A constraints-based theory of senescence: imbalance of epigenetic and non-epigenetic information in histone crosstalk

Felipe A. Veloso *
Ronin Institute, Montclair, NJ 07043, USA
(Revision date: Sep 21, 2021)

Cellular aging has been progressively elucidated by science. However, the fundamental cause of senescence—i.e., why organisms age at the multicellular-individual level—remains unclear. A recent theory of individuated multicellularity describes the emergence and growth of crucial information content for cell differentiation. This information is mostly conveyed in the non-epigenetic (i.e., transcription uncorrelated) histone crosstalk near transcription start sites. According to this theory, the non-epigenetic content emerges and grows at the expense of the information capacity for epigenetic content. If this "reassignment" of information capacity continues after adulthood, it may explain the senescence phenomenon. Here, I present a novel, falsifiable theory describing an uninterrupted growth of capacity for non-epigenetic information at the expense of that for epigenetic information not only during ontogeny but also throughout adulthood. As a byproduct, this continuous "reassignment" of capacity effectively creates an information imbalance in histone crosstalk, which in turn overregulates transcriptional levels. This overregulation is to be understood as transcriptional levels becoming more and more accurate but also less and less precise with respect of the needs of the multicellular individual—up to the point of dysfunctionality. This epigenetic/non-epigenetic information imbalance is the fundamental reason why individuated multicellular organisms senesce.

Keywords: aging; ageing; teleodynamics; naked mole-rat; epigenetics; cancer

1. INTRODUCTION

1.1. Background

Our intellectual endeavors have entertained the prospect of unlimited lifespan for centuries[1], and the scientific endeavor has been no exception[2]. In the 1950s, the immortality of cultured somatic cells was indeed a widely-held belief[3]. That changed only when Hayflick & Moorhead showed that cultured human somatic cells do stop dividing and become less viable once their divisions reach a certain number[4], a phenomenon known today as the Hayflick limit[3]. This loss of replicative capacity and, in general, the process of aging at the cellular level, have been found to correlate with telomere length[3,5,6]. Yet, the number of times human cells can divide in culture exceeds the number of times cells divide throughout our lifespan; there is no significant correlation between human cell replicative capacity and cell donor age[7]. That is, we—and individuated multicellular organisms in general—age before most of our cells do[8,9]. The outstanding question is why.

1.2. Senescence's accepted ultimate cause: a critique

Senescence is widely regarded as an evolutionary consequence of the relaxation of selection on traits that maintain/repair the multicellular individual's functions in later life, because later life would have been rarely realized in the wild with the hazards it imposes[10–12]. Yet, any well-established ultimate cause of senescence must seamlessly integrate with the proximate cause of senescence—i.e., the specific process or mechanism eliciting senescence in multicellular individuals—which itself remains unclear.

Notwithstanding, efforts have been made to develop an explanatory account of senescence that integrates relaxed selection as its ultimate cause with a suggested proximate cause.

The first is the explanatory account dubbed as "disposable soma". This account states that somatic maintenance requires an amount of resources that are often very limited and thus require trade-offs between the components of maintenance (growth, reproduction, and self-repair) in order to maximize evolutionary fitness[13,14]. Here the proximal cause is not fully described but it entails the accumulation of damage over time (somehow leading to senescence) when insufficient resources are spent on self-repair. According to this account, an individual will spend the minimal amount of resources sufficient to reach sexual maturity, after which its soma becomes disposable[13,14].

A number of objections have been raised, such as the fact that variations in reproduction and lifespan are not always associated—as they should be, according to the disposable soma account[15]. Among mammals, naked mole-rats exemplify that reproductive and non-reproductive individuals can display similar maximum lifespans, i.e., no observable association[16].

Recapitulating, it is safe to observe that (i) the proximate cause of senescence is fundamentally unclear (e.g., we remain ignorant of why species such as ours senesce while a few others such as the naked mole-rat display negligible senescence) and, for this very reason,

* Correspondence: veloso.felipe.a@gmail.com

(ii) relaxed selection being the ultimate cause of senescence should not be, at least up to now, accepted as a well-established scientific fact.

1.3. Alternative proximate causes

Other proposed proximate causes of senescence or aging at the multicellular-individual level have been classified into two categories: programmed senescence and senescence caused by damage/error[17]. Recently it has been argued, however, that senescence is not programmed nor is it ultimately a consequence of damage or error in the organism's structure/dynamics[18]. Instead, it may be a byproduct of maintenance and/or developmental dynamics[18,19], themselves underpinned in part by intracellular signaling pathways such as the cell-cycle-related PI3K/AKT/mTOR pathway[18]. Some of these pathways have been shown to modulate aging at the cellular level in species such as the yeast *Saccharomyces cerevisiae*[20].

The analogous notion of aging at the multicellular-individual level as a byproduct of certain functional signaling pathways[18] is, in principle, supported by the fact that a mutation in the *daf-2* gene—which encodes the insuline-like growth factor 1 receptor in the PI 3-kinase pathway—and the deficiency of mTOR kinase—a key component of the PI3K/AKT/mTOR pathway—can double the lifespan of the roundworm *Caenorhabditis elegans*[21,22]. The hypotheses where senescence is the effect of a runaway activity of processes useful in young age that have become harmful in old age have been dubbed "bloated soma" hypotheses[23].

Alas, the fundamental dynamics that make individuated multicellular organisms senescent after adulthood remain unclear and largely lack falsifiable scientific descriptions.

1.4. Towards a constraints-based theory of senescence

Here, I suggest that senescence is a dysfunctional byproduct of functional developmental dynamics as first described by a recently proposed theory of individuated multicellularity[24]. Specifically, I show that the byproduct is a post-ontogenetic, growing imbalance between two different information contents conveyed respectively in two different types of constraints on histone post-translational modifications near transcription start sites (TSSs). Constraints are here understood as the local and level-of-scale specific thermodynamic boundary conditions required for energy to be released as work as described by Atkins[25]. The concept of constraint is crucial because, according to the theory of individuated multicellularity, a higher-order constraint (i.e., a constraint on constraints) on changes in histone modifications harnesses critical work that regulates transcriptional changes for cell differentiation at the multicellular-individual level.

Under the theory of individuated multicellularity, the intrinsic higher-order constraint is the simplest multicellular individual in fundamental terms. In addition, the dynamics of the lower-order constraints must be explicitly unrelated to each other[68] (i.e., statistically independent) in order to elicit the emergence of the intrinsic higher-order constraint. Along with the emergence of this intrinsic higher-order constraint, the theory of individuated multicellularity describes the emergence of critical information content, named in the theory hologenic content, which is about the multicellular individual as a whole in terms of developmental self-regulation. Thus, for the sake of brevity, I here refer to the theory of individuated multicellularity as the hologenic theory.

The constraints on the combinatorial patterns of histone post-translational modifications (PTMs) are generally known as histone crosstalk[27,28]. Histone modifications are also known to be relevant for epigenetic changes[29], which are defined as changes in gene expression that cannot be explained by (i.e., that are explicitly unrelated to) changes in the DNA sequence[30]. Moreover, specific histone modifications are known to be associated with senescence[31] (and references therein). These associations are underpinned by the capacity of histone modifications to convey information content, which has allowed the prediction of mRNA levels from histone modification profiles near TSSs with high accuracy[32].

Based on these considerations and the properties of the nonnegative measure of multivariate statistical association known as total correlation[33] or multiinformation[34] (symbolized by C and typically measured in bits), the overall observable histone crosstalk can be decomposed. That is, histone crosstalk, if measured as a total correlation C, is the sum of two explicitly unrelated C components: one epigenetic (i.e., explicitly related to changes in gene expression) and the other non-epigenetic (i.e., explicitly unrelated to changes in gene expression). This sum can be expressed as follows:

$$\underbrace{C(X_1,\ldots,X_n)}_{\substack{\text{Overall histone crosstalk}\\ \text{(total correlation}\\ \text{of } X_1,\ldots,X_n)}} = \underbrace{C_Y(X_1,\ldots,X_n,Y)}_{\substack{\text{Epigenetic histone crosstalk}\\ \text{(total correlation of } X_1,\ldots,X_n\\ \text{that is explicitly related to } Y),\\ \text{depends on DNA-nucleosome}\\ \text{interactions, and conveys}\\ \text{epigenetic information content}}} + \underbrace{C(X_1,\ldots,X_n|Y)}_{\substack{\text{Non-epigenetic histone crosstalk}\\ \text{(total correlation of } X_1,\ldots,X_n\\ \text{that is explicitly unrelated to } Y),\\ \text{depends on protein/RNA-nucleosome}\\ \text{interactions, and conveys}\\ \text{hologenic information content}}}, \tag{1}$$

where $X_1,\ldots,X_n$ are random variables representing n histone modification levels in specific genomic positions with respect to the TSS and Y is a random variable representing either gene expression level, transcription rate, or mRNA abundance level associated with the TSS. These levels are equivalent for the decomposition because of the strong correlation that exists between them[35] (and references therein).

The hologenic theory describes how the epigenetic component of histone crosstalk (represented by $C_Y(X_1,\ldots,X_n,Y)$ in the sum decomposition of Eq. 1)

conveys information about each cell's transcriptional profile. This component is, in information content terms, the dominating component for any eukaryotic colonial species—such as the alga *Volvox carteri*[36]—and, importantly, also for undifferentiated stem cells.

The second, non-epigenetic component of histone crosstalk (represented by $C(X_1, \ldots, X_n|Y)$ in Eq. 1) is known to grow in magnitude during development until the organism's mature form is reached[24]. This component is described by the hologenic theory as conveying information about the multicellular individual as a whole—starting from the moment said individual emerges as an intrinsic higher-order constraint on the early embryo's proliferating cells.

Importantly, the overall observable histone crosstalk magnitude (represented by $C(X_1, \ldots, X_n)$ in Eq. 1) is not infinite. In other words, the overall histone crosstalk has a finite information capacity, which can be measured in bits. Moreover, the sum decomposition in Eq. 1 implies that the growth in magnitude (bits) of the hologenic (i.e., non-epigenetic) component must be accompanied by a decrease in magnitude of the epigenetic component. That is, the capacity (in bits) for hologenic information content in histone crosstalk is bound to grow at the expense of the capacity for epigenetic information content.

The hologenic theory also maintains that a necessary condition for the evolution of individuated multicellular lineages was the appearance of a class of molecules synthesized by the cells—called Nanney's extracellular propagators (symbolized by $F_{\vec{N}}$) in the theory[24]. These $F_{\vec{N}}$ molecules are predicted to be, in a given tissue and time period, (i) secretable into the extracellular space, (ii) once secreted, capable of eliciting a significant incremental change (via signal transduction) in the magnitude of the non-epigenetic histone crosstalk (i.e., the $C(X_1, \ldots, X_n|Y)$ summand in Eq. 1) within other cells' nuclei, and (iii) affected in their extracellular diffusion dynamics by the geometrical complexity of the extracellular space (i.e., constraints on diffusion at the multicellular-individual level, which cannot be reduced to constraints at the cellular level). Also under the hologenic theory, for the multicellular individual to develop and survive, both hologenic (developmental self-regulation of the multicellular individual overall) and epigenetic (each cell's transcriptional profile) contents must coexist.

One final but important consideration regarding histone crosstalk is that it is the result of constraints which, as mentioned previously, are level-of-scale specific. To exemplify this specificity, consider an internal combustion engine: a single molecule in a cylinder wall or the entire engine do not embody a constraint on the expansion of the igniting gas, yet the cylinder-piston ensemble does. For this reason, histone crosstalk constraints are expected to have relevance for senescence but only at a specific level of scale.

To investigate from a theoretical standpoint if the "reassignment" of information capacity for epigenetic and non-epigenetic (i.e., hologenic) content stops when development reaches the multicellular individual's mature form or instead continues without interruption, one also needs to investigate the "reassignment" (if any) in cancer cells. One of the corollaries of the hologenic theory is a significant loss of hologenic content in cancer cells, because they are no longer constrained by the multicellular individual that normal (i.e., non-cancerous) cells serve and are constrained by. Thus, I developed a falsifiable theory of senescence based on the post-ontogenetic continuation of this "reassignment" process in histone crosstalk.

1.5. How to measure histone crosstalk

Publicly available high-throughput data of histone H3 modifications—because of their high predictive power on transcriptional levels[32]—and mRNA abundance in primary cells can be used to formalize a theoretical description to the senescence phenomenon.

Using these tandem ChIP-seq and RNA-seq data, one can quantify the epigenetic and non-epigenetic (i.e., hologenic) capacities in the crosstalk within a core histone such as the H3 histone (Eq. 1) for some specific level of scale, e.g., for triads of variables $\{X_i, X_j, X_k\}$. These variables represented position-specific histone H3 modification levels, i.e., $C(X_i, X_j, X_k|Y)$ and $C_Y(X_i, X_j, X_k, Y)$ for the non-epigenetic and epigenetic histone crosstalk components, respectively, where Y represents mRNA abundance.

The log-ratio between the non-epigenetic and epigenetic histone H3 crosstalk magnitudes can be thus computed as the dimensionless quantity

$$\log_b \left[\frac{C(X_i, X_j, X_k|Y)}{C_Y(X_i, X_j, X_k, Y)} \right]. \tag{2}$$

Importantly, total correlation C captures all possible associations in the set of (in this example, three) variables $\{X_i, X_j, X_k\}$ that may exist starting from the pairwise level. When b=2 the information capacity represented by total correlation C is measured in bits.

2. A CONSTRAINTS-BASED THEORY OF SENESCENCE

2.1. Characterizing the information capacity "reassignment" in histone crosstalk

At some level of scale—without loss of generality we will assume such level comprises up to triads of variables—for normal primary somatic cells there is a positive and highly significant correlation between the hologenic/epigenetic log-ratio quantity in Eq. 2 and the age of the multicellular individual the primary cells were collected from:

$$\mathrm{Cor}\left(\log_b \left[\frac{C(X_i, X_j, X_k|Y)}{C_Y(X_i, X_j, X_k, Y)} \right]_{\text{normal}}, \, age \right) > 0. \tag{3}$$

On the other hand, at the same level of scale the positive correlation in Eq. 3 exists, for cancer cells the correlation between the hologenic/epigenetic log-ratio in Eq. 2 and the age of the multicellular individual is not statistically significant:

$$\mathrm{Cor}\left(\log_b\left[\frac{C(X_i,X_j,X_k|Y)}{C_Y(X_i,X_j,X_k,Y)}\right]_{\text{cancer}},\ age\right)=0. \quad (4)$$

2.2. The fundamental cause of senescence

Under the falsifiable theory presented here, senescence is to be understood as a dysfunctional byproduct of developmental dynamics: Given that the "reassignment" process for information capacity in histone crosstalk—i.e., a progressive gain of capacity for hologenic information content at the expense of that for epigenetic content—continues without interruption throughout the multicellular individual's lifespan, a growing and ultimately lethal information content imbalance is created in the cells' nuclei. Importantly, this "reassignment" process is underpinned by constraints on the extracellular diffusion of $F_N^{\rightarrow}$ molecules, and the constraints are embodied only at the multicellular-individual level. That is, in histone crosstalk there is a time-correlated loss of capacity for epigenetic information (i.e., less and less epigenetic constraints on histone crosstalk), which causes a global and progressive impairment of biological functions at the multicellular-individual level, eventually causing the death of the individual.

The nature of the epigenetic constraints on histone crosstalk strongly implicates this time-correlated loss of capacity for epigenetic information content (and concurrent gain of that for hologenic content) as the fundamental cause of senescence. Epigenetic constraints are explicitly related to transcriptional/gene expression changes and represented by the $C_Y(X_1,\ldots,X_n,Y)$ summand in Eq. 1. Because they depend on the interactions between the histone-modified nucleosomes and the DNA wrapped around them—allowing or preventing transcription—the epigenetic information content they embody allows precise mRNA (and, ultimately, gene expression) levels from histone modification patterns.

2.3. Senescence as transcriptional overregulation

This age-correlated hologenic/epigenetic information imbalance in histone crosstalk can also be understood in terms of an imbalance between the accuracy and precision of transcription in the cells with respect to the needs of the multicellular individual. That is, more accuracy (i.e., closeness of the mean mRNA level to the mean level functional for the multicellular individual) is reached with age at the expense of precision (i.e., closeness of the resulting mRNA levels from the same pattern of histone modifications) thereby overregulating transcription. This trade-off is unavoidable because (i) the relative growth of $C(X_1,\ldots,X_n|Y)$ implies an increasing constraint on (i.e., regulation of) histone modification patterns with respect to the multicellular individual[24], thus making transcription more accurate and (ii) the concurrent relative decrease of $C_Y(X_1,\ldots,X_n,Y)$ means histone modification patterns become worse and worse predictors of mRNA levels, in turn making transcription less and less precise up to the point of dysfunctionality with respect to the multicellular individual (see schematic in Fig. 1a). Importantly, this theoretical description parsimoniously explains the age-dependent decrease in transcriptional precision—also referred to as increased "transcriptional noise"—observable in different tissues[37–43].

Thus, we can regard senescence under this theory as a global transcriptional overregulation with respect to the multicellular individual's needs—as opposed to cancer, where the dysfunctional effect is typically characterized in terms of the dysregulation of transcription and gene expression[44,45]. Importantly, this global transcriptional overregulation is to be understood under this theory as senescence itself and not as its fundamental cause, which is the previously described epigenetic/non-epigenetic information imbalance in histone crosstalk.

2.4. Senescence's proximate cause

The proximate cause of senescence—i.e., how senescence occurs after a multicellular individual reaches its adult form—according to the theory presented here is described in the following steps:

- the histone H1 protein constrains the accessibility of critical histone-modifying enzymes and chromatin remodeling factors to the nucleosome[46,47]
- the histone H1 variants that accumulate in somatic, terminally differentiated cells are H1.0 (H1 histone family, member 0; also known as H1°, H1(0), H5, H1δ, or RI H1) and, in vertebrates, also H1x (H1 histone family, member X; also known as H1.10)[48,49]
- variants H1.0 and H1x would undergo post-translational modifications in their three DNA-binding α-helical regions
- these PTMs to H1.0 and H1x histones—in particular Lys acetylation and Ser/Thr phosphorylation—would accumulate, in net terms, throughout adulthood
- the immediate effect of these PTMs would be a decrease in the net electric charge of the DNA-binding regions, i.e., rendering their net electric charge less positive, in turn diminishing the DNA-binding affinity of these regions

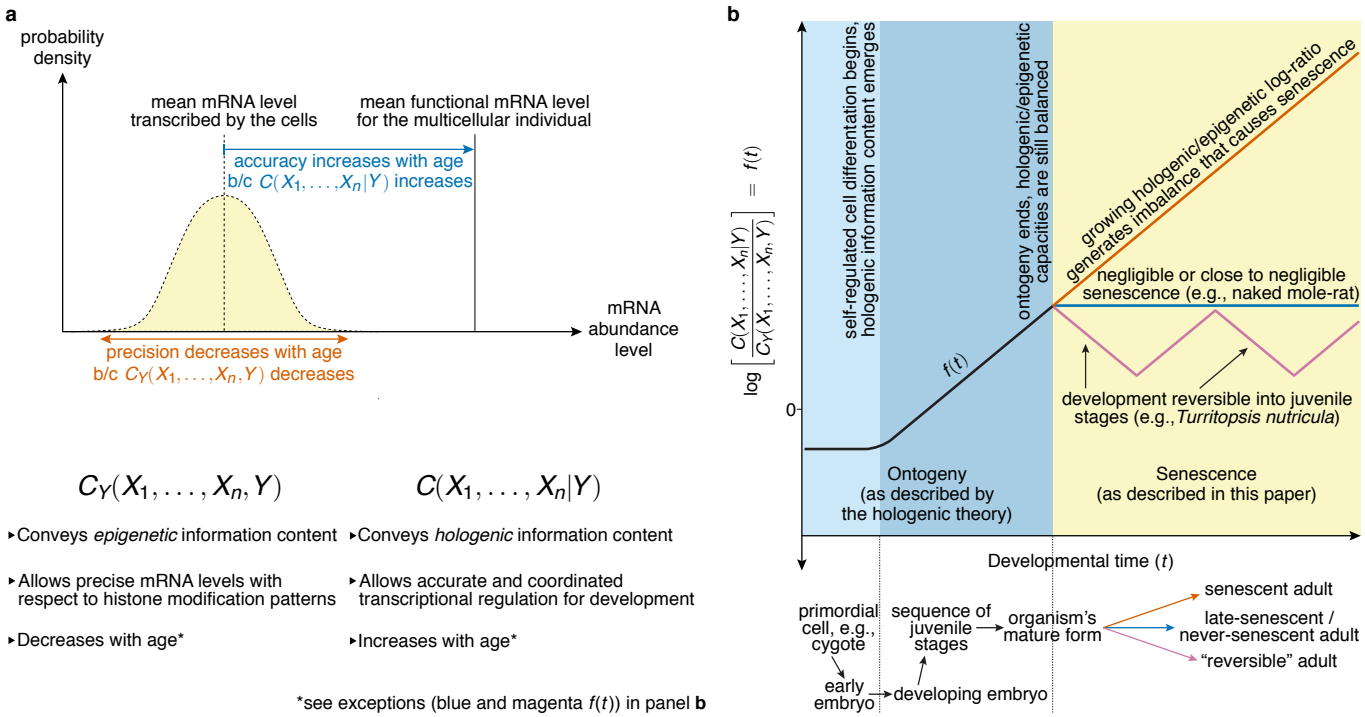

Fig. 1. Schematic of the imbalance between information capacity for hologenic content and epigenetic content in TSS-adjacent histone modification crosstalk as the cause of senescence. (a) The age-correlated increase in $C(X_1,\ldots,X_n|Y)$ and concurrent decrease in $C_Y(X_1,\ldots,X_n,Y)$ overregulates the transcription of any given gene with respect to the multicellular individual's needs, i.e., the transcription of the gene becomes more and more accurate (blue) but less and less precise (orange) up to the point of dysfunctionality. This unavoidable trade-off is explained by histone modification patterns becoming more constrained by regulation at the multicellular-individual level while at the same time becoming worse predictors of mRNA levels. The specific critical level of histone modification crosstalk (i.e., the value of n in $\{X_1,\ldots,X_n\}$) at which this phenomenon occurs may vary across taxa. (b) The log-ratio of non-epigenetic to epigenetic histone crosstalk magnitude increases during development as the embryo grows (black $f(t)$ in darker blue area). After the organism reaches its mature form (yellow area), the log-ratio continues to increase (orange $f(t)$)—with a few notable exceptions (blue and magenta $f(t)$). This continuous increase in turn creates an increasing dysfunctional imbalance of information contents that translates into senescence and, eventually, into death.

- in most species this decrease in net electric charge would be quite drastic—sometimes even resulting in a locally negative net electric charge—making the residence time of H1.0 and H1x histones in their respective DNA binding site significantly shorter
- this progressively shorter residence time would underpin the imbalance of constraints described previously, with the core nucleosomal histones (H2A, H2B, H3, and H4) becoming unable to modulate transcriptional levels as they usually do. In other words, H2A, H2B, H3, and H4 PTMs become worse and worse predictors of transcriptional levels—in non-senescent tissue their predictive power is very high ($R \sim 0.9$)[12]
- transcription then becomes less and less precise—or "noisier"—up to the point of dysfunctionality
- as described previously, this dysfunctional and ever-increasing loss of transcriptional precision is senescence itself, which eventually leads to the multicellular individual's death

2.5. Senescence's ultimate cause

The theory presented in this paper proposes an alternative ultimate cause. Senescence at the multicellular-individual level is, I suggest, not the result of relaxed selection but instead an intrinsic developmental byproduct that would have been already observable theoretically in the emergence of the very first individuated multicellular organisms as described by the hologenic theory[24]. In other words, had the first individuated multicellular organisms been free from any extrinsic hazard in the wild, they would have begun to senesce significantly after reaching a mature form in their development, as opposed to displaying extremely slow or negligible senescence as can be inferred from the relaxed-selection ultimate cause hypothesis.

2.6. Disposable soma or bloated soma?

The theory of senescence presented here may be regarded as a "bloated soma" theory, in the sense that it describes senescence as a dysfunctional byproduct of developmental dynamics, which are not only useful but indeed crucial in early age.

2.7. Falsifiability

Falsifiability will be met by the following experimentally testable prediction, which follows directly from the theory of senescence presented here:

> In any individuated multicellular species and with the random variables $X_1, \ldots, X_n$ representing n histone modification levels in specific genomic positions with respect to the TSS and the random variable Y representing the per-TSS mRNA abundance in a given (fixed) cell type there will be a level of scale $n \leq 4$ such that the following correlation will be both positive and statistically significant:
>
> $$\mathrm{Cor}\left(\log_b\left[\frac{C(X_1,\ldots,X_n|Y)}{C_Y(X_1,\ldots,X_n,Y)}\right],\ age\right) > 0; \qquad (5)$$
>
> with $b > 0$ and the variable *age* representing the age of the multicellular indivudual where the respective primary cells for each tandem ChIP-seq and RNA-seq essay where obtained from. Moreover, since hologenic information content is described as emerging locally and independently in each developmental process[24], the statistical strength of this predicted positive correlation will be further increased—and underpinned by a monotonically increasing function—if all primary cell samples are obtained from the same tissue of the same individual throughout its lifespan.

The notable exceptions to be made for this main prediction are a few species able to undergo reverse developmental processes from adult to juvenile stages. One such species is the jellyfish *Turritopsis nutricula*[50], which is predicted to display an analogous negative correlation in the processes, i.e., "reassignment" in reverse. Another exception for the predictions are species displaying extremely slow or potentially negligible senescence processes[51]. Examples of these are the bristlecone pine *Pinus longaeva*[52], the freshwater polyp *Hydra vulgaris*[53], and the naked mole-rat *Heterocephalus glaber*[54], which, after adulthood, are predicted to display a significant but very weak positive correlation (in cases where senescence is extremely slow), or an hologenic/epigenetic log-ratio invariant with age (i.e., no correlation in cases where senescence is truly negligible; Fig. 1b).

2.8. Can senescence be stopped?

Any theory of senescence is bound to address the question of whether aging at the multicellular-individual level can be artificially stopped. The answer suggested here is that achieving a dynamical arrest of senescence is not a fundamental impossibility but it could well entail a therapeutic safety issue. From a fundamental point of view, methods could be developed to, for example, artificially stabilize the constraints on nucleosome-DNA interactions (thus increasing the capacity for epigenetic information content in histone crosstalk at the expense of that for hologenic content).

Yet, the hologenic theory also predicts that a significant loss of hologenic content is a necessary condition for the onset of cancer. If this is correct, the potential safety problem arises: also under hologenic theory, the *in vivo* balance between hologenic and epigenetic information content is predictably "fine-tuned" as it is individual-specific, cell-type-specific, and also confined to small functional ranges. Thus, there could be an inherent high risk of greatly increasing cancer incidence with a poorly tuned attempt to correct for the hologenic/epigenetic content imbalance. This problem resides in that hologenic constraints, whose growth in magnitude has senescence as a byproduct, are the very constraints preventing an otherwise likely onset of cancer[24].

Based on a mathematical model of intercellular competition, Nelson and Masel have argued that stopping senescence, even if possible, will always elicit the onset of cancer and that senescence is ultimately inevitable[55]. Nevertheless, the existence of individuated multicellular species such the bristlecone pine[52], the freshwater polyp[53], and the naked mole-rat[54] suggests that senescence can be negligible in some cases, however exceptional.

2.9. Age-related cancer as a "pushback" against senescence

The delicate balance between hologenic and epigenetic information described here may shed light on the well-known positive correlation between cancer incidence and age[56]: if the senescent multicellular individual attempts to correct its growing hologenic/epigenetic content imbalance too strongly, it may elicit the onset of cancer. Thus, age-related cancer would be the result of a poorly tuned yet strong enough "pushback" from the multicellular individual against its own senescence. Although the specific dynamics that would underpin the "pushback" are beyond the scope of this paper, this hypothesis is indeed falsifiable by means of the following secondary prediction: the observed log-ratio of non-epigenetic to epigenetic histone crosstalk magnitude in the normal (i.e., non-cancerous) cells closest to an age-related stage I malignant tumor will be significantly lower than said log-ratio observed in the

other (i.e., tumor-nonadjacent) normal cells of the same tissue. (Note: The falsification of this secondary prediction does not imply the falsification of the theory as a whole.)

In turn, the "pushback"-against-senescence hypothesis for age-related cancer has, if correct, an implication we should not overlook. Namely, stopping senescence accurately and eliminating the incidence of age-related cancer should be one and the same technical challenge. In this respect, it is worth noting that in the naked mole-rat both senescence[54] and cancer incidence[57,58] have been described as negligible or close to negligible.

Rozhok and DeGregori have recently highlighted the explanatory limitations[59] of the Armitage-Doll multistage model of carcinogenesis, which regards the accumulation of genetic mutations as the cause of age-related cancer[60]. They further argued that age-related cancer should rather be understood as a function of senescence-related processes[59]. However, their description of age-related cancer is based on Darwinian processes and thus differ from the account suggested here, which can be understood within the concept of teleodynamics[61,62]—a framework of biological individuality based on the emergence of intrinsic higher-order constraints, such as that described in the hologenic theory[24].

If the main prediction resists falsification attempts consistently, further research will be needed to elucidate the specific molecular structures and dynamics embodying hologenic and epigenetic constraints comprehensively.

3. HOW CAN SENESCENCE BE STOPPED?

If senescence is indeed fundamentally caused by an age-dependent information content imbalance in histone crosstalk as proposed here, that fact alone will provide a plausible basis for preventing the imbalance itself.

In an upcoming paper I will specifically address the question of how—from a theoretical standpoint—to confer resistance to both senescence and age-related cancer.

ABBREVIATIONS

H1.0/H1°/H1(0)/H5/H1δ/RI H1: H1 histone family, member 0; H1x/H.10: H1 histone family, member X; PTMs: post-translational modifications; TSSs: transcription start sites.

COMPETING INTERESTS

This author declares that no competing interests exist.

ACKNOWLEDGEMENTS

I wish to thank Angelika H. Hofmann at SciWri Services for editing this paper into an English I could only hope to write. I would also like to express my gratitude to Amy Brock for her valuable comments.

Appendix A: Shannon measures of statistical uncertainty and statistical association

Shannon measures of statistical uncertainty and statistical association are suggested to be used in order to quantify histone crosstalk at TSSs and its relationship with mRNA levels.

Statistical uncertainty

C.E. Shannon's seminal work, among other things, introduced the notion of—and a measure for—the uncertainty about discrete random variables[63]. For a discrete random variable X with probability mass function $P(X)$ its uncertainty (also known as Shannon entropy) is defined as

$$H(X) := -\sum_{x \in X} P(x) \log_b[P(x)], \tag{A1}$$

where $P(x)$ is the probability of $X{=}x$ and b is the logarithm base. When $b{=}2$, the unit for this measure is the bit. $H(X)$ can also be interpreted as the amount of information necessary to resolve the uncertainty about the outcome of X. Shannon uncertainty was the measure used to estimate the uncertainty about the mRNA abundance level to be resolved in normal cells.

$H(X)$ is typically called marginal uncertainty because it involves only one random variable. In a multivariate scenario, the measure $H(X_1, \ldots, X_n)$ is called the joint uncertainty of the set of discrete random variables $\{X_1, \ldots, X_n\}$, and it is analogously defined as

$$H(X_1, \ldots, X_n) := -\sum_{x \in X_1} \cdots \sum_{x \in X_n} P(x_1, \ldots, x_n) \log_b[P(x_1, \ldots, x_n)]. \tag{A2}$$

Another measure important to this work is the conditional uncertainty about a discrete random variable Y, with probability mass function $P(Y)$, given that the value of another discrete random variable X is known. This conditional uncertainty $H(Y|X)$ can be expressed as

$$H(Y|X) = -\sum_{x \in X} \sum_{y \in Y} P(x, y) \log_b \left[\frac{P(x)}{P(x, y)} \right], \tag{A3}$$

where $P(x, y)$ is the joint probability of $X{=}x$ and $Y{=}y$. Importantly, any measure of Shannon uncertainty (or any other derived Shannon measure) that is conditional on a random variable X can also be understood as said measure being explicitly unrelated to, or statistically independent from, the variable X.

Statistical association

A classic Shannon measure of statistical association of any two discrete random variables X and Y is that of mutual information I, defined as

$$I(X;Y) := -\sum_{x\in X}\sum_{y\in Y} P(x,y)\log_b\left[\frac{P(x,y)}{P(x)P(y)}\right] \quad \text{(A4)}$$

$$= H(X) + H(Y) - H(X,Y) \quad \text{(A5)}$$

$$= H(Y) - H(Y|X). \quad \text{(A6)}$$

Note that if and only if X and Y are statistically independent then $I(X;Y)$=0, $H(X,Y)$=$H(X)$+$H(Y)$, and $H(Y|X)$=$H(Y)$. To analyze the magnitude of histone H3 crosstalk at TSSs, the two best known multivariate generalizations of mutual information were used in this work. The first is interaction information[64] or co-information[65], also symbolized by I, which is defined analogously to Eq. A2 for a set V of n discrete random variables as

$$I(V) := \sum_{U\subseteq V}(-1)^{|U|+1}H(U), \quad \text{(A7)}$$

where $|U|$ is the cardinality (in this case, the number of random variables) of the subset U. In the case of interaction information I, Shannon uncertainty H is thus summed over all subsets of V (the uncertainty of the empty subset is $H(\varnothing) = 0$). Importantly, the interaction information of the random variables $\{X_1,\ldots,X_n\}$ can be decomposed with respect to another random variable Y as follows:

$$I(X_1;\ldots;X_n) = I(X_1;\ldots;X_n;Y) + I(X_1;\ldots;X_n|Y). \quad \text{(A8)}$$

Interaction information $I(X_1;\ldots;X_n)$ captures the statistical association of all variables $\{X_1,\ldots,X_n\}$ taken at once, i.e., excluding all lower-order associations, and it can also take negative values in some cases. Interaction information was used in this work as a means to compute total correlation values.

To specifically quantify the magnitude of histone crosstalk, the second multivariate generalization of mutual information I suggest to be used is total correlation[33] (symbolized by C) or multiinformation[34], which is defined as

$$C(X_1,\ldots,X_n) := \left[\sum_{i=1}^{n} H(X_i)\right] - H(X_1,\ldots,X_n), \quad \text{(A9)}$$

i.e., as the sum of the marginal uncertainties of the random variables $\{X_1,\ldots,X_n\}$ minus their joint uncertainty. Importantly, and unlike interaction information I, total correlation C captures all possible statistical associations including lower-order associations or, equivalently, all possible associations between any two or more random variables in the set $\{X_1,\ldots,X_n\}$. This is because the definition of interaction information I in Eq. A7 allows total correlation C to be rewritten as a sum of quantities I for all possible combinations of variables in $\{X_1,\ldots,X_n\}$:

$$C(X_1,\ldots,X_n) = \sum_{i,j} I(X_i;X_j) + \sum_{i,j,k} I(X_i;X_j;X_k) + \ldots + I(X_1;\ldots;X_n). \quad \text{(A10)}$$

This expression for total correlation C as a sum of interaction information quantities I along with the sum decomposition of I in Eq. A8 allows C to be decomposed also as a sum:

$$C(X_1,\ldots,X_n) = C_Y(X_1,\ldots,X_n,Y) + C(X_1,\ldots,X_n|Y), \quad \text{(A11)}$$

where $C_Y(X_1,\ldots,X_n,Y)$ is the sum (analogous to that of Eq. A10) of all interaction information quantities I but now including the random variable Y in each combination of variables in $\{X_1,\ldots,X_n\}$, i.e.,

$$C_Y(X_1,\ldots,X_n,Y) = \sum_{i,j} I(X_i;X_j;Y) + \sum_{i,j,k} I(X_i;X_j;X_k;Y) + \ldots + I(X_1;\ldots;X_n;Y), \quad \text{(A12)}$$

and where $C(X_1,\ldots,X_n|Y)$ is the sum of all conditional interaction information quantities I given Y for each combination of variables in $\{X_1,\ldots,X_n\}$, i.e.,

$$C(X_1,\ldots,X_n|Y) = \sum_{i,j} I(X_i;X_j|Y) + \sum_{i,j,k} I(X_i;X_j;X_k|Y) + \ldots + I(X_1;\ldots;X_n|Y). \quad \text{(A13)}$$

For this work's purposes, total correlation C is proposed as an appropriate measure of statistical association to assess TSS-adjacent histone crosstalk because (i) C is non-negative and thus easier to interpret conceptually, (ii) C is equal to zero if and only if all random variables it comprises are statistically independent, (iii) C captures all possible associations up to a given number of variables (in this work, position-specific histone modification levels) and, (iv) C can be decomposed, as shown in Eq. A11, as a sum of two C quantities: one explicitly related to a certain variable Y and the other explicitly unrelated to Y. Property (iv) was useful to decompose the overall histone crosstalk as a sum of an epigenetic and other non-epigenetic component (Eq. 1).

An additional Shannon measure of statistical association can be used to assess the predictive power of TSS-adjacent histone modification levels on mRNA abundance levels (such power has already been used to predict mRNA levels with high accuracy[32]). The uncertainty coefficient U[66] is defined as

$$U(Y|X_1,\ldots,X_n) := \frac{H(Y) - H(Y|X_1,\ldots,X_n)}{H(Y)}, \quad \text{(A14)}$$

i.e., $U(Y|X_1,\ldots,X_n)$ is the relative decrease in uncertainty about Y when $\{X_1,\ldots,X_n\}$ are known—or, equivalently, the fraction of bits in Y that can be predicted by $\{X_1,\ldots,X_n\}$—and it can take values from 0 to 1. $U(Y|X_1,\ldots,X_n)$=0 implies the set $\{X_1,\ldots,X_n\}$ has no predictive power on Y, whereas $U(Y|X_1,\ldots,X_n)$=1 implies $\{X_1,\ldots,X_n\}$ can predict Y completely.

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