidated, evaluated, and trialed.

There are several limitations relevant to this discussion. The collection of literature is neither systematic nor comprehensive. The ideas are exploratory, and will need refinement or debunking. The papers cited in this review and analysis represents a smattering of literature, and it is likely that many papers have been inadvertently omitted from the list of references. The detailed relationship between glucose metabolism, oxygen consumption, and entropy production require greater study in multiple scenarios, physiologic and pathologic. Systemic infection, hyperthyroidism and exercise all would appear to increase oxygen consumption, metabolism, and entropy production, yet need to be distinguished as they are vastly different. Indeed, few papers have attempted to document a means to measure human entropy production. These and other areas identified throughout the manuscript require further exploration. Nonetheless, we believe it is important to link physiology to non-equilibrium thermodynamics, as life requires both.

6. Conclusions

The goal of this discussion was to explore two traditionally distinct concepts, and apply them to the remarkably complex central nervous system. We observe that there are fractal structures ubiquitously present in time and space in association with the CNS, that there appears to be a link between increased and decreased spatial fractal structure, and increased and decreased entropy production, as measured by glucose uptake. We have hypothesized that the spontaneous appearance of fractal structures occurs principally because fractals are more efficient at dissipating energy gradients, leading to increased entropy production. We hypothesize that human entropy production consists of entropy produced related to mass and energy dispersal, and related to loss of information. Experiments to prove or disprove these hypotheses remain to be performed, with the understanding of limitations, and necessary conditions. The scientific and clinical implications of this work merit further investigation.

Acknowledgments

Author Contributions

Andrew J. E. Seely conceived of the ideas of this paper and was critical to the development of the concepts presented herein as well as contributing to the research, and writing of the manuscript. Kimberley D. Newman contributed to the overall research, preparation and writing of the manuscript. Christophe L. Herry contributed the section on CNS temporal fractal structures and assisted with the editing of the manuscript.

Conflicts of Interest

Andrew J. E. Seely is Founder and Chief Science Officer of Therapeutic Monitoring Systems (TMS); TMS aims to commercialize patent-protected applications of multiorgan variability monitoring to provide variability-directed clinical decision support at the bedside to improve care for patients at risk for or with existing critical illness. Other authors have no relevant conflict of interest to disclose.

References

1. West, B.J. Physiology in fractal dimensions: Error tolerance. *Ann. Biomed. Eng.* **1990**, *18*, 135–149.
2. Peng, C.K.; Mietus, J.; Hausdorff, J.M.; Havlin, S.; Stanley, H.E.; Goldberger, A.L. Long-range anticorrelations and non-gaussian behavior of the heartbeat. *Phys. Rev. Lett.* **1993**, *70*, 1343–1346.
3. Tibby, S.M.; Frndova, H.; Durward, A.; Cox, P.N. Novel method to quantify loss of heart rate variability in pediatric multiple organ failure. *Crit. Care Med.* **2003**, *31*, 2059–2067.
4. Scafetta, N.; Moon, R.E.; West, B.J. Fractal response of physiological signals to stress conditions, environmental changes, and neurodegenerative diseases. *Complexity* **2007**, *12*, 12–17.
5. Goldberger, A.L. Non-linear dynamics for clinicians: Chaos theory, fractals, and complexity at the bedside. *Lancet* **1996**, *347*, 1312–1314.
6. Havlin, S.; Buldyrev, S.V.; Goldberger, A.L.; Mantegna, R.N.; Ossadnik, S.M.; Peng, C.K.; Simons, M.; Stanley, H.E. Fractals in biology and medicine. *Chaos Solitons Fractals* **1995**, *6*, 171–201.
7. Peng, C.K.; Hausdorff, J.M.; Havlin, S.; Mietus, J.E.; Stanley, H.E.; Goldberger, A.L. Multiple-time scales analysis of physiological time series under neural control. *Physica A* **1998**, *249*, 491–500.
8. Stanley, H.E.; Buldyrev, S.V.; Goldberger, A.L.; Goldberger, Z.D.; Havlin, S.; Mantegna, R.N.; Ossadnik, S.M.; Peng, C.K.; Simons, M. Statistical mechanics in biology: How ubiquitous are long-range correlations? *Physica A* **1994**, *205*, 214–253.
9. Atkins, P. *The Second Law*; Scientific American Library, Scientific American Books: New York, NY, USA, **1984**.
10. Lambert, F.L. Disorder—A cracked crutch for supporting entropy discussions. *J. Chem. Educ.* **2002**, *79*, doi: 10.1021/ed079p187.
11. Schneider, E.D.; Sagan, D. *Into the Cool: Energy Flow, Thermodynamics and Life*; University of Chicago Press: Chicago, IL, USA, 2005; p. 378.
12. Schrödinger, E. *What Is life?*; Cambridge University Press: Cambridge, UK, 1944.
13. Aoki, I. Min-max principle of entropy production with time in aquatic communities. *Ecol. Complex.* **2006**, *3*, 56–63.
14. Seely, A.J.; Macklem, P. Fractal variability: An emergent property of complex dissipative systems. *Chaos* **2012**, *22*, doi:10.1063/1.3675622.
15. Di Ieva, A.; Esteban, F.J.; Grizzi, F.; Klonowski, W.; Martin-Landrove, M. Fractals in the neurosciences, part ii: Clinical applications and future perspectives. *Neuroscientist* **2013**, doi: 10.1177/1073858413513928.
16. Di Ieva, A.; Grizzi, F.; Jelinek, H.; Pellionisz, A.J.; Losa, G.A. Fractals in the neurosciences, part i: General principles and basic neurosciences. *Neuroscientist* **2013**, *20*, 403–417.

17. Preissl, H.; Lutzenberger, W.; Pulvermuller, F.; Birbaumer, N. Fractal dimensions of short eeg time series in humans. *Neurosci. Lett.* **1997**, *225*, 77–80.

18. Larsen, P.D.; Elder, D.E.; Tzeng, Y.C.; Campbell, A.J.; Galletly, D.C. Fractal characteristics of breath to breath timing in sleeping infants. *Respir. Physiol. Neurobiol.* **2004**, *139*, 263–270.

19. Perkiomaki, J.S.; Makikallio, T.H.; Huikuri, H.V. Fractal and complexity measures of heart rate variability. *Clin. Exp. Hypertens.* **2005**, *27*, 149–158.

20. West, B.J.; Griffin, L.A.; Frederick, H.J.; Moon, R.E. The independently fractal nature of respiration and heart rate during exercise under normobaric and hyperbaric conditions. *Respir. Physiol. Neurobiol.* **2005**, *145*, 219–233.

21. Hofman, M.A. The fractal geometry of convoluted brains. *J. Hirnforsch.* **1991**, *32*, 103–111.

22. Majumdar, S.; Prasad, R. The fractal dimension of cerebral surfaces using magnetic resonsance imaging. *Comput. Phys.* **1988**, *2*, 69–73.

23. Free, S.L.; Sisodiya, S.M.; Cook, M.J.; Fish, D.R.; Shorvon, S.D. Three-dimensional fractal analysis of the white matter surface from magnetic resonance images of the human brain. *Cereb. Cortex* **1996**, *6*, 830–836.

24. Cook, M.J.; Free, S.L.; Manford, M.R.; Fish, D.R.; Shorvon, S.D.; Stevens, J.M. Fractal description of cerebral cortical patterns in frontal lobe epilepsy. *Eur. Neurol.* **1995**, *35*, 327–335.

25. Kiselev, V.G.; Hahn, K.R.; Auer, D.P. Is the brain cortex a fractal? *Neuroimage* **2003**, *20*, 1765–1774.

26. Milosevic, N.T.; Ristanovic, D. Fractality of dendritic arborization of spinal cord neurons. *Neurosci. Lett.* **2006**, *396*, 172–176.

27. Bullmore, E.; Brammer, M.; Harvey, I.; Persaud, R.; Murray, R.; Ron, M. Fractal analysis of the boundary between white matter and cerebral cortex in magnetic resonance images: A controlled study of schizophrenic and manic-depressive patients. *Psychol. Med.* **1994**, *24*, 771–781.

28. Zhang, L.; Dean, D.; Liu, J.Z.; Sahgal, V.; Wang, X.; Yue, G.H. Quantifying degeneration of white matter in normal aging using fractal dimension. *Neurobiol. Aging* **2007**, *28*, 1543–1555.

29. Zhang, L.; Liu, J.Z.; Dean, D.; Sahgal, V.; Yue, G.H. A three-dimensional fractal analysis method for quantifying white matter structure in human brain. *J. Neurosci. Methods* **2006**, *150*, 242–253.

30. Mandelbrot, B. *The Fractal Geometry of Nature*; French edition published in 1975; Freeman: New York, NY, USA, 1982.

31. Smith, T.G., Jr.; Marks, W.B.; Lange, G.D.; Sheriff, W.H., Jr.; Neale, E.A. A fractal analysis of cell images. *J. Neurosci. Methods* **1989**, *27*, 173–180.

32. Caserta, F.; Eldred, W.D.; Fernandez, E.; Hausman, R.E.; Stanford, L.R.; Bulderev, S.V.; Schwarzer, S.; Stanley, H.E. Determination of fractal dimension of physiologically characterized neurons in two and three dimensions. *J. Neurosci. Methods* **1995**, *56*, 133–144.

33. Fernandez, E.; Jelinek, H.F. Use of fractal theory in neuroscience: Methods, advantages, and potential problems. *Methods* **2001**, *24*, 309–321.

34. Nezadal, M.; Zmeskal, O.; Buchnicek, M. The box-counting critical study. In Proceedings of the 4th Conference on Predicition, Synergetic and More, Zlin, Tomas Bata University, Czech Republic, 25–26 October 2001; pp. 18–24.

35. Fischl, B.; Dale, A.M. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 11050–11055.

36. Ashburner, J.; Friston, K.J. Voxel-based morphometry—The methods. *Neuroimage* **2000**, *11*, 805–821.

37. Waliszewski, P.; Konarski, J. Neuronal differentiation and synapse formation occur in space and time with fractal dimension. *Synapse* **2002**, *43*, 252–258.

38. Goni, J.; Sporns, O.; Cheng, H.; Aznarez-Sanado, M.; Wang, Y.; Josa, S.; Arrondo, G.; Mathews, V.P.; Hummer, T.A.; Kronenberger, W.G.; *et al.* Robust estimation of fractal measures for characterizing the structural complexity of the human brain: Optimization and reproducibility. *Neuroimage* **2013**, *83C*, 646–657.

39. Shyu, K.K.; Wu, Y.T.; Chen, T.R.; Chen, H.Y.; Hu, H.H.; Guo, W.Y. Measuring complexity of fetal cortical surface from mr images using 3-d modified box-counting method. *IEEE Trans. Instrum. Meas.* **2011**, *60*, 522–531.

40. Wu, Y.T.; Shyu, K.K.; Chen, T.R.; Guo, W.Y. Using three-dimensional fractal dimension to analyze the complexity of fetal cortical surface from magnetic resonance images. *Nonlinear Dyn.* **2009**, *58*, 745–752.

41. Blanton, R.E.; Levitt, J.G.; Thompson, P.M.; Narr, K.L.; Capetillo-Cunliffe, L.; Nobel, A.; Singerman, J.D.; McCracken, J.T.; Toga, A.W. Mapping cortical asymmetry and complexity patterns in normal children. *Psychiatry Res.* **2001**, *107*, 29–43.

42. King, R.D.; George, A.T.; Jeon, T.; Hynan, L.S.; Youn, T.S.; Kennedy, D.N.; Dickerson, B. Characterization of atrophic changes in the cerebral cortex using fractal dimensional analysis. *Brain Imaging Behav.* **2009**, *3*, 154–166.

43. Takahashi, T.; Murata, T.; Omori, M.; Kosaka, H.; Takahashi, K.; Yonekura, Y.; Wada, Y. Quantitative evaluation of age-related white matter microstructural changes on mri by multifractal analysis. *J. Neurol. Sci.* **2004**, *225*, 33–37.

44. Mustafa, N.; Ahearn, T.S.; Waiter, G.D.; Murray, A.D.; Whalley, L.J.; Staff, R.T. Brain structural complexity and life course cognitive change. *Neuroimage* **2012**, *61*, 694–701.

45. Esteban, F.J.; Sepulcre, J.; de Mendizabal, N.V.; Goni, J.; Navas, J.; de Miras, J.R.; Bejarano, B.; Masdeu, J.C.; Villoslada, P. Fractal dimension and white matter changes in multiple sclerosis. *Neuroimage* **2007**, *36*, 543–549.

46. Esteban, F.J.; Sepulcre, J.; de Miras, J.R.; Navas, J.; de Mendizabal, N.V.; Goni, J.; Quesada, J.M.; Bejarano, B.; Villoslada, P. Fractal dimension analysis of grey matter in multiple sclerosis. *J. Neurol Sci.* **2009**, *282*, 67–71.

47. Sandu, A.L.; Rasmussen, I.A., Jr.; Lundervold, A.; Kreuder, F.; Neckelmann, G.; Hugdahl, K.; Specht, K. Fractal dimension analysis of mr images reveals grey matter structure irregularities in schizophrenia. *Comput. Med. Imaging Graph.* **2008**, *32*, 150–158.

48. King, R.D.; Brown, B.; Hwang, M.; Jeon, T.; George, A.T. Fractal dimension analysis of the cortical ribbon in mild alzheimer's disease. *Neuroimage* **2010**, *53*, 471–479.

49. Zhang, L.; Butler, A.J.; Sun, C.K.; Sahgal, V.; Wittenberg, G.F.; Yue, G.H. Fractal dimension assessment of brain white matter structural complexity post stroke in relation to upper-extremity motor function. *Brain Res.* **2008**, *1228*, 229–240.

50. Di Ieva, A.; Bruner, E.; Widhalm, G.; Minchev, G.; Tschabitscher, M.; Grizzi, F. Computer-assisted and fractal-based morphometric assessment of microvascularity in histological specimens of gliomas. *Sci. Rep.* **2012**, *2*, 429.

51. Di Ieva, A.; God, S.; Grabner, G.; Grizzi, F.; Sherif, C.; Matula, C.; Tschabitscher, M.; Trattnig, S. Three-dimensional susceptibility-weighted imaging at 7 t using fractal-based quantitative analysis to grade gliomas. *Neuroradiology* **2013**, *55*, 35–40.

52. Ohri, S.; Dey, P.; Nijhawan, R. Fractal dimension in aspiration cytology smears of breast and cervical lesions. *Anal. Quant. Cytol. Histol.* **2004**, *26*, 109–112.

53. Tambasco, M.; Magliocco, A.M. Relationship between tumor grade and computed architectural complexity in breast cancer specimens. *Hum. Pathol.* **2008**, *39*, 740–746.

54. Dey, P.; Banik, T. Fractal dimension of chromatin texture of squamous intraepithelial lesions of cervix. *Diagn. Cytopathol.* **2012**, *40*, 152–154.

55. Streba, C.T.; Pirici, D.; Vere, C.C.; Mogoanta, L.; Comanescu, V.; Rogoveanu, I. Fractal analysis differentiation of nuclear and vascular patterns in hepatocellular carcinomas and hepatic metastasis. *Rom. J. Morphol. Embryol.* **2011**, *52*, 845–854.

56. Di Ieva, A.; Grizzi, F.; Ceva-Grimaldi, G.; Russo, C.; Gaetani, P.; Aimar, E.; Levi, D.; Pisano, P.; Tancioni, F.; Nicola, G.; *et al.* Fractal dimension as a quantitator of the microvasculature of normal and adenomatous pituitary tissue. *J. Anat.* **2007**, *211*, 673–680.

57. Vidal, S.; Horvath, E.; Kovacs, K.; Lloyd, R.V.; Scheithauer, B.W. Microvascular structural entropy: A novel approach to assess angiogenesis in pituitary tumors. *Endocr. Pathol.* **2003**, *14*, 239–247.

58. Passalidou, E.; Trivella, M.; Singh, N.; Ferguson, M.; Hu, J.; Cesario, A.; Granone, P.; Nicholson, A.G.; Goldstraw, P.; Ratcliffe, C.; *et al.* Vascular phenotype in angiogenic and non-angiogenic lung non-small cell carcinomas. *Br. J. Cancer* **2002**, *86*, 244–249.

59. Pezzella, F.; Pastorino, U.; Tagliabue, E.; Andreola, S.; Sozzi, G.; Gasparini, G.; Menard, S.; Gatter, K.C.; Harris, A.L.; Fox, S.; *et al.* Non-small-cell lung carcinoma tumor growth without morphological evidence of neo-angiogenesis. *Am. J. Pathol.* **1997**, *151*, 1417–1423.

60. Ribatti, D.; Vacca, A.; Dammacco, F. New non-angiogenesis dependent pathways for tumour growth. *Eur. J. Cancer* **2003**, *39*, 1835–1841.

61. Wesseling, P.; van der Laak, J.A.; de Leeuw, H.; Ruiter, D.J.; Burger, P.C. Quantitative immunohistological analysis of the microvasculature in untreated human glioblastoma multiforme. Computer-assisted image analysis of whole-tumor sections. *J. Neurosurg.* **1994**, *81*, 902–909.

62. Woyshville, M.J.; Calabrese, J.R. Quantification of occipital eeg changes in Alzheimer's disease utilizing a new metric: The fractal dimension. *Biol. Psychiatry* **1994**, *35*, 381–387.

63. Ahmadlou, M.; Adeli, H.; Adeli, A. Fractality and a wavelet-chaos-methodology for eeg-based diagnosis of alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **2011**, *25*, 85–92.

64. Gomez, C.; Mediavilla, A.; Hornero, R.; Abasolo, D.; Fernandez, A. Use of the higuchi's fractal dimension for the analysis of meg recordings from alzheimer's disease patients. *Med. Eng. Phys.* **2009**, *31*, 306–313.

65. Bullmore, E.T.; Brammer, M.J.; Bourlon, P.; Alarcon, G.; Polkey, C.E.; Elwes, R.; Binnie, C.D. Fractal analysis of electroencephalographic signals intracerebrally recorded during 35 epileptic seizures: Evaluation of a new method for synoptic visualisation of ictal events. *Electroencephalogr. Clin. Neurophysiol.* **1994**, *91*, 337–345.

66. Yuan, Q.; Zhou, W.; Liu, Y.; Wang, J. Epileptic seizure detection with linear and nonlinear features. *Epilepsy Behav.* **2012**, *24*, 415–421.

67. Anokhin, A.P.; Birbaumer, N.; Lutzenberger, W.; Nikolaev, A.; Vogel, F. Age increases brain complexity. *Electroencephalogr. Clin. Neurophysiol.* **1996**, *99*, 63–68.

68. He, L.; Li, C.; Luo, Y.; Dong, W.; Yang, H. Clinical prognostic significance of heart abnormality and heart rate variability in patients with stroke. *Neurol. Res.* **2010**, *32*, 530–534.

69. McKenna, M.; Gruetter, R.; Sonnewald, U.; Waagepetersen, H.; Schousboe, A. Energy Metabolism in the Brain. In *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects*, 7th ed.; Elsevier: London, UK, 2006; pp. 531–557.

70. Sokoloff, L. Energetics of functional activation in neural tissues. *Neurochem. Res.* **1999**, *24*, 321–329.

71. Bouzier-Sore, A.K.; Voisin, P.; Bouchaud, V.; Bezancon, E.; Franconi, J.M.; Pellerin, L. Competition between glucose and lactate as oxidative energy substrates in both neurons and astrocytes: A comparative nmr study. *Eur. J. Neurosci.* **2006**, *24*, 1687–1694.

72. Petit-Taboue, M.C.; Landeau, B.; Desson, J.F.; Desgranges, B.; Baron, J.C. Effects of healthy aging on the regional cerebral metabolic rate of glucose assessed with statistical parametric mapping. *Neuroimage* **1998**, *7*, 176–184.

73. Biessels, G.J.; Staekenborg, S.; Brunner, E.; Brayne, C.; Scheltens, P. Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurol.* **2006**, *5*, 64–74.

74. Correia, S.C.; Santos, R.X.; Carvalho, C.; Cardoso, S.; Candeias, E.; Santos, M.S.; Oliveira, C.R.; Moreira, P.I. Insulin signaling, glucose metabolism and mitochondria: Major players in Alzheimer's disease and diabetes interrelation. *Brain Res.* **2012**, *1441*, 64–78.

75. Craft, S. Insulin resistance syndrome and Alzheimer's disease: Age- and obesity-related effects on memory, amyloid, and inflammation. *Neurobiol. Aging* **2005**, *26* (Suppl. 1), 65–69.

76. Euser, S.M.; Sattar, N.; Witteman, J.C.; Bollen, E.L.; Sijbrands, E.J.; Hofman, A.; Perry, I.J.; Breteler, M.M.; Westendorp, R.G. A prospective analysis of elevated fasting glucose levels and cognitive function in older people: Results from prosper and the rotterdam study. *Diabetes* **2010**, *59*, 1601–1607.

77. Aoki, I. Entropy principle for human development, growth and aging. *J. Theor. Biol.* **1991**, *150*, 215–223.

78. Aoki, I. Entropy production in living systems: From organisms to ecosystems. *Thermochim. Acta* **1995**, *250*, 359–370.

79. Aoki, I. Entropy production in human life span: A thermodynamical measure for aging. *Age* **1994**, *17*, 29–31.

80. Hawkins, S.; Wiswell, R. Rate and mechanism of maximal oxygen consumption decline with aging: Implications for exercise training. *Sports Med.* **2003**, *33*, 877–888.

81. Pardo, J.V.; Lee, J.T.; Sheikh, S.A.; Surerus-Johnson, C.; Shah, H.; Munch, K.R.; Carlis, J.V.; Lewis, S.M.; Kuskowski, M.A.; Dysken, M.W. Where the brain grows old: Decline in anterior cingulate and medial prefrontal function with normal aging. *Neuroimage* **2007**, *35*, 1231–1237.

82. Shen, X.; Liu, H.; Hu, Z.; Hu, H.; Shi, P. The relationship between cerebral glucose metabolism and age: Report of a large brain pet data set. *PLoS One* **2012**, *7*, e51517.

83. Theodore, W.H.; Bhatia, S.; Hatta, J.; Fazilat, S.; DeCarli, C.; Bookheimer, S.Y.; Gaillard, W.D. Hippocampal atrophy, epilepsy duration, and febrile seizures in patients with partial seizures. *Neurology* **1999**, *52*, 132–136.

84. Hajek, M.; Wieser, H.G.; Khan, N.; Antonini, A.; Schrott, P.R.; Maguire, P.; Beer, H.F.; Leenders, K.L. Preoperative and postoperative glucose consumption in mesiobasal and lateral temporal lobe epilepsy. *Neurology* **1994**, *44*, 2125–2132.

85. Lamusuo, S.; Jutila, L.; Ylinen, A.; Kalviainen, R.; Mervaala, E.; Haaparanta, M.; Jaaskelainen, S.; Partanen, K.; Vapalahti, M.; Rinne, J. [18f]fdg-pet reveals temporal hypometabolism in patients with temporal lobe epilepsy even when quantitative mri and histopathological analysis show only mild hippocampal damage. *Arch. Neurol.* **2001**, *58*, 933–939.

86. Bakshi, R.; Miletich, R.S.; Kinkel, P.R.; Emmet, M.L.; Kinkel, W.R. High-resolution fluorodeoxyglucose positron emission tomography shows both global and regional cerebral hypometabolism in multiple sclerosis. *J. Neuroimaging* **1998**, *8*, 228–234.

87. Blinkenberg, M.; Jensen, C.V.; Holm, S.; Paulson, O.B.; Sorensen, P.S. A longitudinal study of cerebral glucose metabolism, mri, and disability in patients with ms. *Neurology* **1999**, *53*, 149–153.

88. Sun, X.; Tanaka, M.; Kondo, S.; Okamoto, K.; Hirai, S. Clinical significance of reduced cerebral metabolism in multiple sclerosis: A combined pet and mri study. *Ann. Nucl. Med.* **1998**, *12*, 89–94.

89. Derache, N.; Marie, R.M.; Constans, J.M.; Defer, G.L. Reduced thalamic and cerebellar rest metabolism in relapsing-remitting multiple sclerosis, a positron emission tomography study: Correlations to lesion load. *J. Neurol. Sci.* **2006**, *245*, 103–109.

90. Cunnane, S.; Nugent, S.; Roy, M.; Courchesne-Loyer, A.; Croteau, E.; Tremblay, S.; Castellano, A.; Pifferi, F.; Bocti, C.; Paquet, N.; *et al.* Brain fuel metabolism, aging, and Alzheimer's disease. *Nutrition* **2011**, *27*, 3–20.

91. Jack, C.R., Jr.; Knopman, D.S.; Jagust, W.J.; Shaw, L.M.; Aisen, P.S.; Weiner, M.W.; Petersen, R.C.; Trojanowski, J.Q., Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* **2010**, *9*, 119–128.

92. Mosconi, L.; de Santi, S.; Li, J.; Tsui, W.H.; Li, Y.; Boppana, M.; Laska, E.; Rusinek, H.; de Leon, M.J. Hippocampal hypometabolism predicts cognitive decline from normal aging. *Neurobiol. Aging* **2008**, *29*, 676–692.

93. Reiman, E.M.; Caselli, R.J.; Yun, L.S.; Chen, K.; Bandy, D.; Minoshima, S.; Thibodeau, S.N.; Osborne, D. Preclinical evidence of alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein e. *N. Engl. J. Med.* **1996**, *334*, 752–758.

94. Small, G.W.; Mazziotta, J.C.; Collins, M.T.; Baxter, L.R.; Phelps, M.E.; Mandelkern, M.A.; Kaplan, A.; la Rue, A.; Adamson, C.F.; Chang, L.; *et al.* Apolipoprotein e type 4 allele and cerebral glucose metabolism in relatives at risk for familial alzheimer disease. *JAMA* **1995**, *273*, 942–947.

95. Minoshima, S.; Giordani, B.; Berent, S.; Frey, K.A.; Foster, N.L.; Kuhl, D.E. Metabolic reduction in the posterior cingulate cortex in very early alzheimer's disease. *Ann. Neurol.* **1997**, *42*, 85–94.

96. Zhao, W.Q.; Townsend, M. Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. *Biochim. Biophys. Acta* **2009**, *1792*, 482–496.

97. Freidland, R.P.; Budinger, T.F.; Ganz, E.; Yano, Y.; Mathis, C.A.; Koss, B.; Ober, B.A.; Huesman, R.H.; Derenzo, S.E. Regional cerebral metabolic alterations in dementia of the alzheimer type: Positron emission tomography with [1818] fluorodeoxyglucose. *J. Comput. Assist. Tomogr.* **1983**, *7*, 590–598.

98. Lewis, D.H.; Toney, L.K.; Baron, J.C. Nuclear medicine in cerebrovascular disease. *Semin. Nucl. Med.* **2012**, *42*, 387–405.

99. Serrati, C.; Marchal, G.; Rioux, P.; Viader, F.; Petit-Taboue, M.C.; Lochon, P.; Luet, D.; Derlon, J.M.; Baron, J.C. Contralateral cerebellar hypometabolism: A predictor for stroke outcome? *J. Neurol. Neurosurg. Psychiatry* **1994**, *57*, 174–179.

100. Shih, W.J.; Huang, W.S.; Milan, P.P. F-18 fdg pet demonstrates crossed cerebellar diaschisis 20 years after stroke. *Clin. Nucl. Med.* **2006**, *31*, 259–261.

101. Metter, E.J.; Wasterlain, C.G.; Kuhl, D.E.; Hanson, W.R.; Phelps, M.E. Fdg positron emission computed tomography in a study of aphasia. *Ann. Neurol.* **1981**, *10*, 173–183.

102. Perani, D.; Vallar, G.; Cappa, S.; Messa, C.; Fazio, F. Aphasia and neglect after subcortical stroke. A clinical/cerebral perfusion correlation study. *Brain* **1987**, *110*, 1211–1229.

103. Kwan, L.T.; Reed, B.R.; Eberling, J.L.; Schuff, N.; Tanabe, J.; Norman, D.; Weiner, M.W.; Jagust, W.J. Effects of subcortical cerebral infarction on cortical glucose metabolism and cognitive function. *Arch. Neurol.* **1999**, *56*, 809–814.

104. Kasenda, B.; Haug, V.; Schorb, E.; Fritsch, K.; Finke, J.; Mix, M.; Hader, C.; Weber, W.A.; Illerhaus, G.; Meyer, P.T. 18f-fdg pet is an independent outcome predictor in primary central nervous system lymphoma. *J. Nucl. Med.* **2013**, *54*, 184–191.

105. Kawai, N.; Miyake, K.; Yamamoto, Y.; Nishiyama, Y.; Tamiya, T. 18f-fdg pet in the diagnosis and treatment of primary central nervous system lymphoma. *Biomed. Res. Int.* **2013**, *2013*, 247152.

106. Kosaka, N.; Tsuchida, T.; Uematsu, H.; Kimura, H.; Okazawa, H.; Itoh, H. 18f-fdg pet of common enhancing malignant brain tumors. *AJR Am. J. Roentgenol.* **2008**, *190*, W365–W369.

107. Makino, K.; Hirai, T.; Nakamura, H.; Murakami, R.; Kitajima, M.; Shigematsu, Y.; Nakashima, R.; Shiraishi, S.; Uetani, H.; Iwashita, K.; *et al.* Does adding fdg-pet to mri improve the differentiation between primary cerebral lymphoma and glioblastoma? Observer performance study. *Ann. Nucl. Med.* **2011**, *25*, 432–438.

108. Palmedo, H.; Urbach, H.; Bender, H.; Schlegel, U.; Schmidt-Wolf, I.G.; Matthies, A.; Linnebank, M.; Joe, A.; Bucerius, J.; Biersack, H.J.; *et al.* Fdg-pet in immunocompetent patients with primary central nervous system lymphoma: Correlation with mri and clinical follow-up. *Eur. J. Nucl. Med. Mol. Imaging* **2006**, *33*, 164–168.

109. Seok, H.; Lee, E.Y.; Choe, E.Y.; Yang, W.I.; Kim, J.Y.; Shin, D.Y.; Cho, H.J.; Kim, T.S.; Yun, M.J.; Lee, J.D.; *et al.* Analysis of 18f-fluorodeoxyglucose positron emission tomography findings in patients with pituitary lesions. *Korean J. Intern. Med.* **2013**, *28*, 81–88.

110. Borbely, K.; Wintermark, M.; Martos, J.; Fedorcsak, I.; Bognar, L.; Kasler, M. The pre-requisite of a second-generation glioma pet biomarker. *J. Neurol. Sci.* **2010**, *298*, 11–16.

111. Zimmer, L.; Luxen, A. Pet radiotracers for molecular imaging in the brain: Past, present and future. *Neuroimage* **2012**, *61*, 363–370.

112. Di Chiro, G.; DeLaPaz, R.L.; Brooks, R.A.; Sokoloff, L.; Kornblith, P.L.; Smith, B.H.; Patronas, N.J.; Kufta, C.V.; Kessler, R.M.; Johnston, G.S.; *et al.* Glucose utilization of cerebral gliomas measured by [18f] fluorodeoxyglucose and positron emission tomography. *Neurology* **1982**, *32*, 1323–1329.

113. Mertens, K.; Acou, M.; van Hauwe, J.; de Ruyck, I.; van den Broecke, C.; Kalala, J.P.; D'Asseler, Y.; Goethals, I. Validation of 18f-fdg pet at conventional and delayed intervals for the discrimination of high-grade from low-grade gliomas: A stereotactic pet and mri study. *Clin. Nucl. Med.* **2013**, *38*, 495–500.

114. Patronas, N.J.; di Chiro, G.; Kufta, C.; Bairamian, D.; Kornblith, P.L.; Simon, R.; Larson, S.M. Prediction of survival in glioma patients by means of positron emission tomography. *J. Neurosurg.* **1985**, *62*, 816–822.

115. Alavi, J.B.; Alavi, A.; Chawluk, J.; Kushner, M.; Powe, J.; Hickey, W.; Reivich, M. Positron emission tomography in patients with glioma. A predictor of prognosis. *Cancer* **1988**, *62*, 1074–1078.

116. Holzer, T.; Herholz, K.; Jeske, J.; Heiss, W.D. Fdg-pet as a prognostic indicator in radiochemotherapy of glioblastoma. *J. Comput. Assist. Tomogr.* **1993**, *17*, 681–687.

117. Herholz, K.; Langen, K.J.; Schiepers, C.; Mountz, J.M. Brain tumors. *Semin. Nucl. Med.* **2012**, *42*, 356–370.

118. Jeong, S.Y.; Lim, S.M. Comparison of 3'-deoxy-3'-[18f]fluorothymidine pet and *O*-(2-[18f]fluoroethyl)-l-tyrosine pet in patients with newly diagnosed glioma. *Nucl. Med. Biol.* **2012**, *39*, 977–981.

119. Lau, E.W.; Drummond, K.J.; Ware, R.E.; Drummond, E.; Hogg, A.; Ryan, G.; Grigg, A.; Callahan, J.; Hicks, R.J. Comparative pet study using f-18 fet and f-18 fdg for the evaluation of patients with suspected brain tumour. *J. Clin. Neurosci.* **2010**, *17*, 43–49.

120. Pauleit, D.; Stoffels, G.; Bachofner, A.; Floeth, F.W.; Sabel, M.; Herzog, H.; Tellmann, L.; Jansen, P.; Reifenberger, G.; Hamacher, K.; *et al.* Comparison of (18)f-fet and (18)f-fdg pet in brain tumors. *Nucl. Med. Biol.* **2009**, *36*, 779–787.

121. Suki, B. The major transitions of life from a network perspective. *Front. Physiol.* **2012**, *3*, 94.

122. Maynard Smith, J.; Szathmary, E. *The Origins of Life: From the Birth of Life to the Origin of Language*; Oxford University Press: Oxford, UK, 1999.

123. Maynard Smith, J.; Eörs, S. *The Major Transitions in Evolution*; Oxford University Press: Oxford, UK, 1995.

124. Macklem, P.T. Emergent phenomena and the secrets of life. *J. Appl. Physiol.* **2008**, *104*, 1844–1846.

125. Macklem, P.T.; Seely, A. Towards a definition of life. *Perspect. Biol. Med.* **2010**, *53*, 330–340.

126. Swenson, R. Emergent attractors and the law of maximum entropy production: Foundations to a theory of general evolution. *Syst. Res.* **1989**, *6*, 187–197.

127. Dewar, R.C. Information theory explanation of the fluctuation theorem, maximum entropy production and self-organized criticality in non-equilibrium stationary states. *J. Phys. A Math. Gen.* **2003**, *36*, 631–641.

128. Dewar, R.C. Maximum entropy production and the fluctuation theorem. *J. Phys. A Math. Gen.* **2005**, *38*, L371-L381.

129. Kleidon, A.; Lorenz, R.D. *Non-Equilibrium Thermodynamics and the Production of Entropy*; Springer: Heidelberg, Germany, **2005**.

130. Dewar, R.C. Maximum entropy production and plant optimization theories. *Philos. Trans. R. Soc. B* **2010**, *365*, 1429–1435.

131. Dewar, R.C. Maximum entropy production as an inference algorithm that translates physical assumptions into macroscopic predictions: Don't shoot the messenger. *Entropy* **2009**, *11*, 931–944.

132. Duncan, T.L.; Semura, J.S. The deep physics behind the second law: Information and energy as independent forms of bookkeeping. *Entropy* **2004**, *6*, 21–29.

133. Duncan, T.L.; Semura, J.S. Information loss as a foundational principle for the second law of thermodynamics. *Found. Phys.* **2007**, *37*, 1767–1773.

134. Jaynes, E.T. Information theory and statistical mechanics. *Phys. Rev.* **1957**, *106*, 620–630.

135. Jaynes, E.T. Information theory and statistical mechanics II. *Phys. Rev.* **1957**, *108*, 171–190.

136. Ben-Naim, A. *Entropy and the Second Law: Interpretations and Miss-Interpretationsss*; World Scientific Publishing Co. Pte. Ltd.: London, UK, 2012.

137. Koroljow, S. Two cases of malignant tumors with metastases apparently treated successfully with hypoglycemic coma. *Psychiatr. Q.* **1962**, *36*, 261–270.

138. Santisteban, G.A.; Ely, J.T.; Hamel, E.E.; Read, D.H.; Kozawa, S.M. Glycemic modulation of tumor tolerance in a mouse model of breast cancer. *Biochem. Biophys. Res. Commun.* **1985**, *132*, 1174–1179.

139. Seyfried, T.N.; Sanderson, T.M.; el-Abbadi, M.M.; McGowan, R.; Mukherjee, P. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. *Br. J. Cancer* **2003**, *89*, 1375–1382.