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Viruses as Living Systems—A Metacybernetic View

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Abstract: The debate over whether viruses are living organisms tends to be paradigmatically determined. The metabolic paradigm denies that they are, while new research evidences the opposite. The purpose of this paper is to deliver a generic model for viral contexts that explains why viruses are alive. It will take a systems biology approach, with a qualitative part (using metacybernetics) to provide deeper explanations of viral contexts, and a quantitative part (using Fisher Information deriving from the variational principle of Extreme Physical Information) which is in principle able to take measurements and predict outcomes. The modelling process provides an extended view of the epigenetic processes of viruses. The generic systems biology model will depict viruses as autonomous entities with metaphysical processes of autopoietic self-organisation and adaptation, enabling them to maintain their physical viability and hence, within their populations, mutate and evolve. The autopoietic epigenetic processes are shown to describe their capability to change, and these are both qualitatively and quantitatively explored, the latter providing an approach to make measurements of physical phenomena under uncertainty. Viruses maintain their fitness when they are able to maintain their stability, and this is indicated by information flow efficacy. A brief case study is presented on the COVID-19 virus from the perspective that it is a living system, and this includes outcome predictions given Fisher Information conditions for known contexts.

Keywords: viruses; living organisms; paradigms; autopoiesis; adaptation; viability; information theory; systems

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1. Introduction

Omicron (a variant of the SARS-CoV-2 Coronavirus, which causes the COVID-19 virus disease) came to public awareness after it was first seen in South Africa. It has since spread around the world faster than any previous variants of the Coronavirus and has been tracked in more than 120 countries [1]. It is also genetically dissimilar from previous pandemic variants, with a remarkable number (50) of mutations, some being extremely rare. Thus, as Hart [2] explains, the Omicron variant does not appear to be a direct evolutionary descendent of the previous variant, Delta. The disease it produces is apparently quite mild and incidental to the main diagnosed causes for hospitalisations [3]. Since its appearance, it has been joined by a relative with a similar unknown and undetected ancestor, and there may well be more in some form of soup of virus variants. While Omicron (variant BA.1) is roughly 500% more infectious than Delta, its new relative (variant BA.2) is about 120% more infectious than that. This means that the original social management techniques, such as the quarantining of contacts, do not work due to Omicron's high infection capability and its shorter incubation period. While BA.2 is still susceptible to the vaccines developed against COVID-19, according to Barnes [4], it is less so. The possibility of a cocktail of variants leads to a concern that more variants may emerge, and some might have very severe impacts. There are thus concerns about future variant appearances, and it suggests that we really need to better understand the processes that are shaping the development and evolution of viruses.

This is not straightforward, as noted by Wessner ([4]: p. 1) when saying:

> "The evolutionary history of viruses represents a fascinating, albeit murky, topic for virologists and cell biologists. Because of the great diversity among viruses, biologists have struggled with how to classify these entities, and how to relate them to the conventional tree of life. They may represent genetic elements that gained the ability to move between cells. They may represent previously free-living organisms that became parasites. They may be the precursors of life as we know it".

That they may be the precursors of life does not mean that they are themselves living, and there are those who advocate this, and those who deny it. Living systems are defined in terms of a set of characteristics that determine their nature and hence their properties, and whether viruses are seen as living or not will be determined by the paradigm adopted to model them.

Wessner [4] further explains that viruses may represent previously free-living organisms that have become parasites, can grow, reproduce, maintain an internal homeostasis (though some deny this [5]), respond to stimuli, and carry out various metabolic processes, and when in populations, are capable of evolving over time. While they may be viewed as living systems, they do not have metabolic processes, and can only replicate within a living host cell. This means that they are non-living. Such a view is exposed by Sanchez and Lagunoff [6], where external viral replication processes are described as occurring through induction, meaning virus determined causal processes.

Kaiser [7] defines viruses as infectious agents with both living and non-living characteristics that can infect animals, plants, and even other micro-organisms, like bacteria or fungi, or even other viruses. Brown [8] argues that whether viruses are living entities or not is a moot philosophical point, this suggesting that it has little or no practical relevance. This may be true if taking a reductionist approach, which involves the investigation of biological mechanisms by breaking them down into ever-smaller components, and analysing them in isolation from other parts of the system. However, this is not so much the case if a systems biology approach is adopted. This seeks to account for system level dependencies, interactions and perturbations, aiming to relinquish reductionism by decoding life in a holistic way. To do this it adopts a complex, dynamic living systems perspective, involving many interrelations that occur over time, space, and physiology [9]. In the systems biology approach, philosophical positions become significant. This is because philosophy provides a means of orienting the perception of relationships, and it also provides opportunities for the exploration of beliefs, values and principles, to facilitate the enhancement of meaning. By philosophy orientation [10] we have in mind the dynamic nature of being, and the provision of a comprehensive account of the interface between cognitively perceived issues and reality. We therefore take philosophy to be a process [11] of inquiry that results in a trajectory enabling complex contexts to be traversed [12]. It is from philosophical positioning that paradigms arise. These are normative sets of group values, beliefs, posited propositions, and explicit assumptions that represent an epistemology in relation to identifiable ontologies, these attributes a function of what it is that constitutes reality. Since the paradigm one adopts to model a virus necessarily influences the outcomes of any analysis of issues (cf. [13]) thereby adjusting meaning, the inclusion of philosophical considerations within a systems biology context is not only appropriate, but essential.

Reminiscent of the historical controversy in physics concerning whether light is composed of particles or waves [14] (now resolved through quantum mechanics and optics), in biology there is a controversy resulting in the dichotomy of whether viruses are alive or not. Farnsworth ([15,16]) explains that there are probably about as many biologists who believe that viruses are alive as those who do not, with a similar number who are unsure. This dichotomy about the nature of living leads us to a comment made by Cleland [17], where she argues that, while there are universal theories in physics and chemistry, there are none in biology. One presumes that when Cleland refers to universal theories, she means dominant discipline-bound theories, otherwise this appears not to be exactly true. In physics there is the well-known proposed unified field theory [18]; in chemistry there is

a proposed unified field theory of chemical reactions [19]; and in biology there is the lesser-known universal principle of biology [20] arising from Bauer's [21,22] general theory of life. Bauer was the first biology theoretician to propose, in the 1920s, a principle of permanent non-equilibrium of living systems in which he adopted thermodynamic principles [23], and this was significantly prior to the work by the biochemist Hans Krebs in 1957 in his work on energy transformations in living matter. The propositions that underlie Bauer's notions of living systems, which do not extend to information- and complexity- based properties as they might do, are that they are autonomous, self-developing and adaptive, this facilitated by its thermodynamic properties.

Grandpierre [24] postulates that such dominant, discipline-bound theories, might be connected to give a universal theory of nature. However, there is an alternative metadisciplinary approach through which such universality can be pursued, and this is through the complexity paradigm [25]. This recognises that complex structures are formed when an arrangement occurs of many differentiable but relatable entities having intricate relationships and interconnections. Complex structures, therefore, can be explored through transdisciplinary/generic theory, noting that this has an intimate relationship with information theory [26,27]. Information theory allows, for Meijer [28], a relatively easy way of describing matter and energy in terms of information. A generic information framework can then be used to generate connected and collective meanings. Meijer notes that such a framework has a fundamental property of *intrinsic information*, and this *produces* matter. Intrinsic information is defined to be the most complete way of describing a contextual object. Not any information theory is adequate to fully investigate complexity, since not all such theories clearly acquire intrinsic information [29]. The explanation for this is that there is a relationship between information that is bound to a context being observed, and information which may be acquired from this through observation, and the latter should be sufficiently close to the former to make it intrinsic [30]. One representation of intrinsic information, Meijer explains, is *Fisher Information* [31] and this arises through core propositions in the paradigm of Extreme Physical Information [32]. In this paper we shall show how Fisher Information operates within autopoietic theory. This theory is core to the description of the nature of living entities through their capacity to reproduce themselves.

The purpose of this paper, then, is to set out and examine the nature of living systems from a generic perspective, and then apply our considerations to viruses, and in particular to Coronaviruses. To do this, the paper will progress its development over its sequentially increasing sections. First it will provide some fundamental concepts that will underpin the discussions in the paper. This will introduce paradigms relevant to microbiology, necessary because their propositions provide a logical basis for arguments. It will be explained that there is no cohesive overarching paradigm for biology. Such a situation can lead to controversy and hence to theoretical fragmentation. Part of the responsibility for this is the dominant neo-Aristotelian/metabolic paradigm, which inadequately defines the nature of living systems, while being overly relaxed about clear evidence of that inadequacy. This paradigm sees living systems in terms of their functionality. In contrast, the generic paradigm we shall introduce rather sees them in terms of organisation. The organisation perspective draws on the concept of autonomy, and we shall explore this and its connection with autopoietic theory. Then, we shall consider the concept of homeostasis, necessary for a living system since it explains their necessary holistic stability.

In the section following, our interest will lie in examining the nature of viruses as parasites that live in a host environment, and survive there through processes of autopoiesis, a term that will be explained in some depth. The virus has an internal metaphysical self, and an external physical extension of self. In particular,

> "Viruses have several common characteristics: they are small, have DNA or RNA genomes, and are obligate intracellular parasites [requiring a host to reproduce]. The virus capsid functions to protect the nucleic acid from the environment, and some viruses surround their capsid with a membrane envelope".
>
> ([33]: p. 19).

Its internal self is composed of the genome (defined as an arrangement of genes) with metaphysical functionality [34] that through epigenetics involves such attributes as stability, adaptation and memory. Here, memory is enabled through a "hidden memory genome" [35], which necessarily involves internal knowledge, indicating cognition. Its physical aspect is provided by its "operative" capsid which interfaces with its environment, and is directly responsible for environmental interaction.

While this paper centres on viruses, it is in essence cross-disciplinary in that it brings cybernetic theory from other fields. It is therefore useful to personify viruses, and thus assign to them abstract qualities or characteristics (initially through metaphor [30]: p. 4). Thus, they may be classed as "purposeful" and "intentional" as they express "interests" and "seek" viability. To understand the relevance of such personifications, one must recognise that a virus has selection processes that enable it to beneficially relieve significant environmental pressures. It has genome expression (its coded information) which acts to regulate its capsid expression (the process by which the information encoded in a gene is used to direct the selective production of requisite proteins, where proteins are biological compounds like enzymes, hormones, and antibodies). The mechanism through which viruses operate is that they respond internally to significant environmental pressures, and these become internally represented as random or adaptive selections. In the case of adaptive selections, autopoietic processes (personified as "intention") correspondingly enable viruses to alter their "regulatory genome". This, according to Alonso et al. [36], regulates gene function, enabling the formation of a fully functioning organism. Wanke et al. [37] notes that the regulatory genome has a noncoding form, so that it does not have any direct association with specific protein production. The genome responds through an autopoietic impulse to the capsid structure that constitutes "purpose", thus signalling it to take actions that reduce significant stresses. Thus, "purpose" can result in "operative adaptation" by issuing requisite proteins to respond to environmental issues. If successful (as either an individual or in a species population), then the virus will maintain viability, thereby extending its durability while simultaneously enhancing a capability for further development. So, to summarise, the capsid has a structure which facilitates behavioural participation in its host environment. There is a regulatory relationship between the genome and its capsid structure, and this enables the selective production of certain proteins that become environmentally active, enabling "purpose" to be reformulated as personified capsid "interest".

Following this we shall explore different aspects of viruses as parasites, operating as autopoietic organisms, with a learning capability, and having evolutionary properties when in their populations. Viruses can adapt to changing host environmental conditions, and this has evolutionary consequences, but sometimes they can function as an adaptive collective whole, through the formation of "mutant clouds".

In modelling the virus, we have already noted that we will adopt the systems biology perspective, with its interest in relevant interrelationships connecting different microbiological entities, and within more or less stabilised functional whole systems (cf. [38]). To progress this, we adopt a cybernetic approach. This comes from von Foerster who, in 1952 [39], used the term meta-cybernetics to refer to metaphysical aspects of cybernetic thought, which deals with concepts like stabilisation, perception, adaptation, recalling, remembering and prediction. But this term was dropped for the publication of his book Cybernetics of Cybernetics [40]. The term has become current again through the meta-cybernetic paradigm [30,41] that Yolles adopts, involving agency theory, and formulated within the metaphysical model that has its origin in the ideas of Eric Schwarz [42]. Agency is an entity that has the capacity, condition, or state of acting or of exerting power. At is simplest, agency may represent a single individual agent, but more generally it has a population of agents that mutually interact. It is through this interaction that they can create collective adaptive processes [43]. The collective is composed of individual viruses that form part of an agency population, and their adaptive processes enable them to purpose-

fully maintain their own viability through their cognitive processes, as they respond to a changing environment.

While our modelling process formulates a qualitative base that is able to provide deep explanations about viral contexts, it also has a quantitative dimension able to take measurements and make predictions about viral situations and options for intervention strategies. To do this it uses Frieden's [32] variational principle of Extreme Physical Information (EPI). EPI derives from Fisher Information [31], which recognises that the observation of a source (e.g., environmental parameters) is deemed to involve uncertainty. This modelling approach will then inform a Coronavirus case study that lends support to the virus being a generic living system.

2. Some Fundamentals

In order to set down a foundation for this paper, we shall first consider the paradigms that are used in biology to describe living processes, and identify their distinctions. All these paradigms are concerned with the organism, though how this is defined varies. The Mosby dictionary of Medicine explains that the term organism comes from the Greek, as: any organic, living system that functions as an individual entity. According to the Merriam-Webster dictionary, an organism may be defined more generally (i.e., not necessarily organically) as: a system of complex structures that has interdependent and subordinate elements, with relations and properties that are, in the whole, largely determined by its function. The functions can be argued to have a dominant, if sub-systemic, relationship with the system as a whole [44]. However, the organism can also be represented in terms of its order and organisation, when functionality takes a more subordinate role. Organisms also have autopoietic properties, but we shall explain that autopoiesis on its own is insufficient for the definition of life, which also requires homeostasis—a property that enables the system to maintain its stability as a whole.

2.1. The Aristotelian Paradigm and Beyond

Aristotle was a Greek philosopher whose ideas in biology dominated in the west from the 4th Century BC for two millennia [45]. His critical empiricism, in which he held that knowledge comes primarily from sensory perception, was melded into reductionism in the 17th Century, as promoted by Descartes in his "Discourses". Aristotle is credited with making the statement that "the whole is more than the sum of its parts", a notion that for Heylighen [46] is ambiguous and controversial, and as noted by Trewavas ([47]: p. 2424) "there is a need to understand how organisms are put together (reductionism) just as in turn there is a need to understand why they are put together in the way that they are (systems; holism)".

Cleland [17] explains that there is a lack of unity in biology due to a tacit commitment to the defective neo-Aristotelian paradigm that reasons about life. This paradigm proposes that there are several abstract functional characteristics that are basic to life, defined as the capacity to self-organise for an extended period against both external and internal perturbations, and the ability to reproduce and transmit adaptive characteristics through evolutionary descendants. The self-organising attribute, for Aristotle, includes nutrition and reproduction that are the basic functions of life, and there is a teleology in which metabolism and genetic-based reproduction require causation that is directed towards future goals. An Aristotelian view is that living things must feed themselves, cannot just be copied, and must reproduce themselves. Systems that do not conform to such a view are not considered to have the property of living. Cleland notes that a neo-Aristotelian perspective is essentially represented by the metabolic definition of life, to which viruses do not conform (cf., [6]). Cleland [17] inherently conforms to Bauer's position by further noting that distinct from the metabolic definition there is a thermodynamic dimension, and beyond this an autopoietic dimension. These together constitute progressive levels of abstraction. Metabolic definitions are reflections of our experiences of life of the planet Earth, and centre on a system of chemical reactions that is sustained by extracting and transforming

chemical energy from its environment. The more abstract thermodynamic definitions of life centre on its physics, this considering the maintenance of its bounded regions of local order as it extracts energy from the thermodynamic gradients of its environment. Autopoietic definitions involve a further level of abstraction, and centre on the "logic" of self-organisation and its capacity to be a self-sustaining viable entity through attributes such as self-reference.

In contrast, Margulis and Sagan [48] identify 7 paradigms concerning life. These are:

1. the metabolic—which considers principles of materials exchange between the organism and its environment occurring in such a way that their general properties are not altered;
2. the physiological—which is concerned with physiological functions like breathing, moving, digesting, a biochemical definition that identifies living systems through an ability to store hereditary information in nucleic acid molecules;
3. the genetic—which is connected with the process of evolution and concerns how information is coded;
4. the thermodynamic—which explains an ability to maintain low levels of entropy that explain order;
5. the physics-based—which sees life as being composed of an ensemble of entities that share information coded in a physical substrate, this able to keep its entropy significantly lower than the maximal entropy of the ensemble;
6. the physical—in which components of life are contained within distinct boundaries (like those of cells) resulting in locally increased order;
7. the autopoietic—where organisms are self-governing, maintain their own identity, have information closure, self-relatedness, self-relational, and are adaptive through autopoietic (self-producing) processes.

However, these may rather be seen as paradigmatic perspectives, where each one contributes to a definition of life. This is illustrated by Álvarez-Vázquez [49], who adopts the autopoietic perspective as part of autonomy, explaining that all biological life is constituted as systems that involve metabolic, physiological, genetic, physical, and inferred thermodynamic processes. This constitutes a move towards a generic approach, where living systems have attributes that enable improved explanatory detail to emerge from the different disciplinary dimensions being considered, a process accompanied by the evolution of the autopoietic concept away from its original definition by Maturana and Varela [50].

An alternative view comes from Barbieri [51], who explains that there are three paradigms that dominate biology, and which coexist, one inside the other, in an embedded hierarchy. At the lowest level is the 'chemical paradigm', the next level is the 'information paradigm', and the top level is the 'code paradigm', where:

- The chemical paradigm (also known as the neo-Aristotelian/metabolic paradigm) posits that life is an extremely complex form of chemistry and is completely described (in principle) by physical quantities. The paradigm has been represented by five basic biological processes that define the form of living: metabolism, temperature regulation, information processing, embryo development, and inheritance [52].
- The information paradigm reflects chemistry through information. It argues that information is not so much a "real observable" but rather a "fundamental observable". While real observables may simply be pragmatic descriptions of a reality being observed, fundamental observables provide fundamental properties [28] that critically characterise it.
- The code paradigm embraces the idea that meaning is the basis of code, and that both information and meaning exist in every living system. This is because they are the inevitable results of the processes of copying and coding from which genes and proteins are produced, and this can be traced to meaning as a fundamental observable. Molecular coding is also an expression of something essential to all observable systems: their levels of complexity.

Hence, living systems have complex chemical processes that are underpinned by the fundamental metaphysical attributes of information and meaning, and their physical observable phenomena enable real, critically measurable information to be acquired about the 'state of complexity' of an organism in its environment. As we shall explain later, system complexity is intimately tied into something called ripple complexity [53], a feature that extends beyond Barbieri's considerations, and which is an essential property with consequences to real-life existence.

Since living organisms are interactive systems, rather than talking of *meaning* in the code paradigm, it is more relevant to refer to *systems of meaning* (referring to relationships between definable entities and the meanings that underpin them). This is because it reflects on the whole organism, and the interactions that it may have with its environment. According to Mahoney [54], systems of meaning can be expressed in terms of causal mechanisms. These are propositionally defined, and provide an argument or description or formal mechanism that explains the means or process or trajectory of a causal-agent and its effects [43]. The causal-agent produces an effect or is responsible for events that result in, and has properties which explain, outcomes and associations. Thus, autopoiesis is a causal-agent, while the causal mechanism identifies the network of processes it uses, and its trajectory.

Dawkins [55], proposed a paradigm that is concerned with natural selection through adaptive processes. In his theory there is a dichotomous distinction between replicators and vehicles [56]. The two are said to have a tension between them as rival candidates in natural selection. Replication is a metaphysical information process, where the replicator is concerned only with *copying*. This is a generalisation of gene function, where genes are self-replicating biological molecules. Seeking support from Fisher's [57] work in natural selection, the genetic complement of asexual organisms is a single gene, and only genes (and by extension the genome) can function as replicators in biological evolution. While the genome of an asexual organism is a replicator, the function of the vehicle (as a generalised organism that houses the replicator) is environmental interaction. Hence, the vehicle may be regarded as a machine programmed to preserve and propagate the replicators that they house. The theory does not posit specific causal connections between the replicator and its vehicle, but rather refers to their relationship being defined through correlations.

For the context of viruses, replication occurs when components of its host cell are used to make copies of itself, forcing the cell to package it [58], and hence (as reproduction) to make new viruses that exit the host cell by either killing it or budding (when it acquires its envelope as a modified piece of the host's plasma or other internal membrane), to then go on to infect other hosts. Living systems have an overall interactive dynamic between the organism as "vehicle", and the gene as "replicator", as it passes on its structure, largely intact, through successive replications [59].

While the theory has supporters [60] and provisional opponents [61], antagonists Griffiths and Day [62] and Wilson [63] view the replicator paradigm through the lens of Developmental Systems Theory (DST). This studies how genes regulate the development of behavioural change. Wilson argues that through processes of evolution, that which is inherited across generations is more than simply genes (against the position promoted by Dawkins). Significant elements of the environment beyond the gene are materially involved. This includes active modifications that occur in the environment due to the organism, that then become important environmental factors that adaptation will in the future need to address. As such, Wilson notes, the conceptual framework that justifies the replicator paradigm is both weak and false.

The generic paradigm, for Bhattacharyya [64], is defined in terms of technical processes that have the ability, through performance, to do that which signifies the act/function of living. Thus, the generic definition of life is represented as a technical process that involves an "ability" to do that which signifies the act or function of living, this reducing to an Aristotelian paradigm if "ability" is interpreted as an inherent and embedded process that is a thing-in-itself, this implying a potential. However, "ability" is something that is produced,

a performance which highlights conditions, constructs, and enables communications, prescriptions and proscriptions through which ability is produced and manifested for operative functionality. Ability as performance is a trajectorial process directed towards the realisation of an acquired constructed potential. The process of life is teleological (through explained purposefulness), and telos (objective, delivered from inherent purpose) is the phenomenological target. Since "ability" is "production", taking living systems to be autonomous and having self, then "ability" becomes self-developed ability that is consistent with the notion of self-production through autopoietic processes.

Let us explore a little further the idea that a generic paradigm can become Aristotelian when "ability" is reduced to an inherent property of a living system. The term *inherent* means an essential character of something, rather than that which is produced. In an autonomous system, such production is self-related. That is, it is autopoietic with a network of processes with causal circularity [65], i.e., it has a dual (forward and reverse) trajectory defined by its causal mechanism. This connects cognition, perception and action, enables the functions of self-organising, self-producing, and self-maintaining, and explains reciprocity between perception and action [66]. Causal circularity is exemplified in a comment by Maturana and Varela ([67]: p. 26) that "all knowing is doing and all doing is knowing". However, for Aristotle, causality relates to form/morphology, concretely embodied in the empirical world [68], and where perception is a form of cognition in that it is incidental, and in general relates to material rather than cognitive contexts [69]. Thus, causality in Aristotelianism, is singular, and appears unable to provide adequate explanation, for instance, of how "living systems both produce and consume meaning" ([70]: p. 145).

The generic paradigm promotes the idea that living systems are autonomous, and can maintain their viability (enabling them to both survive and develop) through adaptive processes that enable them to reorganise themselves. With adaptation new structures emerge that result from processes of autopoiesis, enabling new forms of behaviour to occur that recognise environmental change. For Rosen [71] such systems must necessarily have the property of anticipation (this being a function of autopoiesis [30]), and it is this that distinguishes living from non-living systems. Yolles and Dubois [72] explain that anticipation may occur as a weak model-based or a strong system-based prediction. The difference between them is that in the former, the model has been autopoietically referentially assimilated into the system, while in the latter the assimilated model has been accommodated into the system structure. Thus, reflecting once more on Cleland's ideas and embracing a generic theory that couples concepts associated with self-organisation and autopoiesis that are subject to thermodynamic principles (amplified by, say, Prigogine [73]), we appear to have unintentionally homed in on Bauer's propositions.

2.2. From Controversy to Fragmentation in Biology

Earlier we noted Cleland's [17] realisation that there is a lack of unity in biology, and this originates with controversy in a field that leads to theoretical fragmentation, a consequence of which is the rise of subfields where different independent sets of propositions are adopted to describe similar phenomena, this delivering disciplinary incoherence. As such, it should not be surprising when distinct definitions that are ontologically related become epistemically tangential. This can result in diverse and non-related theoretical trajectories from some arbitrary tangential centre. While scientific development may well reflect some degree of such fragmentation deriving from innovative thinking, some disciplines are more fragmented than others, as seen when they have independent unrelated conceptual derivations [74].

As an illustration of this in biology, major terms surrounding the subject of evolution (like individual or group selection) have taken on multiple and conflicting meanings, and several conceptual frameworks exist that represent themselves as competing theories, though they are just alternative ways of analysing an evolutionary context [75]. Also, in the field of virology, a subfield of microbiology, fragmentation has been exposed through

controversy about the nature of viruses, and whether they are living entities [76]. Typically, biological organisms are defined in terms of a set of characteristic functions that determine their nature and hence their property of living, but differences occur in the definitions that are not supportive of perspective homogeneity. Thus, Tetz and Tetz [77] note a definition of life that has the biological functionalities of reproduction, metabolism, growth, adaptation, stimulus responsiveness, genetic information inheritance and evolution. However, Carter and Scott [78] tell us that life can be defined by the following set of functions: order, sensitivity or response to the environment, reproduction, growth and development, regulation, energy processing, and homeostasis. In the latter area of investigation, homeostasis, it will be discovered that there are two isolated concepts in microbiology: the regulatory genome and the dark matter genome. We have already referred to the regulatory genome, which is considered in the field of neuroscience [37]. However, we shall also soon introduce the concept of the dark matter genome [79], used in the field of molecular biology. Both concepts relate to control of the genome, and both, therefore, appear to be selective application of the same concept, while being unrelated across the literature. However, to be able to relate them, there is a need to have a macroscopic (systems biology) modelling approach that can make those connections which, for viruses, appears to be missing from the literature.

Having noted that biology has some fragmentation, it is a more homogeneous field than others like the social sciences, as explained by Gericke et al. [80]. Here, genetics as a coherent whole emphasizes ontological aspects of content knowledge over epistemological aspects, this resulting in the conflation of different gene concepts that leads to a notion of genetic determinism. This is in contrast with the current understanding of the genotype-phenotype relationships (i.e., genes that deliver manifest traits), and the interplay between genetics, epigenetics [81] (the behaviour-environment relationship connected to gene function), and environmental factors. While there may be fragmentation in biology, history tells us that this is likely to be a temporary condition for disciplines that themselves undergo evolutionary processes. This is illustrated, for instance, in the distinct stances of Mentalism (which proposed principles of genetics, especially for single-gene traits) and biometry (the method of applying mathematics to biology). According to Sarkar [82], Fisher's work (in 1918) provided a partial reduction of 'biometry' to 'mentalism', leading to a synthesis in the 1920s which was mainly one of classical genetics with population genetics, using Haldane's [83] *The Causes of Evolution* as its base theory. It should be noted that Fisher's work also provides the essential groundwork for finding physical laws of growth through use of his "Fisher Information" concept, which shall be adopted later.

2.3. From Functionality to Organisation

While the Aristotelian paradigm has functional characteristics [84], the notion of organisation has more recently become important, this occurring through process and transformation [85]. One reason is given by Collier [86], in that functionality tends to be etiological—with interest in the environmental causes for biological states or conditions of being, this being evidence-backed, where it is realised that observation is paramount in recognising those causes. This mostly ignores the organisational requirements of biological entities, though these may be very important to phenomenological attributes that might be associated with certain functions. By comparison, the sciences of physics and chemistry emphasise *both* organisational and functional aspects of a phenomenon. Their aim is to *derive observed function* from an *assumed organisational principle* (such as conservation of certain physical traits) based on a system-level *mathematical principle* like maximum 'action', entropy or information.

For Mossio and Saborido [87], ascribing a function to a biological entity means locating it in its abstracted system: that is, a system defined by the observer that is able to distinguish between rich interactions between those entities within its boundary, and relatively poor interactions across the boundary, and where the entity is part of a relational structure, where the position of each entity within it conveys an etiological explanation of its existence. Returning to Collier [86], an etiological/evidence-backed theory should be able to provide

physical conditions under which an organism's observed function holds, and it should even suggest alternative conditions under which it should also hold. Niño EL-Hani and Nunes-Neto [88] note the externality of etiological approaches. They also note that in contrast, the organisation approach promoted by Collier sees functionality as an internal contributor to the organism seen as a system. Hence, the organisation approach is internalist and interested in the dynamics of the system's component parts as they contribute internally to functionality, thereby maintaining the system's organisation and autonomy. This occurs where the system's internal organisational closure is greater than its interactive closure ([88,89]). By closure, reference is being made to organised processes connected with functionality that are closed in the sense of their integration and self-maintaining organisation (organisational closure), while also being open with respect to their interaction with other systems contained in the environment (this referring to interactive closure). Bich and Etxeberria [90], also commenting on the organisation approach, recognise that a living system is not characterised by its material or physicochemical processes, but rather by how the interactions it displays are related to producing and maintaining the integrated unity that they are taken to be. Organisation is related to structure, and while structure relates to variant aspects of a living system that includes its physical form, organisation is relevant to invariant topological aspects of its constitution. From this position one may deduce that a living system (one that is able to maintain itself as a whole integrated unity) necessarily has a capacity to self-organise and adapt to environmental changes, thereby modifying its structure and internal organisation.

2.4. From Autonomy to Autopoietic Theory

For Collier [86], autonomy is an essential concept when considering internal functionality. This is because it can provide a rich explanation of the idea of adaptation. Consistent with Collier's view, Carter and Scott [78] recognise that the concept of *autonomy* enables one to identify the *internal dynamics* of a system to be explored. By autonomy is meant the intrinsic, stand-alone property of system function, and by internal dynamics is meant that which occurs inside the system's boundary, beyond which is an external environment. The autonomy of a complex entity involves processes that are in constant movement, especially with respect to actions, reactions, and dynamic change [91]. Arnellos et al. [92] adopt autonomy as a way of exploring living complex biological multicellular organisms in terms of self and identity. They note that autonomy centres on the individual organism that is not dependent on its surroundings for its internal mechanisms. They critically rely on diverse features of the environment like general physico-chemical conditions for viability and energetic/material availability, while continuously generating/regenerating the constraints and mechanisms upon which the use and management of acquired resources is based. Hence, Arnellos et al. argue, there is a continuous interplay between the complex organisation of processes constituting a relatively stable self, where interactions with the environment can trigger internal processes crucial for self-maintenance. As such, they note, autonomy must be conceived in terms of a particular connection/collaboration with external systems.

The word autonomy "implies the ability of a system to continually change its structures, undergoing renewal while preserving its patterns of organisation. It also implies self-regulation that is a manifestation of a central tendency toward the extension, coordination, and integration of function that is a common property of living things" ([43]: p. 563). Arnellos et al. [92] also note that the word is characterised as the ability of an agent to function/operate interactively using only its own resources and processes in a way that is dependent on its functionality, this enabling intentionality which in turn provides meaning. While the notion of autonomy is at times used in biology to explain the idea of living [93,94], it still has not become mainstream [95,96].

In the same way that autonomy can provide a rich explanation of the idea of adaptation, autopoiesis is able to offer an enriched description of the bounded mechanism of life through which other perspectives can be assembled as attributes, where they coincide with a given context. It therefore further improves the explanation concerning the processes

that facilitate life. Autopoiesis is concerned with the processes of organising which occur within an autonomous system as they link, under a dynamic tension, with regulatory and behavioural structures. Living systems maintain their form by the continuous interchange and flow of components which may be chemical-metabolic, physical, and so on, and indeed any attribute that is significant to a particular interest. Through the view of autopoiesis, living systems are seen to be bounded by dynamic materials that the system itself produces and that relates to their ability to adapt. It broadly concerns the metaphysical processes of self-production, self-maintenance, self-repairing, and self-relational functions in living systems. As Boden [97] notes, the core concept of autopoiesis is self-organisation: involving the (complex) process of emergence, and the maintenance of order. Sometimes, Boden says, self-organisation is defined by reference to energy, and sometimes more abstractly (such that the property of living can be applied to a whole variety of phenomena which have no direct association with biology). In other words, autopoiesis is a general concept that applies to biology as it applies to other fields in which there are systems which self-organise and develop, therefore being recognised as viable.

2.5. Homeostasis

As an extension of the more usual notion of epigenetic relationships and processes, while the genome is a regulator for its capsid, the genome-capsid relationship also has a regulator, and relative to the capsid, this is a metaregulator which takes responsibility for homeostasis. Functional and organisational properties in autonomous living systems can be maintained by homeostasis through which the system is able to adapt itself to the environment through processes of learning. If an organism is living, then it must be demonstrated that it has the property of homeostasis. For Billman [98] homeostasis is the central organising principle upon which the discipline of physiology is built. It is a self-regulating process that provides a capability for living systems to maintain their stability, enabling internal conditions that permit it to viably adapt under a changing environment. Turner [99] notes that homeostasis is operationally a persistence of a living system in a state of specified and dynamic disequilibrium that persists during periods of perturbation emanating from its environment, as its order experiences entropic degradation, according to the Second Law of Thermodynamics. Its viability is facilitated through actions enabling it to not only adapt, but to maintain order. Homeostatic systems are also knowledgeable systems, having identity and ability, through their knowledge, to manipulate their environment. As such they must be cognitive systems, able to construct cognitive representations of their environment, embody knowledge of the perceived parametric nature of that environment, and be able to implement a targeted defence of that persistent state while experiencing continuing perturbations. That is, homeostatic systems must be teleological.

Consistent with this perspective, Williams [100] explains that homeostasis refers to constancy in the state of a system, despite the perturbation it is experiencing, and this includes reference to the dynamic organising process of self-regulation. Here, systems adapt their behaviour—a special case occurring through homeorhesis where regulation applies to a trajectory which varies with destination, such as may occur with dynamically shifting environments. Those who deny that a given class of organism is homeostatic might not be considering the homeorhetic context of cellular environments, where there may be multiple interacting species [101]. Homeostasis may thus be represented as a regulator of the dynamics of the autopoietic process of living that enables organisms (or a population of them) to maintain their viability.

Under the condition that a living system is subject to deleterious effects from its environment, its viability is best served when its homeostatic regulator can enable requisite system adaptation to neutralise those effects. This may occur by enabling the system to redefine its structure and processes. A supplementary attribute is the immune system—a functional network of finely attuned higher order regulatory mechanisms that, in order to maintain order, suppresses rather than eliminates the potential for detrimental reactions [102]. However, to facilitate the maintenance of order, it also collects, interprets, and

stores information, while creating an identity of self [103]. We shall refer to this store of information as a pattern of updating knowledge stored as a homeostatic map.

Williams ([100,104]) explains that any system that is stable needs to be homeostatic in its essential variables, and this involves learning to allow homeostatic adaptation that enables the system to become, as defined by Ashby [104]: "ultrastable". Learning occurs in the system's homeostatic regulator, and this acts on the autopoietic couple monitoring and regulating it according to a set of metarules that govern epigenetic events.

If the organism we are discussing is a virus and it is deemed to be living, then it needs to have a homeostatic capability. Interestingly therefore, in the case of Coronaviruses, Russel and others [105,106], explain that they are genetically stable since they have a mechanism for correcting errors that naturally occurs through mutation of their genetic code, and this appears to indicate a homeostatic ability. Further conceptual support that viruses may have a homeostatic system comes from Chi ([107]: p. 275) who explains that:

> "Fifteen years ago, scientists celebrated the first draft of the sequenced human genome. At the time, they predicted that humans had between 25,000 and 40,000 genes that code for proteins. That estimate has continued to fall. Humans actually seem to have as few as 19,000 such genes—a mere 1–2% of the genome. The key to our complexity lies in how these genes are regulated by the remaining 99% of our DNA, known as the genome's 'dark matter'".

This is elaborated on by Bai and Smith ([108]: p. 1), who say that:

> " . . . as much as 98 percent—of our DNA do not code for proteins. Much of this 'dark matter genome' is thought to be nonfunctional evolutionary leftovers that are just along for the ride. However, hidden among this noncoding DNA are many crucial regulatory elements that control the activity of thousands of genes. What is more, these elements play a major role in diseases such as cancer, heart disease, and autism, and they could hold the key to possible cures".

So, genetic variations are often hidden away in the noncoding dark genome. We recall that the distinction between coding and noncoding genes in a genome is that the former are associated with the production of specific proteins, and the latter are not. An exploration of these noncoding elements ([109,110]) reveals a key genetic switch that helps immune responses maintain their metaregulatory stability, and this plays a key role in controlling pathologies.

Thus, to summarise, the genome is an arrangement of coding genes, where genome expression epigenetically regulates capsid expression. Capsid expression involves the emission of specific proteins that are responsible for interactions in cell environments. The dark genome is an arrangement of noncoding genes, and dark genome expression targets genes in the genome which it regulates (cf. [111]). Hence, the dark genome operates as a virus metaregulator.

According to Rogers [112], these dark genomes are quite possibly responsible for personality disorders like schizophrenia and bipolar disorder. Interestingly, the noncoding regulatory genome (referred to earlier) is also a gene regulator [36], and may be associated with schizophrenia [37]. This commonality between regulatory and dark genomes seems more than a coincidence, and suggests that the two are essentially the same. This will be a reflection when we refer to dark/regulatory genomes.

3. Understanding Viruses

Viruses have coevolved with their normal biological hosts, and are structurally remarkably like them [113]. Herrero-Uribe [76] provides a useful background to views on the nature of viruses, starting with Lwoff [114] who defined living organisms to be independent, integrated, and interdependent structures with a set of functions. Viruses were not thought of as living systems because they were not organisms from a neo-Aristotelian perspective. For Luria [115] an organism is an entity that has individuality, historical continuity and evolutionary independence, but where functional independence is irrel-

evant to the definition. For Morowitz [116], the living organism extracts energy from its environment, and uses this to perform chemical and physical work thereby converting energy into organisation. This definition conforms to the nature of viruses as living systems since they use their environment of cell structures and processes to produce organisation. Consistent with this, Harold [117] sees living entities, unlike non-living ones, as having a capacity to both maintain themselves, and to reproduce by processes of extreme organisation. This applies to viruses which have a capacity to modify elements of the host cell and reorganise them such that in very specialized structures they can provide opportunities for viral replication. For Villarreal [118] and Sullivan et al. [119], not only do viruses have a capacity to reorganise their environmental structures and processes, but they are masters of genetic innovation, thus having the ability to learn and adapt. They are thereby able to permanently colonise a host.

In virus development, adaptation is only one part of the story. Genomes are said to mutate, and this may be the result of error processes during replication through "random mutations", or through selected "adaptive mutation". Following Rosenberg ([120]: p. 504):

> "The term 'adaptive' mutation was used by Delbrück to indicate mutations formed in response to an environment in which the mutations were selected. The term does not imply that non-adaptive (unselected) mutations would not also be induced, or that the useful mutations would be induced preferentially (this latter idea being called 'directed' mutation). 'Adaptive mutation' was adopted subsequently by Tlsty in her examination of gene amplification in rat cells. She distinguished mutations that pre-exist at the time a cell is exposed to a selective environment versus (adaptive) mutations formed after exposure to the environment".

Adaptive mutation refers to an ability (via self-production) to relieve selective environmental pressure, where the mutations are more beneficial to the organism against specific stresses, and where their responses include the induction of spontaneous mutation mechanisms. Such beneficiality is consistent with the idea, in more general contexts beyond virology, of purposeful systemic intention that is connected with cognition [30] and consciousness [94], both of which may occur in viruses.

While viruses are all parasites, some are purely pathogenic, while others are symbionts. If viruses are living systems, then they must possess not only autopoietic properties, but also have a capability to learn, and consideration will be given to such attributes.

3.1. The Nature of Viruses

Viruses are organisms with a morphology [101] that is a structured genome of DeoxyriboNucleic Acid (DNA) or RiboNucleic Acid (RNA) encapsulated in a protein shell called a capsid. Just like any living system, it can only durably survive and replicate inside a suitable host environment, and in the case of the virus this is a living cell. As an illustration of structure, the genomes of HIV, Influenza, and Coronavirus are all made of RNA (though Coronaviruses mutate more slowly than the others), this being less stable and more prone to error than the DNA viruses like that of Herpes and Smallpox. Viruses with RNA also mutate more rapidly than those with DNA.

Viruses are more complex than viroids (from which they apparently evolved). Viroids are single-stranded circular RNA molecules that are remnants of RNA from a time prior to the emergence of DNA and proteins. They take the form of rod-like or branched structures of catalytic RNA and can perform many basic functions of life, like replication and processes of evolution [121]. Viruses have a cycle of infection in which virus particles, called virions, are released so that they can infect other hosts.

Viruses are entire particles with a genome that facilitates infectivity, and a nucleic acid inner core. Its outer protein capsid provides viral specificity and cellular interaction. The capsid is a symmetric protein structure that determines a virus's characteristic traits, which when activated promote cellular interaction. Viruses are totally dependent on a host cell for replication, thereby being pegged as intracellular parasites. The replication process involves

using host mechanisms to duplicate the nucleic acid needed for the birth of new viruses. While the nucleic acid may be DNA, Luong [122] explains that for some viruses the generic material is RNA, and during cell infection by such viruses, RNA code is transcribed to DNA (which is more stable), and then to RNA to protein. A reverse transcription process from RNA to DNA also occurs, and viruses that use this mechanism are classified as retroviruses. In large viruses the genome may be quite complex enabling genes to have cellular metabolic cycles, and in such cases, after infection in a host metabolism, it expands its ecological influence, and the distinction between viruses and cellular life becomes unclear [123].

Kaiser [7] explains that viruses can be described as having: many protein folds encoded by viral genomes that are shared with the genomes of cells. They also have an ability to reproduce externally within their environment of living cells, and can mutate. This suggests, Kaiser proposes, a condition of living, even though they have no metabolism.

3.2. Viruses as Parasites

A parasite is an organism that is maintained within another host organism of another species to enable it to benefit by deriving nutrients at the other's expense. Where the parasite depends entirely on its host, it has already been noted that viruses are *obligate parasites*. For example, phytopathogenic fungus is an obligate parasite since it must have a living host on which to grow and complete its life cycle, as is the tapeworm. Both examples are deemed to be living systems. Viruses are also obligate intracellular parasites [33], i.e., they are totally dependent upon the internal environment of the cell to create new infectious viruses. They make contact with and bind to a cell surface to gain entry, and then dismantle their genetic RNA/DNA, encoding instructions for their proteins, and spontaneously assemble this into new viruses creating what is called novo replication. Louten ([33]: p. 20), comparing the nucleic acid structure of cells and viruses, notes that

> "living cells, whether human, animal, plant, or bacterial, have double-stranded DNA (dsDNA) as their genetic material. Viruses, on the other hand, have genomes, or genetic material, that can be composed of DNA *or* RNA (but not both). Genomes are not necessarily double-stranded, either; different virus types can also have single-stranded DNA (ssDNA) genomes, and viruses with RNA genomes can be single-stranded or double-stranded. Any particular virus will only have one type of nucleic acid genome, however, and so viruses are not encountered that have both ssDNA and ssRNA genomes, for example".

Louten further explains that once a virus infects a host, to replicate it must release an infectious virus particle in the host cell with the intention to infect other cells, and as it does this its genome must be protected. Within the extracellular environment there will be enzymes that have the potential to break down or degrade the nucleic acid, physical stresses due to the flow of fluids, or damage by ultraviolet radiation or radioactivity, all of which make virus options to replicate sterile. Its protein capsid has a repeating structure that delivers a strong slightly flexible boundary. The protein capsid is itself protected by a lipid membrane that derives from a cell membrane. The form taken by viruses might typically be a helical or icosahedral structure, but they sometimes have a more complex architecture.

Using the Baltimore classification system, viruses have been classified into types that are dependent on the nature of the genome, its replication strategy, how many strands of RNA it has, and with single-stranded RNA being either positive or negative. A positive strand can be directly translated into proteins, while a negative strand first requires it to be transcribed into positive-strand RNA. Unlike cells, viruses can reverse transcribe by creating DNA from an RNA template.

Viruses are successful key players in evolutionary and ecological processes [124]. All viruses are parasitic in that they benefit from their host through access to its nutrients. However, some are pathogenic delivering nothing but direct harm to a host (for instance by reducing host fitness for their own improved viability), while others are symbiotic,

delivering a more balanced viral-host relationship. For this latter classification, Roossinck and Bazán [125] identify three types: (a) commensal, (b) mutualistic, and (c) antagonistic.

Commensal symbiosis is the condition that is likely most prevalent in nature, where no detectable negative impacts can be determined in the host of a virus. According to Moore and Chang [126], commensal viruses develop in apparent infections which do not usually cause symptoms or disease in a host, and usually result in asymptomatic, persistent infections. As such they have been cited for the potential use in gene therapy against patterns of tumour occurrence.

Mutualistic symbiosis occurs where the virus and host become important beneficial partners, as well illustrated by Pradeu [127] and Roossinck [128]. This is not a new realisation, for instance the mutualistic power of viruses have been recognised for some while, especially where it comes to tackling cancer [129]. As Grasis [130] notes, mutualistic symbiosis can enable benefit to both the virus and its host, creating mutual fitness that increases advantages for evolution and biodiversity.

Antagonistic symbiosis occurs where a viral infection produces no observable cost to the host, but can contribute to coevolutionary processes [131]. Roossinck and Bazán [125] identify at least two models for virus-host coevolution:

(i) the directed arms race—where the host develops resistance and the virus follows by increasing its infectivity, the outcome being a directional evolution of increasing resistance and increasing infectivity. As an illustration of this, Brüssow and Brüssow [132] refer to the Russian flu in 1889, and Sharma [133] to the Spanish Flu of 1918 when the 3rd wave was mild and signalled the end of the pandemic, and suggests this might be the way of COVID-19 with the new Omicron variant;

(ii) fluctuating selection dynamics—where parasites and hosts can experience oscillatory cycles, and where the densities of these interacting species dynamically fluctuate through time, resulting in non-directional evolution [134] where, for example, in marine virus–bacterial systems, viruses might infect different bacterial populations at different times, preventing resistance, this resulting in very high levels of genetic diversity in the host.

While viruses may be antagonistic, they may have dynamic roles that constitute commensal relationships. In fact, the vast majority of viruses that one may come across are commensal. For example, bacteria can house viruses that enable competitors to be killed off while simultaneously providing host protection, and enabling them to invade new environments. Roossinck and Bazán [125] also refer to an extreme form of symbiosis called symbiogenesis, or speciation through fusion, this referring to the genetic fusion of all or part of a virus genome with its host genome, or with another virus. When viruses become part of their host's genome (a process called endogenization), viral DNA integrates, in due course, into the host's descendants.

That viruses can coevolve with their hosts indicates that, through mutations and evolution (when it involves improving fitness, this getting carried through to their populations), they are enabled to successfully respond to their host's immune system. This, in turn, is influenced by the dark/regulatory genome that shapes it [135]. This requires memory [35,136], a capacity to learn and innovatively adapt ([137]: p. 11). We have already referred to the "hidden memory genome" that facilitates memory.

3.3. Viruses as Learners

In contrast to an Aristotelian denial that viruses are living systems, that viruses have a capability to adapt and maintain their viability essentially defines them as living systems. If viruses are to be deemed to be living, then it has already been indicated that they must be capable of homeostasis, and hence have a learning capability. Thus, when their host environment creates an immune system action, learning viruses have a basis for homeostatic regulation that enables them to adapt, as well as a capability to defend themselves against threats through an immune system. Vossen et al. [138] explain this clearly when they note that the coexistence of a parasitic virus and its host provides evolutionary pressure on

both (and this can apply to viroids just as it can to viruses [139]). Vossen et al. also note that viruses vary in size and complexity, large viruses with a larger genome have greater diversity and complexity [140], and greater capability in responding to immune system defences from a host. They consider the case of herpesviruses where, while the host has an immune system able to defend it from the parasitic virus, the viruses have developed evasion against it. In other cases of learning, HIV uses an "invisibility cloak" made up of a host body's own material [141,142], just as Cytomegalovirus, a commensal symbiotic virus, is also capable of cloaking itself [143].

An adaptive capability that enables a virus to acquire a wholly functional and adaptive immune system has been demonstrated [144,145]. The virus, the bacteriophage, is a parasite of the cholera bacteria, and it acquired its immune system which it then used against its host. Zimmer [146] explains the process. In the same way that higher organisms like mammals defend themselves against microbial pathogens through their autoimmune system, so bacteria similarly defend themselves against microbial pathogens using various techniques, like—creating enzymes the action of which destroys an adversary; stealing proteins from viruses prior to their capsid formation, or committing suicide on infection to avoid becoming an incubator for new viruses that would then destroy nearby relatives. Now most bacteria have a genome composed of a chromosome (a circular, double stranded DNA molecule [147]). Their immune system is also able to learn autopoietically. Those that carry genes called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats, specialised stretches of DNA, and responsible for the production of enzymes) are able to capture fragments of invading virus nucleic acid which are then accommodated into those genes. These captured fragments are then used to create defences against the virus. In due course the bacteria create a knowledge base of virus codes. Now, the CRISPR genes are adopted for gene editing, and process transcripts of CRISPR arrays (called crRNAs) are used to facilitate mediated interference processes that guide targeted immunity [148]. Following Deltcheva et al. [149], crRNAs appear to represent a gene model that has been autopoietically assimilated into a microbe and then accommodated into its genome so that new protein behaviour can be anticipated. That such gene editing can occur as designed interference might also be deemed as an explanation of how viruses themselves adapt, since it conforms to the generic model of living systems [30]. The knowledge gained by the bacteria is not lost with its death, for when it reproduces, its CRISPR genes are passed on. The relevance of this for viruses is that they have learned to develop their own defences by producing anti-CRISPR genes which are used to shut down the production of virus-killing molecules. This points to a virus capability to develop its own immune system. Thus, like bacteria, at least some viruses are able to learn, this implying a knowledge base. As such, we shall suppose that viral immune system mechanisms with respect to CRISPR gene production are similar to those of other relatable organisms.

3.4. Viruses as Autopoietic Organisms

Maturana & Varela [67] developed the idea that there must be a common denominator to distinguish living systems from non-living ones. They proposed the notion of autopoiesis which requires that the entity under investigation is regarded as autonomous. Autopoietic systems are able to organise the production of their own components which are continuously re-generated through a network of internal processes. Living systems are thus those that continuously self-produce. While autopoietic theory reflects cellular systems, viruses conform to this definition because they self-organise as is required by the theory. Viral factories are dynamic systems that enable viruses to transform themselves, and that can conceal replicating their nucleic acid from antiviral defences and create conditions to enable their nucleic acid to be replicated. In so doing, viruses evolved strategies that can modify cellular processes for their own use. However, there are differences between Maturana's and Varela's view of the autopoietic process [95,150], and this contributes to the confusions in the field concerning whether viruses are living systems or not.

Before considering these differences, it should be recognised that there is an additional issue with the notion of autopoiesis ([151]: p. 79) that promotes something of mystery. Razeto-Barry [65] explains that autopoiesis is defined in terms of "processes" and "production", but the latter term has not been adequately defined. This has thereby allowed a significant diversity in interpretation. This becomes clear when referring to a dictionary definition for the word "produce", given (e.g., in the Britannia Dictionary) as:

(i) to make or manufacture or create or form something from components or raw materials;
(ii) to cause a particular result or situation to happen or exist.

Villarreal [118] explores viruses in terms of definition (1) using the metabolic paradigm. In contrast, Yolles and Frieden [30] adopt the definition (2) as part of a generic notion of living, with autopoiesis being a network of causal processes. That autopoiesis is causal is reflected in the effects it is directly related to, where, for Turabian [152], a cause-effect relationship is a process that involves displacement or transaction. In a related view by Steward [153], cause may be seen in terms of action which is, in itself, process. Meincke [154] notes that autopoiesis involves a non-linear dynamic causality, and this leads to the idea that living systems are constituted through *process ontology*, meaning that *being* is determined by process. This brings us to return to the differences in definitions of autopoiesis by Maturana and by Varela

Maturana's [155] autopoietic theory explains that any living system is a network of processes that enables a system to causally self-produce elements of itself required for tasks like self-organisation and adaptation. Within this, Luisi [95] notes that an autopoietic system organises the production of its own components, and these are then continuously re-generated so that the system can maintain the very network of processes that produces them, and this involves organisation that maintains identity.

In contrast, the enactive approach due to Varela [156,157] centres on system autonomy and a capacity for self-determination in which the system follows its own rules, and where its environment is unable to specify controls over its intentional behaviour. This indicates that the system is organisationally closed, i.e., has no logical connections with its environment, thus enabling it to create order that is self-determined. Di Paolo and Thompson [158] explain that Varela's approach is concerned with a self-individuating system which occurs under the condition of adaptive autonomy, where the system defines its identity through its own dynamic processes. This involves cognition, which is *an adaptive self-regulation of states and interactions by the system*, and which enables the maintenance of viability. For Yolles and Frieden ([30,159]), living systems not only have cognition, but also consciousness. From Amoroso and Amoroso ([160,161]), one can also deduce that consciousness must imply a subconsciousness due to the sufficient degree of complexity for the organisation required to adequately process information. As we shall see in due course, this subconsciousness provides a capacity to maintain homeostasis and its more dynamic form homeorhesis [162].

So, autonomy is central to living, and by its very nature indicates autopoiesis. Its viability is dependent on a dynamic homeostatic capacity. Here, then, the system as a whole produces itself through a suitable dialogue between its structure (and material fluxes) and its own network of causality. This relationship has been highlighted by Yolles ([163]: p. 167) when he says that "autopoiesis is a property of an *autonomous system* that defines its own boundaries relative to its environment, produces its own network of processes that are themselves part of the processes, and it obeys its own laws of motion. Such systems are self-organising, produce and eventually change their own structures, are self-referencing, and are self-producing in the sense that they produce the network of processes that enables them to in turn produce their own components". It is through self-production that Bhattacharyya's [64] notion of ability arises.

3.5. The Evolution of Populations of Viruses

In his replicator-vehicle paradigm, Dawkins [55] intentionally limits discussion of a causal link between the replicator and its vehicle, indicating only that they are correlated.

This correlation can become evidence for a causal link if the virus is considered to be a living system. Thus, following Herrero-Uribe ([76]: p. 994).

> "An autopoiesis system organises the production of its own components, so that these components are continuously re-generated and the system can therefore maintain the very network process that produces them. Living beings are characterized by their continuous self-production, so they are an autopoietic organization. Even though the theory of autopoiesis is based on cellular life, viruses can fit in this definition [through their own processes of] . . . organisation".

Hence, if viruses are living systems, then the connection between the genome and its capsid is autopoietic. Autopoiesis is a network of processes that produces and reproduces its own components and generates its own structures as it operates through a causal mechanism. It causally connects, in the case of the virus, the genome and capsid, and this connection is responsible for a dynamic tension between them. The components it produces may belong to either the genome or to the capsid, and the tension is therefore a dual autopoietic relationship. From the perspective of an observer in the environment, one part of the duality is an autopoietic causal pathway with an (anterior) trajectory, stretching from a viruses source environment to its target genome. Due to virus replication errors in its host environment, autopoietic selections to the genome may become subjected to mutations through its network of information-based processes that populate its causal mechanisms. This can result in new forms of genome expression, and explains the rise of random mutations. The other part of the duality is the reverse (posterior) autopoietic trajectory which provides imperatives from a genome for new forms of capsid expression. This occurs since the genome is an autopoietic regulator of capsid structure. In the anterior trajectory, adaptive mutation occurs as a process that, for non-lethal selections, mutations are produced that relieve selective pressure independently of any random mutations [164,165]. Since the term mutation indicates a process that generates nucleic acid sequence changes, Foster [164] notes that the term mutagenesis would be appropriate, but it has been used for the process through which mutations are induced by exogenous mutagens. While the term "mutability" means the ability to be mutated, as previously noted, "adaptive mutability" means the ability to be mutated adaptively through intention. Foster points to an illustration involving the *escherichia coli* of bacteria strain FC40, where mutations giving an adaptive phenotype (i.e., their protein shell trait) appear by processes that are distinct from those that produce random mutations during nonselective growth. This is connected with genetic recombination, a process by which nucleic acid is broken down and recombined to produce new combinations of alleles (referring to distinct gene variations). When adaptive mutations are successfully migrated to other viruses in a population, so evolutionary expression occurs. By evolutionary expression, we refer to a population of interactive viruses within which the activation of particular normative traits determines a set of potentials from which an evolutionary trajectory may emerge (cf. [166]), the potentials referring to virus-induced patterns of functionality.

While viruses conform to the same evolutionary mechanisms as all living entities, Darren et al. [167] explain how the dynamic of genetic recombination is a result of natural selection. This generates significant genetic diversity through the creation of genome patterns that can be used during evolutionary development. Any non-random genome patterns, those that identify a sequence of exchange between individual viruses within a species, provide a regulatory structure in a virus population that prevent certain individuals from recombining. Sequence exchange patterns across viral species can also occur, and indicate otherwise undetectable ecological links between species where they exist, and barriers between others.

So, a genome mechanism that exists in the evolutionary process of viruses is adaptive and/or random mutation. Viruses develop and evolve in their populations when their genetic information is modified. Adaptive mutation enables a virus, through purpose, to improve its ability to infect, as explained by Ren et al. [168] in the case of the Coronavirus [168]. It may also occur through random mutation that is the result of error when

copying genetic material [169]. Genes determine traits which characterise the virus structure and its potential for behaviour, and this leads to new capsid characteristic abilities through posterior autogenesis, and a capability to infect a new species, or even to change its character from parasitic-pathogenic to parasitic-symbiotic. Thus, for instance, there is the potential for viruses to become mutualistic, and be harnessed for nerve damage repair in human hosts [170]. They have also been seen as candidates for vaccines against COVID-19, and hence provide a basis for naturally occurring nanobot technology [171,172]. Viruses evolve rapidly due to the way in which they store genetic information, by either DNA or RNA, the latter normally seen in cellular systems as an intermediary for self-production. While cell systems copy stable DNA during replication, we are aware that viruses may replicate stable DNA or the less stable RNA. Since the replication process of viruses occurs in a host environment, where a plurality of viruses participating in replication processes coexist, virus expressions (occurring when its genome expression manifests capsid expression to give mature products, like proteins) can become mixed, so properties of one virus may be fed into another. Whether the impact of this on the genome alleles occurs as adaptive mutation or random mutation might be parametrically deduced, where different alleles exist.

Stern and Andino [173] are also interested in populations of viruses, and recognise that viral infection is highly dynamic, this leading to constant evolutionary changes resulting in genetic diversity in the viral–host interface. However, with a large virus population, selection will be predominant and random drift will be less common. This has an impact on viral alleles. Here, then, deleterious alleles are efficiently removed from the virus population, as adaptive alleles are given the opportunity to dominate it. With a small population size, random effects may dominate processes of selection so that it may not be possible to estimate the mutation rate. During their evolutionary processes, viruses can create very large populations in their host, but the population size becomes subject to bottleneck constraints during transmission between hosts, this reducing selection effectiveness. Domingo et al. [174] explain that due to the extreme heterogeneity of viral populations, very harmful mutations that may occur in viral genomes make them less fit within an evolutionary context, this reducing their viability.

While viruses may mutate easily, following Simmonds et al. [175], there are some (like hepatitis B) that have evolved very little over thousands of years. One explanation for this is that they have optimised their survival fitness for a given host. Short-term mutations reflect viable sequence changes in adapted genomes, while longer-term mutations tend to more closely resemble those of their hosts in a co-adapted virus–host relationship. In contrast, those viruses that jump hosts demonstrate significant adaptive selections in order to maximise their fit to the new host. The result may create an evolutionary stasis in long-term host relationships, so that even while viral evolution can result in rapid adaptation, it is their hosts that determine their longer-term evolution.

Evolutionary processes may be stable in populations of viruses, a condition in which a particular evolutionary trajectory is maintained where alternative strategies exists, even where they may be novel or initially rare. Such stability is enhanced when viruses operate as social entities that cooperate, communicate, and compete with one another, as represented in Social Evolution Theory [176]. Its relative, Kinship Selection Theory, explains cooperative processes between those viruses that share genes, and within it, individual viruses that can distinguish between kin and others, detecting harmful or spiteful behaviours that derive from non-related viruses. [177].

An elaboration of the Social Evolution Theory is Cloud Theory. Viruses form a collective of similar particles that constitute a "mutant cloud/swarm" within which they develop and replicate [178]. Arnold [179] reports research undertaken by Marco Vignuzzi, explaining that DNA viruses are relatively stable because they contain two copies of their genetic information. During replication, errors in the process can thus be eliminated. However, RNA viruses are single-stranded, and during replication, errors are passed on. Hence, new generations of RNA viruses tend to have many errors. After a few generations, a

single virus can become a mutant swarm of similar daughter viruses. As each generation spawns another array of viruses, a mutant cloud develops. If the capsid expression of a virus produces a non-functional protein, the virus can survive because others in the cloud have a good copy. This social cloud therefore compensates for having only a single strand of nucleic acid. This means that the virus adaptive process is shifted from the individual to the cloud under changing host conditions. Virus emissions collectively interact in their cloud, and successfully functioning proteins may emerge with new traits. In a heterogeneous population of viruses, some are able to evade pathological pressures on them, for example from natural host defences or antiviral vaccines. Cloud diversity can therefore result in a dynamic that leads to a changing fitness profile in comparison viruses, seen from an individualist perspective. Virus diversity is thus partly defined by the dynamics that operate in the collective.

Arnold further notes that if the fitness of a virus is determined by how many copies of itself it can make, compared to another virus, then this ignores the social dimension of the cloud. Hence, evolutionary fitness should refer to its ability to mutate in a cloud since an infection is a process of adaptation, where a fitter virus is better able to adapt. This can be explained through agency theory [180], where propositions can be harnessed, deriving from Whitley [181], Dopfer et al. [182] and Dopfer [183,184], and which enables one to explain how a cloud, taken as an autonomous system, is able to self-regulate. The cloud is an agency, and its viruses are its population of agents. They are grouped into configurations of interconnected structures and behaviours. The behaviours are the resulting actions of the emitted proteins arising from capsid expression, from which interactive relationships arise. For viruses these configurations may be seen in terms of populations of daughter agents in a cloud. The protein interactions that result may become institutionalised (being incorporated into a structured and often highly formalised system), this creating a potential for the emergence of generic rule structures that govern the cloud.

4. A Metacybernetic View of Autopoiesis

Here we shall explain the nature of metacybernetics as a qualitative theory of living systems, as developed by Yolles [41]. Initially we shall briefly introduce the theory, and then go on to discuss how it can be used to model living systems. We shall then apply it to viruses, supposing that they are generic living systems. The result is a systems biology representation that is able to explain an extended epigenetics. Metacybernetics is holistic [42,185], and has a quantitative dimension, delivered by Frieden's [32] formal information theory deriving from the concepts of Fisher information. This will allow us to explore viral conditions and capabilities within cell environments, and indicate potentials for viral pathology alleviation.

4.1. The Nature of Metacybernetics

Metacybernetics can be used to model living phenomena with metaphysical attributes, and will be used here to represent viral structure and process. It is a general theory that operates through a superstructure and a substructure [41], but it is being used here to create a generic theory of organisation in that it describes and explains how living systems (represented as agencies—thereby delivering a generic agency theory) can develop. The superstructure involves theory-building that operates through the integration of commensurable configurations [43]. A configuration is a structured knowledge framework that is sometimes called a schema, and which defines a pattern of thought/behaviour and set of relationships that represent effects. It involves propositions relating to their characteristics, relationships and entailments under complexity. Substructure has the dual properties of causal mechanisms and causal-agents. Causal mechanisms are channels/pathways that use processes to enable an outcome to develop from an input, where for instance autopoiesis is a causal mechanism operating through a network of processes. As noted previously, their existence indicates systems of meaning [54] that enable those processes to be represented as

dynamic causal-agents able to produce an effect (or deliver that from which events result) like self-organisation with properties that explain adaptation.

Metacybernetics is essentially a modelling paradigm. For Casti and Karlkvist ([186]: p. 3), models provide a way of representing aspects of the real world in an abbreviated and encapsulated form. Metacybernetics can operate through two modelling approaches. The first modelling approach is qualitative, and it can provide explanation and illustration of the role and functionality of causal mechanisms and causal-agents in life processes, these indicating ontological and epistemological relationships and distinctions. Thus, internal (metaphysical) ontological relationships in a living autonomous system involve the causal mechanisms of autopoiesis (self-production or operative intelligence) and autogenesis (self-creation or figurative intelligence). The second modelling approach is quantitative, using Frieden's theory of Fisher Information that can translate certain features of a natural system into a formal coded structure. In both cases, processes of encoding (through observation) and prediction (through decoding) can be applied to the natural world represented through parameters and data.

Metacybernetics is a cybernetic theory, and cybernetics has been around as a field of study since the 1940s. Attached to systems theory, it is concerned with processes of communication and regulation that are central to the notion of autonomous living systems. Cybernetics is said to operate through different orders of ontology enabling more complex epistemological explorations with increasing order. One way of describing the interests of first order cybernetics is in how systems are controlled, second order in the theory of observing systems, and third order in the theory of living systems [41]. The distinction between each of these orders is indicated by the number of hierarchically arranged ontologically distinct interactive domains they have. A first order cybernetic system has one such domain which provides objective observed positioning of agents towards a system, in contact with an environment. A second order system has two such domains internal to the system, and a third order system has three domains internal to the system. In this paper, our interests clearly lie with third order cybernetic systems.

4.2. General Third Order Agency Model

Consider a living system to be an agency, which we earlier defined as an entity that has the capacity, condition, or state of acting or of exerting power. It may be a singular body as in the case of a cell, or a plural body as in the case of a multicellular organism with a population of agents that mutually interact. Such agencies are adaptive pockets of order in an environment that is subject to processes of entropy [187]. Where agency has a population of agents, its order is due to agent interactions from which emerge collective behaviour that is non-reductively more than that of the sum of individual behaviours [188]. It is due to such emergence that complex interactions between agents are simplified, thereby bringing order to a system that might otherwise be seen to be in random fluctuation ([189]: p. 232). This is due to the natural dynamics of complex processes that result in the formation of regulative structures as described by Dopfer et al. [182]) as previously referred to, and while their work lies in the field of evolutionary economics, the principles that they identify are generic to all living systems able to evolve.

To create order in living systems requires at least self-reference, purpose and regulation. Self-reference is a consequence of some degree of awareness that there is a distinction between agency boundary and environment, and this implies the awareness that self (and therefore identity) exists, even if only as a primitive form [43]. Purpose is connected to functionality via a process of self-organisation. Following Halbe et al. [190], functions that are directly related to systemic need are primary, and this may be associated with a primary purpose. For Mossio et al. [191] a primary function (and hence a primary purpose), is systemic and subject to closure during the self-maintenance required for self-production (an autopoietic network of processes) in autonomous systems [192]. We introduced the term closure earlier, noting that it refers to the idea that no operations can enter or leave the system [193]. The functionality of autopoietic systems is to produce elements of themselves

for their own purposes [151], and they do this through self-regulation. Regulation is the application of controls that create interactive imperatives for agents, this in an agency that might enable it to better maintain stability, and which underpins its capability for viability.

For agency to be identified as a living system (Figure 1) it needs a capability to adapt, which in turn requires an ability to learn. This cybernetic model involves three ontologically differentiable domains that are connected according to a principle originally identified by Eric Schwarz [194]. This is a third order cybernetic model explained in some depth by Yolles [41] and explored with respect to autopoietic processes by Yolles and Frieden [30]. The domains in the model include an operative (or anterior) system of the metasystemic model and its regulatory (or posterior) metasystem, the two together forming an autopoietic couple (constituted as a network of processes) that functions as an operative intelligence ([43,195]). This couple should be seen as an epigenetic structure that explains how various forms of virus expression develop. Yolles and Frieden also explain that these intelligences operate as causal-agents, and the autopoietic couple necessarily involves both cognition and consciousness (as already mentioned). This means that the metasystem must, following Drãgãnescu [161], be associated with an ontologically distinct subconscious (i.e., a meta-metasystem/post-posterior system). As we shall explain, this is represented within a higher order causal mechanism called autogenesis, and as a causal-agent it maintains its network of processes that facilitate homeostatic actions. The hierarchically embedded lower order metasystem has the causal-agent of autopoiesis which transmits information between the regulatory metasystem and its operative system. It also enables source relevant information to become target destination relevant through its network of processes.

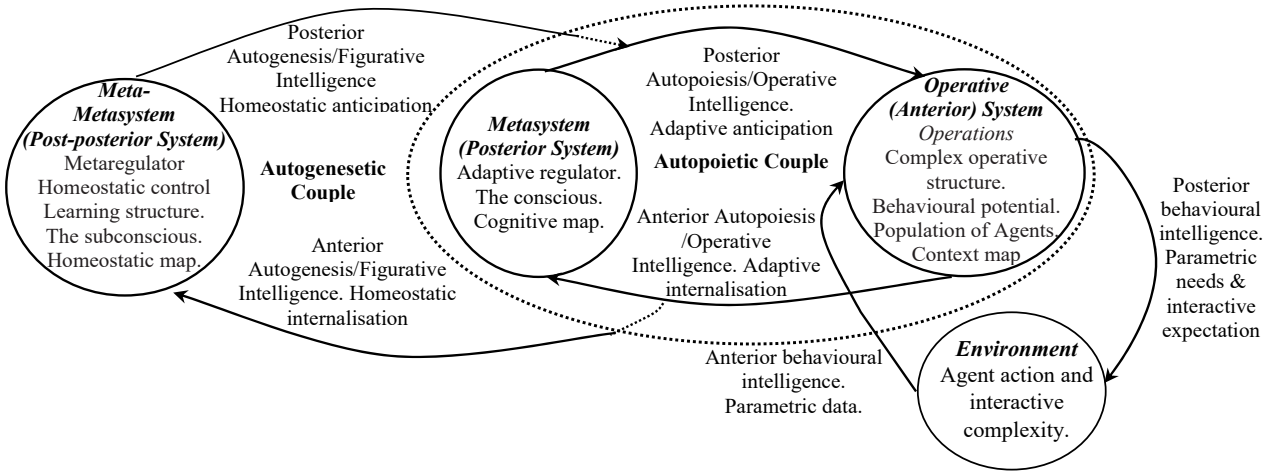

Figure 1. A 3rd Order Agency Model, with a Metaregulator of the Autopoietic Couple.

We can reflect on our earlier discussion in which we considered levels of both abstraction and embedded hierarchy. In principle, the model in Figure 1 is capable of exploring all three of Cleland's [17] (metabolic, thermodynamic and autopoietic) levels of abstraction, together with Barbieri's [51] levels of embedded hierarchy (metabolic, information, coding). The former vectors towards energy, and the latter towards information. Both end up in systems of meaning that constitute causal mechanisms. Metabolic processes are phenomenological as are their thermodynamic properties. This is conveyed cognitively to the conscious dimension of the living system through information flows, through autopoiesis. Then, through autogenesis it provides meaning which underpins coding.

The three systems indicated in Figure 1 exist in a hierarchy of influence, where a higher ontology is hierarchically superior to that of its neighbour. Each of these systems will have a pattern of information that is composed of a collection of data entities, each having a mutually related connection. Together, as a whole, they provide logical meaning. Where the data entities are connected with their parametric origins, they may be considered to form a map of locations and interactions for ontologically inferior contexts. In the operative

system (responsible for system operations) there is a context map, in the metasystem (responsible for regulation) there is a cognitive map, and in the meta-metasystem (responsible for meta-regulation) there is a homeostatic map. A context map identifies the relationships between bounded parametric contexts. A cognitive map identifies the parametric interactive relationship between the operative system and the metasystem, and contains both personalised and social information needed for episodic activities (cf., [196]). A homeostatic map is like a context map, but it refers to the parametric interactive relationship between the autopoietic couple and the meta-metasystem needed to regulate episodic activities.

The autopoietic couple has a dual causal mechanism. One part of the duality defines an anterior trajectory through which processes of internalisation can flow, this manifesting information from a context map of parametric data. Changes to the cognitive map are expressed as a pattern of information that will be assimilated (as a model to be referred to) and may be accommodated (by integrating it into the structure). The other part of the duality has a posterior trajectory through which processes of anticipation occur, this manifesting regulative adjustments from the metasystem to the operative system that leads to operative structure adjustments. The autopoietic couple is connected to the meta-metasystem (effectively the homeostatic regulator) through the dual autogenesetic causal mechanism. The anterior autogenesetic trajectory internalises information from the autopoietic couple which is then manifested in the regulatory homeostat and records this in a homeostatic map (operating as a pattern of knowledge). The other is the posterior autogenesetic trajectory through which processes of anticipation occur, this manifesting regulative adjustments from the metasystem to the operative system, and this impacts on the anterior and posterior autopoietic causal mechanism to create homeostatic adjustments.

The source of the anterior autopoietic trajectory is the operative system, and the target is the metasystem, and vice versa for the posterior autopoietic system. There is a similar relationship between the homeostat and the autopoietic couple. The operative system has a structure that can adapt to environmental change under the regulatory guidance of the metasystem, and in the case of agency with a population of agents, this facilitates or constrains the behaviour of its agents. Similarly, adaptation in regulative structure (from which regulative processes derive) can take place in the metasystem with new autopoietic information arising from the operative system. The autopoietic couple itself always has a potential to become an instrumental (autopoietic) system. Its regulatory control, relative to the operative system, arises in its meta-metasystem. The network of processes that connect the autopoietic couple to the meta-metasystem is called autogenesis (self-creation) that is sometimes referred to as figurative intelligence. The whole assembly forms an autogenesetic couple through which homeostatic regulation occurs. Behavioural intelligence is a causal mechanism that channels a network of information processes. This enables specific parameters to be measured, or phenomenological interactions/behaviours to be ascertained or to occur in the environment, relative to purposes.

The metasystem provides agency self-regulation for the operative system just as the meta-metasystem is a regulator of the autopoietic couple. This is referred to as cognitive regulation. It indicates the self-directed regulation of cognitions, where cognition refers to agency ability to perceive changing features of its internal and external environment and undertakes responses that maintain its viability. Postulating that agency has, in general, limited resources to monitor external inputs, it needs to increase the information content of perceived signals from its environment. This sensory perception is actively shaped by learning and the resulting internal cognitive models that, with anticipation, generate strategies that compensate for limited information that services the need for viability and processes of evolutionary adaptation [197]. Behavioural intelligence is also a network of processes that manifest the potential of the operative system structure pragmatically as actions in the environment. Anterior behavioural intelligence provides the ability for an operative system to satisfy conditions that in effect evaluate its ability to, in turn, satisfy its interests in its environment. Posterior behavioural intelligence is the ability to determine

appropriate behaviour relative to system needs and interests within given contexts, enabling the selection and execution, as required, of effective behaviour in environmental situations.

The autopoietic and autogenesetic causal-agents are important since they enable the system to live, as explained by Yolles and Frieden [30]. Operative Intelligence is the autopoietic network of processes that enables information flow. If this flow is efficacious, then the autopoietic couple is stable as the information received in the metasystem is relatively close to that at the operative source. If it is inefficacious, then the autopoietic couple will be less stable, and the information arriving at the metasystem will involve errors. The autopoietic couple operates as a system in its own right, and hence the figurative intelligence is a second order autopoietic network of processes that creates a higher order autopoietic couple (call it an autogenesetic couple). There is similar stability criteria work for this couple as for the autopoietic couple.

By now it is clear that the intelligences are not only causal networks of processes, but are also channels for information flow across the living system. Behavioural intelligence is an active observer of the contextual environment of the system that can determine the complexity of the context. Through its network of processes, each of which responds to a different contextual parameter, the information is transformed into a structure compatible with operative system requirements. The operative intelligence acquires this information and transforms it, as it is transmitted autopoietically to the metasystem. This is the case since the information introduced into the operative system by behavioural intelligence is manifested in the metasystem. The quality of that information will be indicative of the stability of the autopoietic couple [30]. It thus indicates the degree of order in the couple. The information about the order of the couple is acquired by the figurative intelligence, and delivered to the meta-metasystem which can, in due course, then cause the autopoietic couple to adapt where necessary.

For Miller et al. [162], cognition-based evolution involves variation applied to purposive genetic adjustments as problem-solving, and this recognises that agencies are intelligent. While such considerations apply to biological cells, they also refer to generic living systems, including viruses [198]. Such intelligence should not be seen as some general concept, but rather as process intelligences that operate as networks of transformational processes, like operative, figurative and behavioural intelligence. Miller et al. further note that intelligent cells can receive, assess, communicate, and deploy information to sustain individual states of self-integrity, a process of information assessment inherent to self-reference. It is a knowing, and thus an ability to problem-solve, together with a sense of self that enables distinction from other living entities. This enables agencies to maintain self-determined homeostasis even where states of dynamic flux occur with changing trajectories.

4.3. Modelling Biological Living Systems

It has been said that we shall take a systems biology approach in modelling viruses. This is:

> "an approach in biomedical research to understanding the larger picture—be it at the level of the organism, tissue, or cell—by putting its pieces together. It's in stark contrast to decades of reductionist biology, which involves taking the pieces apart"
>
> ([199]: p. 10).

> "Few scientists will voluntarily characterise their work as reductionistic. Yet, reductionism is at the philosophical heart of the molecular biology revolution. Holistic science, the opposite of reductionistic science, has also acquired a bad name, perhaps due to an unfortunate association of the word "holistic" with new age pseudoscience . . . A fundamental tenet of systems biology is that cellular and organismal constituents are interconnected, so that their structure and dynamics must be examined in intact cells and organisms rather than as iso-

> lated parts . . . [the approach is] "holistic" because [it relies] on the "fundamental interconnectedness of all things . . . "
>
> ([200]: p. 1401).
>
> "Traditionally, science has taken a reductionist approach, dissecting biological systems into their constituent parts and studying them in isolation. Entire scientific careers have been devoted to studying only one gene or protein in order to understand its function. Although scientists have made progress using this method, this reductionist approach limits biological insights into the human body. As a result, efforts to treat many complex diseases have also faced limited success. Reductionism, by its nature, cannot comprehend the complexity of biological systems, the properties of which cannot be explained or predicted by studying their individual components"
>
> ([201]: p. 1).

The approach is characterised by a framework in which the parts of something are intimately interconnected and explicable only by reference to the whole. To enable us to apply this to viruses, and thereby explain in some detail virus epigenetic processes, it is essential that requisite and related reductionist findings are collected and connected, and we shall progress on this journey here.

Trafton [202] explains that living cells contain many types of RNA which have individual roles, like messenger RNA (mRNA), copied from DNA and carrying protein-coding information intended for cell structures, the mRNA directing the assembly of protein through processes called translation. The cell has a structure in which there is a nucleus (containing the cell's chromosomes that encode its genetic material, and which are collected in its interactive mitochondrial and nuclear genomes) and a membrane, the two separated by cytoplasm within which are included organelles—specialised structures (originally perceived as "little organisms") which have certain operative functions that physically maintain the cell, and which together constitute its operative system. However, genomes are not foreign to cells, which can house them within their nuclei as individual chromosome territories [203]. The function of the cellular membrane includes its action to maintain receptors and channels that allow certain molecules that can mediate cellular and extracellular activities, which are then able to interact with the organelles [204].

Living viruses, bacteria and cells have a similar ontological autopoietic structure and causal mechanisms. While the core of a cell is the nucleus (with its genomes), that of the virus is only the genome. Bacteria have a cell wall that is a capsid-like protein assembly that serves as simple metabolic organelles [205]. Unlike bacteria, the virus must use host cellular apparatus for translation in order to convert viral mRNAs and produce the protein products required for viral replication [206]. Thus, a function of the viral capsid is to generate protein mechanisms that can hijack the cell's translational processes for its own purposes. The metaphysical structure of viruses in Figure 1 can thus apply, with slight adjustment, to both cellular structures and to bacteria. There are however physical differences, just indicated by their size, between these three types of life. Viruses tend, as far as we so far know, to be smaller than bacteria or cells. For instance one of the largest viruses, the mimivirus (which is associated with pneumonia), has a capsid diameter (including fibres extending out from the capsid that likely have a cell access function [140]) of about 750 nanometres [140]. This is significantly smaller than the largest bacteria or single cell creatures. One of the largest bacteria, thiomargarita magnifica, has a thread-like single cell of up to 2 centimetres long, holding its genetic material in a membrane sac [207]. Also in contrast to the virus, the largest single-celled organism, the aquatic alga caulerpa taxifolia, can grow to a length of 15–30 centimetres [47].

Returning to viruses, their protein capsid creates a potential for virus behaviour, where the proteins are able to control and influence viral gene expression in the virus genome. Gene expression is an activation process by which information from a gene is used to produce such end products as protein or noncoding RNA (i.e., an RNA molecule that is

not translated into a protein) from which virus traits (phenotypes) arise. They can also influence regulatory processes in a cellular environment. The capsid has viral parametric characteristics that determine its trait behavioural possibilities (connected to its traits) that it can deliver, and part of this is its behavioural style expressed, for instance, through its enzyme actions (e.g., their catalytic properties and the specificity and reversibility of their actions) that its interactive proteins use. Behavioural intelligence is also capable of mapping the parameters of the environment (e.g., the protein expression, which is responsible for the activation of specific proteins, and indicates the observable characteristics of protein structure). It feeds this back to the operative system as acquired information that will update an existing context map concerning the virus protein capsid structure, with the environmental characteristics. It is from this context map that information can then be collected and autopoietically delivered to the genome where it modifies an existing cognitive map, this being able to recall, and decode information about the parametric characteristics of context, and to which an assimilated model is connected.

Viruses differ, some being small and quite simple, while others are large and complex. Viruses having autopoietic processes that have no homeostatic capability become instrumental, this occurring when figurative intelligence is inefficacious, when homeostasis is determined entirely by environmental stability. Instrumental agencies have nowhere to retain knowledge or memories that can enable them to regulate the dynamics that occur in the autopoietic couple or recognise new dynamic processes. As such, the dynamics that occur there are guided by an existing set of strategies, these triggered by the interactive events that occur in the environment.

The biochemical nature of the living system, whether applied to a virus or some other organism like a biological cell or bacteria, has been known for some while, especially through the technical notion of the systems perspective [47], an approach we conform to. To set up such a systemic view, there is a need to identify the different elements of living as considered above, but here it will be useful to summarise them. Following authors like Mokobi [208], Cheriyedath [209], and Wang and Farhana [210], the different elements of virus life can be condensed as follows:

- DNA is a long stable molecule that contains a unique genetic code for a living system.
- RNA is a long (less stable) molecule that processes protein, carrying genetic information of many viruses from the cell to the cytoplasm (material outside the cell nucleus); it has various forms that include mRNA, rRNA, rRNA, tRNA and crRNA [211].
- Messenger RNA (mRNA) carries and transcribes the genetic code of the genome into a form that can be read and used to make proteins, and carries genetic information from the nucleus to the cytoplasm of a cell, and is multifunctional (cf. [212]).
- Ribosomal RNA (rRNA) is located in the cytoplasm of a cell, where ribosomes are found, and directs the translation of mRNA into proteins.
- Transfer RNA (tRNA) which, like rRNA, is located in the cellular cytoplasm and is involved in protein synthesis. Transfer RNA brings or transfers amino acids (protein building blocks) to the ribosome that corresponds to each three-nucleotide codon of rRNA. The amino acids then can be joined together and processed to make polypeptides and proteins.
- CRISPR array RNA (crRNA) is normally discussed within the context of gene editing, but which is also a feature of viruses [213], and that constitutes a model of the environment that has been autopoietically assimilated into a virus, and then accommodated into its genome.
- LncRNA (long noncoding RNA) regulate target gene expression through the interactions between their higher-order structures and major partner proteins in higher order structure connected with the dark/regulatory genome [214]. It is therefore an agency directly connected with dark/regulatory genome metaregulation (cf. [135]).
- The genome of a virus is an arrangement of genes, and regulates the capsid. Genome expression uses coded information that regulates capsid expression. Bacteria and cells also have genomes stored in their chromones (encoded genetic material in DNA

molecules). In cells the chromosome is stored within the nucleus, in bacteria in the nucleoid.

- The capsid is the viruses operative shell. Capsid expression selectively produces certain proteins, which are biological compounds like enzymes, hormones, and antibodies.
- The dark/regulatory genome is part of the nucleic acid that exists outside the known genes, and operates as a virus metaregulator. Dark/regulatory genome expression targets genes in the genome which it regulates, and influences the viruses immune system where it has one.
- Epigenetics refers to the relationship between the expression of the dark/regulatory genome, the genome and the capsid, and the environment.
- Protein synthesis occurs through translation, and during transcription an element of the genome is transcribed (copied similarly but not identically to the source) into mRNA which is then translated to produce a protein; during translation, mRNA along with tRNA and ribosomes (RNA and proteins responsible for assembling the proteins of the cell) work together to produce proteins. We note that in a virus the source element may be either DNA or RNA.
- Proteins are biological molecules in cells used for functions that vary from cellular support to cell signalling and cellular locomotion; illustrations are antibodies, enzymes and some hormones. Some proteins are enzymes capable of creating some substances and decomposing others; viral enzymes catalyse the integration of virally derived DNA into the DNA of a host cell in the nucleus; this forms a provirus that can be activated to produce viral proteins.
- Cytoplasm consists of all the contents outside of the nucleus (a structure containing a cell's hereditary information which controls its growth and reproduction) and enclosed within the cell membrane of a cell and has various functions like protein synthesis and hormone and cellular waste removal.

We therefore postulate that rRNA takes the process role of behavioural intelligence in that it directs the translation of mRNA into proteins. The role of mRNA is taken to be that of a causal-agency. It operates through autopoiesis as a network of anterior processes that enables the genetic information that has been assembled (as part of the context map) in the protein capsid from the cellular environment, to be communicated to the genome, and adjustments made. A low efficacy of mRNA in doing this may result in information error that impacts on the genome, resulting in a mutated virus. Recombination is the process by which the genome can be adjusted when there is a high efficacy in the information transmission. The anterior mRNA process regulates genome expression, determining which aspects of the genome to activate. At this early modelling juncture, it looks very much like the operative system can represent the protein shell of the virus from which various proteins can emanate to interact in the cellular environment. Its metasystem contains the coding genome which is capable of modifying the potential of the protein shell, and the two are connected autopoietically as a coupling, apparently through mRNA. The connection between the protein shell and the cellular environment might well occur through tRNA. Questions then arise concerning how the autopoietic couple is itself regulated. This will then be an issue that will be examined soon.

The description so far enables us to propose Figure 2 (as a derivative of Figure 1) for a virus as an instrumental system that functions autopoietically with no learning capacity. However, it has already been explained that viruses can have a learning capability, and for this to occur there needs to be a meta-metasystem that, as previously explained, houses an immune system repository that is shaped by a dark/regulatory genome [135]. This higher order system is a homeostatic controller, and its operations use the knowledge that it acquires. The communicator between the autopoietic couple and the homeostat involves the process of transcription, which gene therapists may use (called metatranscription [148]) to alter the gene coding for therapeutic purposes. One way of seeing this is that the gene therapist will modify, in a way perceived appropriate for a therapy, the information being

transmitted autopoietically as part of the transcription process. Transcription, it must be recognised, is one of the fundamental genome processes. It involves turning DNA (for DNA genomes) into RNA, the role of which is to act as a messenger and carry instructions from DNA to control the synthesis of proteins, even though in some viruses it is RNA as opposed to DNA that holds the genetic information. The proteins that are synthesised determine the characteristic (behavioural trait) properties of the virus, for instance whether its parasitic nature is pathogenic or symbiotic, and if so in what way. The communication between the dark/regulatory genome and the genome occurs through transcription factors that mediate the regulation. Following Lawton et al. [215], genome transcription is a network of processes by which the viral genetic information is presented to the host cell protein synthesis machinery. There it produces the viral proteins needed for genome replication and progeny virus assembly. Transcription factors [216] are proteins involved in the process of converting, or transcribing, DNA into RNA, or stimulating or repressing transcription of the related gene.

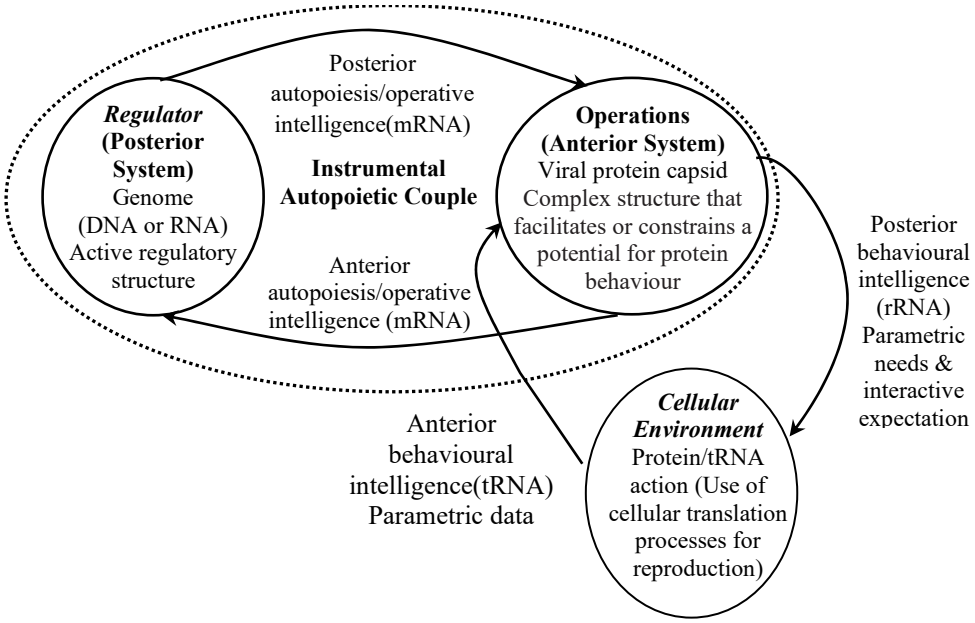

Figure 2. Instrumental Model of a Virus.

The operative intelligence is an autopoietic network of processes that involves internalisation (which includes assimilation of a model, like a microbe's crRNA, that is internally referenced by a system, and accommodation where the model is integrated into the structure), and anticipation that determines the adaptive potential for the system. Thus, in the case of a virus, this determines the structure of the protein capsid that guides the behaviour intelligences of purposive behaviour through, for instance, enzyme actions. As indicated earlier, genome change may occur through random mutation, or it may occur under virus intention as processes of adaptation called adaptive mutation.

Reflecting on Figure 2 and its autopoietic intelligence networks of processes, in the case that a viral genome is DNA based, then we know that it has mechanisms of autopoietic processes, permitting the expression of certain genes to change [217]. If, however, a virus is RNA based, then it too has such properties. According to Frederick [218], RNA molecules are responsible for regulating their own formation through feedback, that is, using both anterior and posterior autopoietic processes. If there are too few RNA molecules, then the host cell initiates transcription to create more. If there are too many RNA molecules, then transcription is halted.

The regulatory genome provides information concerning when and where molecules (like RNA or DNA) are produced within an organism [219]. If a learning cell (or virus) is to function properly, required proteins must be synthesized in a timely way, and this is

regulated from information encoded in their DNA (or perhaps RNA for the relevant virus). The process of *gene expression* enables a gene to produce RNA (through transcription) and protein, or DNA (in the case of reverse transcription). This process is represented in Figure 3, which should be recognised as a dynamic cybernetic tension between the genome and the individual body as a phenomenological representation of the organism. The function of the meta-metasystem is a homeostatic regulator as part of the metaregulator to the virus, as agency. Transcripts deliver crRNAs (processed transcripts) to the immune system repository where they can be used as accommodated models to regulate the autopoietic couple. The meta-metasystem is also a domain in which the dark/regulatory genome sits, also part of the virus metaregulation, and a regulator for the autopoietic couple that connects the genome with the capsid.

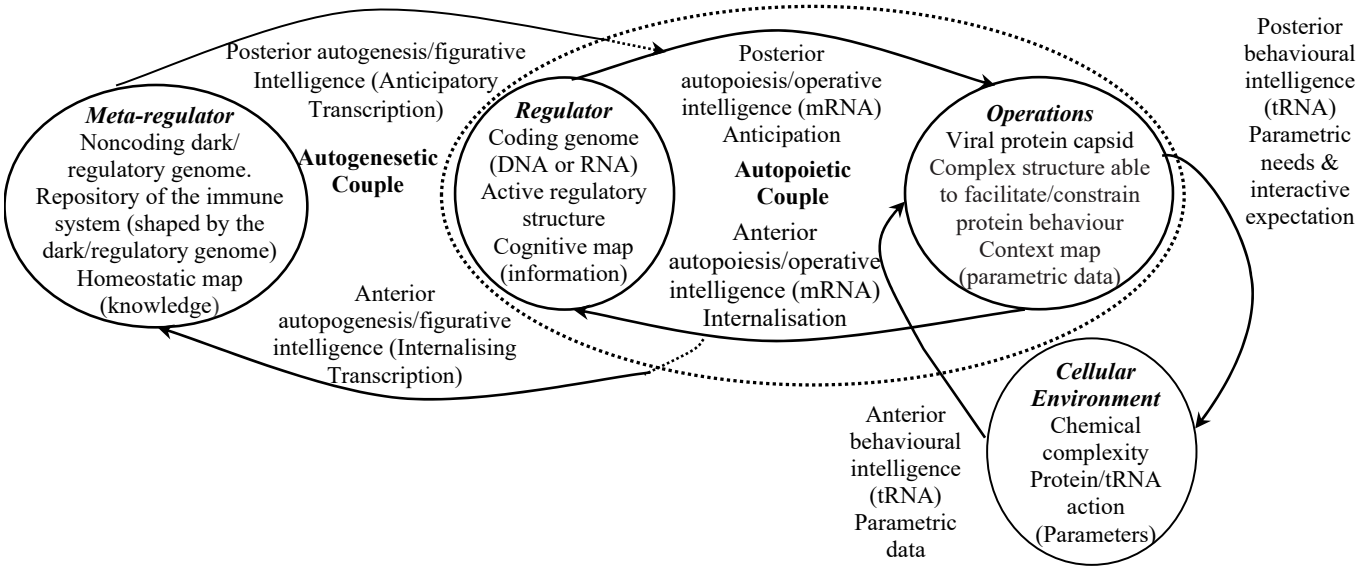

Figure 3. Tentative Agency Model for a Homeostatic Regulator.

The causal mechanism functionality in Figure 3 can be described as follows. Internalisations occur through the anterior autopoietic trajectory defined by the network of mRNA processes. They create crRNA that is referenced in the cognitive map during assimilation, when genome expression may be influenced. If the crRNA is accommodated into the genome, then the genome expression will mutate adaptively. The new expression of the genome will then impact on the posterior autopoietic mechanism, when the network of mRNA processes will, in anticipation mode, influence capsid expression. The mechanism for this is beyond the current scope of this paper, but it is explained through CRISPR processes [73].

The transcription network of processes that occur in the autogenesis causal mechanism are not totally clear. However, internalising transcription occurs through the anterior autogenesetic trajectory where LncRNA acts as an agency to target dark/regulatory genomes. Perhaps this might use a form of crRNA that will be assimilated and/or accommodated into the dark/regulatory genome therefore modifying dark/regulatory genome expression. This in turn will influence the posterior autogenesetic trajectory, enabling the system to anticipate a new regulatory interconnection between the genome and its capsid. The posterior transcription processes will provide metaregulatory information that applies to the genome and its capsid, again with LncRNA functionality.

4.4. Evolutionary Processes

Consider having a population of viruses the behaviour of which is determined by the operative system constituted as its protein capsid. Also consider that a complex operative system houses agencies in rich interaction, where the specific interactive relationships that

promote behaviour are unknown. These relationships are regulated from the metasystem by related entities that, as a structure, create a potential of imperatives for agency interactions. If the relationships between these entities is known, they might be expressed mathematically [43], thereby explaining bifurcations [73] and the development of emergent structures through metamorphosis [220].

Multiple viruses from either a single population, or multiple populations, interact within the cellular environment. These interactions occur through the enzymes that they produce from their protein capsids. The properties of these enzymes are a function of the structure of the protein resulting from capsid expression. In the case of viruses from the same population, behavioural trends develop that are autopoietically fed back to the viral genome to create regenerated evolution. In the case where there are viruses from different populations, i.e., different viruses, then the behavioural properties of one may influence that of another through the anterior autopoietic trajectory, this resulting in their genome adaptation. This is the mechanism adopted when viruses, which have crossed over from one species to another, evolve and become relevant to the new species. It can also represent the cloud/swarm dynamics of virus evolutionary processes. This calls on the principles borrowed from evolutionary economics [181–184] and where, as discussed earlier, the interactions that occur between the viral proteins may in due course result in the emergence of new genome regulations. Figure 4 is representative of this process.

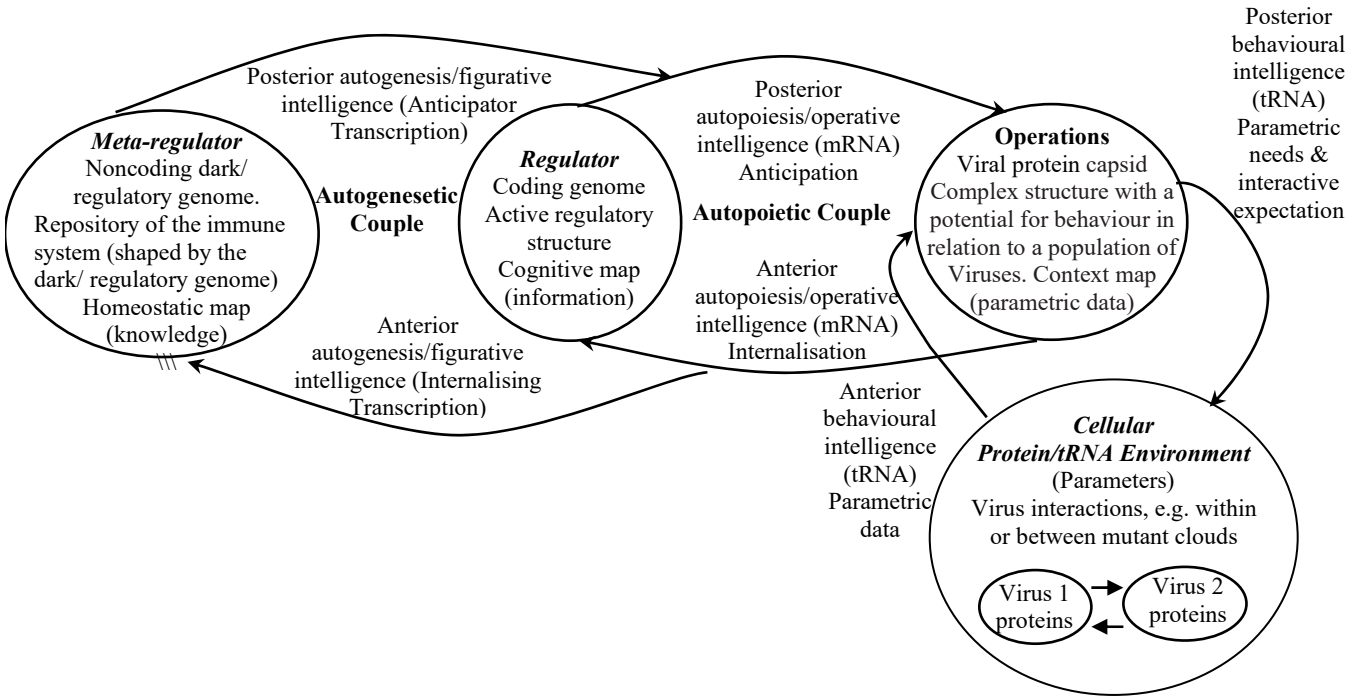

Figure 4. Postulated Model of an Agency as an Evolutionary Virus Process.

While the different intelligences are explained in Yolles [41], Yolles and Fink [43] and Yolles and Frieden [30] as networks of processes that manifest information from one domain to another related domain, the efficacy of these intelligences in undertaking their transformative function is really important if one is to understand the viability of a living system. To determine such efficacy, it is useful to adopt Frieden's [32,221] information theory that derives from Fisher Information. It should be noted that when Fisher Information is given as a measurement value, this is also a measure of process intelligence efficacy.

Figures 3 and 4 are agency models that not only represent the virus as a living system, but also that of its cellular environment where the genome is replaced by a nucleus (with its own genomes). This can therefore describe how virus mRNA, when introduced into the cell, instructs it to build new viruses that conform to its interests.

4.5. Causal Agency Efficacy: The Intelligences as Information Channels

Recognising that agency involves causal mechanisms that are channels of information, it is of value to explore the efficacy of the system's process capability in this using an appropriate information theory. This allows us to introduce a quantitative dimension of metacybernetics, from Extreme Physical Information (EPI), which is demonstrably coherent with it [43]. This is an information theory that uses Fisher Information, and is suitable for probabilistic exploration of complex dynamic systems. The causal mechanisms are information channels for system process intelligences, and from this one can (for instance) evaluate system stability [30]. This can lead to the exploration, in general terms, of the efficacy of viral autopoietic information transmission, and what this means with respect to virus dynamics.

Intelligences are not only networks of processes that manifest observed attributes of a given domain (e.g., for anterior trajectories, behavioural intelligence from the environmental domain, operative intelligence from the operative system domain, and figurative intelligence from the domain of the autopoietic couple) and manifest them to another, but they are also channels for information which is manifested with some degree of efficacy [30]. This can be determined from EPI theory [221], where Fisher Information enables measurement of the amount of information that an observable random variable x carries about an unknown parameter a of a distribution that models x. EPI is concerned with determining the nature of an observable context by taking data samples through a set of relational parameters, with quantitative parametric descriptors that broadly describe it.

The theory supposes that data values y to be measured obey

$$y = a + x \tag{1}$$

for some x and with a unknown parameters defining the system's state. Where the data y is known, a is computed via some required function of the data (like a simple average). The apparent "noise" values x is supposed to be due to phenomenological fluctuation that defines the phenomenological effect driving the system. This obeys a probability distribution $p(x)$ that describes knowledge uncertainty about the effect. The distribution $p(x)$ is unknown, and to be found, data y also ultimately determines the total amount of information I carried by the system. This must obey the principle of Extreme Physical Information (EPI), i.e., that $I = maximum$. Note: Historically, this was in the past called the principle of Maximum Physical Information. The maximisation process is algebraically determined, given knowledge of all known constraints on $p(x)$ (like mean value $<x>$). Knowledge of the parameters involved depends on the narrowness of the distribution $p(x)$ which indicates how much information is collected in the data. EPI thus refers to observed systems that obey the condition $I = I_{\max}$, where I can represent such measures as entropy, order, or complexity, depending on context [221,222].

The nature of I is the information acquired from the context and is a measured representation of the bound information J. The numbers I and J are Fisher Information [32] values. While I is not a perfect measure of J, the relationship between them is indicative of an information flow represented as:

$$J \to I \tag{2}$$

In general we can suppose, for ease of modelling, that the context at some time t is specifiable by a single parameter a which is generally a fixed and definite vector of numbers that derives from measures of context. Here, a is indicative of a set of relationships that exist between the parametric components, and which deliver the observed values y. Practically, y is not representative of a since there is also a random value x as shown in Equation (1). The nature of x is that it is an intrinsic fluctuating effect, and is indicative of an anomaly like observational error. The total number of possible intrinsic fluctuations x define a probability law $p(y \mid a)$, and knowing this, one can provide an indication of the quality of contextual observations that create I. In effect, therefore, EPI is concerned with identifying the maximum attainable change of Fisher Information subject to the constraints

that are determined from the context. If one has confidence in the constraints, then there will be equal confidence in the solution for $p(x)$.

Now, the value I for observation y is defined to obey Fisher Information as

$$I = <[d/dx(\log(p(y \mid a)))]^2>. \quad (3)$$

Here d/dx is a derivative of the log argument with respect to x; also brackets $< >$ indicate an expectation in the presence of the probability (likelihood) law $p(y \mid a)$. This defines the probability of each possible observation y in the presence of a given state value a. Now, if fluctuations x in Equation (3) do not depend on the size of a (case of "additive noise"), then $p(y \mid a) = p(y - a) = p(x)$. Putting this in Equation (3) gives (ignoring a multiplier 4) gives

$$I = <[d/dx\ (\log(p(x)))]^2 = \int dx q'^2(x), \text{ with } q' = dq/dx \text{ and } p(x) = q^2(x). \quad (4)$$

The information is, then, expressed merely as a simple integral over, now, the amplitude function $q(x)$ describing the phenomenon (where it may be noted that in quantum theory, this amplitude function $q(x)$ is usually denoted as the complex function $\Psi(x)$). In summary, if $p(y \mid a)$ is known then so is $p(x)$ known, as is then $q(x)$ and then information I. In evaluating Equation (4) for various laws $p(x)$ it becomes apparent that I is a measure of the width of $p(x)$.

A *wider* probability law $p(x)$ means, via Equation (1), that more widely "random" values of x are present. As discussed below, this results in a less accurate estimate of the parameter a from an observation y. Thus, less-fine prediction is possible, expressing inadequate observation. This is intuitively why I will take on a small value.

Conversely, a locally narrow law $p(x)$ means a larger value of I. Thus, Fisher information I measures the information about an unknown parameter (or parameters) in a given context, enabling it, by its size, to 'recognise' hidden structure in an observable effect.

This also ties in with the 'unexpectedness' or 'surprisal' nature of Shannon's information measure (noting that Shannon's measure is the discrete limit of Fisher information due to 'coarse graining' the data.) That is, the Fisher information for a highly complex phenomenon $p(x)$ obeys alternate zones x of high and low unexpectedness.

The premise is that all information is conveyed from a phenomenon to an observer. The observations are outputs from a channel, defined by an output probability law $p(t)$ or $p(x)$, depending on whether time or position are being observed. All such events convey Fisher Information that satisfy Equation (3).

Now, as an elaboration of Equation (1), consider information received as observation values y given as

$$y_n = a + x_n, n = 1, \ldots, N. \quad (5)$$

The aim of taking all such data is to estimate the value of the system parameter a specifying its state. The value of a is, then, *to be estimated* out of the data y_n as some function of them (such as their arithmetic mean, or geometric mean, or ...). In general, the data may be *biased*, i.e., their arithmetic average a does not equal the true value a but, rather, some function $b(a)$ of them.

Now, Frieden [53] explains that I can be used as a measure of the level of disorder of a source being measured, or its degree of complexity. As an illustration, minimal complexity is used as a defining property of cancer growth [223]. To appreciate the relationship between cancer and viruses, McLaughlin-Drubin and Munger [224], explain that viruses can encode proteins that reprogram host cellular signalling pathways (like transcription) that control its attributes. This relates to: proliferation, differentiation, cell death, genomic integrity, and recognition by the immune system. The cellular processes respond to complex and regulatory networks and are monitored to ensure that aberrant cells are eliminated. The viruses target cellular regulatory nodes and inactivate surveillance mechanisms that would usually recognise and extinguish such abnormal cells. In another area of research,

interest lies in how viruses are able to cure cancer. In particular, Coronaviruses have been recognised to have an impact on cancer [225–227], this leading to considerations about the design of viruses for disease control. For instance, Howells et al. [228] explain that oncolytic virotherapy can be used to design viruses that attack cancer cells, useful since they do not have the side effects that more traditional therapies have. There are various ways through which this can occur, one of which is to manipulate the protein capsid so that infection is targeted to receptors only found in cancerous cells.

Returning to Gatenby and Frieden [223], cancerous tissue can grow, but can no longer function properly as would be normal, hence it has given up a large amount of complexity. This property, when used in an application of EPI to cancer growth, gives rise to the law of growth for breast cancer, where I is a measure of the *ability to know.* Here, then, information I also determines how well the state of a biological molecule can be estimated by a generally imperfect observation of its position. The mean-squared error e^2 in any unbiased estimate obeys the law [229]

$$e^2 \geq 1/I \tag{6}$$

called the "Cramer-Rao" inequality. As noted by Frieden [32], when the lower bound

$$e^2{}_{min} = (1 + db/da)^2 \ / \ I \approx 1/I \tag{7}$$

is reached then an efficient value of I has been achieved, where b is the derivative of a function $b(a)$ with respect to a, and that $b = b(a)$ is the amount of 'bias' present in any observation of the system of parameter value a. The 'bias' measures systematic bias away from the true value a in any observation y (i.e., data value y). Thus, the equation for $e^2{}_{min}$ is indicative that the minimum mean-squared error goes inversely as I *regardless of* that level $b(a)$ of systematic bias. Thus, the information dominates the error effect, whatever the 'foibles' and failings of the data-taking setup.

Now, Equation (7) describes, on the face of it, how well the system state a is known by observing data Equation (1) from it. A further premise is that only if the value of a is well-enough defined a priori can that system 'effect' *be known* to have happened. To 'hesitant' or conservative observers, only if that value of I or a larger one occurs that can be believed unequivocally, is it convincing that that the effect has, indeed, occurred. This will be quantified in due course.

The value of I is connected with gene expression which influences parameter descriptions. For Awazu et al. [230], gene expression levels can be classified as conforming approximately to the Gaussian power law. By the power law we mean a functional relationship between two quantities, where a relative change in one quantity results in a proportional relative change in the other quantity, independent of the initial size of those quantities: one quantity varies as a power of another. The law is important because it reveals an underlying regularity in the properties of systems. Highly complex systems have properties where the changes between phenomena at different scales (or foci in a hierarchy of embedded systems) are not dependent on the particular scale being used to observe it. Gene expression may evolve, and this is a major source of trait/phenotype diversity [231]. The dynamics driving the growth and evolution of genomes is the Fibonacci "golden ratio" that describes predictable patterns that occur in all dynamic systems, and it is an indicator of balance [232]. This ratio has also been found in the human genome within the frequencies of different nucleotides (the basic building block of nucleic acids—the primary information-carrying RNA or DNA molecules that make up genetic material). The numerical value of this ratio is 1.618, and arises even in *non-biological cases* in the EPI answer for the law $p(t)$ as the form $t^{1.618}$ for *any* mass growth scenario arising, at $t = 0$, out of zero mass.

4.6. Virus Autopoietic Efficacy

We are aware that information flows along the causal mechanisms, which we can now examine individually. Consider behavioural intelligence, the function of which is to

observe a contextual environment, recognise its parametric and other characteristics, and take measurements that conform to the EPI principle (of maximum Fisher Information), then deliver this to the operative system (the virus protein capsid) to update the context map. Operative intelligence observes and selects information available in the context map, manifesting it to the metasystem (the virus genome), where I is an indicator of autopoietic stability/order [30]. Figurative intelligence observes the processes that occur in the autopoietic couple taking heed of parameters like autopoietic efficacy, regulatory structures and adaptive system changes, and manifests its findings to the meta-metasystem (the homeostat) that creates viral coherence through the improvement of order. To determine the efficacy of either operative or figurative intelligence, parameters are needed for environment and the autopoietic couple. In this section, however, our interest lies in information flow from the former, along the autopoietic channel.

In order to understand viral information processes, consider the basic relation between Fisher I and level of ripple complexity [53] of order R, defined as

$$R = (1/8)L^2 I \tag{8}$$

whereby the level of complexity we are referring to is that which may be due to randomness and/or intention in the level of structural x detail in the probability law $p(x)$ describing it and exhibiting structured organisation and detail, primarily in its "ripples". L is the maximum extent of the system (e.g., $2r$ for a sphere of radius r). In the case of the virus capsid, it can be represented as a sphere covered by spikes, where L indicates the length from spike to opposite spike. So, it would then be the diameter of that sphere. Or, if it is instead a partly squashed sphere (like a 'flying saucer') it would be the largest diameter of that shape, with I the Fisher Information. On this basis, ripple complexity R and information-loss level I vary directly: R is large if I is large, or small if I is small. So, by Equation (1), our thesis is that nature produces phenomena of maximum information level I. Proteins active in cell environments propagate according to this effect.

It may be noted that Equation (8) is consistent with Chaitin's [233] definition of complexity in observable data, and where the system has maximum complexity R if its level I of Fisher Information is at its *maximum value*, where, as the system grows and evolves, so its level of Fisher Information grows thereby satisfying the EPI principle.

Let us now consider Figure 4 in which a cellular environment involves interactions between proteins. While these interactions may occur between the parameters associated with different viruses, they may also occur between parameters of a parasitic virus and its host cell environment. Let us suppose that there is a virus with enzymic parameter that is a reflection of a relational cellular enzymic parameter, and let this parameter be represented by $\boldsymbol{\tau}$. Let us call the host's cellular parameter $\boldsymbol{\tau}_{good}$ since it is of benefit to the host, and that of the virus $\boldsymbol{\tau}_{bad}$ which is of benefit to the virus but not to the host. Both forms of the $\boldsymbol{\tau}$ will likely result in different levels of 'structure' in the infected cell; therefore, there will be different levels of order R and I. Perhaps this is a case where a system (here a host's infected cells), obeying the EPI principle, can have *either good or bad* outcomes, depending upon which of the $\boldsymbol{\tau}$ forms prevails. The most beneficial for the host is the one giving a lower value of the Fisher Information loss I (from the level J that, in theory, allows the process '$\boldsymbol{\tau}_{good} + \boldsymbol{\tau}_{bad}$' to occur). However, at this point it is not clear whether one choice or the other *always* gives the lower value of I, or if the process outcome just depends on the individual host.

Consider a gene therapy approach where there is an interest in minimising the impact of the virus on the cell. This is achieved by understanding the $p(t)$ laws that govern them. Respectively information level $J - I$ for $\boldsymbol{\tau}_{good}$ is greater than that for $\boldsymbol{\tau}_{bad}$. Identifying $p(t)$ would help in identifying the trajectory of virus infections that do not harm the host, as compared to incurring ones that do. Both forms $\boldsymbol{\tau}_{good}$ and $\boldsymbol{\tau}_{bad}$ will likely result in different levels of 'structure' in the infected cell; and therefore, in different levels of order R and corresponding I. Let J represent the minimum required level of I that allows the virus to

take hold of, and enter, the host cell. This implies that the host system, obeying the EPI principle of

$$J - I = minimum, \text{ with } J \text{ fixed and } I \leq J \tag{9}$$

can have *either good or bad* outcomes, depending upon which of the two $\boldsymbol{\tau}$ proteins prevail. The most beneficial for the host is the one giving a lower value of the Fisher Information loss I (closer to minimum required level J) and, therefore by Equation (2), a larger gain of structure and information. This therefore models the creation of the $\boldsymbol{\tau}_{bad}$ variant: The minimum information loss $J - I$ in Equation (6) should be larger than that for the $\boldsymbol{\tau}_{good}$ version. We note that, since J is fixed, accomplishing the *minimum* shows that this also expresses a principle for attaining *maximum* Fisher information I in the system.

On the other hand, hosts (as *victims* of a viral infection) want the parameters expressing that information loss I in Equation (9) to be a maximum value (i.e., less potent). That is, for a minimally bad COVID-19 effect we want I to be maximum of size (so that it maximally subtracts from maximum possible value J possible).

So, in summary, there is a two-pronged problem:

(i) show how a virus infection arises naturally, out of Equation (9), and
(ii) show what biological parameters affect the value R and therefore what values of them tend to maximize R, thereby weakening the strength of the effect.

Either case requires an information measure that parametrically connects the interaction between the virus with its cellular environment, where I updates the capsid context map through the anterior behavioural information trajectory, and the updates are autopoietically transformed and transmitted to the genome through the anterior operative intelligence trajectory, thereby determining a requisite need for the genome to adapt its structure through processes of adaptive mutation. Such genome adaptation is consistent with the idea that viruses evolve through either error and /or intention. There will be such an information level for $\boldsymbol{\tau}_{bad}$, and for $\boldsymbol{\tau}_{good}$. Both growth effects obey the minimum principle of Equation (9), where J is the fixed, maximum level of I needed for, respectively, $\boldsymbol{\tau}_{bad}$ or $\boldsymbol{\tau}_{good}$ to 'successfully' infect the host cell.

Notice that information I is a loss from an incident level J of information, so that the loss $J - I$ is positive or zero. The loss is, phenomenologically, incurred by the 2nd law of thermodynamics, which says here that information is lost as the incident particle travels through a medium. Phenomenologically, that loss is affected as increased disorder (e.g., in cancer) in the infected host cell. As in all growing systems, this increased disorder is expressed as increased randomness in the cell structure. The information associated with $\boldsymbol{\tau}$ (call it ${}^{I}\boldsymbol{\tau}_{good}$ and ${}^{I}\boldsymbol{\tau}_{bad}$), for cell viability, will require that ${}^{I}\boldsymbol{\tau}_{good} > {}^{I}\boldsymbol{\tau}_{bad}$. This formulation will be applied below.

5. Case Study

In this case study we shall consider how the theory so far constructed reflects on our knowledge of the Coronavirus. Interest lies mainly in the relationship between the virus capsid and its host cell environment. We shall first consider capsid expression which we earlier explained enables the activation of proteins in the cell environment that are of interest in virus-host cell management. Then we shall consider in more general terms the relationship between capsid expression and how it relates to the EPI principle. Finally, we shall consider virus learning capacity, this relating to its possible homeostatic capability and hence its condition as a living organism.

5.1. SARS-CoV-2 Capsid Expression and Cybernetic Interactive Processes

Capsid expression results in the emission and activation of proteins that can be used to alter host cell activity for virus benefits. Viruses have receptors that during infection provide a point of attachment to a target cell, and this enables events that lead to fusion with the cell membrane and entry of the virus. Receptors are highly spe-

cialised proteins that have limited tissue distribution, and examples are growth factor and neurotransmitter receptors.

A hormone is a chemical messenger, and Angiotensin is a hormone protein that causes blood vessels to become narrower, helping to maintain blood pressure and fluid balance in the body. ACE is an angiotensinogen-converting enzyme—and its function is to convert angiotensin 1 (Ang1) into angiotensin 2 (Ang2). ACE is a key enzyme in regulating pressure through the renin-angiotensin system [234], and it is a protein receptor that can be found attached to the membrane of cell surfaces [235]. High levels of ACE activity lead to increased formation of Ang2, this in turn leading to potent vasoconstriction, and hence hypertension.

ACE2 is an enzyme that regulates ACE [236]. To infect a host cell, the SARS-CoV-2 virus mediates entry into a cell (through its surface spike protein) by binding ACE2 on host cells to initiate molecular events that release the viral genome intracellularly [237, 238]. During COVID-19 infections, the virus initially targets the lungs since it likes to infect the ciliated cells that occur in the lung bronchioles [239] causing tissue damage and inflammation. To limit this, drugs, called ACE inhibitors, are used which limit the formation of Ang2, thus bounding tissue damage and inflammation. ACE inhibitors help relax the veins and arteries to lower blood pressure as it restricts Ang2 production.

Pagliaro and Penna [240] explain that ACE2 is a negative regulator of classical ACE. The two enzymes are involved in maintaining the homeostasis in the renin-Ang system, by regulating blood pressure and fluid and salt balances. In almost all relevant pathological conditions, especially those of the cardiovascular system, there is an increase in the ACE/ACE2 ratio in relevant organs and systems. An ACE/ACE2 ratio imbalance is caused by downwardly regulated ACE2 levels, and this alteration in ratio disturbs homeostasis. Since SARS-CoV-2 connects with ACE2 to enter the targeted cells, this leads to downregulation of ACE2. Thus, with low ACE2 levels or activity, the ACE/ACE2 ratio increases, and difficulties arise for the human host. This indicates an increasing risk of having a worse outcome in COVID-19 infection. Below, we shall explore this ratio through Fisher Information.

The action of SARS-CoV-2 to create the COVID-19 disease delivers an inflammatory response in the host. ACE and ACE2 operate at the cell surface and compete for the same substrates (cell surface). A gene therapist might well be interested in investigating how to force domination of the ACE2 protein's presence in the infected cell, over that of the ACE. A bit short of this goal, we shall show how to favour ACE + ACE2 as a population class in the infected cell. Now, there are two opposite downstream effects from the two enzymes:

- ACE as a 'bad' enzyme ($\boldsymbol{\tau}_{bad}$) causes activity leading to vasoconstriction (the narrowing of blood vessels by small muscles in their walls), oxidative stress (a phenomenon caused by imbalance between production and the accumulation of oxygen reactive species), inflammation and apoptosis (programmed cell death);
- ACE2, the 'good' enzyme ($\boldsymbol{\tau}_{good}$) counters the preceding activities of ACE by altering ratios of hormones and amino acids (the two types of protein that form a basis for life).

We have already discussed the relationship between $\boldsymbol{\tau}_{bad}$ and $\boldsymbol{\tau}_{good}$. Now, the host may be more prone to inflammation where ACE prevails. When this happens, the result is the accumulation of a toxin that exacerbates inflammation resulting in acute respiratory distress syndrome and severe diffuse cardiac inflammation.

To understand the virus targeting of ACE2 requires an appreciation of the cybernetic relationship between the virus capsid and its host cell environment. The interaction between them is determined by the causal mechanism of behavioural intelligence that has two reverse trajectories: a posterior (feedforth) trajectory from the capsid to the cell environment, and an anterior (feedback) trajectory from the cell environment to the capsid, and for this we refer to Figures 2–4. The posterior trajectory anticipates requisite virus conditions through the release of proteins to be activated in its host. The anterior trajectory provides the ability for the virus to determine cell environmental conditions that can

satisfy its infection interest in the host cell. This interest includes creating opportunities for infection and replication.

Now, the cell structure is composed of a membrane supported by the cytoskeleton, and a nucleus, where the two are separated by cytoplasm. The parametric nature of the cell is highly complex [241], but anterior trajectory parametric data needs to be relevant to virus infection options, like that of the protein ACE2. The Fisher Information associated with the anterior trajectory will indicate how adequately parametric data has been acquired from the bound information in the cell environment. Suppose that the anterior trajectory, where parametric data is carried to the capsid, has a Fisher Information of I_a. A small value of I_a will represent a poor representation of the cell environment, and a large value will provide a good representation. For virus viability, I_a should be large.

The posterior trajectory concerns the Coronavirus and its intended interactive behaviour in the cell environment. It is reflective of the ability for the virus to determine appropriate behaviour relative to its needs and interests within the context of cell infection and reproduction, enabling the selection and execution, as required, of effective behaviour in the cell environment. It thus carries information that is connected with the virus parameters. These parameters are reflected in the four main structural proteins that it has, and these include spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins [242], but principally the spike protein is capsid specific, and a measure of this is its ripple complexity. It has already been noted that the main function of the spike protein is to connect with the receptor ACE2, enabling it to enter the host cell. The spike protein thus plays a crucial role in the first step of infections in causing disease. The capsid ripple complexity indicates the surface shape of the Coronavirus and hence its fitness to infect. Now, recall that by Equation (8) the ripple complexity of the capsid will be proportional to the Fisher Information I for a given virus architecture. Consider that I_p is the Fisher Information associated with the posterior trajectory, through which proteins that are released through capsid expression seek to create adjusted parametric conditions in the cell. If I_p is small, then the virus has more uncertainty in the protein releases that it will make. This is because of Equation (6) where $e^2 \geq 1/I$, and this indicates that there is error in the ability of the virus to locate a vulnerable point on the cell surface, perhaps occurring because feedback through the anterior causal mechanism leading from the cell to the capsid has a small value of I_a. Thus, a small value I_p would give large error for the capsid ripple complexity which diminishes the fitness of the virus to infect. In contrast, a large value of I_p will indicate greater certainty about the cell environment and the actions of the proteins emitted during capsid expression, this suggesting greater virus viability.

Returning to ACE and ACE2, both forms will likely result in different levels of 'structure' in the infected cell; therefore, different levels of order R and Fisher Information I_p will result. This is a case where a host system (here a person's infected lung), when it obeys the EPI principle, can have *either good or bad* outcomes depending upon which of the ACE forms prevail.

Each host cell experiences a differing balance between ACE and ACE2. The cell is more prone to inflammation where ACE prevails. When this happens, the result is the accumulation of a toxin that exacerbates inflammation resulting in acute respiratory distress syndrome and severe diffuse cardiac inflammation.

One may also reflect on the viruses auto-immune system in Figures 3 and 4. One can begin by assuming that all viruses have a potential for such a system, though in the higher order autopoietic couple that connects the immune system to the autopoietic couple, there may be very little coherence so that autopoietic Fisher Information I_a is small and the homeostatic autogenesetic couple is unstable, this leading to an ineffective immune system. The virus is only capable of homeostasis when its autopoietic regulator functions effectively, implying the need for a large autogenesetic I_a.

5.2. Capsid Expression and the EPI Principle

It is of value to review the idea behind the EPI principle with respect to capsid expression—the selective activation of proteins to be released in the cell environment to deliver purposeful interactions. For $J - I = minimum$, J is any level of information the virus (here the 'observer') gains about the location of a *vital position* on that cell, with the aim of causing onset of the COVID-19 infection after it is pierced. So, here the event a in data obeying Equation (4) is actually two joint events: (1) the cell location a, and (2) discrete positions on the virus that, when meeting with the lung cell, can pierce it so as to parasitise it. Hence, by the *independence* of events (1) and (2) location quantity I is here the sum of the information in both events (1) and (2). They are obviously independent, so that for the latter purpose, the 'observer' virus deforms its surface selectively through an imperative from the capsid expression through the causal mechanism of posterior behavioural intelligence. Since the Fisher Information generally measures the amount of 'gradient' in its law $p(x)$ (see Equation (3)) the virus increases its degree of surface roughness. This takes the form of relatively long, sharp spikes.

Now, under the condition given in Equation (7), a "weak spot" can be identified in the COVID-19 system infection process. In this case the system "state" a identifies a parameter that indicates the true location of a spike on the viruses protein surface. This spike position also defines an entry point position on the cell surface. The more uncertainty associated with this entry point location, the less likely it is that the host cell will be entered, and hence, the less likely it is that a COVID-19 infection will occur.

Suppose we now wish to analyse the growth of the information system at hand. To do this, consider an incoming Coronavirus and the host cell surface it is impinging upon. The virus enters the cell if any one of its spikes pierces the cell surface. Thus, the event "virus enters cell surface" is to be considered. Any one spike suffices. Also, since a relatively wide range of cell surface positions can be entered by the virus, the efficiency of the virus-host system is mainly that of the virus spike per se.

Let the system "state" a identify the parameter defining *the true position* of a spike on the *virus*' surface. For the event "virus enters cell" to occur, this spike position must be well defined, i.e., it should represent a high net level of Fisher information for the virus-host system. On the basis that J was the highest effective information value needed for the "virus entry" event to happen, the information difference $J - I$ should be minimized, i.e., Equation (8) must be obeyed. In fact, that principle was used [243] to derive the growth law $p(t)$ that COVID-19 should obey.

It should be noted that this is COVID-19 growth *solely within the individual 'host' that catches the virus*. Further growth, purely by contagion from one host to another, is another possible route (see below). This growth within the individual host obeys a simple power-law relation

$$p(t) = t^b. \tag{10}$$

For this to have physical significance, the power b must equal the Fibonacci constant 1.618 ... That value maximizes its level of information I, through obeying $J - I = minimum$, where J is any fixed, very high level of the information. This Fibonacci golden constant, or mean, as it can be referred to, is a "golden ratio" that describes predictable patterns that occur in all dynamic systems, and it is an indicator of balance. The EPI approach, in itself, gives the number 1.618 ... as the power of the power-law $p(t) = t^{1.618\ldots}$ [221].

In fact, despite its lack of biological assumptions the law Equation (10) *is confirmed*, by the power-law effects $p(t)$ *empirically observed* for the first months of the COVID-19 pandemic for South Korea and Japan (and we shall return to this).

We note that the Fibonacci golden mean is a "golden ratio" that describes predictable patterns that occur in all dynamic systems, and it is an indicator of balance. It naturally occurs, e.g., when the number of events (say, number of rabbits in a biological population) at a given generation (i.e., given time t) equals the sum of the rabbit numbers for the preceding two generations. It assumes that no losses occur due to death (since rabbits breed so fast that virtually no deaths occur between generations).

Now, by Equation (7) it can be observed that the uncertainty e^2 in spike position grows as $1/I$, meaning that the infection is less apt to occur if information I about the spike location is reduced. What does this mean in practice? Biologically, for a given amount of virus surface mass, this means that its spikes become more bluntly shaped. That is, they become less sharp and, also, shorter in length. Such a prediction is sensible since it is both the length and sharpness of the spikes that allow them to "latch on" to the cell. Thus, the complexity of the viruses spike structure unites the two phenomena of "ripple complexity" and biological virus growth. The COVID-19 pathogen then becomes more dangerous when it evolves to have spikes that are sharper, taller and denser. Ripple complexity R therefore grows with its corresponding Fisher Information value.

Seeing that COVID-19 takes hold in a host using its spikes, it suggests that an information-based offensive can be adopted based on Fisher Information. To explain this, note that any physical effect, such as COVID-19, needs information to engage it, since its activation state (here, where the virus pierces the lung cell membrane and infects the person) is defined by the Cramer-Rao error formula in Equation (7). It has been indicated that the higher the level of I, the more "crisply" the virus is defined and, hence, the more effective it is in infecting the lung cell. Thus, the ability for the virus to infect grows directly with its level of I. Conversely, a virus having minimum I has less ability to infect. This occurs when its spikes become shorter and blunter, thereby incurring a lower level of I and hence of ripple complexity R, which we recall is proportional to I.

This could be engineered, or it might occur naturally, or if the precursor viruses (where existing before the enhanced spikes of the SARS-CoV-2 virus had evolved) allow it to replicate under ideal conditions, perhaps induced through viral management techniques. Then the 'weaker' viruses, those with the shorter and blunter spikes, would tend to survive: (a) at first, equally with the better fit (longer and pointier spikes), and then (b) more often since the latter spikes, to survive, and presumably requiring a lot more resources (and information) to 'burn', this no longer available in its natural cellular environment.

One may ask why this didn't occur naturally in the first place, that is, why did the first deadly SARS-CoV-2 viruses, with longer, sharper spikes, not die out within but a few generations of their growth? The answer is that they, instead, started growing ripple complexity and information by contaminating the human population. This is abundantly clear from the early curves of COVID-19 growth, country-by-country, published by health information sources [244]. The curves of lowest COVID-19 growth were for the two countries (Korea and Japan) that took great pains to socially isolate infected people. So growth by contagion occurred minimally. They also obeyed the following growth curve of COVID-19 virus mass m over time t where:

$$m(t) = t^b. \tag{11}$$

All other countries, which did not enforce social isolation so stringently, obeyed the law, and with power much exceeding 1.7, with values of even 10 or higher. In fact, the lowest empirical value 1.7 was a good approximation to the theoretical golden ratio of 1.618 [221], obeying theoretical growth according to the Fisher principle for which Fisher Information loss is minimum. Note that the minimum loss of information corresponds to its maximum gain, thereby minimizing error e^2 in Equation (7).

So, why might there be loss of information in the first place? Biologically this occurs because of an expenditure of resource just before it reaches the 'output' of this information channel, as determined by some observation. For this detector to itself function optimally, by Equation (7), it needs its input signal to have a high level of information. Now, for any real phenomenon there is a maximal level J of information I that will certainly suffice for this purpose. Then any value of input information $I \leq J$ will suffice if the reduction $J - I$ is small enough, satisfying Equation (9). The process continues, in sequence, to all other channels of information of the overall process.

This can be related to Figure 4, noting that the spikes of the SARS-CoV-2 virus are one of its characteristic parameters. A gene engineering approach would be to quash the level of

that Fisher Information just prior to its 'creation.' This therapy could apply to causal agency of behavioural and/or operative intelligence. In a homeostatic virus, capsid expression is determined by anterior operative intelligence in the autopoietic couple of Figure 4 through adaptive mutation. As a result, the posterior operative intelligence causes adaptation of the capsid in order to adjust the capsid expression. However, where anterior autopoietic Fisher Information is small, adaptive mutation is overcome by random mutation. Where anterior behavioural Fisher Information I is small, the spike feature of the capsid is disrupted, where for instance $I_{\min}$ may be approached. According to Paulsson-Habegger et al. [245], in the latter case this may be possible through a therapy that involves the TMPRSS2 mRNA enzyme. Such a strategy is the *opposite* of a usual Fisher Information requirement that seeks $I_{\max}$.

This ties into recent work regarding the elimination of the spike in the first place. It amounts to a direct, intuitive approach to getting at the virus ("don't let it make a beachhead, in the first place"). Here, by contrast, we see that it arises out of considerations of information and ripple complexity content, a two-pronged attack, either of which by itself could accomplish reducing these values. In gene therapy there is thus the possible tactic of simply removing the spike. However, from Mousavizadeh and Ghasemi [246] it can be recognised that under certain known natural conditions, the Coronavirus can grow and produce spikeless and non-infectious viruses. This is the strategy that companies like Pfizer and Moderna have followed. By modifying the mRNA coding through a vaccine, the cells are instructed to produce a SARS-CoV-2 virus with spikes that have less accessibility to cell environments, this overriding virus mRNA codes.

Past tactics on reducing pandemics have centred on outbreeding the highly pathogenic version of the virus with a harmless version. The relatively harmless version could be attempted here as well. Here then, there is a need to breed a species of SARS-CoV-2 that has some of the features: (1) no spikes, (2) small spikes, or (3) blunted spikes. In all cases, the ripple complexity R is vastly reduced, as required, by EPI. It also has to out-breed the SARS-CoV-2 (which, in itself, is just another tactic to increase its total ripple complexity R for that generation).

It should be realised that the efficacy of the posterior anticipatory autopoietic trajectory in Figure 4 is dependent on anterior internalising autopoietic trajectory. If anterior autopoiesis is inefficacious, the assimilated model in the genome will be poor (cf., [30]), and this will also have impact on the posterior autopoiesis of anticipation that carries adaptive information to the capsid. During the internalisation process, if I is small, then the genome is subject to mutations which may also impact on the ability of the spike parameter to be maintained. When I is large, the genome will adapt through recombination to satisfy intended changes. As a result, the genome will change according to the value of I, and the way in which regulative anticipation occurs in the virus will determine the protein structure and hence the potential for virus behaviour.

5.3. SARS-CoV-2 as a Learning Virus

Using the metabolic paradigm, Thomas [247] informs us in a discussion concerning Coronavirus SARS-CoV-2 that viruses are not living systems since they are devoid of their own metabolism. Thomas's particular interest, however, lies in the Membrane protein that is used to mediate cell interactions, and is an envelope of the capsid which is a small integral membrane protein involved in several aspects of the viruses life cycle [248]. For Kapinder [249] Membrane proteins represent conserved structural proteins that have an important function in both packaging virus RNA and providing virus behavioural stability by maintaining the shape of the viral envelope and preserving virus homeostasis. So, if a virus is an autopoietic system that involves both internalisation and anticipation (conditions that together indicate living), and has a homeostatic capability that indicates a capacity to learn, then necessarily the virus must be considered to be a living system. Here, then, lies the dichotomy of whether viruses are living or not. While this may not impact on the discussion concerning the Membrane proteins, it could affect considerations concerning the

complex processes of Coronavirus adaptive development. In this, the idea of ontological distinctions serviced by causal mechanisms can significantly simplify the explanatory logic.

In our alternative generic paradigm, we adopt the position that Coronaviruses are living systems, where Figure 4 should then be a reasonable representation of the Coronavirus ontology. In this model viruses have a higher order homeostatic regulator that has embedded within it a learning structure that houses its knowledge based immune system repository, influenced by the regulatory genome. So, we can look at virus behaviour to determine if this conforms to the model.

We have already noted that if viruses are viable living systems, then they have effective homeostatic regulators. Where they are not viable, this impacting on their ability to adapt appropriately to environmental perturbations and thus not develop or evolve, then their homeostatic regulator is either unstable, or their figurative intelligence (network of autogenetic processes) is inefficacious (having a small to zero value of Fisher Information I). Thus, for instance, from Figure 4, unstable mRNA proteins with the same function but encoded by a different gene (called an isoform) affect the ability of a virus to develop because the isoforms play an important role in the generation of biological diversity during evolutionary processes [250]. Such autopoietic instability is likely to be caused in part by state instability in the regulatory genome.

This leads to the question as to whether Coronaviruses are instrumental or learning systems, the former case indicating that it is the cell environment that effectively controls the autopoietic couple processes and hence viral behaviour, while in the latter case ultrastability options are implied. Instrumental viruses have a repertoire of genomic expression options available to them that have likely been developed through random mutations, fortuitously allowing their survival. The capability to develop through adaptive mutations, however, requires homeostatic memory, this suggesting a condition of living.

Earlier we introduced the idea that viruses have a dark/regulatory genome. It is likely that they exist in SARS-CoV-2. Here, then, the mechanism by which its genome is regulated (even before the new organism appears 'on the scene'), occurs through the dark/regulatory genome, which must *by itself* provide a sizeable amount of Fisher Information. This would take the form of one or more spikes of occurrence in the cell $p(x)$ curve over that dark genome region that is the homeostatic domain. We might, then, suggest that this dark genome region of the cell be searched for such mathematical spikes. These should take some tangible form, such as transport vesicles (small sacks that help move materials, like proteins and other molecules, from a source to a target destination) destined for the plasma membrane or some other vital organelle.

6. Discussion and Conclusions

This paper, which we must admit is a little dense and verbose, has contemplated viruses as living systems, taking a timely detour into the COVID-19/Omicron microevolution. It is a theoretical paper ... some might even call it "speculative". However, this word has more than one meaning. Speculation can be defined in at least two ways. In the Oxford Lexico it is: "the forming of a theory or conjecture without firm evidence". This definition has negative connotations, since conjecture may be defined as a conclusion deduced by surmise or guesswork, and therefore having little validity. Another problem with this definition is that it does not make clear what it is that constitutes evidence, let alone what it is that constitutes *firm* evidence. It is *firm* because it is based on *facts* which

> "attempt to validate a view of that reality. The nature of facts, however, very much depends upon the context and framework from which one views them. Stafford Beer has called facts 'fantasies that you can trust.' Now, trust is 'a firm belief in the honesty, veracity, justice, strength, etc., of a person or thing.' Since trust occurs through belief, it should be realised that it can vary from individual to individual, from group to group, or from time to time. Beliefs are also culture based"
>
> ([163]: p. 42).

Then there is the problem of what it is that constitutes evidence. Qualitative evidence is descriptive, providing information that enables improved meaning and understanding of complex phenomena that is the subject of inquiry, and the relative associations, conditions, interventions and their consequences. Quantitative evidence is information that can be quantified, counted or measured, and given a numerical value. It is often associated with empiricism, which refers to information acquired by observation or experimentation. These considerations lead us to seek an improved, less condescending, definition of the word speculation, and this can be found from the Merriam-Webster dictionary as: "theoretical rather than empirically demonstrable".

Using the latter definition, the research here is necessarily speculative in that it derives from metatheory [43] (a higher order theory able to deliver particular context-specific theories), essential to the construction of a systems biology approach. This is so since context-specific theory is designed to selectively embrace reductionist evidence, this provided from microbiology inquiry into highly complex systems, where interventions may well produce unexpected new complexity. When constructing context-specific models using the metatheory, as has been done here for viruses, the creation of a systems biology model might, in some of its aspects, be tentative, if there is insufficiently clear supportive reductionist explanation or empirical evidence that can be brought to the modelling process.

Both metacybernetics and EPI are instances of metatheory, and both are propositionally formal in the sense that they are formulated through a set of propositions, the logic of which has been explored to indicate relational correctness. They are therefore not only propositionally sound in their construction, but also philosophically sound through an adherence to critical realism [30,41,43,221,251]. They also both have demonstrable empirical support in their history of publications, and the theories (in the case of metacybernetics, through its original "higher order cybernetics") goes back to the 1990s.

Metacybernetics has been used in social sciences, for instance, to investigate green marketing, to examine marketing performance, in exploring the transformative processes in the banking sector, in explaining the development of newly industrialised Asian countries, and in personality theory where, for instance, it has provided new methodology to empirically identify personality pathologies. EPI arises from principles that have purely *physical* origins and original intent, *and it has already generated many purely biological* effects; e.g., (a) the Hodgkin-Huxley equations of ion-cell interaction, and (b) the unique power-law equation governing viral growth and early-cancer growth. Moreover, the very power 1.681 . . . , in this power-law equation, is well-known to characterise many different *biological* growth processes (where it is called the Fibonacci "golden mean"). A few of the constructs with respect to virus morphology are indeed speculative, but only in that they await empirical support.

The paper is lengthy, but there is a rationale for this. It is set up to complement a developing series of papers on the metacybernetic paradigm, which provides new insights into the exploration of metaphysical aspects of generic living systems, i.e., those that may not be classed as only biological in nature. This is why the paper has spent considerable time in creating a foundation for the generic paradigm, using language that works not only for biological systems, but also for those beyond biology. The most controversial biological system to which to apply such a paradigm is, of course, the virus, since there is so much confusion over whether or not it is alive.

The length of the paper reflects that which has already been argued, that to properly identify a new paradigm there is a need to explore philosophical aspects. Beyond this, in the field of microbiology, one cannot simply introduce a new paradigm without exploring the existing paradigms, with attempts to show them for what they are. Thus, the neo-Aristotelian/metabolic paradigm is shown to be conceptually perforated when comparing its propositions to new evidence. The 7-paradigms of life are shown not to be distinct paradigms at all, but aspects of a larger paradigm. The Dawkins paradigm is similarly limiting in its capacity to represent that which has been found empirically. The fact that its epigenetic constructs are purely empirical (through correlations), is a major failing. The

Barbieri paradigm acts as an excellent basis to explain the distinctions between physical chemistry, and metaphysical information and meaning. Then, Bhattacharyya's ideas form a strong basis for the generic paradigm. The structure of this paper has been designed to help the reader transgress it, where each section is effectively a chapter (as a significant specified unit) belonging to the overall theme.

Finally, relative to the length of the paper, the case study of the COVID-19 is brief. The intention here is to show that the modelling process has some empirical microbiological support, where mensuration using Fisher Information is possible. To provide a full case study would itself require a full paper. In a sense, therefore, this case should be seen as the application of the principles of this paper into observed COVID-19 phenomena, and vice versa. But then this is how early research develops.

The paper, which has been concerned with living organisms, clearly shows that there is controversy in the field of biology over whether viruses are living or not. Mostly, deniers are holders of the neo-Aristotelian paradigm that requires a belief (sometimes maintained in the face of apparent pragmatic contradiction) that all biological functions (including reproduction) must not only be self-determined, but must also occur internally to the system. Thus, the recurrent "Mule problem", which delivers the question of whether Mules (which are infertile) are actually living, requires an argument to be made as to why they, and other infertile hybrids, are "obviously" living [252] while ignoring that the specificity of the metabolic paradigm is not being adhered to.

Recent evidence is available indicating that viruses are living. For instance, genome feedback processes have been found to occur, and this is consistent with autopoietic principles that define life. Also, viruses have been shown to have a capacity to maintain homeostatic immune systems, a function that necessarily means that they are capable of learning. This clearly indicates that viruses can be living entities.

Due to the coevolution between viruses and their host cells, the virus generic model tentatively suggested in Figure 3 also broadly applies to the host cellular system. It portrays a living system with process intelligences that offers an extended representation of epigenetics. It has a coupled structure with an operative protein capsid that is cognitively regulated by the genome, the two being connected by a causal mechanism that channels autopoietic processes (itself a network of operative intelligence processes recognised to be cognitive in nature). The couple is regulated by a homeostat that, with respect to the capsid, is a metaregulator that promotes living system ultrastability. The metaregulator operates as a homeostat and houses an immune system which is conditioned by the dark/regulatory genome. The living system is structured as a system hierarchy, its subsidiary autopoietic couple being a dynamic, inherently instrumental, system that is homeostatically regulated through its own causal mechanism of autogenesis. This is a network of cognitive figurative intelligence processes. The capsid itself interacts operatively with the cell environment through the other causal mechanism of behavioural intelligence. The dark/regulatory genome (which is uncoded), the genome (which is coded to specific genes), the capsid and its proteins, each have their own forms of expression. The intelligences have very specific functions, and enable the virus to develop requisite responses to the challenging events that they experience in their environment, thereby maintaining their viability.

The generic modelling approach adopted takes viruses to be living autonomous systems with self-identity, and able to self-organise. The metaregulatory system enables the virus to adapt through objectives relating to the maintenance of stable dynamic self-organising processes through self-regulation. The inherently instrumental system has its objectives that may be modified by its superior autogenesetic couple, but where there is no learning, its predefined repertoire of goal objectives limits its potential for viability, which bounds its survival fitness.

As an epigenetic model, the viruses operative protein capsid expression determines protein and enzyme emissions, the actions of which correspond to regulations arising from its coding genome. The operative capsid structure can be adapted through the autopoietic network of processes, as can the dark/regulatory genome through its autogenesetic network

of processes. Autopoiesis is a causal-agent that provides a dual (anterior and posterior) movement of Fisher Information within the autopoietic couple that connects the capsid with the genome. It explains how the virus environment is internalised through the anterior autopoietic trajectory, and how this leads to anticipation through the posterior autopoietic trajectory which enables adaptive responses to the environment. It thus provides regulatory epigenetic explanations for virus viability.

In Coronaviruses, contextual Fisher Information flows between the virus and the cell may show high and low levels of information. The level impacts on the pathological severity of virus infection. Higher/lower information levels implies higher/lower levels of complexity in the viruses capsid structure, due to the increased/decreased variation in the spike profile. For instance in the SARS-CoV-2 virus, a complex surface profile of the capsid has sharper and longer spikes, enabling enhanced COVID-19 infection. This connects 'increased complexity' with an increased rate of infection which improves the fitness of the virus to infect, but this is not so beneficial for the parasite's hosts where the virus is purely pathogenic.

We have shown that it is feasible to construct a tentative model of viruses that conforms to a generic theory of living systems. We can reflect on the idea that such a generic theory, when supported by, say, Prigogine's thermodynamic principles, would appear to move us further towards the unified theory of living as proposed by Bauer, this in turn providing a potential for the development of a universal theory of nature as argued for by Grandpierre [24]. However, a universal theory may alternatively arise using the veil of complexity. According to Kelty-Stephen and Dixon [253], there is demonstrable information synergy between cognitive, biological, physical and thermodynamic systems. Information is a fundamental observable for complexity, and hence it is essential to seek the intrinsic information that critically describes it. Fisher Information represents this *intrinsic* information (from which physical and thermodynamic [221] and cognitive [30] properties can be produced), and it more completely describes the complex structures under investigation.

Epigenetic processes are enabled through causal mechanisms. Of the three forms of causal mechanism we have introduced, behavioural intelligence is a network of processes that delivers causal-agent functionality that facilitates parametric measurement in the cell environment. This data is delivered as anterior Fisher Information flow to a context map in the capsid. The efficacy of this flow is determined by the value of the Fisher Information. In Coronaviruses Fisher Information is an indicator of the shape of the capsid. When the virus has "digested" this information internally, it can create a potential for protein expression (when specific proteins are activated). Through the internalising autopoietic causal mechanism, the value of Fisher Information can indicate the efficacy of the various proteins in satisfying virus goal functions arising from protein expression (which is determined from gene expression when there is autopoietic stability). This necessarily influences the chemical reactions that occur in the microbiological environment of the host. If the efficacy of the anterior flow is small, then the capsid is less complex with flatter spikes, making the virus less able to infect cells. As such, it may be argued that Fisher Information can act to trigger chemical actions (due to specific protein releases) in the cellular host environment.

We have not really discussed in pragmatic terms the causal mechanism of operative intelligence, which transforms parametric data from the capsid context map to the genome cognitive map. The efficacy of the transformation process from one map to the other is indicated by the value of the Fisher Information of the autopoietic causal-agent, and is an indicator of virus autopoietic instability. If Fisher Information takes a small value, then this indicates that the virus is more prone to random mutation, as opposed to adaptive mutation when the Fisher Information value is large. Nor have we discussed the figurative intelligence causal mechanisms that relate the adaptive ability of the virus to its metaregulatory capacity. The dynamic autopoietic interaction between the capsid and genome provides parametric information that is transformed through figurative intelligence, and

this updates patterns of knowledge in the homeostatic map. This is then used to regulate the adaptive processes of the virus.

If viruses are living systems, then necessarily, they must conform to certain mechanisms that, in this paper, constitute findings. Through behavioural intelligence, changes in parameters are delivered to the context map through Fisher Information. At the next phase, and as part of the virus autopoietic network of processes linking the genome and the capsid, two things may occur: internalisation and anticipation. By internalisation we can consider that autopoietic Fisher Information, being information acquired from the context map, is manifested in the cognitive map. Where this indicates that contextual changes have occurred, requisite adaptive mutations can be indicated. Fisher Information is also capable of representing non-adaptive, random, mutations that arise from errors in the environment. However, in the case that the virus is part of a mutant cloud, such errors may be minimised due to collective agency processes.

The genome will assimilate the autopoietic Fisher Information referentially in order to determine what changes are required. If it is accommodated into the genome structure, genome adaptive mutations occur. As a result, posterior anticipative autopoietic Fisher Information is manifested as requisite adaptive capsid change. This alters the capsid structure and hence its expression, which results in a potential for new proteins that can be released and activated through protein expression. The resulting chemical dynamic will modify the interactions occurring in the host environment. This is an ever-ongoing cybernetic cycle that enables the virus to adapt. When this process is subject to pathologies due to the introduction of random events, the stability (indicated by Fisher Information) of the dynamic can be threatened.

So, what does this suggest with respect to the nature of viruses? Firstly, the cybernetic model obviates the usual biological need for a virus to develop, mature and reproduce before assaying whether its fitness has been increased or decreased as required. The model is supported through recent research evidence as cited in the paper, and indicates that virus anterior feedback loops actually exist, these occurring between a developing capsid, its genome, and indeed, between their interactive autopoietic processes and its dark/regulatory genome (where it has one). These relationships can be changed selectively even before a virus attempts reproduction. This novel finding is a consequence of coupling the qualitative cybernetic theory with the EPI principle. The existence of causal mechanisms in the virus has a profound impact on how they should be viewed, and intimately links host environmental processes with virus mechanisms.

If one were interested in exploring dark/regulatory genomes further through EPI, there would be a need to identify autogenesetic transport channels, like vesicles, located in that dark matter genome region, that ultimately connect with the genome nucleic acid. That would "complete the circuit" needed. We are clear that cellular and virus processes operate similarly due to their coevolution, and in the host cell, protein events are often stored in the cell cytoplasm before going on to the nucleus. There should therefore be 'spike sources' of Fisher Information in that dark genome region. This is because spikes are strong sources of Fisher Information—being *the very mechanism the SARS-CoV-2 virus uses to infect*. Such spikes suggest actual vesicles there that will transport the nucleic acid to the nucleus that houses the genome. Noting that in Figure 3, the autogenesetic causal mechanism is defined in terms of a network of transcription processes, the transport channels may well be found since (in accord with the findings by Foster and Bridger [254]) most dark/regulatory genome transcripts are associated with known genes.

Recognising these epigenetic processes provides an insight into the creation of new vaccines, where the model in Figure 3 can also be used to generally represent the host cell. Its autopoietic processes are indicated to be mRNA, which thus has a role in mutations of the genome (or in the case of the cell, the nucleus). There are a variety of mRNA vaccines for the Coronavirus, and the way that they work is to use a fragment of mRNA to deliver instructions to host cells to produce a single protein with a "spike". The epigenetic mechanism for this can be explained [255], recalling that our virus model is also broadly

applicable to the cell (and to bacteria). Cells susceptible to infection are autonomous living systems with both regulatory and metaregulatory structures. The presence of the pathogen, when recognised, will, through processes of autopoiesis and autogenesis, trigger its immune system to take appropriate action. This mechanism, as used by mRNA vaccines, uses a single protein responsible for the virus spikes. When introduced to the potential virus host, the spike protein is recognised as a foreign pathogen, and remembered as such through the hidden memory genome, presumably residing in the dark matter region. The vaccine contains instructions in the mRNA about how to make the protein, so that potentially susceptible host cells can produce it. The mRNA fragment is packaged in a capsule (using a lipid nanoparticle [256]) which acts as a delivery vehicle to enable the mRNA to enter the host cell. It is then used by the cells to produce the protein, which causes a cellular immune response. The protein is then broken down by the cell. The spike that appears on the surface of each SARS-CoV-2 virus is recognised by the host immune system, and protein antibodies are delivered to deal with this. When the spike protein is again encountered, then the host immune system can recall this, and react much more quickly.

The arrival of mRNA vaccines came with the promise of safe dosing, low-cost manufacturing, a rapid development capability, and high efficacy [257]. Low production cost does not mean low sales cost, and safe dosing does not mean unintended outcomes. Thus, while AstraZeneca's traditional vaccine and the Pfizer-BioNTech mRNA vaccine both have similar production costs, the former company sells its product, per vaccine jab, at about the cost of production (around €5), while the latter charges roughly four times that per vaccine jab [258]. This has brought accusations of profiteering to Pfizer, having made a profit of around €20bn during 2021, more than double its 2020 profit [259]. Curiously, the AstraZeneca vaccine has uniquely been troubled by coordinated misinformation [260] that has damaged its uptake, and therefore has cost lives [261].

Both the AstraZeneca and Pfizer vaccines have been associated with unintended and undesirable collateral functionality. While the former has been connected with the very rare, low risk, incidence of blood clotting [262], interest here lies in the latter. The mRNA vaccines are created through an mRNA sequence, coded for a specific pathogen. The sequencing used to target the pathogen can vary according to architectural design [263], so that different mRNA designers may possibly produce different sequences to achieve similar outcomes. The vaccine operates by inducing complex functional reprogramming of innate immune responses, where its broad effects are unknown (for instance as to whether they have combined actions on innate and adaptive immune responses). Any mRNA intervention will interfere with the immune system, the result of which could be a contribution to, or an impeding of, a more balanced inflammatory reaction, and the Pfizer vaccine appears to suppress the immune system [264,265]. However, it is not only the immune system that might suffer. The Pfizer vaccine has also been found to induce myocarditis and pericarditis into previously unaffected subjects, these being types of tissue inflammation connected to heart, and both requiring medical treatment [266,267]. Such discoveries of the unexpected impact of the vaccine should not be a surprise in mRNA intervention strategies, considering the complex microbiology dynamics involved (e.g., in immune responses [268]).

We can now posit a tentative explanation of mRNA intervention issues with respect to the model of Figure 3. Since the vaccine involves complex functional reprogramming of mRNA, during the gene editing process it is therefore easy to imagine that the mRNA fragment introduced to the host will unexpectedly alter its dynamic posterior internalising autopoietic processes. This is likely to influence autopoietic stability (indicated by a lower Fisher Information value), and will result in genome mutation. Anterior internalising transcription is then activated, which delivers transcription factors to the homeostatic system, this affecting the differentiation and function of elements in the immune system. The cyclic nature of transcription means that the posterior anticipatory transcription activation processes are also influenced. There appears to be evidence for such an explanation [269].

In the worst-case scenario, these transcription effects might influence homeostatic stability of the system, thereby potentially reducing the capacity of the immune system to requisitely respond to needs. This could result in the host functioning instrumentally, thereby limiting its ability to adapt to changing conditions and thus impacting on its fitness. This should be testable by finding values for the Fisher Information.

A final takeaway from this paper is that disease has vulnerable points that make sense from the standpoint of analysis, and in particular through Fisher Information. These have been partially exploited by new approaches to pathogenic therapies that recognise the importance of process intelligences. Here, attempts have been made to suitably pragmatise the generic theory, thereby hopefully providing a real advance from the scientific point of view.

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