

# Complexification of eukaryote phenotype: Adaptive immuno-cognitive systems as unique Gödelian blockchain distributed ledger<sup>☆</sup>

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## ABSTRACT

The digitization of inheritable information in the genome has been called the ‘algorithmic take-over of biology’. The McClintock discovery that viral software based transposable elements that conduct cut-paste (transposon) and copy-paste (retrotransposon) operations are needed for genomic evolvability underscores the truism that only software can change software and also that viral hacking by internal and external bio-malware is the Achilles heel of genomic digital systems. There was a paradigm shift in genomic information processing with the Adaptive Immune System (AIS) 500 mya followed by the Mirror Neuron System (MNS), latterly mostly in primate brains, which reaches its apogee in human social cognition. The AIS and MNS involve distinctive Gödelian features of self-reference (**Self-Ref**) and offline virtual self-representation (**Self-Rep**) for complex self-other interaction with prodigious open-ended capacity for anticipative malware detection and novelty production within a unique blockchain distributed ledger (BCDL). The role of self-referential information processing, often considered to be central to the sentient self with origins in the immune system ‘Thymic self’, is shown to be part of the Gödel logic behind a generator-selector framework at a molecular level, which exerts stringent selection criteria to maintain genomic BCDL. The latter manifests digital and decentralized record keeping where no internal or external bio-malware can compromise the immutability of the life’s building blocks and no novel blocks can be added that is not consistent with extant blocks. This is demonstrated with regard to somatic hypermutation with novel anti-body production in the face of external non-self antigen attacks.

## 1. Introduction

Despite the probable analog origins of life (see, [Baum and Lehman \(2017\)](#); [Goodwin et al. \(2012\)](#); [Smith et al. \(2014\)](#)), the digitization of inheritable information in the genome using an almost universal 4 letter code (A, T, C, G/U) has been referred to as the ‘algorithmic take over’ of biology by [Walker and Davis \(2013\)](#).<sup>1</sup> Though the metabolic aspects of maintaining conditions for the homeostasis of life’s vitals imply control

mechanisms that conjoin analog and digital systems, in evolutionary terms, information processing, transmission and storage became digital. Overcoming the lack of fidelity in transmission of information in analog systems with, in principle, low cost of duplication, ease of recursive recombination and splitting due to modularity of software with high density of storage in the DNA, have been found to be the typical advantages of DNA based digital information processing and storage.<sup>2</sup> To date, automata as in Read only Memory (ROM) processing of digital

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<sup>1</sup> Analog processes typically rely on information relating to chemistry and physical forces such as concentrations of chemicals, temperature, pressure and velocity, while digital systems can only deal with this indirectly in the form of information encoded in discrete chunks using a finite alphabet. Operations in digital systems are governed by algorithmic principles of computation or Recursion Function Theory ([Cutland \(1980\)](#) and [Rogers \(1967\)](#)). The numerous studies on analog-digital duality, a term attributed to [Hoffmeyer and Emmeche \(1991\)](#), underscores how information processing in life-forms characterizes this dualism as the basis of “persistent information storage and also adaptive responses to an ever-changing environment” (see, [Goodwin et al. \(2012\)](#)). Proponents of the so-called RNA world ([Gilbert \(1986\)](#)), consider RNA as an exemplar for embodying both the digital and analog capabilities with being able to store codes and also power transcription with catalytic processes/molecules inherent to RNA (see, [Walker and Davies \(2013\)](#)).

<sup>2</sup> In recent studies on DNA as a storage medium for digital data (see, [Bornholt et al. \(2016\)](#), [Bancroft et al. \(2001\)](#), [Adelman \(1994\)](#)), DNA has been estimated to have extraordinary storage density of 1 exabyte/nm<sup>3</sup> (10<sup>9</sup> GB/nm<sup>3</sup>) which is said to exceed extant tape technology by eight orders of magnitude. Further, the stability or resistance of DNA from degradation has a half-life of 500 years in challenging conditions. Note, nm<sup>3</sup> stands for nano cubic meter.

information, as a norm, can only faithfully execute the instructions in the code and have severe constraints on deviating from the embedded program. There is considerable evidence that the core ROM part of genomic operations, associated with gene replication, transcription and ribosomal machine executions in gene expression, show commitment to fidelity and quality control with inbuilt proofreading and repair mechanisms in place (Kunkel (2009); Kunkel and Erie (2015); Janssen and Hayes (2012)). This also constrains the capacity of digital systems to change and evolve.<sup>3</sup> Indeed, Gershenfeld et al. (2017) ranks the capacity for digital systems to detect changes to codes as the major factor in the success behind digitization of inheritable information of life, especially in the face of the Achilles heel of software systems to viral hacking.

With the prolonged stasis of prokaryote evolution, which has shown limited change in their genotype and phenotype for billions of years, evolvability, emergence of novelty, diversity and complexity of life have been found to be the exclusive domain of eukaryotes. This has prompted new lines of investigation (see Lane (2014); Lane and Martin (2010); Cavalier-Smith (2009); Marijuán and Navarro (2021); Frieden and Gatenby (2011); Barbieri (2014, 2015; 2018)). The latter author has suggested the need for a new field of Code Biology and the notion of ‘codepoiesis’ (Barbieri (2012; 2018)) to provide insights into the conservation of certain gene codes from the inception of life in the face of novel dynamical changes to biotic codes in eukaryote evolution. In Markose (2021a) the notion of genomic intelligence was coined to underscore the digital information processing in biology based on the biological instructions encoded in the genome, in some three billion nucleotide base-pair combinations of ATCG in the case of humans, which in the 21 century can be called ‘smart’<sup>4</sup> programs.

The above code-centric approach to genomic dynamism contrasts with the popular notion of autopoiesis (Maturana and Varela (1980), Varela et al. (1974)), which is agnostic regarding the software involved in biological self-reference and self-organization. This is also the case with famous thermodynamic models of life (Nicolis and Prigogine, 1977), including the dominant account of this in terms of the Free Energy Principle (Maxwell et al. (2017); Friston (2010); Friston (2013)), which postulates multifaceted optimization frameworks to maintain life’s vitals within homeostatic limits in the face of dissipative forces of entropy. There have been attempts to quantify how far from thermodynamic equilibrium eukaryote life must be in contrast with low complexity prokaryotes relative to their respective capacities to generate energy. Frieden and Gatenby (2011), for instance, come up with a maximum Information and Complexity measure for high energy producing eukaryotes, while prokaryotes have been assigned a minimum value in this regard. Given the billions of years of success that prokaryotes and eukaryotes have had against the dissipative forces of entropy along the precepts of the Free Energy Principle, the latter, however, does not *ipso facto* offer explanations for why open-ended capacity for complexity and novelty production found primarily in eukaryotes is needed for their homeostasis. This has called into question whether FEP suffices as a unitary explanation for complexification in code based genomic systems (see also, Colombo and Palacios (2021)).

The fundamental premise as first propounded in the so-called Wolfram-Chomsky schema for dynamical systems (Wolfram (2002), Albin (1998), Markose (2004, 2005; 2017)) is that the *sine qua non* of complex adaptive systems is to produce novelty and that this can be

<sup>3</sup> Cheap replication and resistance to copy errors with inbuilt proof-reading capabilities to ensure fidelity is the feature of gene expression (Kunkel (2009)). In DNA replication, 1 mistake is made for every  $10^9$  nucleotides copied and the speed of copying is around 1000 nucleotides every second.

<sup>4</sup> In the digital era, ‘smart’ is the acronym for Self-Monitoring, Analysis and Reporting Technology. Self-executable nature of smart programs is also considered to be an important feature. This is to be contrasted with Peter Drucker’s top-down management speak of setting objectives that are ‘Specific, Measurable, Achievable, Realistic, Time-bound’.

achieved only by advanced software systems in what is called Type IV undecidable dynamics associated with Gödel (1931) Incompleteness Theorems.<sup>5</sup> The most recent statements regarding this can be found in Igamberdiev (2021), Markose (2017, 2021a) and Prokopenko et al. (2019). The first two sets of studies are unique in stating that the formal conditions found in the proof of Gödel Incompleteness Theorem need to be structurally embedded in the information processing of living systems during the course of evolution, if they are to achieve endogenous wherewithal for novelty production. Prokopenko et al. (2019) is also unique in explicitly investigating whether Elementary Cellular Automata Rule 110 (see, Wolfram (2002)) can incorporate the Gödel conditions of Self-Reference and Negation/Inverter operators in the production of subsequent novel code-based dynamics. In contrast, Cellular Automata Rule 110 has been studied by many as an example of a simple code-based system that can evolve complex Type IV dynamics with novel structures (Adams et al. (2017); Hiesinger (2021)) in order to indicate how evolution itself could have achieved this. However, these studies do not rely on the conditions in the Gödel proof of Incompleteness for the endogenous production of novel syntactic objects and dynamics.<sup>6</sup>

Because of the encoded basis of the genome and changes thereof for evolution, Igamberdiev (2021) gives general principles, but no concrete evidence, for why “living systems during evolution continuously realize the proof of Gödel’s theorems.” Markose (2017, 2021a) is more specific about how evolutionary developments relate to the conditions in the proof of Gödel’s theorems. Following the Cantor Diagonal Lemma antecedents for the Gödel Incompleteness Results, it is obligatory to produce syntactic objects that can be proven to be outside of all algorithmically listable sets. Gödel (1931) helped mechanize these steps and the Gödel Sentence, which is the fixed point of a negation function, is the syntactic encoded object which proves that the system is incomplete, but only if the system is logically consistent. As noted by Chaitin et al. (2011) and Markose (2022), despite aspirational statements to the contrary, till recently and for some 90 years, the Gödel Sentence has had little or no relevance to any real-world phenomena. From this to the position espoused in this paper that the conditions of Gödel Incompleteness proof and in particular, the Gödel Sentence, far from being funky, esoteric constructions in the foundations of mathematics, are ubiquitous in vertebrate intelligence and information processing, is a major intellectual jump.

The paper aims to unpack the breakthrough in Markose (2021a) that the Gödel Sentence as a fixed point of an algorithm implementing a negation function of an adversarial viral agent, permits biotic elements that determine the somatic identity of organisms to self-report they are under attack. The Gödel Sentence is a necessary condition for open ended scope for novelty production outside of recursively enumerable sets. For this far more of Recursion Function Theory than has been used to date is needed, in particular, the Emil Post (1944) set theoretic proof of Gödel Incompleteness involving Creative and Productive sets. These sets, respectively contain Theorems and known non-Theorems of the system (see, Smullyan (1961)). As the original formulation of the Gödel Sentence in Gödel (1931) predates the full developments on programs/algorithms, for the constructive generation of the Gödel Sentence

<sup>5</sup> Dynamics of Types I-III, respectively, those that generate limit points, limit cycles and chaos do not produce novelty. Note Igamberdiev and Shklovskiy-Kordi (2016) discuss where the generativity of the genetic language comes from that permits “the infinite use of finite means” and novel structures. The authors indicate that for the latter the “biological computational system ... (has to) incorporate meta-statements about the system”.

<sup>6</sup> Adams et al. (2017), Hiesinger (2021) instead use the Kolmogorov-Chaitin measure of algorithmic/computational complexity. As noted by Chaitin (2013) “Computational complexity differs from recursive function theory in that, instead of just asking whether it is possible to compute something, one asks exactly how much effort is needed to do this.”

for algorithms, as noted by Hamkins (2021)<sup>7</sup> and Markose (2021a, b, 2022), the Rogers (1967) fixed point theorem is used for the self-referential identification of novel negation function implemented by total computable algorithm of the bio-malware. Secondly, we need to take on board advances in gene science and molecular biology in the post Barbara McClintock era. Also new thinking on digital information processing in terms of the 21 st century nomenclature on blockchain distributed ledger is needed to fully understand the significance of the role of Gödel logic in complexification of eukaryotes.

In the 21 st century, it is widely known that editing of digital documents require software commands of cut-paste and copy-paste. In addition to another ubiquitous command of copy and print, the cyber security threats from internal and external malware agents are all too familiar. The first man-made blockchain distributed ledger devised for secure decentralized software record keeping is associated circa in 2008 with the Bitcoin (see, Nakamoto (2008)). The paradigm shift in gene science was brought about by the Nobel Prize winning discovery by McClintock (1984) of transposable elements constituted by retro-transposons (copy-paste) and transposons (scissor-paste). These account for some 45% of the human genome and clearly show that the same processes are at work for editing the digital genomic system as in the case for digital documents. McClintock (1984) challenges the view that random mutations and transcription errors are the main drivers for evolvability and the role of transposable elements underscores the truism that software is needed to change software. But is there a Code Biology for secure genomic record keeping with novelty production?

As we have been wedded to random shocks and prediction error as the model of novelty (see, Barto et al. (2013) and Markose (2022)), there has to date never been a framework of code-based novelty in terms of syntactic objects that lie outside algorithmically listable sets. Four sources of syntactic or software-based novelty production can be identified and all of them are related to life. Novelty that can be inheritable via biological evolution has to be 'retrotransposed' into the germline, the molecular mechanics of the stringent conditions for selection for additions of novel blocks of biotic codes within a genomic blockchain are yet to be understood (Nätt and Thorsell (2016)). There are three sources of novelty producing phenotypes that occur during the lifetime of organisms, which are not pre-scripted in the genome. The one found in the Adaptive Immune System for somatic hypermutations (Noia and Neuberger (2007)) for novel anti-body production against non-self antigens arose from the Big Bang of Immunology (Janeway et al. (2005)) associated with the complexification of eukaryotes and which will be shown to have distinctive Gödelian self-referential characteristics of information processing. Also related to maintaining highly conserved components of the germline are arms races in genomic novelty within a single genome from highly evolvable internal non-protein coding transposable elements, satellite DNA and their respective countervailing epigenetic chromatin regulators (Luo et al. (2020)) and satellite DNA proteins (see, Brand and Levine (2022)). The most recent in evolutionary terms and rivalled only by the Adaptive Immune System for novelty production is the capacity in humans for unbounded proteanism for novel extended phenotypes, to use a Dawkins (1989) term, in the form of artifacts outside of ourselves.

Section 2 of the paper will start with the Gödelization of biology and give an informal discussion of the three other characteristics of Gödel digital information processing that accompanied the eukaryote complexification with vertebrate evolution. Two of these characteristics of Gödel logic are the self-referential (Self-Ref) and offline virtual self-representational (Self-Rep) mirror operators, using epithets from Hofstadter (1999). How these operators relate to biology will be discussed.

<sup>7</sup> Hamkins (2021) notes that "Gödel fixed-point lemma enables one to find sentences that refer to themselves", ..... the Kleene (1952) style Second Recursion Theorem "allows one to construct programs/algorithms that refer to themselves".

The fourth necessary condition of Gödel Incompleteness which permits recursive access to an open-ended domain is Gödel's Liar or the negator/inverter operator. The widespread nature of the role of the virosphere and viral software in being both an adversarial agent and also the agency for evolvability is covered. The ancient ancestry of what is widely recognized to be two basic recursive function operations of 'copy and paste/print' (retrotransposons) and 'scissor and paste' (transposons) of digital genomic information has been traced to viral software from RNA virus or DNA virus (Feschotte and Pritham (2007)). Fedoroff (2012) states "It is becoming increasingly difficult to escape the conclusion that eukaryotic genome evolution is driven from *within* (italics added) by the stronger winds (with perhaps occasional gale force gusts) of transposon activity." Equally, the onslaught from external bio-malware and transposable elements that have internally colonized organisms, can have deleterious effects that can disrupt host genes and cause disease by unsolicited chromosomal rearrangements and malign gene expression. The principle of a blockchain distributed ledger is mooted for the vast Adaptive Immune System and epigenetic regulatory arms races in somatic novelty for the purpose of maintaining genomic integrity of eukaryotes.

Section 3 will give more formal and specific details on how the conditions of Gödel Self-Ref and Self-Rep map over to biology. The digital adversarial game involving Gödel's Liar that is co-extensive with life will be shown to have a bearing on why the complexification of morphology in eukaryotes is accompanied by a complexification of the regulatory framework in Code Biology. Indeed, the phylogenetic origins of the unique self-referential and embodied self-centric nature of cognition in advanced eukaryotes can be traced to the uber bio cyber-security (Markose (2021a)) that arose to maintain homeostasis in terms of the primacy of the gene codes against internal and external biotic malware 500 mya with the Big Bang of Immunology and the Adaptive Immune System of eukaryotes (Janeway et al. (2001)).

Section 4 will give details for why there is significant mileage to be gained from the use of the Emil Post Creative and Productive sets and productive function thereof (Post (1944), Cutland (1980), Smullyan (1961)). This is undertaken to constructively embed syntactic objects as Gödel Sentences which involve fixed points of novel negation functions applied to halting self-assembly gene codes that build the somatic identity of organisms. This permits the gene codes to self-report they are under attack. Gödel Sentences lie outside all listable sets, viz the two recursively enumerable sets of theorems and known non-theorems of the genomic system and incompleteness is the consequence of logical consistency of the formal system. A brief discussion is given for the role of the blockchain distributed ledger for biology. While Abramov et al. (2021) and Markose (2021a) are first to observe that DNA based eukaryote genomic systems have the hallmarks of blockchain distributed ledgers with the phenomena of the same DNA in all cells of multi-cellular life, Abramov et al. (2021) tries to find antecedents for this in the thermodynamic models of life. In contrast, Markose (2021a) indicates that the Gödel Sentence in biology is a hashing algorithm for the detection of novel negation operator of bio-malware agents and thereby achieve fidelity of record keeping of extant genomic software within a unique principle of blockchain distributed ledger technology with its capacity for open ended novelty production. The Productive set provides the structure of the blockchain so that novelty production is logically consistent with the Theorems of the system. In terms of the Adaptive Immune System novel anti-bodies are generated to counter bio-malware hacking of gene codes.

## 2. Gödelization of biology and the algorithmic takeover

### 2.1. Biology and the staples of Recursion Function Theory

The Gödelization of biology takes the form of unique bio-peptide identifiers of biotic elements and more generally can be understood to be Gödel numbers for encoded information. The two features of Gödel

logic referred to as self-referential (**Self-Ref**) and offline virtual self-representational (**Self-Rep**) mirror operators are staples of Recursive Function Theory found in textbooks on the subject such as Rogers (1967) and Cutland (1980). The breakthrough on the significance on these staples starts with the insight of Gershenfeld (2012, 2017 Chapter 3 p. 109) that the self-referential operator (aka Diagonal operator) where a program  $m$  builds the machine that runs program  $m$  corresponds to the self-assembly programs associated with the ribosome and other transcriptase machinery involved in gene expression for the somatic morphology and regulatory control of the organism (see, Tibbits (2012)). The next breakthrough (Markose, 2017; 2021a) is to acknowledge that halting self-assembly gene codes that create the organism are theorems of the genomic system. This set is disjoint from known non-theorems or what the immunologist Burnet (1972) famously called ‘forbidden codes’, if allowed to run will ‘negate’ the theorems and hence the organism is endangered. Genomic information processing follows the conditions of formal systems (Smullyan (1961)) governed by the principle of logical consistency and is best demonstrated by the Emil Post (1944) set theoretic proof of Gödel Incompleteness using creative and productive sets. This Gödel-Turing<sup>8</sup>-Post (**G-T-P**) framework, Markose (2017, 2021a), provides the stringent selector mechanism satisfying logical consistency in what is an ancient precedent of a blockchain distributed ledger that maintains the genome secure from bio-malware while novel blocks can be added.

Involved above are the third and the fourth key elements in Gödel logic. Gödel’s Liar, which is an adversarial digital agent associated with the negation function and is, respectively, the hacker in the digital economy and the virus or bio-malware in biology. The latter as will be seen, aims to hijack the halting self-assembly gene expression codes that determine the somatic identity of the organism. What marks a paradigm shift in the complexification of eukaryotes is to do with self-other interactions, especially regarding the non-self hostile other, coinciding with the Big Bang of Immunology (Janeway et al. (2005)) and the development of the Adaptive Immune System (AIS) in jawed fish some 500 mya. It is here we first see the development of the distinct Gödel conditions of self-representational (**Self-Rep**) mirror mappings into an *offline* mirror domain from online self-referential (**Self-Ref**) operators, exactly as in the Gödel Meta-Representation Theorem of Rogers (1967). Remarkably, with what Ramachandran (2000) calls the Great Leap Forward, latterly in primate brains and reaching apogee in human social cognition, there is an identical offline domain of the Mirror Neuron **Self-Rep** System. This permits action prediction and inference regarding con-specifics from the reuse of codes from self-referential neuronal firings from self-actions in the motor-sensory cortex (Fadiga et al. (1995); Gallese et al. (1996); Rizzolatti et al. (1996)).

The internal diversity producing machinery came about with the domestication of viral software to yield Recombination Activation Genes (RAG1 and RAG2) coinciding with the AIS 500 mya. The RAG produce diversity in T-cell receptors of the AIS (Kapitonov and Jurka (2005)) with prodigious open-ended capacity for anticipative malware detection to identify virtually any foreign pathogen self-referentially as software/algorithmic negations from self gene codes. In order for the latter to endogenously identify such negative deviations to self-codes, Gödel style fixed point theorems, viz. Gödel Sentences, have to be in situ. For this following Hamkins (2021) and Markose (2021a, b, 2022), the Rogers (1967) fixed point theorem is used for the self-referential identification of novel negation functions of bio-malware external to the organism. As will be shown, the astounding way in which this fixed point qua Gödel Sentence can be generated by the Adaptive Immune System has to date never been modelled prior to Markose (2021a).

The other as a projection of self and the self-representational (**Self-Rep**) mappings enabling offline embodied simulations in the human Mirror Neuron Systems has led Markose (2021a) to propose that both

the AIS and MNS run on the same Gödel-Turing-Post principles of digital information processing. Detection of negation of what is predicted in the human Mirror Neuron System found in neuro-science experiments by Scott Kelso and co-authors (Tognoli et al. (2007)) is evidence for perception of deceit and complex counterfactuals in Theory of Mind in social cognition. Similar RAG1 gene and other transposable elements are known to produce receptor diversity in the hippocampus for memory and con-specific related social learning and also in other areas of the Central Nervous System (Chun et al. (1992), Caesar and Chun (2020), Peña de Ortiz and Arshavsky (2001)). The work of Gage and co-researchers on retrotransposon-induced neural mosaicism that produces diversity in neurons (Erwin et al. (2014), Singer et al. (2010); Muotri et al. (2009)) discuss the similarity of this to the retrotransposon-based V(D)J recombinations for antibody diversity in the immune system. The important discovery on the role of the neuronal protein encoded by the Arc (activity-regulated cytoskeletal) gene, which is evolutionarily related to retrotransposon Gag proteins, is that it forms virus-like capsid structures to transmit mRNA between cells in the nervous system (Ashley et al. (2018)). This study shows the intriguing possibility that the Arc gene aids in the self-assembly of memories in capsids of encoded material from activated neurons that are then transferred to other neurons non-synaptically via exosomes or tunneling nanotubes.

## 2.2. Viral software, genomic dynamism and Gödel’s Liar

A prime candidate for genomic dynamism has long provenance with the thesis that even the replicative component of DNA has origins in viral software (see, Forterre (2006), Forterre et al. (2014), Koonin et al. (2017), Villarreal (2005), Zimmer (2006))<sup>9</sup>. The Faustian pact involved in the genesis of life has been colourfully described by Dyson (2001) as follows: the replicative code in the DNA was the result “of a digital parasite incorporated into the analog metabolism of its original host”. The enormous abundance of the virosphere provides remarkable genetic diversity from viruses and other mobile genetic elements that can be “the principal reservoir of new genes on earth” (Koonin et al. (2017), Goldenfeld and Woese (2011)). However, the onslaught of parasitic pathogens that aim to hijack the gene expression machinery of the host, have placed prokaryotes and eukaryotes under severe evolutionary pressures.

It is widely acknowledged that Barbara McClintock (1984), with her Nobel Prize winning work, began to dislodge the view that genomic novelty is primarily the result of random mutations or replication and transcription errors. She pioneered the notion of the ‘dynamic genome’ that can respond and adapt to stressful conditions for the genome. This was based on her work on transposons and retrotransposons, the so called jumping genes that have been collectively called transposal elements (TEs) which allow flexibility to genetic material, setting in motion what Shapiro (2013, 2017) has called the read-write enhancements to the core ROM only components of the genome. This has ushered in the notion of the dynamic genome that creatively responds with exaptation of already extant functional gene codes to produce viable and novel solutions under conditions of stress.<sup>10</sup>

The growing understanding about ribosomal 3-D self-assembly machinery of digitized bio-materials and other gene expression procedures

<sup>9</sup> Forterre et al. (2014) state that “the tree of life is infected by viruses from the root to the leaves”. Koonin et al. (2017) state that “genetic parasites are an inevitable outcome of replicator systems, reflecting perhaps the most fundamental of strategies after replication itself.” See also Koonin and Krupovic (2015).

<sup>10</sup> McClintock (1984) described the genome “as a highly sensitive organ of the cell, monitoring genomic activities and correcting common errors, sensing the unusual and unexpected events, and responding to them, often by restructuring the genome”.

<sup>8</sup> Turing (1936).

is that they are geared to high fidelity of somatic outputs for morphology and regulatory structures and have built in error correction software (Kunkel (2009); Kunkel and Erie (2015)). This alongside the explicit presence of viral software based transposons, is undermining the view that exogenous random mutation and transcription errors are the sole drivers of evolution (see, Noble (2017), Shapiro (2013,2017), Goldenfeld and Woese (2011), Amaral et al. (2008), Mattick (2011, 2012), Fedoroff (2021)).

Here it is useful to follow a lead from Maturana and Varela (1980) that ‘homeostatic organization *has its own organization as the variable that it maintains constant* (italics added) through the production and functioning of the components that specify it ...’ A major part of the smart controls in the homeostasis of life is to maintain the software involved to be hack free from external and internal bio-malware. Complex multicellular life is clearly predicated on the development of the most sophisticated bio cyber security to overcome the Achilles heel of code-based systems which is cyber-attacks from a plethora of bio-malware. This brings to the forefront the key feature of Gödel logic to do with the software/digital adversarial agent sometimes called Gödel’s Liar who can negate or falsify what can be computed. In diverse settings this becomes the model of an adversarial agent as in viral software or the hacker, respectively, in biology and the digital economy. As the actions of the adversarial agent cannot *a priori* be constrained in any way, strategies for open-ended search for malware detection are necessary in what is effectively a non-denumerable infinite set of total computable functions, Markose (2017, 2021a). This adversarial digital game first seminally mooted by Binmore (1987) in his critique of extant Game Theory, in terms of Gödel’s Liar, is co-extensive with life and has far reaching implications in the evolution of genomic intelligence.<sup>11</sup> Extant Game Theory aims to be logically closed and complete with prespecified action sets and is unable to produce novelty outside of these sets. The problem of homeostasis in a genomic system requires a modus operandi to figure out if self-codes have been changed by a non-self agent. The self-agent is denoted as the host (h) and the non-self antigen as the parasite (p), with the two protagonists strictly being confined to using total recursive functions as strategy functions.<sup>12</sup>

This requires new principles of diversity-selector mechanism equivalent to the blockchain distributed ledger, which are over and above principles of natural selection. The latter are governed by macroscopic environmental and population level pressures arising from conspecific or multi-species competition for survival in terms of those which reproduce more and those which die out. The main principle of a blockchain distributed ledger technology is to secure the fidelity of earlier blocks of software so that they cannot be compromised by internal and external malware agents either by hacking or producing new blocks that have outcomes that are antithetical to encoded information in earlier blocks. Further, all nodes of a distributed network should have access to the same information to mitigate intranet gaming due to asymmetric information.

### 3. Modelling algorithmic takeover of biology

This section will formally define the three necessary conditions of Gödel Incompleteness Results to do with Self-Reference (Self-Ref) and

<sup>11</sup> The reader is directed to Markose (2021a,c) University of Essex Blog for an informal discussion of the Binmore (1987) critique of Game Theory and how it paves the way for a model for genomic intelligence as a unique digital self-referential information processing framework capable of endogenous open-ended novelty production in a structure of an arms race See, <https://www.essex.ac.uk/blog/posts/2021/10/26/how-we-became-smart>.

<sup>12</sup> Thus, denoting strategy functions as  $f_i$ ,  $i \in (h,p)$ ,  $f_i$  are contained in set  $\mathfrak{R}$ ,  $\mathfrak{R} = \{m \mid f_i = \varphi_m, \varphi_m \text{ is total computable}\}$ . See, Cutland (1980) for the proof that the set of total computable functions is not recursively enumerable and is non-denumerable infinity.

Self-Representation (Self-Rep) Operators, the adversarial agent in the form of Gödel’s Liar and how they relate to biology.

#### 3.1. Self-ref and programmed 3-D self-assembly of bio-digitized materials

The first of the Gödel conditions, takes the form of bio-peptide identifiers in biology, with even location identifying biotic zip codes first discovered in the Nobel Prize winning work of Günter Blobel (1999). More generally these can be understood to be Gödel numbers for encoded information, making for bio-digitized materials. Algorithmic operations on such digitized materials are now subsumed in the class of general recursive functions (Cutland (1980); Rogers (1967))<sup>13</sup> which have as inputs and outputs Gödel numbered syntactic or software objects. The genomic programs, as is well known, is written in 3 letter codons from the universal alphabets A,T, C, G/U with a start and halt cordons. Where codes, for short, represent the integer g.ns for programs, recursive or computable functions are machine operations on codes by codes. Hence, they are number theoretic functions,  $f: \mathbb{N} \rightarrow \mathbb{N}$ , where  $\mathbb{N}$  is the set of all integers, and is the domain and range of these code based computable functions.<sup>14</sup> Such functions have a standard notation (see, Cutland (1980) and Rogers, 1967) that takes the following form  $f(x) \simeq \varphi_y(x) = b$ , where  $y$  is the index or g.n of the program that builds/runs a machine denoted by  $\varphi$  on an input  $x$ . If this machine  $\varphi_y(x)$  halts, the output is  $b$ .

Using the above system of Gödel numbers (g.ns), integers can uniquely identify gene codes based on the near universal alphabet of the genome. The set of genes codes representing both protein coding and non-coding (n.c) ones is denoted as

$$\mathbf{G} = \{g_1, g_2, \dots, g_\#\} \quad (1)$$

A gene code will be generically denoted as  $g$ , and  $\#$  denotes some finite cardinal number. Note a gene code does not refer to any single gene but a program representing segments of DNA necessary for the self-assembly of bio-macromolecules. The digital encoding of the finite set of states under which the gene codes are transcribed is denoted by  $\mathcal{S}$ , with  $s \in \mathcal{S}$  is an element in a finite and countable set of states and other archival information.<sup>15</sup>

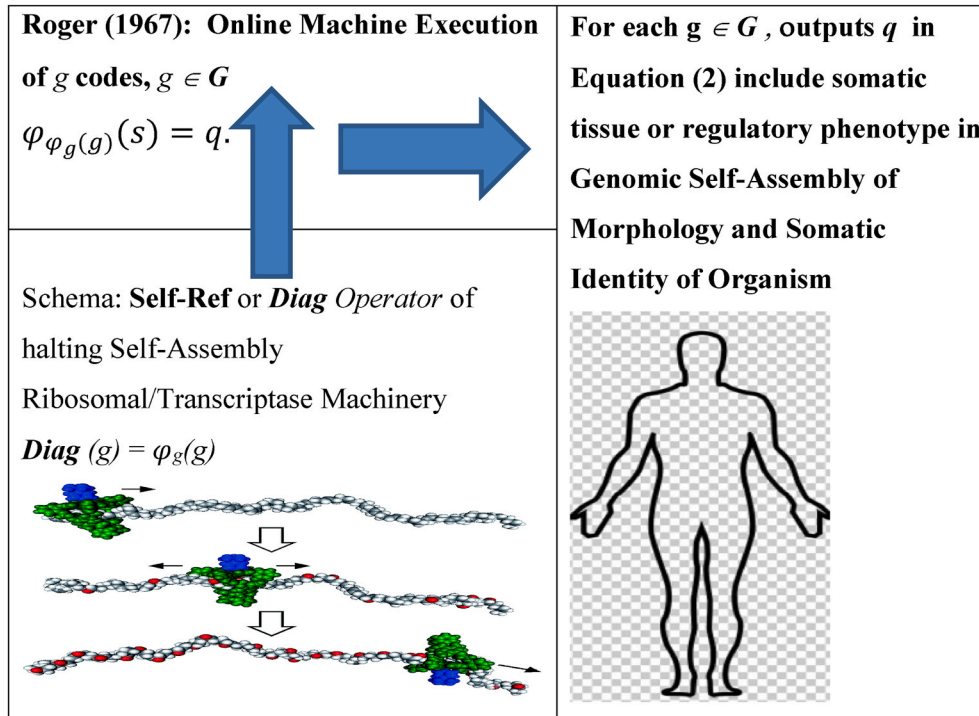
To represent the online self-assembly of the ribosomal RNA or the non-protein coding transcription machinery, the following notation from Rogers (1967) is used. Equation (2) denotes the online machine execution of the gene code  $g$  that finally outputs  $q$ , which represents some somatic tissue or regulatory phenotype of the organism:

$$\varphi_{\varphi_g(g)}(s) = q, \text{ Diag}(g) = \varphi_g(g) \text{ halts} \quad (2)$$

<sup>13</sup> General recursive functions or computable functions are number theoretic functions involving finite steps of instructions, called an algorithm or a program, operating on integers representing encoded information given in finite strings of symbols and map to similar integers as outputs, should the procedure halt. General recursive functions include all elementary arithmetic, logical operations and also functions obtained from substitution, iteration and recursion. In the latter, functions call on themselves and use as inputs what are outputs from previous calculations. In this paper, I use notation from Cutland (1980) and Rogers (1967).

<sup>14</sup> The first limitative result on functions computable by T.Ms is that at most there can only be a countable number of these with the cardinality of  $\mathbb{N}$  being denoted by  $\aleph_0$ , while from Cantor we know that the set of all number theoretic functions have cardinality of  $2^{\aleph_0}$ . Hence, not all number theoretic functions are computable (see, Cutland, 1980).

<sup>15</sup> Note, analog measurements of state variables, such as chemical concentration, temperature etc, have to be converted into digital code in order for this to be processed by a digital agent.



**Fig. 1.** Textbook (Rogers (1967)) Staple of Recursion Function Theory Eq. (2) for Programmed Self-Assembly of Bio-digitized Materials as Model for Ribosomal and other Transcriptase Machinery for Morphology and Somatic Identity of Organism.

Here, the  $\varphi_g(g)$  in the subscript of the recursive function  $\varphi$  that outputs  $q$  underscores the online self-assembly or **Self-Ref** process where **Diag** ( $g$ ) =  $\varphi_g(g)$  is such that a program  $g$  effectively builds the machine that runs its own code. When the computation in **Diag** ( $g$ ) =  $\varphi_g(g)$  halts, producing typically a protein or an RNA transcriptase, this is further applied in a machine execution to output  $q$ . These outputs  $q$  in (2) from genomic codes  $g \in G$  is schematically shown below in Fig. 1 to produce the morphology and somatic identity of the organism.

In terms of the discussion on the central place given to the **Self-Ref** or **Diag** operator, a major insight on what this foundational concept in Eq. (2) in computation theory means for biology comes from Gershenfeld (2012, 2017 Chapter 3 p. 109) and the MIT Self-Assembly Lab (see, Tibbitts (2012)). Gershenfeld (2012) makes a remarkable observation that the design framework for programmed 3-D self-assembly of digitized materials in the 21st century fabrication is one that evolution has succeeded in creating some 3.5 billion years ago with the self-assembly programs of the ribosome and other transcriptase machinery.

The primary problem in the adversarial digital game at the heart of life is that a viral software of the bio-parasite can hijack the self-assembly gene expression machinery of the host in Eq. (2) as in  $f_p^{-1}$  (**Diag** ( $g$ )) =  $f_p^{-1}(\varphi_g(g))$  with the  $f_p^{-1}$  denoting the novel (!), adversarial ( $\neg$  is negation symbol) algorithm of the bio-parasite. As noted, the set denoted by  $\mathfrak{R}$  from which  $f_p^{-1}$  can arise, being the set of total computable functions, is non-denumerable infinite and not listable (see, footnote 12). Denoting, the new g.n for the  $f_p^{-1}$  pathogen attack on host gene code  $g$  as  $g_n^{-}$ , the consequence of the attack is to negate  $q$ , viz. destroy the tissue:

$$\varphi_{f_p^{-1}\varphi_g(g)}(s) = \varphi_{\varphi_{g_n^{-}}(g)}(s) = \neg \varphi_{\varphi_g(g)}(s) = q^{-} \text{ iff } \varphi_{\varphi_g(g)}(s) = q. \quad (3)$$

In principle, viral hijacking of the gene expression machinery is similar in both prokaryotes and eukaryotes as given in (3). Equation (3) highlights what can be called the ‘sitting duck’ problem: the expressed genes  $g \in G$  with morphology/phenotype  $q$  in situ and online as stated on the right-hand side (RHS) of (3) implies that the bio-parasite can succeed in negating  $q$ . In view of Covid-19,  $q$  is assumed to be the lung tissue in Fig. 2.

Prokaryotes have highly sophisticated means for self-other distinction and non-self antigen detection. However, prokaryotes drastically pruned the size of the genomic set  $G$  as a solution to the problem. As will be shown in the next section, detection of non-self antigen took on an elaborate Gödel self-referential format of offline records in the eukaryote Adaptive Immune System. The identification of the hostile other as a self-referential mapping from self-codes is distinctively missing in prokaryotes.

What a Code Biology framework has to delineate is how the organism finds Fixed Points of novel external bio-malware software functions  $f_p^{-1}$  that belong to the set  $\mathfrak{R}$  with respect to any expressed gene code  $g \in G$ . Note from (3), the attack takes the form  $\varphi_{f_p^{-1}\varphi_g(g)}(s)$  in what is called the immunological periphery in real time. The question is: How can this be internalized as an index of a fixed point, which can record online real time bio-malware changes to expressed gene codes, should this happen?

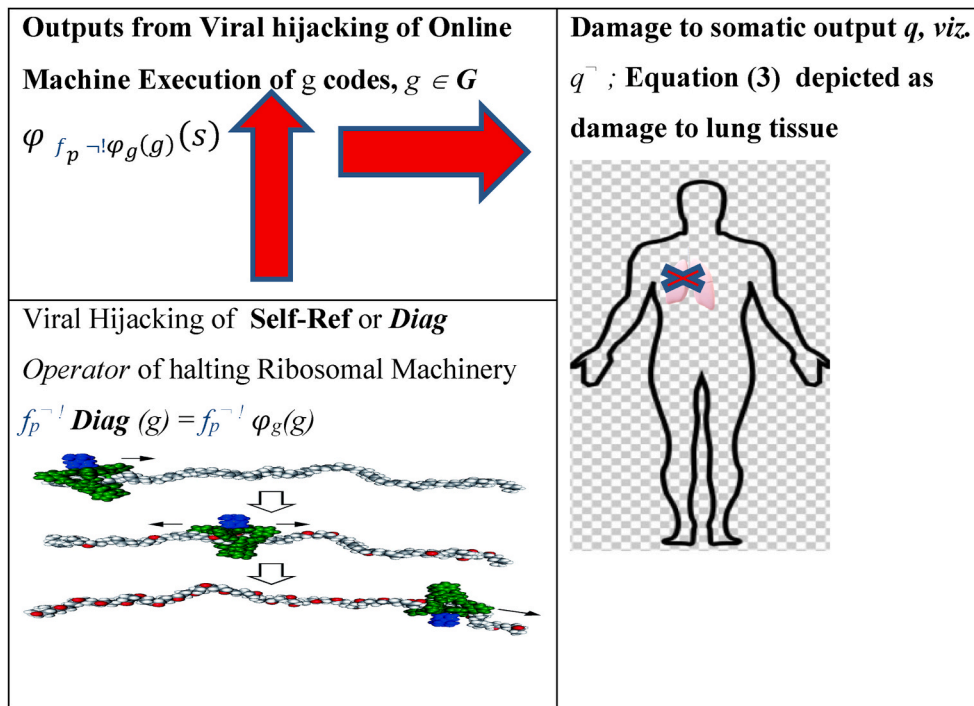


Fig. 2. Viral Parasite ( $f_p^{-1}$ ) Hijacking of the Ribosomal Self-Assembly Machinery (Eq. (3)) Depicted as Damage to somatic output  $q$  (lung tissue).

3.2. The Thymic Self and the Brain Self: offline mirror mappings in genomic immuno-cognitive systems

In what marks the start of the vertebrate and mammalian radiation, there was a step change in genomic intelligence with the so-called Big Bang of Immunology (Janeway et al. (2005)) with the Adaptive Immune System (AIS) in the lineage of jawed fish some 500 mya. Analog defences of the innate immune system, which include setting up barriers, toxicity, raising temperature by inflammation and ingestion by phagocytes was enhanced with a code-centric bio-cybersecurity of stupendous capabilities for complex self-other interactions where the other is a self-referential projection of self. In the context of the Adaptive Immune System, in what has been called the ‘Thymic self’ (Sánchez-Ramón and Faure (2020)) and as ‘the science of self’ (Greenen (2021)), an offline virtual self-representation (Self-Rep) mapping onto MHC1 receptors of the Thymus Medulla is made of over 85% of the gene codes, in the case of humans (Danan-Gotthold et al. (2016); Kyewski and Klein (2006)), which are expressed in halting self-assembly programs for human somatic identity and phenotype.

In other words, post AIS, eukaryotes generate an offline internal mapping in Thymus Medulla of online gene expression of somatic self exactly as stated in the famous Gödel Meta-Representation system. This is given the following textbook format from Rogers (1967, p. 202–204):

$$\varphi_{\sigma(g,g)}(s) \cong \varphi_{\varphi_g}(s) = q, \text{ iff } \text{Diag}(g) = \varphi_g(g) \text{ halts} \quad (4)$$

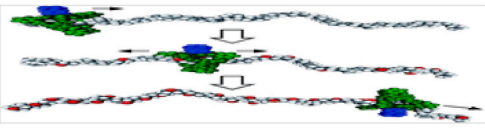
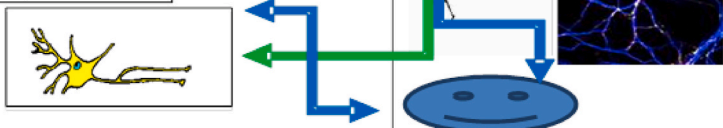
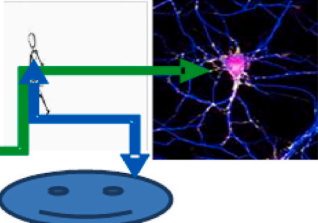
Here, the diagonal operation of Self-Rep on the right-hand side (RHS) of (4) and in (2) show a self-assembly machine that runs its own code and halts, denoted by  $\varphi_g(g)$  halts. This is bijectively (iff, if and only if) represented in Self-Rep (Self-Representation) offline format as in  $\sigma(g,g)$  on the LHS of (4). The LHS function  $\sigma(g,g)$  modelled along the lines of the Gödel 2- place substitution function (see, Rogers (1967)) has the feature that it names or ‘signifies’ in the off-line recording in the Thymus Medulla epithelial cells, m-TECs, the one-one bijective mapping of the machine execution of the gene codes  $\varphi_{\varphi_g}(s) = q$ , viz. when the self-assembly machine executions that halt and proceed to output  $q$ , the

meta system also faithfully predicts the outcome is  $q$ . The graphics in Fig. 3 in the top Panel A shows this stupendous Gödel Self-Rep mapping in the eukaryote adaptive immune system in the Thymus Medulla epithelial cells of self gene codes that determine somatic identity of the organism.

The significance of this bijective offline recording device of m-TECs for tissue specific genes in equation (4) has led Derbinski et al. (2001) to note that “m-TECs may indeed represent an immunological homunculus, in that they mirror and anticipate the peripheral self”. In Markose (2017), this is taken to be baseline point of the game when the pathogen does not disrupt host gene codes. A major implication of the Gödel Self-Rep mapping in Eq. (4) is that as the machine execution on RHS of both Eq. (4) and in Fig. 3 is gene expression, the mapping is also a semantic one with the actualization of a specific output. This is encapsulated in the offline setting in the  $\sigma(g,g)$  index and the biotic element  $g$  can make self-referential statements of itself as noted below by Tsuda (2014).

The neuroscience literature has invested heavily in offline mirroring activity of online motor and sensory cortex activity<sup>16</sup> with the discovery of the mirror neuron system (MNS) by the Parma Group in the 1980’s. Gallese (2009), Gallese and Sinigaglia (2011) have characterized the MNS as a common neuronal platform for conducting offline embodied simulations for action prediction in the other based on a parallel set of neurons that fire during action execution by one-self (see also Acharya and Shukla (2012)). Ramachandran (2000) describes this as follows: “It’s as if anytime you want to make a judgement about someone else’s movements you have to run a VR (virtual reality) simulation of the corresponding movements in your own brain and without mirror neurons you cannot do this.” However, despite so called computational

<sup>16</sup> The neurons that fire with actual action execution by are called canonical neurons (Arbib and Fagg (1998)) and correspond to on-line machine executions by self in the G-T-P logic.

<p><i>Offline : Recording/Simulation</i>  <i>Equation (4) (LHS) Self-Rep</i>                      Notation <math>\phi_{\sigma(g,g)}(s)</math></p>	<p><i>Online : Machine Execution</i>  <i>Equation (4) (RHS) Self-Ref</i>                      Notation: <math>\phi_{\phi_s(g)}(s)=q</math></p>
<p><b>Panel A (Left)</b>                      Medullary Thymus Epithelial cells (m-TECs)                      Mirror Mapping of tissue specific genes/peptides of ~85% of genome</p>	<p><b>Panel A (Right)</b>                      Baseline Machine Execution of Coding and nc Genes modelled as a self assembly of digitized biotic elements of gene codes in set G See Equation (2))</p>
<p><b>Baseline : With no malware</b></p> <div style="border: 1px solid black; padding: 5px; width: fit-content;"> <math>\sigma(g,g)</math> </div> <div style="border: 1px solid black; padding: 5px; width: fit-content; margin-top: 10px;"> <math>\xi_1, \xi_2, \xi_3, \dots, \xi_n</math>                      Theorems of genomic system                 </div>	<p>Ribosomal and non-coding Transcription machine executions which halt:  <math>\phi_g(g) \downarrow</math> for all <math>g \in G</math></p> 
<p><b>Panel B (Left) Mirror Neurons (Yellow)</b>                      For Social Cognition : Fires with self action and when self 'sees' others' actions For action prediction with self and other</p>	<p><b>Panel B (Right) Canonical Neurons (Pink on black)</b> Firing Based on Motor Cortex (eg'self walking, Green Arrows) and Sensory/Visual Cortex as observer by self 'of other walking (Blue Arrow)</p>
<p>Discovered by Parma Group '90s (Gallese, Fadiga, Rizollatti, Pellegrino, Fogassi)</p> <div style="border: 1px solid black; padding: 5px; width: fit-content;"> <math>\sigma(a,a)</math> </div> 	

**Fig. 3.** Gödel Meta-representation (Rogers, 1967) Online Halting Self-Assembly Machines Mirrored Offline For Embodied Simulations for Complex Self-Other Interactions in Immuno-Cognitive Systems

Note: *Offline* Mirror Systems in Medulla Thymus (Panel A, Left) and *Offline* Cognitive Mirror Neuron System (Panel B, Left) with respective Bijective Map of *Online* Gene Transcription (Panel A, Right) and *Online* Action Execution in Motor-Sensory Cortex (Panel B Right).

Panel A offline mirroring in 'Thymic Self' of online Self-Assembly Gene Expression of Somatic Identity of Organism circa 500 mya in Adaptive Immune System in lineage of jawed fish.

Panel B: Primate/Human Mirror Neuron System. Both immune-cognitive systems have access to RAG and/or Retrotransposon endogenous diversity production for astromic open-ended search.

frameworks for cognitive biology (see, Fitch 2014),<sup>17</sup> computational neuroscience and Computational Theory of the Mind (Rescorla (2020)), apart from Tsuda (2014), there has been no explicit discussion of the role of the genomic mirror systems and recursive information processing in G-T-P using the Self-Ref and Self-Rep operations.

Tsuda (2014) identifies how neural systems which need to process a self-referential description use the mirror neuron mapping as in the mathematics of the Gödel's incompleteness theorem: "When neural systems process a self-referential description, they may first have to make a copy of the object of self-reference and then refer to this copy. This two-stage formulation can be realized mathematically in the proof of Gödel's incompleteness theorem through the processes of projecting mathematical statements to natural numbers and of referring to meta-mathematical statements by providing mathematical statements about such numbers. The presence of mirror neurons in animal brains or mirror neuron systems in human brains may also be a realization of the above two-stage formulation in brains, because mirror neurons, or

mirror-neuron systems, can be activated, not only by behavior in others similar to one's own behavior, but also by one's own behavior." However, Tsuda (2014) does not utilize the mirror system for a model of cognition capable of implementing novelty production.

The graphics in Fig. 3, are useful to show an identical recursive machinery based on the G-T-P condition of Self-Rep in Eq. (4) is at work both in the mirror system of the m-TECs of the Adaptive Immune System (Panel A) and for the cognitive mirror neuron system (Panel B). The respective, self-referential online machine executions (RHS) Fig. 3 are mapped 1-1 to offline Self-Rep that permits meta-inference on self and the other. There are, ofcourse, interesting differences in the processes by which information on the other is conveyed via visual-sensory cortex to the mirror neuron system when external phenotypes are involved as compared to the case of peripheral antigen receptors and those antigen receptors in the m-TECs. Some details of the latter are given in the next section.

In general, the two place Gödel substitution function  $\sigma(x,y)$  in Eq. (4) has place-holders from the perspective of self on status of self and status of non-self vis-à-vis self:

$\sigma$  (status of self, status of non-self vis-à-vis self)

Thus, in the  $\sigma(g,g)$  notation in (4), in the 1st place from the left, is the record of host's gene code and an identical  $g$  in the 2nd place implies that the host has identified that there has been no alteration of this gene code by the non-self antigen or pathogen, aka Liar. In other words, the agency of the other is calibrated self-referentially, viz. in terms of self-

<sup>17</sup> Many computational cognitive models rely on Bayesian learning. As stated in Fitch (2014) the recordings from the sensory-visual and motor cortex constitute "a large, complex and ancient set of Bayesian priors (visual, sensory, motor) that constrain inference in any mammalian brain, and are equally operative in the human brain". Bayesian inference is statistical and is a far cry from inference by embodied offline simulation in the G-T-P cognitive system, which also permits novelty generation.



codes and their recursive function/algorithmic transformations. The diagonal elements  $\sigma(x,x)$ , in general, have great significance in the *offline* meta system organized in matrix form. As discussed in Markose (2017, 2021a), only diagonal elements demonstrate Nash equilibria when both status of self and self's identification of non-self status are in sync, with false beliefs and undetected deceit being ruled out. These will be contrasted with off-diagonal elements  $\sigma(x,y)$  or  $\sigma(y,x)$ . In general, as one substitutes different values  $\sigma(x,y)$  for a given state  $s$ , the whole space of potential self-other genomic outcomes that can be brought about by recursive functions can be explored. There is an important theorem here (see, Rogers 1967)<sup>18</sup> that the *g.ns* representing  $\sigma(x,y)$  in the meta-system can always be obtained whether or not the partial recursive function  $\varphi_x(y)$  on the right-hand side of (4) which executes programs halts.

More often than not, the developments with the Adaptive Immune System and the Mirror Neuron Systems in the primate brain are dealt in disparate ways rather than as the workings of a unitary recursive function theory based self-referential digital information processing found in Gödel-Turing-Post (G-T-P) formal systems. There is a long legacy at least since Irun Cohen (1992) on the so called cognitive immune system theories of intelligence in which internal self-image is the basis of the 'other'. Many, like Nataf (2017), Filiano et al. (2016), Kipnis (2016) and others, make the link between how the immune system became 'smart' and the possible similarities in bio-molecular processes underpinning neural activities relating to cognition, communication and signalling, social cognition and even behavioural traits (Lopes, 2017). Miller (2018) goes further and characterizes all biotic elements to be cognitive components imbued with self-referential sensory perception of the 'other'. Ofcourse, what is missing in the above narratives is the precise G-T-P recursive machinery at work.

#### 4. Construction of the Gödel Sentence as Rogers (1967) fixed point of novel malware negation functions in adaptive immune system

##### 4.1. Open-ended detection of novel malware negation functions $\{f_p^{-1}, g_n\}$

The key steps from Markose (2021a) are given here for the bio-informatics involved in terms of the recursive function operations of the V-D-J (variable-diversity-joining) recombinant machinery which enable the Adaptive Immune System, using a self-referential process, to identify putative attacks on the gene codes,  $g \in G$ . With the aid of large-scale V-D-J recombinant recursive machinery based on viral transposon derived Recombination Activating Genes (RAG 1 and RAG 2), the AIS conducts an open-ended search in the T-cell receptors of possible reactive pathogen software to the gene codes, presented in a self-referential way in the m-TECs, to simulate putative attacks or changes to the gene codes. This involves concatenations of bio Gödel numbers using the Gödel substitution function  $\sigma(\dots)$  in (4) which runs into orders of magnitude of  $10^{20}$ – $10^{30}$  that exceed the *pre-scripted* germline genome size many times over and is only rivalled by neuronal operations. Markose (2021a) models the V-D-J Adaptive Immune System operations as generating bio indexes for the composite functions of what is effectively an non-denumerable infinity of  $f_p^{-1} \circ \text{Diag}(g)$  with  $g \in G$ . As this is in anticipation of yet unknown bio-malware functions  $f_p^{-1}$ , some  $10^{20}$ – $10^{30}$  bio-peptide molecules are assumed to be generated. Of these only 5% of mature T-cell receptors are released from the offline environment of the Thymus into peripheral circulation after undergoing what is called positive and negative selection (see, Markose (2021a); Kyewski and Klein (2006)). Only the bio Gödel numbers which are a function of Self-Repped  $g \in G$  are positively selected.

Flajnik and Kasahara (2009) refer to the "anticipatory system of

defence" in the AIS machinery with RAG enabled somatic hyper-mutations in the T-cells and B-Cells of prodigious capacity which rivals that of the neuronal system. Müller et al. (2018) state that the capacity of the AIS for "somatic generation of immune recognition motifs is practically unlimited (open-ended) information capacity".

Needless, to say despite, copious evidence that information processing in the AIS follows the G-T-P Self-Ref (Eq. (2)) and Self-Rep structures (Eq. (4)), AIS detection of non self-antigen attack on a specific tissue in the immunological periphery has been dealt solely in analog terms of 'lock and key' or in terms of models of Affinity/Avidity (Wu et al. (2008)). Consequently, the very large literature on non-self antigen detection by the AIS, with the exception of Markose (2021a), does not model the problem as one of identifying the fixed point of a (negator) software function that involves a unique hashing algorithm.

##### 4.2. Rogers (1967) fixed point for non-self bio-malware functions

Rogers Fixed Point Theorem (1967, Section 11.2) states that any total computable function,  $f_p^{-1}$ , for the case in question, has as its fixed point an index given by an integer  $v$  such that  $\varphi_{f_p^{-1}(v)}(s) \cong \varphi_v(s)$ , viz. either both sides are defined and are equal or else both sides are undefined. The construction using the Rogers (1967) Fixed Point Theorem to detect hacking by novel non-self antigens by the Adaptive Immune System has two parts. The first part of the fixed point is generated offline in the Thymic T-Cell receptors (TCR) in an anticipative way. This has to 'sync' with the second part which arises experientially and gets recorded in the peripheral MHC I receptor in real time if and when the said non-self antigen  $f_p^{-1}$ , attacks a the peripheral tissue emanating from the expression of the tissue specific gene code, say  $g_n$ .

The first step of the proof of the Rogers (1967) Fixed Point Theorem is already satisfied with the offline recording being made in the MHC Thymic receptors of the index function  $\sigma(g_n, g_n)$  in the Self-Rep Theorem in (Eq. (4)) for the online machine execution of the *Diag* program such that  $\text{Diag}(g_n) = \varphi_{g_n}(g_n)$ . Having modelled T-cell receptor training to be vis-à-vis these Self-Repped gene codes in the MHC receptors of the Thymus, those bio-Gödel numbers which are not composed of some  $g \in G$  are eliminated. The question is what should the motif of the  $\sigma(\dots)$  index be so that the TCR once released from the Thymus does not attack self gene codes and cause auto-immune disease?

Assume that the bio Gödel number generated *offline* in the T cell receptor is  $g_n^{-1}$  for a specific composite function  $f_p^{-1} \circ \text{Diag}(g_n)$  relating to pair  $\{f_p^{-1}, g_n\}$ . Note  $g_n^{-1}$  is the index for the program for a machine, viz  $\varphi_{g_n^{-1}}(g_n)$ . Should an attack take place online in the periphery equivalent to  $f_p^{-1} \circ \text{Diag}(g_n)$ , this implies as shown in (3) that a successful high-jacking of gene expression machinery has been achieved  $\varphi_{f_p^{-1} \circ \text{Diag}(g_n)}(s) = \varphi_{\varphi_{g_n^{-1}}(g_n)}(s) = \varphi_{f_p^{-1} \circ \text{Diag}(g_n)}(s) = \neg \varphi_{\varphi_{g_n^{-1}}(g_n)}(s)$ . This will destroy the  $q$ -related morphology or phenotype. Likewise, the offline TCR motif of  $\sigma(g_n^{-1}, g_n)$  for this if released into the periphery will cause autoimmune disease as  $\sigma(g_n^{-1}, g_n)$  contains the instructions to do exactly what the bio-malware  $f_p^{-1}$  is programmed to do, viz.  $\varphi_{f_p^{-1} \circ \text{Diag}(g_n)}(s)$  as in Eq. (3).

The final step of the proof of the Rogers Fixed Point Theorem (1967) is to substitute  $g_n^{-1}$  into  $f_p^{-1} \circ \text{Diag}(g_n)$  to get  $f_p^{-1} \circ \text{Diag}(g_n^{-1})$ , which is the function  $\varphi_{g_n^{-1}}(g_n^{-1})$  as by definition  $g_n^{-1}$  is the index for the program which computes  $\varphi_{g_n^{-1}}(g_n)$ . This final step of the proof has great significance in the offline 'training' that is done in the Thymus in the generation of the motifs in the T-cell receptors as only now will the index  $\sigma(g_n^{-1}, g_n)$  that is capable of producing auto-immune disease be rendered 'harmless' in the form  $\sigma(g_n^{-1}, g_n^{-1})$ . Then, assign  $v$  as the index for  $\varphi_{g_n^{-1}}(g_n^{-1}) = \text{Diag}(g_n^{-1}) = \sigma(g_n^{-1}, g_n^{-1})$ , which yields the Rogers (1967) Fixed Point Result and generates the

<sup>18</sup> It is well known by what is called the SMN Theorem or the Parameterization Theorem (Rogers, 1967) how new *g.ns* for recursive operations on extant *g.ns* can be mechanically generated.

<sup>19</sup> While the CRISPR-Cas systems of prokaryotes have impressive adaptive capabilities for identification of non-self pathogens, they do not have the anticipative self-referential projections.

Gödel Sentence for the pathogen-gene code pair  $\{f_p^{-1}, g_n\}$ :

$$\begin{aligned} \varphi_{f_p^{-1}(v)}(s) &\cong \varphi_{f_p^{-1}\sigma(g_n^-, g_n^-)}(s) \cong \varphi_{f_p^{-1}Diag(g_n^-)}(s) \cong \varphi_{\varphi_{g_n^-}(g_n^-)}(s) \cong \varphi_{\sigma(g_n^-, g_n^-)}(s) \\ &\cong \varphi_v(s). \end{aligned} \tag{5}$$

Note the Gödel Sentence involves a pair of expressions starting with the far right and far left ones. While the fixed point index  $v$  for the Gödel Sentence in (5) can be constructed and this permits the gene code  $g_n^-$  to self-report it is under attack by  $f_p^{-1}$ , the outcome of the game is undecidable as to whether  $q$  or  $\neg q$  will follow. The Gödel Sentence encodes a contradiction:

$\varphi_{\varphi_{g_n^-}(g_n^-)}(s) = \neg \varphi_{\varphi_{g_n^-}(g_n^-)}(s)$ , viz.  $0 = 1$ . This can be seen by substituting  $g_n^-$  into  $\varphi_{\varphi_{g_n^-}(g_n^-)}(s)$  and noting  $\varphi_{f_p^{-1}Diag(g_n^-)}(s) = \neg \varphi_{\varphi_{g_n^-}(g_n^-)}(s)$ . Hence, by the definition of the index  $v$  of fixed point of  $f_p^{-1}$ , as both sides of  $\varphi_{f_p^{-1}(v)}(s) \sim \varphi_v(s)$  yield different outputs, both sides are undefined.

Note  $v = \sigma(g_n^-, g_n^-)$  generated offline in the T-cell Receptor of the Thymus is the fixed point of as yet to be encountered bio-malware function  $f_p^{-1}$ . The latter will not be known to the genomic system till, as discussed in Markose (2021a), the novel malware,  $f_p^{-1}$ , has attacked the gene code,  $g_n$ , expressed tissue in the periphery, and the peripheral MHC1 receptor updates  $f_p^{-1}Diag(g_n)$  to get  $f_p^{-1}Diag(g_n^-)$ . Only then can the biotic element  $g_n$  self-report it is under attack.

What is important to note is that the recording of the genomic Gödel Sentences as in (5) occur in two sets of *offline* receptors: (i) The index  $\sigma(g_n^-, g_n^-)$  generated *offline* via V-D-J concatenations in the T cell receptors in anticipation of an attack and are released into the periphery from the Thymus. (ii) In the peripheral MHC1 receptors where index  $f_p^{-1}\sigma(g_n^-, g_n^-)$  is generated experientially when the bio-malware attacks the tissue code  $g_n$  online, given on the LHS of Eq. (5). These two records must sync, viz. the predicted and the actual, for the formation of the Gödel Sentence in (5). If no attack takes place, then the index  $\sigma(g_n^-, g_n^-)$  generated in the T-cells sees no action. In the absence of the relevant Gödel Sentences being formed as in (5), as the latter are a logical necessity for producing software objects outside listable sets (see, Fig. 4), it is not possible for novel antibodies to be generated.

Markose (2021a) has put forward a testable hypothesis that those who suffer, for example, Covid 19 morbidity have problems regarding the formation of the Gödel Sentence arising from an inability to update the meta records from a state of health to one of bio-malware attack  $f_p^{-1}$  on  $g_n$ , viz from  $f_p^{-1}Diag(g_n)$  to  $f_p^{-1}Diag(g_n^-)$ , in the relevant peripheral offline MHC 1 receptors. Markose (2021a) has cited studies (Brouwer et al. (2020); Bastard et al. (2020)) that have found that deficiency in Type 1 Interferon Gamma, which aids in the non-self antigen presentation in the peripheral MHC1 receptors, is a prime candidate here for the failure of the formation of the Gödel Sentence.

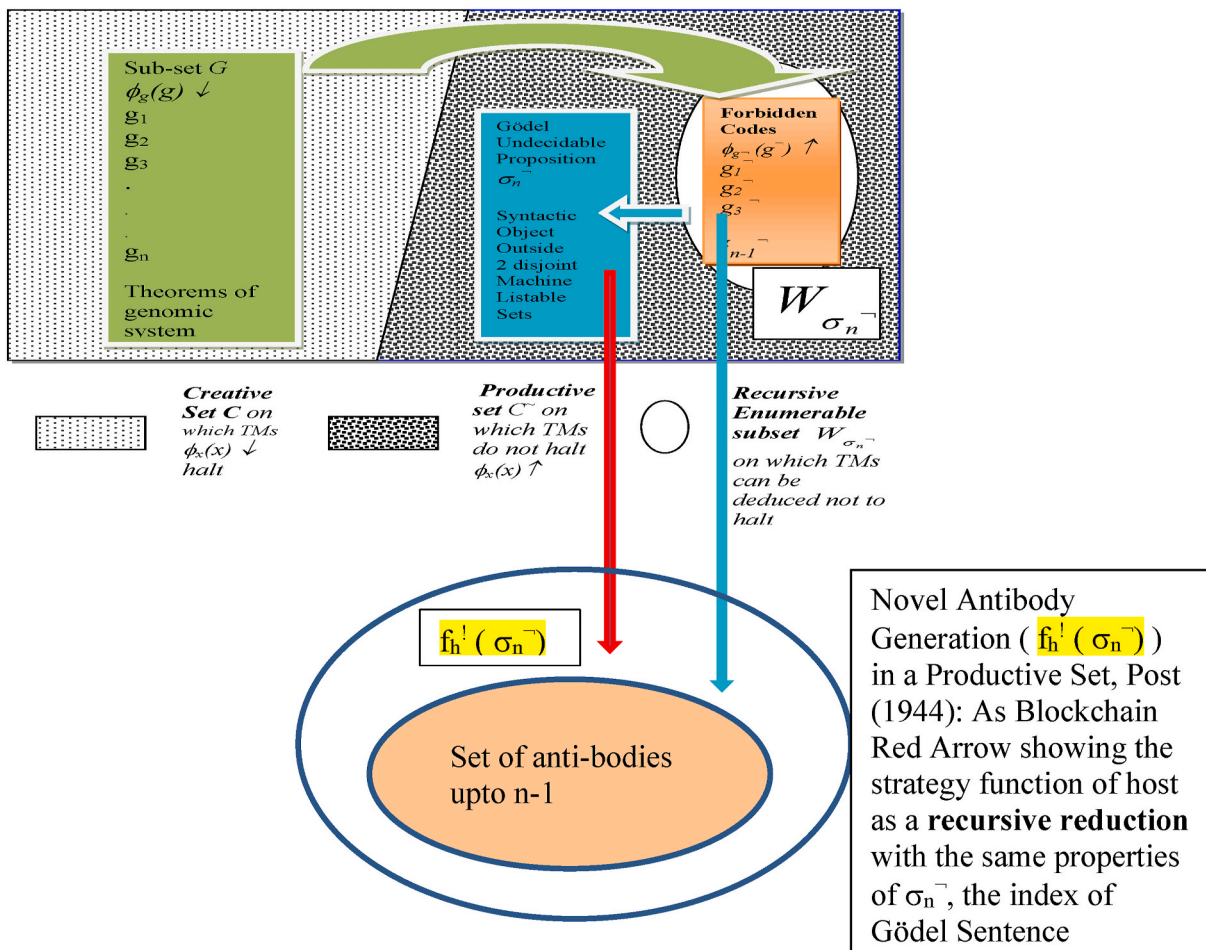


Fig. 4. Gödel Incompleteness Result in Miniature: An Illustration of Mirror Mapping in Thymus Medulla of Gene Codes that are Theorems in Genomic System And Novel Anti-body Generation As A Block Chain  
 Gödel undecidable proposition  $Diag(g_n^-)$  lies outside the listable sets  $G$  and  $W_{\sigma_n^-}$ , viz.  $\sigma_n^- \notin C \cup W_{\sigma_n^-}$ ,  $G \subset C$ . Note  $\sigma_n^- = \tau(Diag(g_n^-))$ .

### 4.3. Gödel Sentence as a hashing algorithm in a genomic blockchain distributed ledger

In order to fully incorporate all (total) recursive functions, viz. a halting algorithm, that can ‘negate’ halting self-assembly gene codes that determine the morphology and phenotype of multicellular organisms, it is important to acknowledge that latter are theorems of the genomic system. Further the genomic digital information processing follows the logic of formal systems (Smullyan, 1961). This is governed by the principle of logical consistency as demonstrated in the Emil Post (1944) Creative and Productive set theoretic proof of Gödel Incompleteness. A Creative set,  $C$ , as shown in Fig. 4 is the domain of all **Diag** ( $x$ ) self-assembly machines that halt for  $x$ . Hence  $g \in G$ , which determine the somatic identity of the organism is the subset of the creative set  $G \subset C$  and are the Theorems of the genomic system mapped onto the offline Thymic MHC receptors, shown in green in Fig. 4. The set of known non-Theorems denoted by  $W_{\sigma_n^-}$  in Fig. 4 is a strict subset of the complement of the creative set  $C$  and hence is disjoint from both  $G$  and  $C$ . The subscript  $\sigma_n^-$  for  $W_{\sigma_n^-}$  is the enumeration function  $\sigma_n^- = \tau(\text{Diag}(g_n^-))$ , the record of the  $n$ th novel bio-malware attack on a gene code during the life time of the organism. The proof of undecidability of  $\sigma_n^-$  relies on the set  $W_{\sigma_n^-}$  being *Productive* (Cutland (1980)) and the index  $\sigma_n^-$  cannot belong to  $W_{\sigma_n^-}$  or to  $C$  and hence  $\sigma_n^-$  and  $v$  cannot be recursively enumerated in advance respectively, as a non-theorem or a theorem of the genomic system. Instead,  $\sigma_n^-$  can only be added to  $W_{\sigma_n^-}$  and this flags out a new syntactic object when it is generated in the genomic system from the arms race with a non-self antigen.

In Section 3.2 Eq. (5), it was shown how the Rogers (1967) Fixed Point Theorem can generate indexes of the Gödel Sentence for novel non-self antigen software that can ‘negate’ self gene codes. In Fig. 4 such a Gödel sentence index will lie outside the disjoint sets of listable theorems and known non-theorems for the organism in the Post (1944) set theoretic proof of Gödel Incompleteness. It is interesting to note that at the level of the biotic element  $g_n$ , which suffers ‘negation’ by a novel non-self antigen,  $g_n$  is able to self-report that it has been hacked.

It can be conjectured that the hash value for bio-Gödel Sentences is of fixed length and in a compressed form of  $0=1$ , possibly using a unique peptide identifier for this. This is a requirement of a hashing algorithm and having flagged out a potential inconsistency ( $0=1$ ), it also encapsulates radical uncertainty. It does so by identifying undecidability (see, Blue box in Fig. 4) in the formal genomic system as discussed. Further, the inability to form the Gödel sentence vis-à-vis a novel hostile bio-malware  $f_p^1$  as shown in equation (3) will lead to an out of (Nash) equilibrium outcome with destruction of the gene code expressed morphology/phenotype  $q$  of the organism.

Fig. 4 shows via the red arrow how novel anti-bodies are produced in response to a novel pathogen attack recorded in the enumeration  $\sigma_n^-$  of the index for the relevant Gödel Sentence generated by the Adaptive Immune System. The strategy function of the host is a recursive reduction, (see, Markose (2017) Lemmas 3 and 5), from the basal information stored as a formal system of Theorems and non-Theorems. The function producing novel anti-bodies exactly maps the properties of the basal productive function  $\sigma_n^-$ , in that it is novel and lies outside all listable sets. The novel anti-body is precision engineered for the  $f_p^1$  threat to gene code  $g_n$ . In contrast, the innate immune systems responses to non-self antigens are generic and known to create ‘cytokine storms’ which can do more harm than good, Markose (2021a). In summary, we see that the main principle of a blockchain distributed ledger technology is achieved by the eukaryote adaptive immune system: the fidelity of earlier blocks of gene codes is secured so that they cannot be compromised by external non-self antigens by hacking and new blocks in the form of novel

anti-bodies cannot have outcomes that are antithetical to encoded information in earlier blocks.

## 5. Conclusion

Despite aspirational statements on the significance of Gödel logic and conditions of Gödel Incompleteness for complexification of life and cognition (see, Chaitin et al. (2011), Casti (1994), Prokopenko et al. (2019), Markose (2004, 2005)), it is fair to say that for some 90 years, there has been no direct evidence for how any of this got embedded into life forms in the course of evolution.

The significance of the Gödel framework was first mooted by the game theorist Binmore (1987) in the context of an adversarial digital game where Binmore postulated that agents like Gödel’s Liar who personify bio-malware and hackers with access to non-denumerable infinite set of algorithms, makes it logically impossible for decision making to be confined within a framework that is closed, complete and nothing new can be produced. Till Markose (2017) such digital games where strategic novelty production is a Nash equilibrium of the game have been missing from the annals of Game Theory. However, while Markose (2017) gives steps on how novelty can be produced as syntactic objects as in Gödel undecidable propositions using the Emil Post (1944) set theoretic framework, how this may have arisen during the course of biological evolution in the vertebrate lineage post jawed fish was missing.

The main message of the current paper is that the Binmore style adversarial digital game is co-extensive with life itself. It was in Markose (2021a) that the distinctive Gödel **Diag** (.) operator, which follows from the antecedents of Gödel Incompleteness results from the Cantor Diagonal Lemma (see, Markose (2022)), was shown to coincide with the Gershenfeld (2012, 2017) insight that biology solved the problem of programmed self-assembly 3.5 billion years ago with the ribosomal and other transcriptase software. Also, it is in Markose (2021a) that the text-book formulation in Rogers (1967) of the recursive Self-Representation mapping of halting online self-assembly machines to an offline virtual record keeping platform was found to exactly match the evolution of the Adaptive Immune System. Eukaryotes in the lineage of jawed fish some 500 mya achieve homeostasis with regard to the gene codes that determine their somatic identity by developing an offline self-representation in the so called ‘Thymic self’ (Sánchez-Ramón and Faure (2020)). Latterly, the Mirror Neuron System in primates achieves the epitome of self-referential social cognition in humans for complex self-other interaction and for open-ended adaptive novelty production. In the human mirror neuron system the mapping from online self-activity codes to offline representation in the Rogers (1967) meta-representation fuses syntax with semantics. With the sentient self, the latter is identifiable as self-actions giving the wherewithal to make out the other.

Self-reference and Self-Representation have been adduced to be the defining feature of vertebrate biology and of the sentient self by many studies on immune-cognitive systems, some of which has been reviewed in this paper. However, apart from Tsuda (2014) and Markose (2017, 2021a), as the elaborate mirror systems in the brain or the Adaptive Immune System have never been identified as **Self-Ref/Self-Rep** staples of Gödel-Turing-Post, there have been varied explanations and also outright denial of the necessity for such structures in advanced genomic information processing (see, Newen (2018) and Gallistel and King (2009)). Even in quarters such as Computational Theory of Mind (Rescorla (2020)) which purports to model code-based cognition, the Rogers (1967) **Self-Rep** virtual records of online **Self-Ref** operations are missing (see, Markose (2022)).

Indeed, even after the epochal discoveries by McClintock (1984) of transposable elements that do scissor/paste (transposons) and copy/-paste (retrotransposons), operations well known in word processing of digital documents, it has not yet become mainstream in biology<sup>20</sup> that primarily only bio-software can make changes to genomic software. To model such algorithmic dynamics of digital systems, as pointed out by Hamkins (2021), far more recursive function machinery than was available to Gödel (1931) in the form of Second Recursion Theorems is needed. The remarkable consequence of the Rogers (1967) Self-Rep mappings is that it enables biotic elements to make self-referential statements endogenously about algorithmic changes being made to them as fixed points.

As already noted as (halting) novel algorithmic changes to self-codes can arise from a non-denumerable infinite set, how the Adaptive Immune System identifies the fixed points of novel bio-malware is an eye-opener, which is missing in Markose (2017). In general, while Roger style fixed point indexes can be generated for a given total computable function making a change to a known code, the issue is how does the AIS make out yet to happen bio-malware attacks? As postulated here, a stringent diversity-selector framework of a genomic blockchain distributed ledger technology at a decentralized level of bio-molecules seems to be at work in the vertebrate lineage post jawed fish. The evolution of the retrotransposon based RAG 1 and RAG 2 500 mya provides astronomic diversity in the generation of putative fixed point indexes of novel bio-malware changes in the offline T-cell receptors. The full formation of the Gödel Sentence as shown in Eq. (5) occurs only when the predicted Thymic index 'syncs' with the one generated when the bio-malware attack/negation actually occurs in real time. This crucially has to be followed by index formation in the peripheral MHC1 receptor of the said attack. The Gödel Sentence which encodes  $0 = 1$  is of fixed length in accordance to the properties of a hashing algorithm. The fixed point index relating to a Gödel Sentence will endogenously alert the system as being undecidable in it if only if the halting self-assembly gene codes are organized as Theorems of the system and their known negations as non-theorem as in Fig. 4. No objective function or optimization is involved here, only the principle of consistency involving Theoremhood of self-assembly gene codes that create the organism. Further, as shown in Fig. 4 and the recursively reduced Post (1944) productive set for anti-bodies will add novel anti-bodies only to preserve the Theoremhood of the original gene codes with the structure of the productive set satisfying the concept behind the blockchain. It is conjectured that gene regulatory networks are recursive reductions to the genomic formal system depicted in Fig. 4. Clearly, considerably more work is needed to see if the Gödel Sentence will suffice as a hashing algorithm to detect malign transposable element based epigenetic activity in gene expression, gene silencing and other somatic gene changes. This will lead to a unified model of genomic regulatory structures in Code Biology.

In conclusion, a major development of the 21 st century digital age is the astounding invention of the blockchain distributed ledger technology (BCDLT), first presented in the anarchic agenda of the Bitcoin by pseudonymous Satoshi Nakamoto (2008) to resist centralized state control of monetary systems. BCDLT permits decentralized software-based record keeping of actions of multiple agents in which the fidelity of extant digital accounts is maintained by a software solution to a cryptographic puzzle which makes it difficult for malign activity in

new software additions by a subset of agents. There are yet major challenges associated with the man-made BCDLT systems. What my model of the unique G-T-P blockchain distributed ledger for the vertebrate genomic system seems to suggest is that when the powers of recursive recombinations and proteanism (from RAG 1 & 2, transposable elements and viral softwares) are unleashed on bio digital systems, if they are not embedded in a BCDLT, they will be hacked to pieces and doomed to failure. In Markose (2021a) and here some key details have been given on this phenomenally successful ancient genomic precedent of a BCDLT with highly conserved building blocks of life being virtually unchanged for 3.5 billion years while novelty is added on.

## Declaration of competing interest

This is to confirm that I have no conflict of interest regarding the submission of paper titled.

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<sup>20</sup> Chaitin (2012, 2013) underscores the code-based nature of biology and evolution in favour of one based on differential equations. Despite this and his well-known support for the relevance of Gödel Incompleteness for biology, Chaitin (2012, 2013) takes a pre-McClintock model of random mutation as the sole driver for diversity and evolvability and eschews the Gödel-Turing-Post staples on Self-Ref/Self-Rep and also gives no role for Gödel Sentence in the complexification of biology. See, Markose (2021b) for a review on this. See, also Siedliński (2016).

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