International Journal of Astrobiology (2022), **21**:4 243–259
doi:10.1017/S1473550422000246

RESEARCH ARTICLE

Curbing the fruitfulness of self-replicating machines

Alex Ellery

Department of Mechanical & Aerospace Engineering, Carleton University, 1125 Colonel By Drive, Ottawa, ON. K1S 5B6, Canada
Author for correspondence: Alex Ellery, E-mail: aellery@mae.carleton.ca

Received: 1 February 2022; **Accepted:** 1 June 2022; **First published online:** 08 July 2022

Key words: Galactic exploration, grey goo scenario, population control, self-replicating machines, SETI, telomeric restriction

Abstract

The self-replicating machine has high utility by virtue of its universal construction properties and its productive capacity for exponential growth. Their capacity is unrivalled. They can be deployed to the Moon to industrialize it using local in-situ resources in the short term to open up the solar system and thence deployed on interstellar spacecraft to explore the entire Galaxy by exploiting in-situ stellar system resources. Nevertheless, there are significant concerns regarding the inherent safety of self-replicating machines. We consider the general problem of runaway population growth in physical self-replicating machines to prevent the grey goo problem, the number of offspring spawned by self-replicating machines may be controlled at a genetic level. We adopt a biologically-inspired approach based on telomeres, DNA endcaps that are progressively shortened during cellular replication. This acts as a counter that imposes a limit to the number of replication cycles (Hayflick limit). By examining the biological process in detail, we can obtain some insights in implementing similar mechanisms in self-replicating machines. In particular, we find that counting mechanisms are vulnerable to cancerous runaway.

Contents

Introduction

We have been developing aspects of a physical self-replicating machine for deployment on the Moon using only local in-situ resources (Ellery, 2015*a*, 2017*a*). Self-replicating machines deployed on the Moon exploit their exponential growth capability to rapidly construct a production-based industrial infrastructure to support the low-cost settlement of the Moon (Ellery, 2016). We have examined the lunar resource requirements and the required processing of lunar raw materials within a lunar industrial ecology in detail (Ellery, 2020; Ellery *et al*., 2022). The self-replicating machine we consider here has grander applications – interstellar spacecraft with a self-replicating payload can explore the entire Galaxy at a low-cost (Freitas, 1980). Indeed, it might be considered a natural extension from

self-replicating machines within the solar system to beyond with minimal cost. We have been 3D printing crucial components to demonstrate universal construction properties. We have demonstrated 3D printing of electric motors which are a key component of kinematic machines (Elaskri and Ellery, 2020). We have yet to 3D print active computational devices but this activity is ongoing (Prasad and Ellery, 2020). We have explored the possibility of a bio-inspired control architecture for the industrial ecology based on genetic regulatory networks (Ellery, 2021). The self-replicating machine has high utility by virtue of its universal construction properties and its productive capacity for exponential growth which suggest inevitability. However, there are significant concerns regarding the inherent safety of self-replicating machines primarily associated with its exponential growth potential – this is the grey goo scenario. We have explored several approaches to this problem (Ellery and Eiben 2019) including (i) the implementation of kill switches (through the salt and tunicose contingencies) that deny centralized supplies of resources; (ii) the implementation of error detection and correction codes (EDAC) at a genetic (memory) level to prevent evolutionary divergence. Only the latter would be applicable to a self-replicating interstellar probe. But there are further, more subtle biomimetic approaches that we explore here relating to maturation such as ageing and cancer.

Problem of uncontrolled self-replication

Humankind blessed them, and Humankind said to them, 'Be fruitful and multiply; but fill not the earth nor subdue it; you have no dominion over the fish of the sea, nor over the birds of the air, nor over any living thing that moves on the earth or elsewhere.' Then Humankind said, 'Behold, we have supplied you the element-yielding minerals of the Moon, and the rocks in which are the element-yielding minerals; to you it is food…. but consume frugally'. Forgive the literary adulteration but it forcibly illustrates the immense power and implicit responsibility bestowed upon humanity in pursuing self-replicating machine technology. One of the thorniest problems in developing self-replicating machines is the fear of an unrestrained population explosion – the grey goo scenario. It is imperative that this problem is addressed in a robust manner that satisfies not only the real threat but also the perceived threat (Kahneman and Tversky, 1979) which, frankly, is magnified out of all proportion (Joy, 2000) but nevertheless must be allayed. It has been suggested that runaway self-replication of machines on Earth will yield at least a 4 °C global temperature rise within 2 years which would be readily detectable (Freitas, 2001). Similarly, the release of self-replicating machines throughout the Galaxy has been deemed as irresponsible that no intelligent species would undertake (Sagan and Newman, 1983). It is worth noting that uncontrolled replication is not inherently undesirable – it is the end to which it is deployed that is the determinant of its ethical character. Uncontrolled self-replication has been proposed to spread vaccines through self-spreading viruses as a vector (Lentzos *et al*., 2022). In this case, viral evolution is suppressed by limiting viral lifetimes. However, the efficacy of such genetic manipulation is unproven in the wild – a dynamic, complex and uncontrolled environment. Nevertheless, the sheer utility of self-replicating machines renders it unlikely that self-denial of such technology is realistic – its universal construction and exponential growth capabilities render it extremely high economic utility (Ellery, 2017*b*). It behoves us therefore to address the risk of proliferation directly.

In previous work, we have addressed some issues regarding the control of self-replicating machine populations (Ellery and Eiben, 2019) – we had specifically addressed the implementation of genetic redundancy and error correction codes to prevent evolutionary variance as the population grows through the self-replication process. One safeguard that might be implemented is restrictions on offspring population. In this paper, we continue to address the problem of control of self-replicating machine populations by focussing on imposing limits on the number of offspring that any individual self-replicating machine can spawn – a Hayflick limit – and inherent (rather than external) kill switch approaches. We shall examine in detail how biological constraints on cellular division are imposed to explore if there are biomimetic lessons that we can learn in implementing our technological solutions. Our focus will be on the implementation of counters and their biological counterpart, the telomeres.

https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

How biological cells count

Prokaryotes demonstrate that biological organisms can propagate indefinitely with continuous repair without suffering senescence. Unlike prokaryotes in which DNA is circular however, eukaryotic DNA is packaged into linear chromosomes with free ends requiring telomere endcaps. The relationship between Hayflick limits and the concept of telomeres, telomerase and senescence was first described by Alexei Olovnikov (1996). Telomeres are protein-DNA complexes at the ends of eukaryotic chromosomes that act as buffers by forming molecular caps to protect them. They are characterized by non-coding sequences of many short tandem repeats of species-specific motifs. These motifs comprise 5–8 base pairs including G-rich sequences at the 3' end of the chromosome, e.g. the 6 base-pair $(TTAGGG)_n$ in vertebrates (Neidle and Parkinson, 2003). They are usually identical tandem repeats but there can be variants. Telomeric repeats are highly conserved in different eukaryotic groups from yeast to humans (Moyzis *et al*., 1988). The average length of telomeric repeats varies between species but the average length correlates with variability rather than genome size – in humans, telomere length is 2–15 kbases but in mice, it is >30 kbases.

Most of the G-rich strand is duplex but a single (lagging) strand protrudes 100–300 bases (in humans) beyond the complementary C-rich (leading) strand, i.e. the G-rich strand is longer than the complementary C-rich strand resulting in a G-rich 3' overhang (G-tail) of 100–300 single-stranded repeats which binds to part of the ds region forming a (telomere) t-loop. The telomeric repeats are primarily double stranded $(TTAGGG/CCCTAA)_n$ and the single-stranded overhang $(TTAGGG)_n$ is much shorter than the double strand. It is the single-stranded DNA extension that differentiates the telomere endcaps from double-strand breaks (DSB). Double strand breaks during replication are detected and processed through S-phase checkpointing. Single strands prevent telomeres from being treated as DSB, especially nonhomologous end joining (EJ) of the broken ends (McEachern *et al*., 2000). Non-homologous EJ involves the DNA ligase and the DNA-PK kinase protein binding to the DNA end. The single-stranded G-tail overhang forms a terminal (t) loop structure at the end of the double-stranded telomeric repeats which acts to protect the telomeres (Griffith *et al*., 1999). The tandem repeats serve as binding sites for specific proteins and repressor sites for nearby gene expression. Shelterin is a protective protein complex comprising six telomere-binding proteins that bind to telomeric repeats and prevent double-strand break repair mechanisms. In mammals, the six telomere-binding proteins are a core of TRF1 and TRF2 (telomere repeat binding factors) which attract RAP1 (TRF1-interacting protein), TIN2 (TRF1-interacting factor), POT1 (protection of telomeres 1) and TPP1 (adrenocortical dysplasia homologue). They bind to both double and single-strand regions of the telomere. TRF1, TRF2 and POT1 bind to double-strand telomeres with high specificity; POT1 binds to the single strand overhang; TN2 tethers TRF1 and TRF2; TPP1 tethers POT1 to TIN2. TRF1 inhibits telomere elongation but TRF2 renders telomeric ends into t loops thereby protecting against double-strand break response of senescence or apoptosis (Kierszenbaum, 2000). The t loop is formed by the 3' single-stranded overhang bonding with the double-stranded telomeric repeats in the presence of TRF2 and requires sufficient double-strand length for t loop formation (Collins, 2000). T loop formation requires TRF2 that renders the chromosome end non-sticky to p53-dependent DNA damage repair activity. In fact, there are a host of molecules involved in telomere function such as CST which comprises three proteins (Venkatesan *et al*., 2017).

During telomere replication, the C strand replicates through lagging strand synthesis and the G strand through leading strand synthesis. DNA polymerase synthesizes the continuous DNA leading strand in the 5'-to-3' direction. The lagging strand of the replication fork requires discontinuous Okazaki fragments to be joined by laying a short 10–16 nucleotide RNA primer to initiate DNA synthesis. Once the RNA primer is removed at the 3' end, 50–200 bp of the lagging strand end cannot be replicated. 5'-to-3' DNA synthesis by DNA polymerase leaves the overhanging G-rich strand of DNA $(TTAGGG)_n$ at the 5' end incompletely replicated because the lagging C-rich strand is recessed. Leading strand DNA replication halts prematurely because of a lack of a template for the 3' overhang resulting in incomplete replication at telomeric chromosome ends (Kelleher *et al*., 2002). The double-

https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

strand telomeric DNA constituting the bulk of telomeric DNA is packaged into chromatin and replicated; the single strand telomeric DNA is not packaged into chromatin and is not replicated. Hence, at each cell division, the single strand 3' end of the telomere is not replicated causing telomere shortening of 50–200 bases per replication cycle. Thus, telomeres shorten progressively from their maximum length of 10–15 kb to a critical length of 4–6 kb in size, whence cell senescence is invoked. Cell senescence is invoked by DNA damage, telomere loss, de-repression of cyclin-dependent kinase inhibitor (CDKN2a) and other cellular stressors. Indeed, levels of CDK2Na expression are a good indication of cellular ageing. This limits the number of times cells can replicate to around 50 ± 10 cell divisions (varying in culture from 80–90 times in newborn tissue to 20–30 times in elderly tissue) – this is the Hayflick limit whence cellular senescence ensues (Hayflick, 1984) though cellular senescence typically occurs long before this limit (of $\sim 10^{15}$ cells after 50 doublings) is reached (Hayflick, 1979). Accelerated ageing syndromes such as Werner's syndrome and Trisonomy 21 are characterized by reduced replicative capacity. Indeed, it has been demonstrated that telomere shortening acts as a clock that causally induces replicative senescence (Chiu and Harley, 1997; Bodnar *et al*., 1998). Hence, telomere shortening acts as a mitotic replication copy counter. When a few telomeres become critically short, the G-rich binding sites for proteins are no longer functional in telomere replication and end capping. Short telomeres even occur in tissues with low replication rates. As well as replicative cycle losses of telomeres, there are also random telomere losses due to oxidative damage to sensitive G-rich DNA of telomeres (Lansdorp, 2005). Ageing correlates with diminished DNA repair capacity of regulatory telomeres which accumulate damage (Kruk *et al*., 1995).

There is a mechanism of alternative lengthening of telomeres (ALT) in which DNA is copied from telomere to telomere through homologous recombination (HR) using telomeres as copy templates (Dunham *et al*., 2000). This is a type of recombination involving gene conversion that maintains extremely long telomeres (Kass-Eisler and Greider, 2000). However, we do not pursue this mechanism here.

In the germline cells (and cancers) but not healthy somatic cells, telomeres may be maintained indefinitely by telomerase. Germline cells are effectively immortal due to telomerase activation – telomeric DNA extension is coupled to DNA replication during the S phase. Telomerase is a specialized ribonucleoprotein (RNP) that binds to telomeric DNA. It incorporates a reverse transcriptase enzyme subunit but, unlike conventional reverse transcriptases which are pure proteins, includes an RNA subunit (Stone, 2018). Telomerase is a RNP enzyme comprising the hTERT (human telomerase reverse transcriptase) protein and hTERC (human telomerase RNA component) RNA (Blackburn, 1992). The hTERT enzyme catalyses the DNA sequence repeats from the TERC RNA template. TERT has highly conserved reverse transcriptase protein signatures because it generates DNA from its non-coding RNA template. Reverse transcriptase evolved from RNA-dependent RNA polymerases while telomerases originated with ancestral eukaryotes from retrotransposons (Nakamura and Cech, 1998). TERC is the non-protein-encoding RNA transcribed by RNA polymerase II and is polyadenylated. The human telomerase RNA segment is 451 bases in length containing an 11-base RNA region 5'…CUAACCCUAAC…3' (Simonsson, 2003). It is this RNA sequence of telomerase that acts as a template from which the telomere DNA tandem repeats are copied. Telomerase adds new single-stranded telomeric tandem repeats to the 3' chromosome end using its RNA template from which it only generates and elongates G-rich DNA strands. Complementary strand synthesis completes the double-strand segments up to the overhang. Telomerase requires a DNA primer onto which telomeric repeats are added in the usual 5' to 3' direction. The DNA polymerase-primase complex is crucial for telomere maintenance through elongation of multiple repeats. Telomerase thus lengthens chromosomes with repetitive sequences to compensate for telomere shortening. Regulation of transcription of hTERT is the limiting step in telomerase activation (Aisner *et al*., 2002). hTERT mRNA exhibits differential splicing into different tissue-specific splices that regulates the amount of telomerase enzyme.

Telomerase adds 390–420 base pairs of telomeric repeats to a telomere while oxidative stress can shorten telomeres by 100–600 base pairs per deletion depending on the degree of oxidative stress so cellular lifespan enhancement requires oxidative attrition to be below ~400 base pair deletions (Arkus, 2005). Mitochondrial DNA is essential for oxidative phosphorylation in the eukaryotic cell

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– cellular ageing is associated with mutations in mtDNA with high ageing rates in cells with high energy demands such as muscle and nerve cells (Nagley and Wei, 1998). However, there is no direct relationship between longevity in mammals and metabolic rate based on the assumption that ageing results from the accumulation of molecular damage due to genetic errors or toxic metabolites (Austad and Fischer, 1991). TERT regulates the level of mitochondrial oxygen radicals (Ait-Aissa *et al*., 2016). DNA integrity checkpoints control the balance between telomeric shortening and lengthening (Chakhparonian and Wellinger, 2003). Telomere homoeostasis implements a dynamic balance between lengthening and shortening which maintains a telomere length of 9–15 kbp in length (Bodnar *et al*., 1998). Telomeres are switched either open or closed to telomerase activity. Cdc13p recognizes a minimal 11 nucleotide single strand sequence as a G-rich overhang (t-loop) and initiates telomerase activity by opening the telomere. Telomere maintenance involves several steps (Dubrana *et al*., 2001): (i) telomere unfolds so that the tree end is open to enzymes; (ii) telomerase and DNA replication together synthesize the C-rich strand regulated by length-sensing feedback and second-strand synthesis; (iii) telomere refolds into its protective terminal.

Once a critical shortness of telomere length is reached in germ cells (but not somatic cells), telomerase activity can be activated during the late S phase of the cell cycle. It is the shortest telomeres rather than the average length that determine cellular response (Armanios and Blackburn, 2012). Telomerase is expressed only in germ cells but not somatic cells except during early embryonic development in somatic tissue (Wright *et al*., 1996). Embryonic stem cells possess very long telomeres that lengthen due to high TERT expression and adult stem cells also exhibit telomerase activity but this diminishes with adult stem cell age (Flores and Blasco, 2010). Indeed, during development, there is a major shift in telomere behaviour (Bekaert *et al*., 2004). During early development of the germline, telomere length is maintained by balancing shortening induced during cell division against lengthening by telomerase which becomes particularly active after fertilization. During later differentiation into specialized somatic cells, prior to the differentiation of sex, shortening begins to dominate as telomerase activity is repressed, starting the molecular clock. Hence, telomere shortening contributes to ageing. As ageing occurs, telomerase activity declines. If telomerase is overexpressed, telomere slippage during cell replication causes excessive replication resulting in cancer.

When biological counting stops

There are mechanisms for genome maintenance to prevent mutation into oncogenes including multiple repair mechanisms all of which are highly conserved across evolutionary timescales (Hoeijmakers, 2001). There are four main repair systems in mammals – nucleotide excision repair (NER), base excision repair (BER), HR and EJ. NER repairs helix-distorting lesions that affect base pairing and prevent transcription. BER repairs chemical changes in bases. Many environmental insults yield characteristic genetic mutations, e.g. UV light converts the base cytosine into thymine and are characteristic of melanomas. The less frequent DSB which are more dangerous than single-strand breaks are repaired through HR which generates a second copy of DNA for aligning breaks and EJ when there is no second copy. NER is the most versatile of repair mechanisms with two subpathways – the global genome is scanned for helix-distorting damage and transcription-coupled repair focuses on the damage that blocks RNA polymerase elongation. HJ and ER are the main repair modes, however. Paediatric cancers are rare but concentrated in the brain, bone and white blood cells, all of which have undergone rapid recent evolutionary change or subject to strong host-parasite selection, suggesting that evolutionary disequilibria have not yet been corrected. Carcinogenesis is an evolutionary process that involves natural selection between genetic variations in somatic cancer cells, especially those that eliminate genetic repair mechanisms (Crespi and Summers, 2005). Such genomic instability with inactivation of DNA repair pathways is characteristic of the development of cancer malignancy (Tubbs and Nussenzweig, 2017). The tissue organization theory regards cell proliferation as the natural state of all cells (Soto and Sonnenschein, 2004). This places cellular replication as a fundamental default process in cellular life because it has evolved so – this will not be the case for a self-replicating machine.

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If DNA repair cannot restore genetic integrity, there are two main cellular responses to damage – cellular senescence and programmed cell death (such as apoptosis), the latter killing the cell and the former irreversibly preventing cell replication. They are both invoked by common triggers such as DNA damage or oncogenic stress and involve common regulatory mechanisms such as the p53 pathway. p53 is activated by short telomeres initiating cellular senescence or apoptosis depending on the tissue. The default state of the p53 gene is inhibited by protein MDM2 to low-level activity until environmental stresses decouple MDM2 (Eisenstein, 2022). This activates p53 to regulate the expression of a cascade of gene products that invoke apoptosis. However, some tumours produce excess MDM2 even without p53 mutations. Cellular senescence is a stable cell cycle arrest that occurs due to cellular damage such as DNA mutation or telomere loss. Senescence is characterized by a distinct secretion profile of inflammatory cytokines and degraded proteins due to cellular damage which determines the response of neighbouring cells. Cell senescence induced by critically-shortened telomeres is the causative agent of ageing and its associated diseases (Xi *et al*., 2013). The characteristic feature of cellular senescence is the halting of cell division. It occurs when telomere uncapping invokes the loss of the single-strand overhang which activates double-strand break repair processes. Cellular senescence is initiated when telomeres still retain several kbases of tandem repeats due to p53 and p21 activation (Wright and Shay, 1995). It is also a response to a wide variety of stresses including DNA damage, oxidative exposure, tumorigenesis, etc in which cells halt cell division for tumour suppression (Ben-Porath and Weinberg, 2005). Cancer is also linked to cell senescence in which cell senescence blocks tumour formation (Finkel *et al*., 2007). Cellular senescence also occurs in embryonic development and is dependent on p21 regulated by the tumour necrosis factor pathway (Munoz-Espin *et al*., 2013).

Programmed cell death occurs in all multicellular animals, of which apoptosis is the most prominent. Apoptosis is an essential biochemical pathway for metazoans especially in embryonic development, adult tissue homoeostasis and defence against mutation (Danial and Korsmeyer, 2004). Apoptosis is an altruistic cell behaviour that induces cell suicide (programmed cell death) without inflammation (a defining characteristic of necrotic cell death) in response to noxious stimuli. For example, in neurodegeneration, neuron apoptosis is induced by oxidative stress (Krantic *et al*., 2006). Psychological stress is associated with higher oxidative stress which reduces telomerase activity and shortens telomerase length (Epel *et al*., 2004). Similarly, epithelial cells die through apoptosis when detached from other epithelial substrate cells – carcinomas result when apoptosis is suppressed. While apoptosis is a genetically-controlled, well-ordered process, necrosis is reactively invoked by the leakage of protein-digestive enzymes (cathepsins) from ruptured intracellular lysosomes due to increased intracellular Ca^{2+} ions.

There are two major signalling pathways for apoptosis – death receptor pathway and mitochondrial pathway (Gupta, 2001). The death receptor pathway includes the CD95 death pathway and the tumour necrosis factor pathways which are associated with immune response through T cell proliferation. Each T cell carries a distinct T cell receptor that recognizes a specific antigen presented at the surface of an invading cell. The thymus generates a wide variety of immature T cells (thymocytes) which undergo selection through programmed cell death. During apoptosis, the cell cytoplasm shrinks in volume followed by organelle and chromatin condensation while the cell membrane bulges. The DNA and lipids are packaged to enable neighbouring cells to recycle these resources through phagocytosis (Bar, 1996). DNA is cleaved into fragments of 180–200 bp in length by Ca^{2+}-dependent endonucleases during apoptosis rather than the random cleaving by lyzosomes that occurs during necrosis. In fact, this internucleosomal cleavage between histones ~180–200 bp in length is one type of cleavage – there are others including fragmentation into large 50–300 bp segments prior to internucleosomal cleavage corresponding to chromatin loop domains, and single-strand cleavage (Bortner *et al*., 1995). There are at least two endonucleases with different mechanisms involved in DNA fragmentation during apoptosis – caspase-dependent DFF (DNA fragmentation factor) and caspase-independent mitochondrial EndoG (endonuclease G) (Zhang and Xu 2002). Caspase 1, caspase 4 and caspase 5 promote lytic cell death triggering inflammation. Caspase 8 promotes cell death by inflammation. The destruction of

https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

DNA suppresses inflammatory response. The cell membrane pinches off to form multiple internal vesicles containing fragments of the cell contents. Apoptotic cells secrete lysophospatidylcholine (LPC) chemicals that invite phagocytes. Apparently, the situation is more complex as reduced apoptosis can prevent cancer progression by reducing cell division and so mutations (Luria-Delbruck theory) (Wodaerz and Komarova, 2007).

When biological counting runs amok

Ageing is primarily caused by DNA damage (Schumacher *et al*., 2021) which induces (i) genome instability that prevents transcription and regulation despite constant repair mechanisms, (ii) telomere dysfunction due to progressive rather than critical shortening, (iii) epigenetic changes due to modifications of DNA methylation and polyADP-ribosylation of histones, (iv) proteostatic stress resulting in protein misfolding and (v) mitochondrial dysfunction due to reactive oxygen species damage from oxidative respiration for which there are fewer repair mechanisms. Such DNA damage invokes cell senescence which evolved as a mechanism to prevent cell over-proliferation (cancer). It is unlikely that the average human lifespan can extend beyond 85 years unless cancers can be controlled (Olshansky *et al*., 2001), and even if this is the case, such longevity increases are likely to be modest (Turner, 2004). Cancers are due to the accumulation of somatic mutations resulting in around 30% of deaths in developed countries. Cancer is ubiquitous among metazoans including mammals – although higher cancer rates occur in larger, long-lived organisms within species as expected, there no is evidence of such correlation between different species (Peto's paradox).

There are four main cancer markers: (i) evasion of apoptosis via mutation; (ii) expression of telomerase inducing limitless replication; (iii) angiogenesis that grows tumour blood supplies; (iv) tissue invasion and metastasis which causes 90% of cancer deaths. Cancer involves a succession of distinct genetic mutations (most commonly acquired rather than inherited) in specific tumour suppressor genes and proto-oncogenes that convert normal cells into cancer cells that proliferate into malignant tumours due to their resistance to cellular apoptosis (Fadeel and Orrenius, 2005). Genetic mutations can affect interdependent signalling pathways that interact in multiple ways contributing to multiple steps in the development of cancer (McCormick, 1999), e.g. there are multiple cellular checkpoints in metabolic pathways such as Ras, p53, p16, etc which must be circumvented in tumourigenesis. Tumour suppressor genes slow cell division while proto-oncogenes aid cell growth. Oncogenes are cellular genes that have been captured into viral genomes through reverse transcriptase, e.g. src gene of Rous sarcoma virus that infects chickens. Proto-oncogenes are commonly involved in cell replication and differentiation. Oncogenes can inhibit autophagy which acts as a tumour suppressor. Autophagy is a coordinated series of processes that are fundamental to anti-ageing. Oncogene activation is a major driving force in the development of cancer. They generate stalled replication forks which tend to collapse into DSB. There are multiple processes through which normal proto-oncogenes are converted into active oncogenes (Land *et al*., 1983). If the mutation occurs in a tumour suppressive gene that controls cell division or other crucial apoptotic genes, then the cell does not undergo apoptosis and can allow cancer to emerge. Proto-oncogenes mutate in cancer-generating oncogenes that remain switched on. While oncogenes are activated (switched on) through chromosomal rearrangements or gene duplication, tumour suppressor genes such as TP53 are switched off (occurs in greater than 50% of human cancers).

Telomerase activity is repressed in somatic cells but is reactivated in cancer cells resulting in tumour growth (Kim *et al*., 1994). The majority of cancer cells exhibit high telomerase activity suggesting that senescence through telomere shortening is a malignant tumour-suppression mechanism that is activated in response to oxidative stress preventing telomerase expression (Vixtorelli and Passos, 2017). Telomerase activity is present in 85–90% of all human tumours. Cancer is usually associated with shorter telomeres ~2–4 kbases than in healthy cells in conjunction with telomerase activation (Autexier and Greider, 1996). Tumour cells initially reproduce rapidly, generating shortened telomeres. Genomic instability arises due to the shortest telomeres rather than the average telomere length increasing the prospect of tumour growth (Lundblad, 2001). Such short telomeres indicate DNA damage and

https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

initiate cancer. Only subsequently, short telomeres are subsequently maintained through telomerase activation. Hence, telomeres in cancer cells are smaller than in normal cells because cancer cells synthesize telomerase only after the onset of uncontrollable replication. Cancer cells become immortalized through the activation of hTERT telomerase expression to actively maintain stable telomere lengths (Masutomi *et al*., 2003). Telomerase (TERT) suppression can lead to tumour cell apoptosis or senescence. Telomerase inhibitors such as PNA, hammerhead ribozymes or antigens could potentially be deployed against telomerase-mediated cancers (White *et al*., 2001). Oncogenes such as Myc and Wnt act as transcriptional regulators of telomerase. Telomerase then allows further replication but with shortened telomeres. Cancers are caused by mutations in DNA repair genes that cause deficient DNA repair enzymes and so accelerate mutation rates. Telomeres on the short arm of chromosome 17 are shorter than telomeres on other human chromosomes on average – this chromosome includes the p53 gene.

Tumour suppression genes regulate a range of cell processes including p53 transcription factor which regulates cell cycle checkpoints as the genomic gatekeeper (Sherr, 2004). p53 offers two broad functions – it induces cell senescence responses to stress and regulates metabolic activity. Cell senescence is controlled by tumour-suppressor pathways of which the most prominent in human cancers are p53 and pRB which also interact with each other in several ways (Campisi, 2001). Tumour suppressor genes prevent abnormal cell growth by inducing repair, senescence or programmed cell death. The TRP53 gene which encodes the p53 protein is a tumour suppressor and exhibits the commonest mutation in human cancers. Because p53 also regulates glucose metabolism, this prevents cancer from upregulating glycolysis and so glucose consumption required for cell proliferation is mediated by activating AMP-activated protein kinase (Warburg effect) (Bensaad and Vousden, 2007). It regulates the transcription of TIGAR (TP53-induced glycolysis and apoptosis regulator) and the SCO2 (synthesis of cytochrome c oxidase 2) proteins involved in glucose and mitochondrial oxidative respiration respectively. p53 activity resists cancer but promotes ageing. pRB regulates transcription more indirectly through interaction with transcription factors. Activation of p53 transcription factor positively regulates transcription of p21, a cyclin-dependent kinase inhibitor that causes cell cycle arrest characteristic of cell senescence (Sahin and DePinho, 2010). Both p53 and p16 must be inhibited for cell proliferation to occur.

Somatic mutations in the p53 gene are frequent (up to 50%) in most cancers and germline mutations in the p53 gene causes Li-Fraumeni syndrome which predisposes to a large variety of early cancers – most such mutations are multiple incidences of single amino acid changes rather than frameshift or nonsense mutations, 25% of which are C:G > T:A substitutions at CpG sites (Olivier *et al*., 2010). p53 is a tumour suppressor gene activated by DNA damage that induces arrest of the cell cycle in the G1 phase for DNA repair processes and/or apoptosis. If the p53 gene is mutated, cancer cells are permitted to survive and proliferate without restraint. p53 upregulates Bid, Bax and Bad, three of several proteins of the bcl-2 family that activate apoptosis by decreasing the stability of phospholipid bilayers of the outer mitochondrial membrane by forming channels through it. Genetic instability arises from several sources but most notably from deactivated DNA mismatch repair gene (MSH2 and MLH1) mutations generating mutation rates two or three orders of magnitude higher than in normal cells (Cahill *et al*., 1999). If genes for DNA repair enzymes mutate, mutational errors accumulate at a much higher rate leading to cancers (Pray, 2008). Germline mutations in mismatch repair genes are associated with cancer predisposition in humans including colon cancers (Radman *et al*., 1995; Peltomaki, 1997). As replication proceeds uncontrollably in cancers, tumours grow and invade neighbouring tissue, sometimes detaching and travelling to other distant tissues and generating new tumours. This is metastasis.

Some 10–15% of cancers are not characterized by telomerase activity but exhibit extremely long telomeres maintained through ALT (Bryan *et al*., 1997; Blasco and Hahn, 2003). ALT occurs in most cases of solid tumours (10–15% of cancers) which recombine telomeres from different chromosomes. ALT is believed to have derived from homologous repair. ALT-based tumours cannot be treated

with telomerase inhibitors. ALT cancers have poor prognosis and telomerase-based cancers can switch to ALT cancers under selection due to therapeutic intervention.

There are epigenetic effects in cancer growth that do not involve underlying genetic mutations. Epigenetic phenomena include methylation and histone modification. DNA methylation involves reversible attachment of a methyl group to a cytosine nucleotide located next to a guanine nucleotide (CpG site). Methylated CpG sites act as binding sites for proteins that alter DNA's structure which prevents transcription (with CpG/CpC ratio>0.6), i.e. switches the gene off. Because 5'-CG-3 is palindromic, C on one or both strands may be methylated (hemi- or homo-methylated respectively). DNA methylation is mediated by methyl-CpG-binding proteins. DNA is wrapped around histone proteins to which acetyl groups can be attached which switches the gene on (acetylation) or removed which switches the gene off (deacetylation). Seven mammalian sirtuin proteins act as NAD-dependent deacetylases for genome stability. Histones may also be modified by methylation. Small forms of RNA (RNAi) can interfere with gene expression by attaching to other RNA molecules. Many cancers exhibit hypomethylation of oncogenes switching them on and hypermethylation of tumour suppressor genes switching them off (Balmain, 1995). The silencing of tumour suppressor genes through methylation is as effective as genetic mutation but unlike mutation are reversible (Plass and Soloway, 2002).

Role of viruses

Transposable elements are DNA sequences that can be cut-and-paste from and into the genome (jumping genes). They are classed into two types: (i) DNA transposons were active during early primate evolution until 37 My ago since when they have been inactive; (ii) retrotransposons form RNA intermediates which are then reverse transcribed into DNA for insertion into the chromosome as (a) long terminal repeats (LTR) or human endogenous retroviruses (HERV) and (b) non-LTR including long interspersed elements (LINE), Alu or SVA elements. Around 45% of the human genome comprises transposable elements which have causative roles in human rapid evolution, genetic instability and cancer (Ayarpadikannan and Kim, 2014). Around 8% of the human genome comprises fossil endogenous retroviral (ERV) genes in addition to other random insertions of retrotransposons such as Alu and LINE elements. Evolution of ERVs is dependent on the high error rate of reverse transcriptase and recombination through its jumps (Blikstad *et al*., 2008). Retroviruses comprise RNA genomes from which a double-strand DNA copy is constructed through reverse transcriptase and the viral DNA is integrated into the host chromosomal DNA using viral integrase enzyme forming a provirus ~7–11 kb in length (Temin, 1972). Retroviruses generally integrate at random locations in host chromosomes but have preference for active locations – others such as ALV have distinct target preferences. Integration of retroviral DNA into the host chromosome enhances the expression of adjacent downstream host genes – if the activated gene is an oncogene, tumour growth may result. Retroviruses may have simple genomes (alpha, beta, gamma and epsilon) or complex genomes (lentivirus, deltavirus and spumavirus) but only simple retroviruses have become endogenous in their hosts. Endogenous avian leukosis virus (ALV) is an alpha-retrovirus that infects chickens similar to Rous sarcoma virus (RSV) inducing B-cell lymphomas – ALV (5'LTR-gag-pol-env-LTR3') does not transform fibroblasts but RSV (5'LTR-gag-pol-src-LTR3') does (Weiss, 2013). The order of structural genes is conserved in all retroviruses: gag gene encodes for virion structure; pol encodes for reverse transcriptase and other enzymes and env encodes envelope proteins for host cell recognition. Env and gag markers were inherited as a single host locus. Each of the LTRs comprises unique U3 and U5 regions separated by an R segment. The transformation-capable RSV genome is 20% greater than the transformation-defective genome due to the inclusion of a cancer-causing src gene near the 3' end. Endogenous retroviruses have evolved from retroviral infections in the ancestral germline which subsequently became fixed and then vertically transmitted from parent to offspring. This has been occurring since retroviruses emerged 500 My ago. The env sequence of a HERV provirus on chromosome 7q21.2 has been co-opted to express protein Syncytin-1 in the placenta (Jern and Coffin, 2008). There

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are around 30 human ERV (HERV) families in the human genome, most of which have accumulated mutations so they do not offer uninterrupted open reading frames. Of the 4000 endoviral env loci in the human genome, only 16 retain intact open reading frames that encode an Env protein (De Parseval *et al*., 2003). HERV gag and pol have even lower ratios of 17/9500 and 13/20 900 loci respectively. There are no known replicative HERV in the human genome including HERV-K(HML-2) which is the most active HERV family and was provirally integrated some 200 000 years ago. ERVs have been implicated in tumourigenesis including HERV, an infectious example of which is human T cell leukaemia virus 1 (HTLV-1) (Ruprecht *et al*., 2008). Oncogenes of retroviruses are copies of host cellular proto-oncogenes that are implicated in carcinogenesis (Bishop, 1983). ERV can induce cancer through two mechanisms: (i) oncogene capture involves infection by transforming retrovirus rapidly causing tumour growth due to the expression of a viral oncogene (v-onc) derived from host cell proto-oncogenes (c-onc) that were inserted into the retroviral genome through recombination during reverse transcription; (ii) insertional mutagenesis involves the integration of proviral genomes close to host cell proto-oncogenes that activate them or into tumour-suppressor genes which are disrupted and inactivated allowing slower tumour growth in both cases. Immunosuppressive domains are present in 10 of the 16 HERV elements containing complete env genes in the human genome suggesting that HERV act as tumour antigens that elicit anti-tumour immune response. ERV also jump between species (xenotropism) – RD114 is a feline ERV found in the tabby but not spotted cats that was infected from a primate as it is found in baboons (Weiss, 2006). There are well-known exogenous viruses that are associated with human cancers. Human tumour-inducing viruses yield prolonged latency to malignant growth and include Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), human T cell lymphotropic virus (HTLV-1) and Kaposi's sarcoma virus (KSV) constituting 15–20% of human cancers globally (Javier and Butel, 2008; Martin and Gutkind, 2009). Oncolytic viruses preferentially lyse cancer cells by activating dormant tumours to activate immune response but operate best in combination with other therapies (Melcher *et al*., 2021). Cancer forms a co-evolving ecosystem in which cancer therapies can eradicate most cancer cells but also promote clonal evolution of drug resistance (Ushijima *et al*., 2021). Interferon, a type of cytokine regulatory transcription factor, is the first viral defence in mammals that blocks the spread of viral infection through the body by invoking cell death of infected cells (Sen, 2001). Some use double-stranded RNA as cofactor that activates promoters for their activity against RNA viruses. They act through different cell surface receptors. Most viruses have evolved defences to maintain a dynamic equilibrium between interferon and virus. Oncolytic viruses are viruses that attack tumours, e.g. the modified adenovirus Onyx-015 targets cancer cells that have mutated p53 genes (in its unmodified form, it possesses genes that inactivates p53). They can work with checkpoint inhibitors such as ipilimumab. Rapamycin is a TOR signalling network inhibitor as a treatment for malignant tumours. A chimaeric antigen receptor has been engineered to modify a T lymphocyte to act as an OR gate in recognizing two cancer antigens – CD19 or CD20 – to prevent escape by mutation.

Biomimetic lessons in counting

It has been proposed that there is a tiny erosion of mean telomere length per generation of any species that very gradually leads to critically short telomeres and genomic instability in the germline inducing species extinction (species clock hypothesis) (Stindl, 2004). Such a process would be too short for a self-replicating machine. Alternatively, an ageing process may be envisaged – in biological organisms, the accumulation of spontaneous somatic mutations is the primary mechanism of ageing (Curtis, 1963). Post-reproductive lifespans extending the onset of senescence will evolve only when the offspring and other relatives benefit (Hamilton, 1966). There are two primary theories of ageing (Partridge and Barton, 1993; Rando, 2006). The pleiotropic theory of ageing predicts that genes that are advantageous in early life are selected even if they are disadvantageous in later life (Williams, 1957; Bell 1984) due to the decline of selection pressure with age particularly after reproductive maturation (Charlesworth, 2000), e.g. the onset of Huntington's disease occurs after reproductive prime. Cancer is a direct –

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though not universal – result of the pleiotropy theory of ageing (Campisi, 2005). The mechanism of pleiotropic theory of ageing may be that telomeric shortening inhibits cancer formation in early life but simultaneously involves progressive degradation with age (reserve capacity hypothesis) (Weinstein and Ciszek, 2002). Consistent with the pleiotropic theory of ageing is the disposable soma theory that increased longevity imposes metabolic costs for the maintenance of somatic tissue against deterioration (Kirkwood and Rose, 1991). Both may be incorporated into a single stochastic dynamic programming model based on the Gompertz ageing equations (Mangel, 2001). Reliability theory of ageing predicts exponential mortality rates with age (Gompertz law) in biological systems rather than power law mortality rates with age (Weibull law) in engineered systems (Gavrilov and Gavrilova, 2001). Biological systems' extensive adoption of multiple, overlapping functional redundancies renders an exponential profile that begins with infant mortality failures and increases rather than the bathtub power law profile of high infant-reliability of engineered components. The Gompertz model estimates the maximum human lifespan at 120 years – death grows exponentially with age until a plateau at 105–113 years, following which there is a sharp growth in mortality beyond 113. By implementing high-reliability manufacture, test and recycling of components, a self-replicating machine can exhibit a Weibull power law ageing profile.

If evolutionary selection is not operational in a self-replicating machine, senescence may be imposed by energetic limitations to controlling the growth of errors in information-based molecules (Kirkwood, 1977). It has been demonstrated in animal models that treatment with the non-integrative adeno-associated virus expressing TERT to activate telomerase yielded improved health and longevity without increasing the incidence of cancer (De Jesus *et al*., 2012; De Jesus and Blasco, 2013). We must ensure that there is no such happy valley between senescence and cancer for our self-replicating machine.

Biomimetic lessons into engineering design

Our first consideration concerns the physical implementation of our genetic instruction store for a self-replicating machine. Based on the material resources available on the Moon (Ellery, 2020), we propose that magnetic core memory constitutes the most appropriate medium of information storage. Magnetic core memories were used for RAM over the period 1955–75 and are tolerant of radiation with high reliability – they were used in the Apollo Guidance Computer and Space Shuttle Flight Computers. The chief advantage of magnetic core memory over solid-state electronics is its much lower susceptibility to radiation errors increasing the reliability of data storage. Magnetic core memory has many of the basic materials and components required in a dc electric motor (Elaskri and Ellery, 2018). There are several magnetic core materials. Soft iron loses its magnetization when the field is removed. It can concentrate fields up to 2 T but suffers from eddy currents due to its good electrical conductivity generating waste heat. Laminated silicon steel reduces its electrical conductivity and so hinders eddy current formation. Powdered iron coated in a thin layer of insulation is an alternative. The core is typically constructed from ferrite (Fe_3O_4) ceramic through which wires are passed to convey read and write signals. Each core stores one bit of information non-volatilely as zero or one depending on the direction of the core's magnetization. The toroidal shape of the core allows close packing of the cores. Tiny magnetic toroids are formed in the cores forming arrays of cores. The unit cell of magnetic core memory comprises a toroidal hysteresis loop of magnetically hard material to act as a transformer core material (high remanence but low coercivity material such as cobalt ferrite or AlNiCo) through which several (aluminium) wires pass for reading/writing non-volatile binary data. Electric current passing through the wires set or reset the bit stored magnetically in the core. The cores are magnetized clockwise or anticlockwise to represent binary 1 and 0 or vice versa. A set of three wires (X, Y, Sense/Inhibit) through the centre of the core carries current to generate a magnetic field concentrated by the core. A grid of horizontal (x) and vertical (y) wires generate the write current while two perpendicular diagonal wires are the read wires. Only at the junction where the x and y wires cross (logical AND) is there sufficient current to magnetically write a bit. Any change in magnetic state induces a voltage pulse in a read line

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which in turn invokes a re-write. The invention of the coincident current system enabled a small number of wires to control a large number of cores in 3D stacks. A large number of small ferrite toroidal cores are held on layers of XY grids of wires through the toroidal centres. Only where the combined magnetic field from X and Y lines cross exceeds a threshold will the magnetic polarity reverse. Although non-volatile, reading data resets the core so a re-write cycle is required to restore the data after reading. In the 1960s, the limit of memory storage density was $\sim$1 kbit l^{-1}, i.e. 1 Mbit m^{-3}. Although there exist today a suite of manufacturing technologies that may increase this density, this is currently conjectural. If we assume that the genetic program will be invariant, the program can be woven into read-only core rope memory which is renowned for its high reliability in space applications. Binary data was stored either as wire threaded through the core (1) or around the core (0) which was read as a current pulse. This offers a higher storage density of 2.5 Mbit m^{-3} than that of magnetic core memory with higher reliability.

We propose that the physical design of the genetic memory module of the self-replicating machine comprises a volumetric array of magnetic core memory cells. Copying of uninterpreted genetic instructions from a parent self-replicating machine to an offspring self-replicating machine is a fundamental requirement of self-replication (von Neumann and Burks, 1966). Memory copying from one storage location to another is a fundamental capability in computing, e.g. memcpy in C. We assume arbitrarily that a copying head scans the original magnetic core memory array serially and/or in parallel to copy it onto an identical blank magnetic core memory array. It is important to note that biological template copying is of a different nature to artificial copying – in the dividing cell, the parent DNA unwinds in which both daughter cells each retain one original parent DNA strand from which to re-constitute the double strand. In effect, the parent no longer exists – during this process of replication, telomeres in both daughter cells are shortened. Any further replication cycles will undergo further shortening in offspring. In artificial self-replication, the parent and offspring are distinct entities. In order for analogous telomeres to act as counters, the parent telomere must be truncated as well as those of the offspring copies. We suggest that analogous to biological telomeres, a physical linear tail of blank memory cells feeds into the original to-be-read memory array, the number of cells corresponding to the maximum number of replications (Hayflick limit). For example, to limit the population of self-replicating machines to 1.5 million, the number of replications (generations) is limited to 13 (assuming two offspring per generation) by $P = (1 + r)^i$ where P = population, r = number of offspring/generation, i = generation number. However, two offspring per generation offers double the population growth rate over a single offspring – a population of 1.5 million requires 13 generations compared with 20–21 generations of single offspring. Greater than two offspring per generation offer diminishing returns in terms of rapidity – three offspring per generation requires over 10 generations to yield a population of 1.5 million. For Galactic colonization, 24 generations yield a population of 424 billion machines assuming two offspring per generation, i.e. the maximum number of offspring is constructed by the first generation of probes at 48.

Both parent and any offspring must exhibit telomeres that are reduced by $C_{i+1} = C_i$-1 – physical reduction provides greater robustness than logical reduction implying that a blank memory cell of the tail is physically removed as the initial step in self-replication of any offspring. This must be repeated for every subsequent generation of offspring manufactured by the original parent. The magnetic core memory array of each generation of offspring is copied from the parent in four stages applied *at each generation*: (i) parent tail counter is shortened by a single memory cell; (ii) a second counter controls the subsequent processes in determining the number of offspring per generation (nominally two); (iii) a blank hardware substrate is assembled including the reduced tail counter; (iv) data copying from parent memory to offspring memory. As each offspring inherits a reduced counter tail, subsequent offspring will generate further generations with telomeric tails in lockstep with the original parent. This system will be reliable for a single offspring every generation. The implementation of two offspring with identical counters per generation requires an additional counting loop to be incorporated such as a toggle switch. This introduces an additional mechanism and a concomitant greater chance of error including the prospect of uncontrolled replication if the additional counter malfunctions.

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This is exactly analogous to biological cancer in which telomerase genetic expression malfunctions leading to uncontrolled proliferation.

We can also implement computer viruses stored in magnetic core memory that are instantiated under undesirable conditions through physical interrupts to infect the neural network architectures such as if the outer counter exceeds two offspring per generation. Computer malware is a family of malicious computer programs that include spyware, ransomware, adware, rootkits, Trojan horses, worms and viruses. Computer viruses are executive software programs designed to interfere with computer operations that replicates itself through computer networks (Cohen, 1987; Denning, 1988). Unlike a worm which is an independent self-replicating program, it cannot exist independently of a host program. The Trojan horse part of the virus is the functional code that implements the payload of the virus by writing its own code into the host program. The payload may implement cyber-attacks such as physical attack on hardware devices and their drivers, e.g. SCADA; reconnaissance attacks searching for vulnerabilities through traffic analysis, denial-of-service, access attacks through network ports and privacy attacks. The virus is triggered as a logic bomb that activates it once an event or condition occurs. In our case, this event is the initiation of a third circuit around the number of offspring per generation loop. To minimize the size of the viral payload, the payload must cripple a crucial capability systematically. We decided to specifically attack the computational system.

Our computational system is based on analogue neural networks comprising networks of neuron modules based on a modified version of the Yamashita-Nakamura neuron (Yamashita and Nakamura, 2007; Prasad and Ellery, 2020). Specifically, the neural network architecture configurations of fixed (pre-trained) connection weights are stored in magnetic core memory. One relatively straightforward approach would be to initialize all stored connection weights to zero. This would then print all analogue neural network circuits with severed synaptic links to ensure that all computational circuits are defunct. However, metal whisker growth is a well-known but poorly understood phenomenon which can occur under a variety of environmental conditions which could potentially grow undesired conductive paths between the severed analogue neurons. Alternatively, a quine is a self-referencing program that copies its own code. It is implemented by a virus that modifies memory. The neural network quine is any neural network that learns to output its own weights on inputs defining the coordinates of the connection weight, i.e. self-replicating (Chang and Lipson, 2018). The loss function is defined as the difference between the weight and the predicted weight output: $L = \sum_i \lfloor y_i - w_i \rfloor^2$. Although it is possible for the self-replicating neural network to perform auxiliary tasks, this degrades its ability to self-replicate. Hence, training for self-replication will degrade the network's ability to perform other functions which is desirable. However, the network must not be input with predicted weight outputs as this would iteratively shrink the weights towards zero, i.e. severed connection links which introduces the aforementioned problem. Nevertheless, the implementation of a virus in magnetic memory that reconfigures all neural network weights to a quine configuration would effectively disable self-replicating machines' ability to procreate.

Conclusions

We have examined the biology of telomeres in implementing the Hayflick limit to biological cellular replication. Reliable imposition of a Hayflick limit will be essential in preventing uncontrolled replication of self-replicating machines. We propose a physical telomeric counter that is operational prior to the copying of genetic instructions that limits the generation number from a parent machine and any subsequent offspring. However, introducing the flexibility of multiple offspring per generation opens up the prospect of cancerous replication cycles. This illustrates the necessity for multiple layers of mechanisms to enhance reliability to prevent uncontrolled replication. A final safety layer would be a stored virus invoked under certain conditions such as replicating more than two offspring per generation that propagates through memory to initialize all neural network circuits with weights that output their own values, i.e. in effect, viral induction of brain cancer.

https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

Conflict of interest. There is no conflict of interest associated with this paper.

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https://doi.org/10.1017/S1473550422000246 Published online by Cambridge University Press

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