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Biological constraint as a cause of aging

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Abstract

Aging rate differs greatly between species, indicating that the process of senescence is largely genetically determined. Senescence evolves in part due to antagonistic pleiotropy (AP), where selection favors gene variants that increase fitness earlier in life but promote pathology later. Identifying the biological mechanisms by which AP causes senescence is key to understanding the endogenous causes of aging and its attendant diseases. Here we argue that the frequent occurrence of AP as a property of genes reflects the presence of constraint in the biological systems that they specify. This arises particularly because the functionally interconnected nature of biological systems constrains the simultaneous optimization of coupled traits (interconnection constraints), or because individual traits cannot evolve (impossibility constraints). We present an account of aging that integrates AP and biological constraint with recent programmatic aging concepts, including costly programs, quasi-programs, hyperfunction and hypofunction. We argue that AP mechanisms of costly programs and triggered quasi-programs are consequences of constraint, in which costs resulting from hyperfunction or hypofunction cause senescent pathology. Impossibility constraint can also cause hypofunction independently of AP. We also describe how AP corresponds to Stephen Jay Gould's constraint-based concept of evolutionary spandrels, and argue that pathologies arising from AP are bad spandrels. Biological constraint is a missing link between ultimate and proximate causes of senescence, including diseases of aging. That this was not realized previously may reflect a combination of hyperadaptationism among evolutionary biologists, and the erroneous assumption by biogerontologists that molecular damage accumulation is the principal primary cause of aging.

Keywords: aging, antagonistic pleiotropy, biological constraint, hyperfunction, hypofunction, programmatic aging, trade-off

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1. Introduction

Among animal species, lifespans vary over several orders of magnitude from adult mayflies living a mere few days to *Arctica islandica* clams living up to half a millennium (Butler et al., 2013). Thus, the process of senescence (not to be confused with *cellular senescence*, sensu Hayflick) is largely genetically determined, and a feature of the normal phenome as specified by the wild-type genome. In humans, senescence, including the manifold diseases of aging, is also influenced by diverse environmental factors that are relatively well understood. By contrast, far less is known about how the main causes of senescence arising from wild-type biological function lead to development of cardiovascular disease, cancer, chronic obstructive pulmonary disease (COPD), Alzheimer's disease, osteoarthritis and the very numerous other evils that beset us in old age.

Our understanding of many human diseases, and the treatments based on that understanding, follow from the premise that disease results from disruptions of normal function from such factors as infectious pathogens, mechanical injury, poor nutrition, toxin exposure, and gene mutation (somatic, inherited). But the main, primary cause of senescence is

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something quite different: it is the process of evolution. Diseases of aging are to a large extent evolutionary diseases, arising from evolutionary mechanisms that shape wild-type function (Brüne and Schiefenhövel, 2019; Nesse and Williams, 1994).

Aging and its many diseases evolve not because they provide any benefit but, principally, because the force of selection against gene variants with harmful effects later in life declines with increasing age (Hamilton, 1966; Medawar, 1952). Many genes are pleiotropic, affecting multiple traits, and some show antagonistic pleiotropy (AP), i.e. in different ways both improving and impairing biological function, and fitness (Paaby and Rockman, 2013). AP genes with beneficial effects earlier in life, but pathogenic effects later can be favored by selection, thereby promoting the evolution of senescence (Williams, 1957). The role of AP in aging is now well established, and there are many examples of pleiotropic genes with benefits early in life that promote diseases of aging, including cancer, cardiovascular disease, COPD and Alzheimer's disease (Supplementary Table 1) (Austad and Hoffman, 2018; Byars and Voskarides, 2020; Carter and Nguyen, 2011; Zhao and Promislow, 2019). What is largely missing, and necessary to understand the causes of aging and its many diseases, is an account of the proximate mechanisms determined by genes that exhibit AP. While we understand the evolutionary (ultimate) causes of senescence, these proximate biological mechanisms of aging remain poorly defined.

In this article we explore the role of biological constraint in the evolution of aging. This topic has in the past been relatively neglected, possibly because the extent to which the characteristics of organisms are adaptive has tended to be over-estimated, relative to the determinative effects of biological constraint (Gould and Lewontin, 1979) and historicity (phylogenetic legacy) (Nesse and Williams, 1994; Williams, 1992). Our exploration is aided by the recent emergence of several principles of programmatic aging, including run-on-type and triggered quasi-programs, costly programs, hyperfunction and hypofunction (Blagosklonny, 2006; Gems et al., 2021; Kern and Gems, 2022; Maklakov and Chapman, 2019) (described below, and see Glossary). It is also supported by an expansion of the typology of biological constraint, to include interconnection constraint, impossibility constraint, clock constraint, mixed constraint, molecular constraint, multiplex constraint, sexual dimorphism constraint, and asynchronous and synchronous constraint. Such conceptual developments have enabled us to define several categories of ultimate-proximate mechanism involved in aging. These include AP arising from interconnection constraints (causing pathogenic costly programs and triggered quasi-programs); and AP-independent determinants arising from impossibility constraints (causing pathogenic hypofunction). This article builds upon an earlier account of AP in the context of programmatic theories of aging (Gems, 2022).

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1.1 Defining antagonistic pleiotropy

Before considering the proximate mechanisms involved, a clear definition of AP is required. AP can occur when a given gene has both beneficial and detrimental effects on evolutionary fitness, function or health (Paaby and Rockman, 2013). Considered from the perspective of the evolution of aging, the term AP is often used to refer to a benefit earlier in life and a detriment in later life. But AP effects of genes can occur in many ways, in terms of the different contexts in which benefits and detriments are manifested (Figure 1).

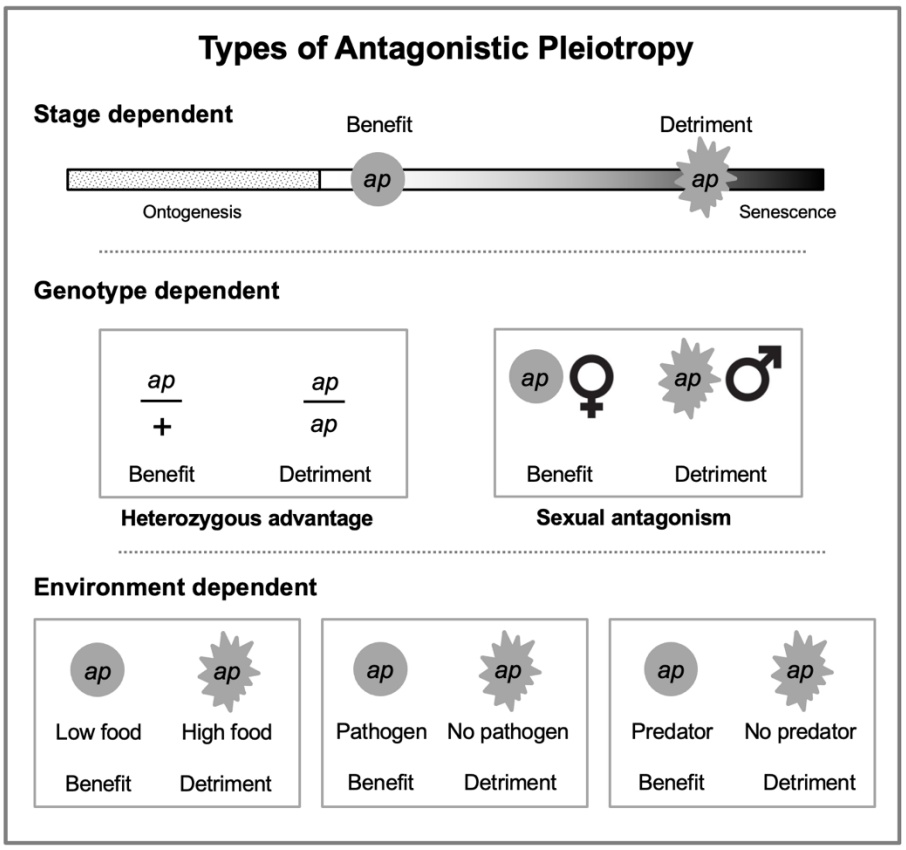

Figure 1. Some of the different forms of antagonistic pleiotropy. AP effects of a gene (allele), *ap*. Top, stage-dependent AP, as proposed by the evolutionary theory of aging. But detriments and benefits may occur at any point in the life history, including the same stage, and also at different locations (cell types, tissues, organs). Middle, genotype-dependent AP. Heterozygous advantage (overdominance) and sexual antagonism (intra-locus sexual conflict) are two examples, but there are others. Bottom, environment-dependent AP. This includes pathologies arising from mismatch between current and former environments where return to the former environment is possible. Selected examples shown; in all contexts apart from heterozygous advantage, the benefit and detriment may be reversed.

Benefits and detriments can occur at different points in the life history of an individual, as in *ORL1* (lectin-like low-density lipoprotein receptor 1) alleles that promotes immune defense but also cardiovascular disease (Predazzi et al., 2013); or they can also occur simultaneously as in *AR* (androgen receptor) alleles that reduce risk of breast cancer but increase that of ovarian cancer (Levine and Boyd, 2001; Rebbeck et al., 1999). They can also occur in different individuals due to various sorts of difference in the genotypic or environmental context in which the gene is expressed. Genotypic differences include a difference in sex (i.e.

intra-locus sexual conflict, or sexual antagonism) (Gavrilets and Rice, 2006), and whether the allele is heterozygous or homozygous (usually heterozygous advantage, overdominance), as in sickle cell anemia. A gene may exert beneficial or detrimental effects depending on the environment in which it is active, and such factors as presence/absence of pathogens, parasites and predators, food availability, and ambient temperature. For example, mutations in tumor suppressor genes can provide benefits in extreme cold (e.g. by reducing apoptosis) but this also increases cancer risk (Voskarides, 2018; Voskarides, 2019).

Defining AP becomes more difficult when considering a species which experiences an environmental change, such that a formerly beneficial gene becomes detrimental or vice versa. This is particularly relevant to humans, where it is thought that a number of diseases are caused or exacerbated by mismatch between modern environments and our genotype, which evolved to match the very different world of our recent ancestors. For example, increased availability of calorie rich food contributes to hypertension and type 2 diabetes (Di Rienzo and Hudson, 2005) and improved hygiene to various inflammatory diseases (Rook, 2019; Zhang and Gems, 2021). In the case of a permanent change in environment, in which an allele becomes deleterious but not beneficial, it no longer exhibits AP. However, regarding human environmental mismatch diseases, in some parts of the developing world no such mismatch exists; moreover, the wise student of recent history will regard as unsafe any assumption that mismatched features of modernity (hygiene, high food availability) are now a permanent condition for our species. Thus, for humans at least, mismatch diseases involve AP.

2. By what proximate mechanisms does antagonistic pleiotropy lead to senescence?

The AP theory provides an account of how senescence evolves, and predicts that wild-type genes with AP effects cause senescence. What it does not provide is detail of the biological mechanisms (biochemical, cellular, endocrine) that actually cause aging. One possible mechanism is proposed by the disposable soma (DS) theory. This is based on the assumption that aging is the result of accumulated damage (particularly molecular damage) and insufficient activity of cellular maintenance processes (e.g. DNA repair, antioxidant defense). It argues that aging evolves as the result of trade-offs between resource investment into reproduction and somatic maintenance, where an optimal strategy entails levels of investment into somatic maintenance that are insufficient to prevent aging (Kirkwood, 2005; Kirkwood, 1977) (Figure 2A). The DS theory featured strongly in biogerontological thinking in the 1990s and 2000s, and remains influential, yet it seems likely that it is largely erroneous. Empirical support for it is still limited and some evidence clearly argues against it (Blagosklonny, 2007; Grandison et al., 2009; Piper et al., 2017; Speakman and Król, 2010; Zajitschek et al., 2019). Moreover, the theory is dependent on the damage-maintenance paradigm and, while molecular damage (particularly DNA damage) is certainly a major, primary

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causal mechanism in certain forms of senescent pathology (e.g. cancer), for many others, such as cardiovascular disease and type II diabetes this is far from clear (Blagosklonny, 2006; Blagosklonny, 2013; Gems and de la Guardia, 2013).

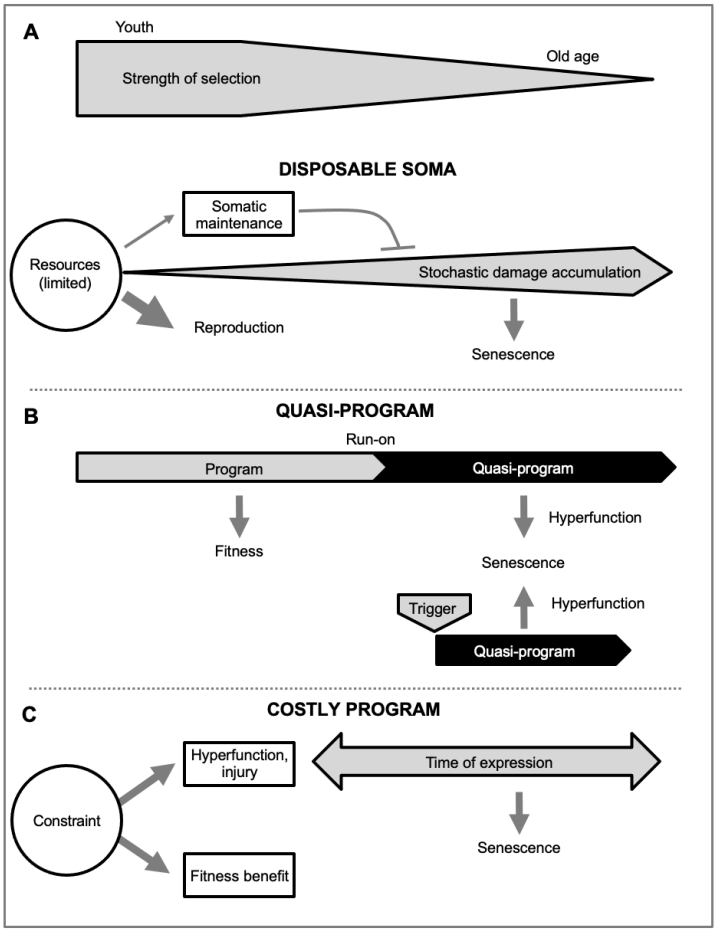

Figure 2. Alternative models for mechanisms by which antagonistic pleiotropy causes senescence. A, The disposable soma theory. Here senescence is caused by stochastic molecular damage accumulation, and the inadequacy of somatic maintenance mechanisms that could prevent it (Kirkwood, 1977). Constraint results from limited resource availability to optimize both reproduction and somatic maintenance. **B**, Quasi-programs. Here senescence results from non-adaptive continuation or activation of wild-type biological programs (Blagosklonny, 2006). Quasi-programs may occur due to futile run-on of wild-type programs (as in presbyopia), or they may be triggered by other events. The possible role of constraint in quasi-programs is discussed below. **C**, Costly programs. Here senescence results from hyperfunctional effects of programs that promote fitness, which arise due to organizational constraints. Timing of expression of injury as senescence varies; often it lies latent, and is unmasked later by wider senescence. The three models are not mutually exclusive. Costly programs are likely to be more important in semelparous organisms and quasi-programs in iteroparous ones (Gems et al., 2021). Disposable soma could in principle play a minor role in either.

2.1 Programmatic mechanisms of aging: quasi-programs and costly programs

If AP is not attributable to disposable soma, then what? George Williams, who developed the AP theory, gave relatively little thought to the question of the proximate mechanisms of AP. However he did suggest one hypothetical illustration. In it, a new allele appears that promotes fitness by enhancing calcification of bone during development, but in later life causes calcification of arteries, promoting arteriosclerosis (Williams, 1957). Senescence in this example arises due to non-adaptive, futile gene action later in life. Here

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senescence is programmed in the mechanistic sense (genetically determined, and involving concerted, wild-type biological activity), but not in the adaptive sense (Galimov et al., 2019). This highlights how the word “programmed” has two meanings (Mayr, 1961), whose conflation is wont to cause confusion. To avoid this, the disambiguation *quasi-programmed* was introduced (Blagosklonny, 2006). The term *quasi-program* describes a complex, non-adaptive, development-like process arising from wild-type biological function (Figure 2B). In Williams’ hypothetical example, a program for calcification of bone later becomes a quasi-program for vascular calcification. Recent advances in aging theory, drawing on experimental findings over the last two decades, have been exploring the possible role of programmatic mechanisms such as quasi-programs in the wild-type aging process (Blagosklonny, 2006; de Magalhães and Church, 2005; Gems, 2022; Gems and de la Guardia, 2013; Maklakov and Chapman, 2019).

It was long assumed that senescence arises due to a largely passive process of damage accumulation, analogous to that affecting inanimate objects such as machines. By contrast, the pathogenic effects of quasi-programs result from the *action* of biological processes, what has been described as *hyperfunction* (Blagosklonny, 2006; Gems, 2022). Hyperfunction describes a level of activity in a biological process that is higher than that which would result in optimal function and fitness, or an activity where it would be better if it were not there at all. Quasi-programs are hyperfunctional.

Quasi-programs may arise through the unregulated continuation or non-adaptive triggering of gene action later in life, and involve various forms of programmatic process (developmental, reproductive, reparative) (Blagosklonny, 2006; de Magalhães and Church, 2005; Gems, 2022). Support for the contribution of quasi-programs to senescence comes from laboratory animal-based experimental data and diverse examples of their involvement in human senescent pathology (Blagosklonny, 2006; Kern and Gems, 2022). As a simple example, presbyopia (long-sightedness with age) results from the futile run-on of eye lens growth resulting in excessive lens thickening (Strenk et al., 2005).

Another mode of programmatic aging involves costly programs, where a biological process that promotes fitness also incurs a cost. Such costs can result from various forms of hyperfunction. These include costly repurposing of somatic resources through active recycling of cellular biomass (Figure 2C). This occurs to a high degree in semelparous organisms such as monocarpic plants, but also more subtly in iteroparous ones, as in bone consumption to release calcium for lactation in mammals (Gems et al., 2021; Speakman, 2008). Costly programs also occur when defenses against an acute, potentially severe threat to health cause collateral injury to tissue, e.g. neutrophil migration which injures lung tissue, contributing to COPD (Sapey et al., 2014; Voynow and Shinbashi, 2021). This is analogous to the damage caused by the water from firefighters’ hoses (*firehose-type costly program*). A third form of costly program is enacted in social trade-offs, as in *adaptive death* (programmed organismal

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death, c.f. programmed cell death), a phenomenon largely restricted to organisms with a colonial lifestyle, such as colonial microbes (Galimov and Gems, 2021; Lohr et al., 2019). In adaptive death, altruistic suicide is a costly program to individuals that provides benefits at the higher, colony level; similarly, from the perspective of the dying cell, programmed cell death is a costly program that benefits the organism.

2.2 Hypofunction: genetically-determined deficiency that promotes senescence

The existence of a different sort of programmatic pathophysiology, unrelated to hyperfunction, has been proposed (de Magalhães and Church, 2005). At the end of ontogenesis or reproduction, some aspects of biology show a slow decline, for example plasma IGF-1 levels. This, it has been argued, could reflect a form of programmatic insufficiency (de Magalhães and Church, 2005), subsequently referred to as *hypofunction* (Maklakov and Chapman, 2019). While it is true that many facets of living organisms show a gradual decline with age, the concept of hypofunction is problematic in certain respects.

First, in some cases decline (such as atrophy, breakdown) is caused by active mechanisms, as where osteoporosis is caused by osteoclast hyperfunction, loss of tissue integrity due to “senescent” fibroblast hyperfunction (Campisi, 2013), or mTOR-promoted stem cell loss (Blagosklonny, 2008a). Thus, it can be difficult to distinguish between decline caused by hyperfunction from that where the initial cause is a lack of function. The collapse of protein folding homeostasis in young adults of the nematode *Caenorhabditis elegans* was suggested as a possible instance of hypofunction (Maklakov and Chapman, 2019). Yet this proteostatic collapse is actively promoted by germline signaling (Labbadia and Morimoto, 2015), and might serve either to unfetter protein synthetic capacity, consistent with AP, or possibly to promote fitness by causing adaptive death (Lohr et al., 2019). In either case, it is the product of active, programmatic function, rather than hypofunction. Second, in contrast to hyperfunction, the causes of evolution of hypofunction have remained relatively undefined, beyond being a consequence of evolutionary neglect due to the presence of the selection shadow in later life. Possible determinants of the evolution of hypofunction are described below.

3. AP and biological constraint

The claim that AP is important in the evolution of aging implies that many genes must exhibit AP. But why should so many genes have this property? The likely answer here lies in the existence of a high degree of biological constraint, arising from the highly integrated nature of biological systems (Gould, 1997; Gould and Lewontin, 1979; Mauro and Ghalambor, 2020) (Figure 3). As Stephen Jay Gould put it, when discussing the evolution of anatomy: “any adaptive change in a complex and integrated organism must engender an automatic (and often substantial) set of architectural byproducts” (Gould, 1997). This means that a new allele that

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alters one trait in a way that enhances fitness can easily affect other traits adversely. To use a simple example: for fundamental thermodynamic reasons increasing ATP production rate reduces ATP yield and vice versa (Pfeiffer et al., 2001). Therefore a mutation increasing ATP production rate will exhibit AP and reduce ATP yield; here ATP yield is traded off against production rate. This illustrates how AP can arise not only from properties of the molecular biology of genes or their RNA or protein products, which tend to be the focus of accounts of pleiotropy (Hodgkin, 1998; Mauro and Ghalambor, 2020; Paaby and Rockman, 2013), but also from properties of the systems that those products impact.

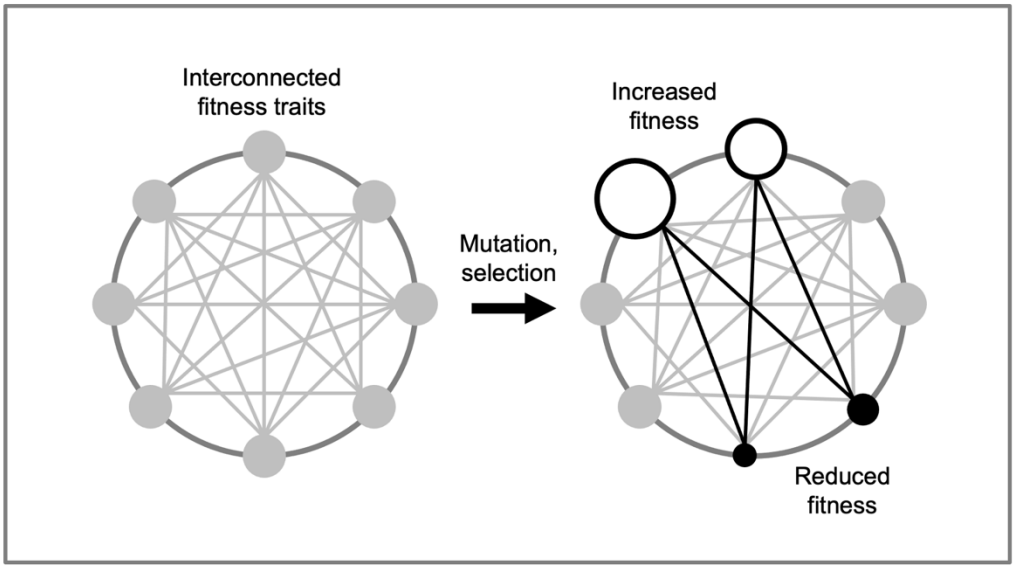

Figure 3. **Interconnection constraints.** The highly integrated nature of biological systems leads to organizational constraint (interconnection constraint). Top: Hypothetical example of interconnected traits (each trait represented as a circle). Here mutation followed by natural selection leads to a beneficial change in two traits (represented as increased circle size). This leads to non-adaptive, accompanying changes in two other traits that reduce fitness (reduced circle size).

3.1 A typology of biological constraint

Key to a full understanding of AP action, we suggest, is a clear account of the nature of biological constraint. A variety of different facets of biological constraint have been described in different ways (Antonovics and van Tienderen, 1991), and enumerating these is beyond the scope of this essay. However, a useful unifying scheme was recently proposed by Luis Acerenza, at the Universidad de la República (Montevideo, Uruguay) that gives a systematic overview of constraint, to which the following discussion owes a great deal (Acerenza, 2016).

According to Acerenza's scheme, two major forms of biological constraint are *selective constraints* and *organizational constraints*. Selective constraints result from ecological factors leading to different and conflicting forces of selection. As an example, males of the guppy *Poecilia reticulata* have brightly colored patches which attract females but also increase visibility to predators, such as pike cichlids (Endler, 1980). Here conflicting selection pressures act, usually on a single trait, to affect trait *presentation*.

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Organizational constraints affect trait *production.* They commonly arise from the interconnected nature of biological traits, as in our prior example of ATP production rate and yield where maximizing both traits is not possible. Constraints of this type, which for convenience we will refer to as *interconnection constraints*, are highly diverse and affect all levels of biological function, from the level of genome and biochemical pathway level, through the whole cell and organ level to the organismal and even population level. They can affect many facets of biology, including composition, kinetics, regulation and structure (Acerenza, 2016). As argued: “the mechanisms that cause senescence may not be mistakes but compromises carefully wrought by natural selection” (Nesse and Williams, 1994). The reason why compromise is necessary is the existence of organizational constraints involving interconnection.

A few illustrations follow. At the genome level the existence of genes within chromosomes means that if selection changes the frequency of an allele at a given locus, this will also affect the frequency of alleles to which it is linked (linkage disequilibrium). This can lead to genetic hitch-hiking, where selection for a beneficial allele can co-select linked alleles, including deleterious ones (Maynard Smith and Haigh, 1974). At the cellular process level, the evolution of enzyme function can be constrained in many ways, depending on whether a new reaction is catalyzed or, particularly, the same reaction with a different rate law (Acerenza, 2016). The complex topology of protein interaction networks is another potential constraint; in a study of budding yeast protein interaction networks, it was noted that proteins associated with aging have greater levels of connectivity, and are more pleiotropic (Promislow, 2004). An example at the organelle level is membrane leak, which in mitochondria leads to energy dissipation but also reduction of production of reactive oxygen species (Brand, 2000), which can cause molecular damage. At the whole cell level there exist protein occupancy constraints, due to the fact that a given cell volume or membrane space has a limit to the amount of protein that it can contain (Acerenza, 2016). This is expected to result in competing selection pressure on different classes of proteins; this might account for observed competition in *Escherichia coli* between expression of ribosomal proteins for growth, and stress response proteins for stress resistance (Nyström, 2004). Such competition results in growth vs survival trade-offs, and AP in genes that regulate such trade-offs.

Regarding constraints acting at the organismal level, there has historically been much discussion of developmental constraints that restrict the evolution of animal morphology (Arnold, 1992; Brakefield and Roskam, 2006; Maynard Smith et al., 1985). Here a major constraint is the highly complex and interconnected process of embryonic development, including pattern formation, morphogenesis and coordinated growth. This includes constraint due to action of given signaling components (e.g. hormones and growth factors, receptors, signaling kinases, transcription factors) in diverse contexts (*signaling constraint*) (Mauro and

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Ghalambor, 2020). But of particular interest in the present context are constraints affecting not just development to adulthood, but the entire life history, encompassing ontogenesis, maturational and reproductive development during adulthood, and senescence (discussed below). At the population level, organizational constraints are expected to occur in highly social species, such as eusocial insects and colonial microbes, leading to social trade-offs. For example there is some evidence that, due to the constraint of limited food availability, individual *C. elegans* constrain their reproduction in order to increase food availability for existing larvae better able to develop to the dispersal (dauer) stage before food depletion, thereby increasing colony fitness (Galimov and Gems, 2020; Galimov and Gems, 2021).

Acerenza's selective vs organizational constraint categorization corresponds to Richard Lewontin's conception of genotype and phenotype maps to connect genotype and phenotype (Lewontin, 1947). In Lewontin's scheme, the average genotype of a population can be viewed as a point in the space of all possible genotypes (G space), and the average phenotype of the same population as a corresponding point in the space of all possible phenotypes (P space). Selective constraints reduce the *accessible* P space, by limiting the persistence of phenotypic variants. While selective constraints do not alter the P space of all possible phenotypes, organizational constraints restrict the P space because they affect trait production.

3.2 Impossibility constraints

Acerenza also defines a second type of organizational constraint, using an enzymological example. If two molecules of ethanol are chemically combined to form a single molecule of n-butanol, energy is released. This means that an enzyme that catalyzed this synthesis would be an efficient means of n-butanol synthesis. Yet no such enzyme exists. Why not? The answer may lie in the fact that the number of reaction mechanisms underlying enzyme catalysis is limited (Acerenza, 2016; Bar-Even et al., 2012). Given the existing toolbox of enzymatic mechanisms, it is simply not *feasible* for enzymatic conversion of ethanol into butanol to evolve. By contrast, some characters may be feasible, but evolutionarily *unreachable*, as where genes are lost from a lineage (e.g. uricase in higher primates, which contributes to gout)(Kratzer et al., 2014). Such *impossibility constraints* are distinct from interconnection constraints, though both are organizational constraints. An major difference between them is that while interconnection constraints are expected to give rise to AP, impossibility constraints are not. However, functional defects resulting from both interconnection and impossibility constraints are programmatic in origin insofar as they are part of the wild-type phenome, specified by the wild-type genome. The hierarchy of the main forms of constraint is depicted in Figure 4.

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3.3 Mixed constraints

Trade-offs can arise due either to selective constraints or organizational constraints. They can also arise from a combination of the two - what we can term *mixed constraint* trade-offs. For example, considering the relationship between fertility and infection resistance, it has been suggested that immune defense not only increases resistance to infection but also the probability of spontaneous abortion (Westendorp, 2015). Given that half the genes in an embryo come from the father, they are foreign to the mother's immune system and, as a result, the embryo is vulnerable to immunological rejection. The constraint operative here is that on optimizing both fertility, an internal function, and resistance to infection, an external, environmental factor as much as the aforementioned guppy-eating pike cichlids.

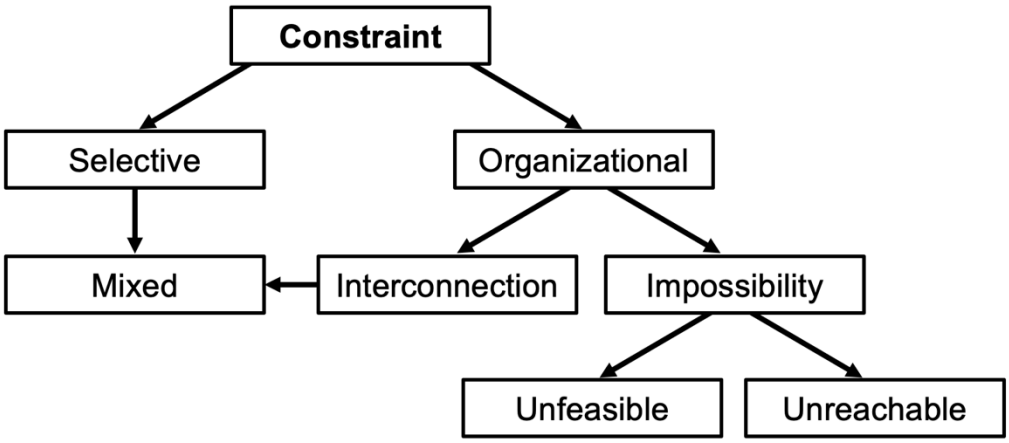

Figure 4. Hierarchy of major categories of biological constraint. Inspired by Acerenza (2016). Unreachability constraint includes phylogenetic constraint, in which the capacity to generate a particular phenotype has either not yet evolved or been lost (Sinervo and Svensson, 1998).

4. How constraint causes aging

This brings us to the main questions posed in this article. Are the AP mechanisms that contribute to senescence the result of biological constraint, and if so at what level(s) of organization? The type of trade-off by which AP is thought to promote aging is the life history trade-off, where mutations have a positive effect on fitness at one, earlier stage in the life history, but a negative effect at another, later stage (Acerenza, 2016; Sinervo and Svensson, 1998; Zera and Harshman, 2001). Yet what remains unclear is how constraint might lead to life history trade-offs, including senescent changes. The preceding discussion also raises a number of new questions. Biological constraint can generate AP, but where constraint leads to aging does this inevitably involve AP? And is AP always a consequence of constraint? Are quasi-programs a consequence of constraint? (We argue below that the answers here are, respectively, no, no and sometimes).

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4.1 How do constraints promote aging?

How might constraint give rise to AP in *programmatic* aging? A fundamental form of constraint giving rise to life history trait trade-offs is limited availability of resources (e.g. food); thus, different fitness components compete for available resources (Guillaume and Otto, 2012; King et al., 2010; van Noordwijk and de Jong, 1986). For example, in birds, increases in egg size or brood size can increase fitness, but both cannot be maximized simultaneously. (The disposable soma theory provides a potential account of how resource availability constraint could contribute to AP in *damage-maintenance* mechanisms of aging, as previously discussed (Kirkwood and Rose, 1991; Lemaître et al., 2015)).

One possibility is that such constraints involve differential resource allocation but of a different sort to the disposable soma theory. Costly programs are active at high levels in semelparous organisms that die as the result of suicidal reproductive effort, such as Pacific salmon and rice plants (Gems et al., 2021). Here, rapid senescence is due, at least in part, to breakdown of tissues and organs to provide resources for reproduction. This mechanism does involve a disposable soma of a kind, but not in the sense meant in Kirkwood's theory. The harm here is from active self destruction, rather than failure to invest in protection against damage. Such costly programs exemplify aging where AP results from interconnection constraint. It is not possible to maximize simultaneously both autophagic processes to support reproductive effort, and retention of somatic biomass.

The presence of a different type of programmatic constraint can be deduced from the existence of programmatic rate-of-living or methylation clock effects (de Magalhães, 2012; Gems, 2022; Raj and Horvath, 2020). At higher temperatures, fruit flies develop faster and reproduce sooner (benefit) but also senesce faster (cost). Thus, faster development is traded off against faster aging. Here the existence of the program (possibly running on into quasi-program) is itself a constraint; but critically, the operative constraint is that increasing play rate promotes both fitness and aging. In other words, the relationship between clock speed and temperature is fixed: there is a *clock speed constraint*. Clock speed constraint might also account for AP in the effects of growth pathway genes on development and programmatic aging. Growth promotion pathways increase both development rate, and aging rate, as reflected in increased tick rate of Horvath's methylation clock (Blagosklonny, 2018; Cole et al., 2017; Consortium, 2021; Petkovich et al., 2017; Wang et al., 2017).

4.2 Developmental constraint and quasi-programs

Returning to Williams' AP scenario of a Ca^{2+} deposition program that promotes bone growth but then vascular calcium deposition (Williams, 1957): does constraint play a role here? Here it would appear that, owing to the late-life selection shadow, the program of calcifying

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bone is simply left running with pathogenic consequences. Thus, one might conclude that constraint plays no role. By the same token, quasi-programs resulting from complex program run-on would seem not to involve biological constraint either.

Yet on closer inspection, the Ca^{2+} deposition gene can be seen to be subject to interconnection constraint of a sort not discussed hitherto. The aging process involves mechanisms shared with that of development (ontogenesis) (de Magalhães and Church, 2005; Gems, 2022; Maklakov and Chapman, 2019). Developmental processes are subject to constraint. Consider the example of the panda's thumb, where selection for evolution of an additional digit in the hand led to non-functional evolutionary changes in the equivalent bones of the foot (Gould, 1991). In this case, an interconnection constraint is operative, due to similar developmental processes determining morphology in hands and feet. Here the constraint, like that linking ATP production rate and ATP yield, acts at the same time (synchronously) on hand and foot development.

But the process of development involves traits that are separated in time as well as in space. This suggests that interconnection constraints are likely to exist between processes operative at different stages in ontogenesis, and perhaps in later, adult development. In other words, it is likely that there exist *asynchronous* as well as synchronous developmental constraints. This would be consistent with observed pleiotropic effects of genes at different stages in development. For example, in *C. elegans* the DAF-4 TGF-β/BMP receptor inhibits entry into dauer diapause early in larval development, and then directs male tail development in later larval stages (Estevez et al., 1993). In mammals, genes orchestrating development and morphogenesis act at multiple times in development and may therefore be subject to asynchronous developmental constraint. As an example, the morphogen sonic hedgehog (SHH) contributes to the development of deciduous (milk) and permanent teeth at different stages in development (Hosoya et al., 2020). Different possible ways in which interconnection constraint could contribute to the evolution of aging are summarized in Figure 5.

The existence of asynchronous developmental constraint, leading to trade-offs and AP, provides an interesting perspective for considering the possible evolutionary origins of quasi-programs. Here a sequence of developmental stages creates a series of distinct biological contexts in which a given biological function (e.g. gene action) impacts fitness. Returning to Williams' Ca^{2+} deposition gene, this suggests a scenario in which a context emerges in late life in which the increased activity of this gene is pathogenic. Here the Ca^{2+} deposition quasi-program is triggered, rather than being a consequence of run-on. This argues that asynchronous developmental constraint promotes evolution of triggered quasi-programs but not run-on-type quasi-programs.

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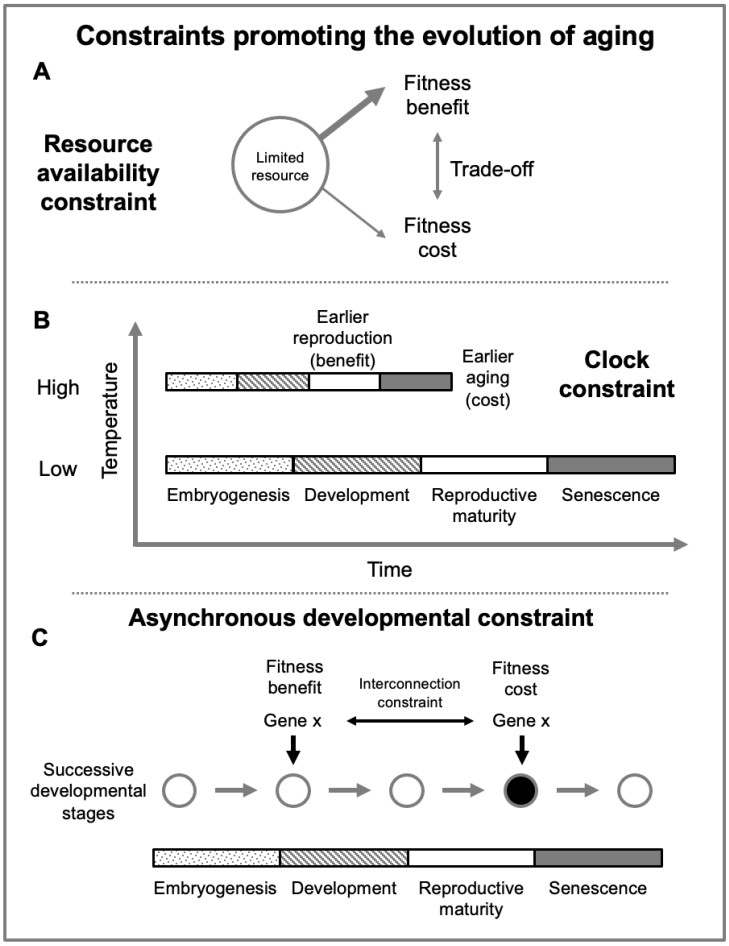

Figure 5. How constraint can cause programmatic senescence. **A**, Resource availability constraint, e.g. costly programs, disposable soma. **B**, Clock speed constraint, where rate of the entire development and aging process is altered e.g. by changes in ambient temperature (poikilotherms only), and perhaps altered growth regulators (e.g. GH, mTOR), and evolutionary change. The constraint is imposed by the necessary relationship between biological process rate determinants (e.g. temperature) and biological process rate. **C**, Asynchronous developmental constraint, where developmental effects of a process (e.g. gene action, such as Ca^{2+} deposition) provide a fitness benefit on an early developmental stage, but a fitness cost at a later stage. Dark fill denotes deleterious change.

According to this scenario (Figure 5C), during aging a context appears in which the Ca^{2+} deposition gene becomes pathogenic. Interconnection constraint prevents optimization of the Ca^{2+} deposition gene activity level in both contexts. A virtue of this account is that, as outlined above, triggered quasi-programs appear to play a greater role than run-on-type quasi-programs in the etiology of late-life diseases (Kern and Gems, 2022).

Viewing Williams' Ca^{2+} deposition gene parable in the light of the programmatic theory provides one further, rather striking perspective. He argued that a mechanism to suppress the pathogenic effect by switching the Ca^{2+} gene off in later life could in principle evolve, but this does not occur due to lack of late-life selection (Williams, 1957). Viewing development and aging as related phenomena: ontogenesis is a process of many corrections, where developmental trajectories are shaped by an orchestrated series of developmental-genetic adjustments to generate the final, adult phenome. Williams' missing off-switch suggests a

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scenario where diverse quasi-programs emerge due a deficiency of later developmental adjustments (Figure 6). This deficiency is a consequence of the selection shadow and asynchronous developmental constraint.

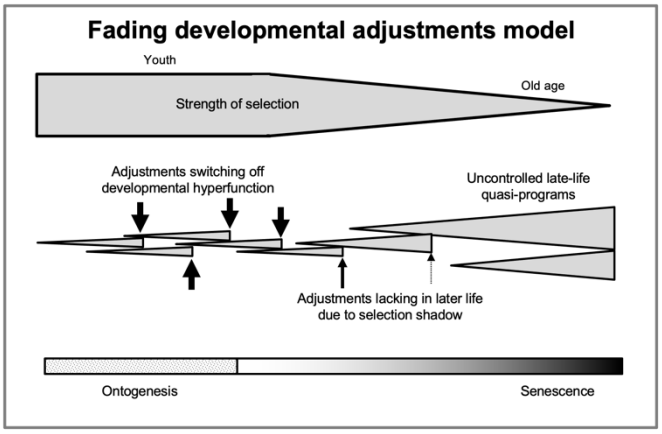

Figure 6. Fading developmental adjustments model. Hypothetical scheme. During ontogenesis, diverse mechanisms of programmatic adjustment prevent run-on of program into quasi-program, and shape normal development. In later life, due to the selection shadow, such adjustment mechanisms fade away. Cf the absent late-life off switch for Ca^{2+} deposition in Williams' hypothetical example (Williams, 1957). Developmental programs are depicted as triangles, with increased maximum triangle height (right) denoting quasi-programs.

A final point about asynchronous vs synchronous constraint is that while the former will generate trade-offs and AP that are asynchronous, the latter can generate asynchronous as well as synchronous ones. This is because costs may remain latent and only emerge to affect fitness later in life. For example, rapid pumping of the pharynx in young *C. elegans* adults optimizes food ingestion, but also causes mechanical damage to the pharyngeal cuticle. This increases susceptibility to infection that spreads later in life, probably due to wider organismal senescence, and increases mortality (Zhao et al., 2017).

4.3 Evolutionary origins of hypofunction

The term *hypofunction* was coined by Alexei Maklakov and Tracey Chapman to describe an inherent, programmatic insufficiency of function that contributes to senescence (Maklakov and Chapman, 2019). From the above account of biological constraint, it is possible to deduce two different ways in which hypofunction could evolve, the first involving interconnection constraint, and the second impossibility constraint.

Regarding interconnection constraint: if a given function produces a cost and a benefit, and selection to reduce the cost is greater than that to promote the benefit, a deficiency in the beneficial action will result, i.e. hypofunction. This can be illustrated by AP exhibited by the *AAT1* gene. This encodes α1-antitrypsin which inhibits neutrophil elastase. Migration of neutrophils to sites of infection in the lung causes tissue damage, including breakdown of elastin, which promotes COPD (Voynow and Shinbashi, 2021), and more so during aging (Sapey et al., 2014). The *AAT1* Z allele reduces AAT levels, which elevates elastase activity,

increases COPD risk but protects against myocardial infarction (Listì et al., 2007). It has been suggested that the latter occurs because neutrophil elastase breaks down elastic tissue in the arterial wall, altering the distensibility of the vessel wall in a way that reduces blood pressure and cardiac load (Dahl et al., 2003). Thus, the harm to cardiovascular health arising from wild-type *AAT1* is, according to the Dahl et al. hypothesis, deficiency in a corrective mechanism that would otherwise reduce hypertension, i.e. hypofunction.

That interconnection constraints can give rise to both hyperfunction and hypofunction is amply illustrated by a survey of examples of AP (Supplementary Table 1; Supplementary Discussion). For particular genes that exhibit AP, it is not uncommon for multiple different forms of AP to be present, involving distinct forms of constraint and programmatic mechanisms. That a given gene can be subject to such *multiplex constraint* is consistent with the highly integrated nature of biological systems, particularly in metazoa.

Regarding impossibility constraint: here, functional deficiency in later life occurs not as a cost linked to an earlier benefit, but because of inability of the function to evolve. As possible examples of hypofunction of this type, we offer the aging of elephants' teeth, and the human menopause. The jaws of elephants have on average one massive tooth (a molar) on each side. As these molars are worn down, they are replaced by new ones developing from the back of the jaw and moving horizontally forward (successional teeth). Elephants can live up to about 75 years, during which time each set of molars is replaced five times (Lee et al., 2012). Feeding in elephants surviving into their eighth decade is increasingly impaired as their last teeth wear down, leading to starvation and death (Finch, 1990).

But why in old elephants does odontogenesis stop? One possibility is weakened selection in late life, yet this seems unlikely given that some elephants in the wild die as the consequence of their inability to produce new teeth. During elephant evolution there occurred a switch from all adult teeth emerging at once to the molars appearing one at a time. Elephant longevity is promoted by their eking out one at a time their limited stock of premolars and molars. The occurrence of death from starvation due to tooth loss in elderly elephants suggests that the nature of the odontogenetic developmental program is an unsurmountable constraint to the evolution of further rounds of tooth replacement, i.e. an impossibility constraint.

Elderly elephants become toothless due to an odontogenetic program with a clear endpoint due to depletion of a limit resource (here tooth buds). This is analogous to a sand clock (hourglass), where the number of grains of sand is a determinant of the time at which the clock reaches its end. A similar sand clock-type depletion mechanism is operative in the human ovary, and contributes to the timing and onset of menopause. Menopause occurs due to depletion of oocyte stocks that form prior to birth; by contrast spermatogenesis continues throughout adulthood in males. This depletion is accelerated by a rapid age increases in the rate of follicular atresia, such that increasing initial oocyte stock size would be expected to

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delay menopause only marginally. Notably, females of other higher primates keep reproducing until nearly the end of their lives, and reproductive span in women is little different to those of chimpanzees; the age at last birth in female chimpanzees and women is 42 and 45, years respectively, though maximum lifespans are 53.4 and ~110 years, respectively (Robson and Wood, 2008). It has been argued that the human menopause evolved not because it promotes fitness in any way, but because as hominin longevity increased, production of a longer reproductive span in hominin females was simply not possible (Austad, 1994; Marlowe, 2000). Thus, menopause results from an impossibility constraint.

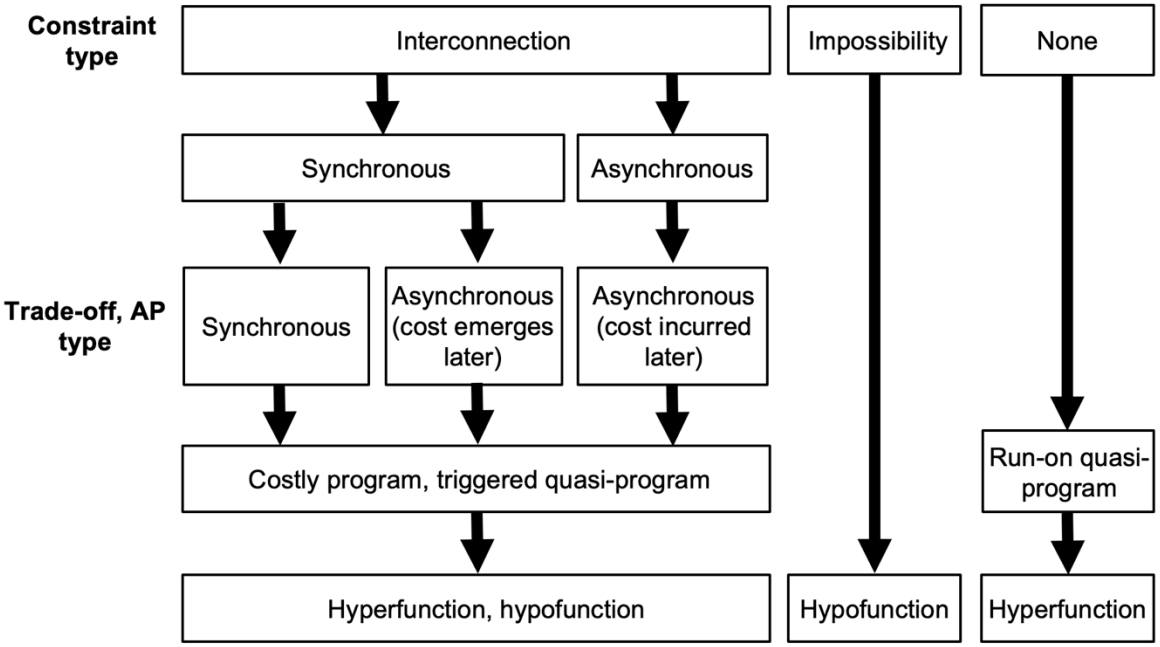

Figure 7. Biological constraint and programmatic mechanisms of aging. Simplified overview. The possibility that run-on-type quasi-programs can be a consequence of constraint may warrant further consideration.

In these examples, it can be seen that hypofunction is programmatic insofar as it is, in a broad sense, an outcome of the wild-type genome. Yet, in contrast to hyperfunction, it is not that wild-type gene function actively makes it happen. One can say that the presence of fins on a goldfish is a consequence of gene action, but one cannot say the same of their lack of wings. By the same token, phenotypic insufficiency caused by hypofunction is not the result of wild-type gene hyperfunction. The absence is, in a manner of speaking, a non-adaptive design feature.

An overview of how biological constraint can lead to distinct modes of programmatic aging is shown in Figure 7.

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5. Constraint, AP and aging in a wider context

5.1 AP and the spandrels of San Marco

A cogent discussion of the importance of biological constraint in evolution is Gould and Lewontin's well-known essay "The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist program" (Gould and Lewontin, 1979). This used an architectural analogy to explain how organizational constraint can lead to the generation of new traits. In architecture, a spandrel is the triangular space between the shoulders of adjoining arches and the ceiling above (Figure 8). Spandrels arise as a secondary consequence of the construction of adjoining arches, rather than from any from intention of the architect to create spandrels, due to geometric constraint. Similarly, due to the presence of organizational constraints, selection for new traits generates spandrel-like secondary changes.

Likely examples of evolutionary spandrels mentioned by Gould include the presence in mammals of nipples on males and the clitoris in females, the rudimentary thumb on the foot of pandas, the masculinized genitalia of female hyenas, the umbilicus of snails, and various miracles of human cognition (Gould, 1980; Gould, 1991; Gould, 1997). Male nipples and, seemingly, the clitoris are a consequence of what one may call *sexual dimorphism constraint*. This arises from the fact that males and females of a given species share a common embryogenetic process. Consequently trait changes in one sex can easily bleed through to the other (male nipples from the program for mammary gland development, and the clitoris from that of penis development). This constraint is important in the evolution of human aging; for example, human longevity likely evolved due to selection for increased late-life reproduction in men and, due to the sexual dimorphism constraint, is also present in women (Gems, 2014; Marlowe, 2000).

Let us return once more to ATP synthesis, and the relationship between organizational constraint and AP. As discussed, increasing ATP production rate reduces ATP yield and vice versa; thus, a new allele, favored by natural selection because it increases ATP production rate will also reduce ATP yield, thus exhibiting AP. Notably, the reduction in ATP yield is an evolutionary spandrel. In fact, in all examples of AP resulting from constraints, the cost coupled to the benefit arises from a spandrel. The depiction of interconnection constraints in Figure 3 for instance also includes spandrels. Antagonistic pleiotropy is the spandrel principle viewed through the lens of evolutionary genetics.

Regarding AP as a cause of aging, a notable difference to Gould's architectural analogy is that the selected and unselected traits are separated in time in the former and space in the latter. We postulate that the main form of constraint operative in the delayed onset spandrels through which AP causes aging is the asynchronous developmental constraint. According to this perspective, forms of senescence that arise from constraint (Figure 7), and the diseases

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that they cause, are noxious spandrels. Williams approved of the architectural analogy, defining a spandrel as "a structure arising as an incidental consequence of some evolutionary change" (Williams, 1992), yet seemingly did not register its relevance to AP. In his Ca^{2+} deposition gene example, the accumulation of Ca^{2+} in blood vessel walls is a bad spandrel (Figure 8, bottom). Late-life diseases arising from programmatic aging can be understood as bad spandrels (insofar as they arise from constraint). Osteoarthritis, COPD, prostate cancer, Parkinson's disease: plausibly these are all to an extent the spandrels of San Marco, but decorated with demons and skeletons rather than saints.

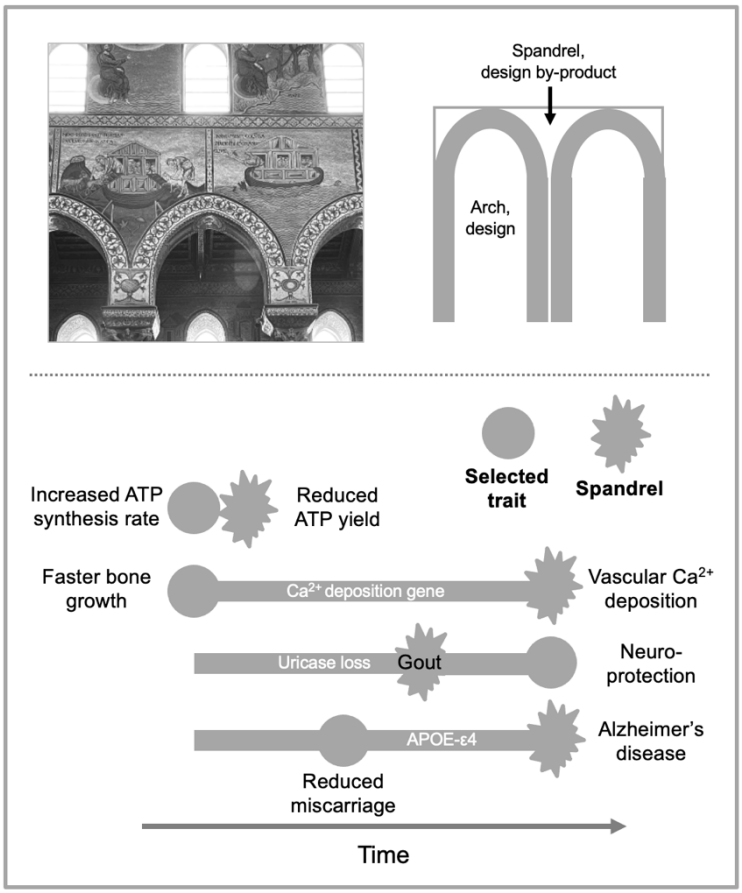

Figure 8. Constraint, AP and the spandrels of San Marco. Top, the spandrels concept. Left, decorated spandrels, similar to those under the dome of St. Mark's Basilica which triggered Stephen Jay Gould's reflections during a visit to Venice (Gould and Lewontin, 1979). The spandrels shown here are from Monreale Cathedral, Sicily, and bear depictions of the story of Noah's ark (photo, D. Gems). Right, a spandrel is the area between the tops of two adjoining arches. Here, the architect's purpose is to create two arches; the spandrel appears as an unintended consequence (cf. pleiotropy). Bottom, four possible examples of spandrels arising from biological constraint, involving AP, and varying in terms of relative timing of benefit and cost. First: ATP synthesis. Here increasing ATP synthesis rate synchronously reduces ATP yield (spandrel) due to interconnection constraint. Second, Williams' Ca^{2+} deposition gene example (Williams, 1957). Here a developmental change enhancing bone growth early in life promotes arteriosclerosis later in life (spandrel), due in principle to an asynchronous developmental constraint. Third, uricase gene loss. Here, uricase hypofunction is neuroprotective (Hong et al., 2015; Lu et al., 2016; Pakpoor et al., 2015; Weisskopf et al., 2007) but causes gout (spandrel) due to urate accumulation. Fourth, the *APOE4* allele reduces miscarriage (van Exel et al., 2017) but increases late-life disease, including Alzheimer's disease (spandrel). Notes that run-on quasi-programs may not be the product of constraint, yet as "incidental consequences of evolutionary change" they are spandrels.

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5.2 Constraint and programmatic damage

Recent discussions emphasizing the importance of programmatic mechanisms view the accumulation of molecular damage as a relatively minor determinant of the aging process, at least in terms of its primary causes (Blagosklonny, 2008b; de Magalhães and Church, 2005; Gems, 2022; Maklakov and Chapman, 2019). Accepting that molecular damage accumulation does contribute to aging to some extent, one may ask: what is the relationship between constraint, AP and programmatic mechanisms on the one hand and molecular damage accumulation on the other?

Considering this relationship allows three sources of molecular damage to be distinguished (Figure 9). First, molecular damage that is not the result of programmatic mechanisms, and is wholly stochastic in origin. This would include damage due to extrinsic stressors such as solar UV radiation or tobacco smoke. Second, molecular damage occurring when pathology leads to major loss of homeostasis, as in anoxia followed by reperfusion damage due to stroke (brain hemorrhage); such damage caused by (rather than causing) senescence is probably the main source of molecular damage occurring towards the end of life (Blagosklonny, 2008b). Third, molecular damage arising as a consequence of biological constraint. Some molecular damage can be understood as the consequence of wild-type processes, what Vladimir Dilman described as “regular stochastic processes” (Dilman, 1994).

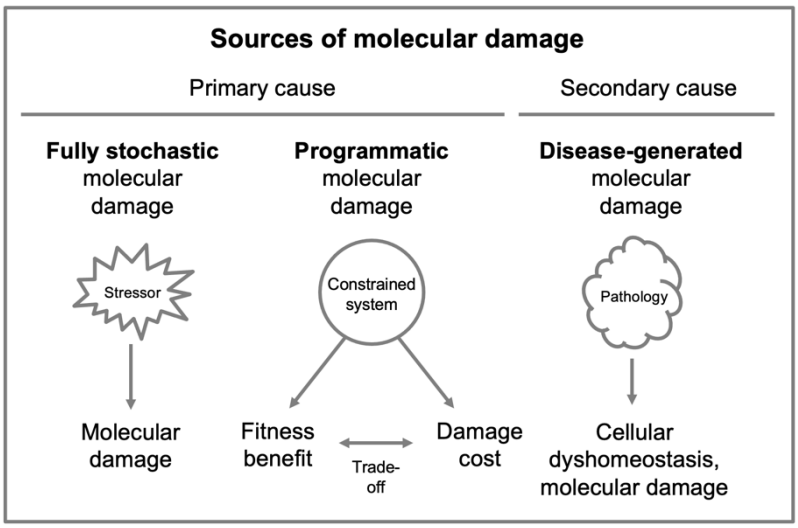

Figure 9. Programmatic molecular damage. Three sources of molecular damage accumulation that contribute to senescence. Left, fully stochastic damage, e.g. due to exposure to solar UV radiation or tobacco smoke. Center, molecular damage arising from constraint and AP, e.g. reduced end-to-end joining of chromosomes and reduced telomeric DNA repair, due to the shelterin complex (Fumagalli et al., 2012). Right, molecular damage caused by pathology arising from other causes, e.g. oxidation arising from reperfusion damage after stroke.

Regarding constraint: processes exist where it is impossible to set all fitness benefits to optimal, and fitness costs include molecular damage. This may be described as *programmatic molecular damage*. For example, during protein translation it is not possible to

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optimize both protein translation rate and translation fidelity (Conn and Qian, 2013). Potentially, increasing protein translation rate to support rapid growth may lead to increased levels of protein aggregation (i.e. molecular damage). This would exemplify programmatic molecular damage, arising from constraint, and trade-offs set by genes that would be expected to exhibit AP. It was recently reported that a mutation in the *Drosophila rps23* (small ribosomal subunit) gene improves translational accuracy and increases lifespan but reduces development rate (Martinez-Miguel et al., 2021); whether the increased lifespan is due to reduced protein aggregation is not known. Another example of programmatic molecular damage relates to ROS generated by NADPH oxidases (Nox and Duox enzymes) which serves various functions (e.g. in innate immunity, signal transduction, biochemical reactions) but contributes later to inflammaging and its various associated diseases (Lambeth, 2007).

Another example of programmatic molecular damage that may contribute to aging involves telomeres. Naked DNA at chromosomal ends is prone to end-to-end joining, leading to aneuploidy. This is prevented by the telomeric shelterin complex, including TRF2 (telomeric repeat binding factor 2). However, the presence of this complex also impedes DNA repair at telomeres, leading to increased DNA damage and telomere shortening (Fumagalli et al., 2012). Here an organizational constraint prevents simultaneous optimization of prevention of aneuploidy and telomeric DNA repair.

6. Final remarks

The development of the programmatic theory has, we believe, helped inch the aging field closer towards possession of an effective explanatory paradigm, something that it has lacked until now (Gems and de Magalhães, 2021). In this essay we have endeavored to build upon foundations created in particular by Williams, Blagosklonny and de Magalhães, to elaborate and extend this paradigm. In particular, we show how consideration of the role of constraint in the evolution of aging helps to make sense of programmatic mechanisms of aging. This creates a broader ultimate proximate account of the causes of aging, that includes an expanding family of programmatic mechanisms and a growing toolbox of new terminology (see Glossary), which we hope will be helpful in enabling new ways of thinking about programmatic aging. Supplementary Table 1 includes diverse examples of spandrels arising from constraint unconnected to known AP genes, and constraints to which neither spandrels or AP genes have been associated, as well as many actual examples of AP. Detailed discussion of selected examples is presented in the Supplementary Discussion. This includes several examples of constraint due to gene action differing between cell types; the manifold constraints arising from multicellularity may explain why programmatic senescence occurs more at the tissue level than the cellular and subcellular levels (Gems, 2022). That constraint arises from proximate mechanisms but shapes the evolutionary process also illustrates the limitations of Ernst Mayr's

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ultimate proximate dichotomy (Mayr, 1961; Sinervo and Svensson, 1998). Finally, our account raises two last questions, relating to wild-type function as a cause of disease, and why the key role of constraint in aging has not been appreciated previously.

6.1 Wild-type genes cause disease

As a broad approximation, diseases of aging result from two principal causes (Gems, 2022). First, disruptions of wild-type function, e.g. due to infectious pathogens, mechanical injury, mutation, malnutrition etc. Second, and more importantly, the wild-type genome, whose later, pathogenic action is ultimately caused by the process of evolution, including selection shadows and constraint, which gives rise to AP.

This binary scheme includes a distinction between genes that cause disease because they are mutant (disrupted, defective) and wild-type genes that cause disease due to AP. But do all genes that cause disease fall clearly into one of these two categories? Following this argument through to its logical conclusion, let us consider variation at the *Htt* (Huntingtin) locus. Here alleles with higher numbers of CAG repeats, leading to longer polyglutamine tracts, cause Huntington's disease (HD), a severe and fatal neurodegenerative disease with mid-life onset. *Htt* alleles that cause HD can also increase resistance to cancer (McNulty et al., 2018; Sorenson et al., 1999), perhaps due to increased expression of the pro-apoptotic tumor suppressor protein p53 (Eskenazi et al., 2007)(Supplemental Discussion). Thus *Htt* alleles that cause HD exhibit AP and should therefore be considered to be wild-type. Thus, though HD is a defining example of the principle of late-acting mutation accumulation as an evolutionary cause of aging (Haldane, 1941), it is in fact an example of AP.

As a second example, consider the F508del allele of *CFTR* (cystic fibrosis transmembrane conductance regulator) which when heterozygous promotes resistance to cholera infection (Gabriel et al., 1994; Meindl, 1987) but when homozygous causes cystic fibrosis. Thus, F508del is a wild-type allele that is disease-causing due to AP. Here, instead of providing early-life benefit and late-life disease, as in disease-causing *Htt* alleles, it benefits the heterozygote and causes disease in the homozygote.

While this view of disease-causing *Htt* and *CFTR* alleles might initially seem counterintuitive, it should be remembered that the more common *Htt* alleles increase cancer susceptibility, while those of *CFTR* increase cholera susceptibility: *they are also disease-causing alleles*. Moreover, AP at wild-type alleles is perhaps the main cause of late-life disease and death. However, most AP genes are undetectable, due to absence of alleles with different effects on the antagonistic traits. That AP genes where allelic variation exists often also exhibit overdominance (Table 1) is due to the inevitable balancing selection in such cases, as fitness is increased in the heterozygote and decreased in the homozygote. The impossibility of

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optimizing fitness in both the heterozygote and the homozygote represents a further form of constraint (*allele dosage constraint*).

6.2 AP and biological constraint: a blind spot in evolutionary theory

The idea that AP arises from biological constraint is not counterintuitive, and a puzzle to us was that it had not been explored previously by evolutionary biologists, George Williams for one. To explain this surprising oversight, we suggest two explanations. The first relates to Williams' own AP example involving the Ca^{2+} deposition gene (Williams, 1957) which, as we have argued, involves asynchronous constraint. By contrast, discussions of constraint usually involve synchronous constraint, as in the examples furnished by Acerenza. Perhaps for this reason Williams did not consider the role of constraint in AP in relation to aging.

As a second possible explanation, we suggest a hypothesis relating to the history of ideas about the evolution of aging. The role of developmental constraint in evolution for a time appears to have been the subject of a degree of suspicion among evolutionary biologists, particularly during the 1980s and 1990s (Harvey and Purvis, 1999; Harvey and Zammuto, 1985; Promislow, 1993; Williams, 1992). In some ways this period marked the culmination of a project to increase scientific rigor in evolutionary biology. For this emphasis was placed on the role of individual selection and adaptation in shaping evolutionary outcomes, and use of rigorous data- and mathematical modelling-based approaches. This endeavor was in part a reaction against mushy thinking in the field, for example facile just-so speculations about aging as "beneficial death" which Williams found so irritating (Williams, 1966). It led to something of a purge of ideas that were, or were taken to be, pre-Darwinian, including some relating to allometric relationships between size and other traits (Huxley, 1932). One target was the idea that constraining developmental mechanisms such as those determining animal bauplans (the generalized structure body plan of organisms in a major taxon) should lead to preferred directions of evolution. Such ideas carry a risk of conflation with pre-Darwinian ideas about orthogenesis, the view of evolution as a goal-driven process (Stevens, 2009), a teleological and mystical view of evolution that is anathema to evolutionary biologists, quite correctly.

While this dose of rigor was healthy for the field of evolutionary biology, it did have the effect of inhibiting discovery in some areas. One was the possibility of programmed adaptive death (altruistic suicide), which can evolve under certain conditions (Galimov and Gems, 2021; Lohr et al., 2019). Another, we suggest, was the importance in evolution of organizational constraint - which one might say was the baby thrown out with the allometric bathwater. The idea of bauplans as constraining evolution was scorned by Williams, who described it as "misguided and dispensable" (Williams, 1992). Yet the claim that developmental constraint is highly determinative in evolution is clearly correct (Gould, 1997; Gould and Lewontin, 1979).

These historical circumstances may explain the aversion to the notion that constraint shapes the evolution of aging: this sort of idea was, at the time, non U.

However, since the end of the scorched earth phase of evolutionary biology of the 1980s and 1990s, a new field of biology has emerged, that of evolutionary developmental biology (evo-devo), which studies how mechanisms of development and natural selection interact to produce evolutionary outcomes. The appearance of evo-devo has led to a shift from a strictly gene- and adaptation-focused perspective, grumpily referred to by Gould as hyperadaptationism (Gould, 1997), to a more multifactorial account of evolution (Brakefield, 2006; Stevens, 2009). It is perhaps worth noting the faint irony in hyperadaptationism acting as a constraint on advances in evolutionary understanding.

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Glossary

Adaptive death: Synonymous with programmed organismal death. Here death of an individual is a selected trait, providing a direct benefit in terms of inclusive or group fitness (Lohr et al., 2019).

Allele dosage constraint (new term): Where it is not possible to simultaneously optimize the effect of a given allele in both the homozygous and heterozygous state. This give rise to overdominance (heterozygous advantage).

Antagonistic pleiotropy *(AP)*: Where action of a given gene is both beneficial and detrimental to fitness. If the latter occurs later in life and is therefore subject to weaker selection, such a gene may be favored by natural selection, and promote aging (Williams, 1957).

Asynchronous constraint (new term): A form of biological constraint where fitness traits that cannot be simultaneously optimized occur at different points in the life history. This can be due to differences in the timing of selection or trait appearance.

Asynchronous trade-off (new term): Trade-off where cost and benefit are temporally separated, which can result from either asynchronous or synchronous constraints.

Asynchronous developmental constraint (new term): Where a change to a developmental program leading to a trait change necessarily causes an additional later trait change. This is a cause of antagonistic pleiotropy acting through programmatic mechanisms (e.g. where the later trait change is quasi-program driven).

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Biological constraint: A property of organisms and/or their ecology that prevents the evolution of traits that would increase fitness. This includes selection and organizational constraints. The latter includes impossibility and interconnection constraints.

Clock speed constraint (new term): Where changes in overall rate of development and aging occur, the relative timing of reproduction and aging is fixed (constrained). Thus, a more rapid rate of living leads to earlier reproduction (potential fitness benefit) and earlier aging (potential fitness cost).

Costly program: A biological program that simultaneously promotes fitness and incurs a cost in terms of pathological changes to tissues or organs where the program is executed. One form of programmatic mechanism involving hyperfunction by which AP causes senescence (cf. quasi-program) (Gems et al., 2021).

Disposable soma: Theory proposing that natural selection favors investment of limited resources into reproduction rather than somatic maintenance, accelerating damage accumulation and, therefore, senescence (Kirkwood, 1977).

Firehose-type costly program (new term): Where a function providing protection against an acute, potentially severe threat to health causes collateral injury to tissue, e.g. degranulation by phagocytes. The analogy is with the damage caused by the water from firefighters' hoses.

Hyperfunction: Where wild-type gene function actively leads to senescent pathology, as opposed to passive random damage or wear and tear (Blagosklonny, 2006).

Hypofunction: Where deficiency in function encoded by the wild-type genome promotes pathology (Maklakov and Chapman, 2019). Hypofunction can result from impossibility constraints or interconnection constraints.

Impossibility constraint (new term): Where a function that would provide a fitness benefit is absent due to the impossibility of its evolution. Impossibility constraint gives rise to hypofunction manifesting as phenotypic insufficiency. For example, the human menopause likely exists due to an impossibility constraint having blocked the evolution of capacity to produce viable oocytes over a longer period. Impossibility may result from traits being either *unfeasible* (e.g. production of additional teeth by elderly elephants) or *unreachable* (e.g. after gene loss, as in uricase in higher primates).

Iteroparous: Possessing the capacity for more than one cycle of reproduction.

Mixed constraint (new term): Where it is impossible to simultaneously optimize a selection constraint and an organizational constraint, which can lead to pathology arising from the latter. This may particularly affect interactions between infectious pathogens and the evolution of immune function.

Molecular constraint (new term): Where organizational constraint exists because a protein possesses more than one biochemical activity, and optimizing all activities at once is not possible. E.g. *AR* (androgen receptor), see Supplementary Discussion.

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Multiplex constraint (new term): Where organizational constraints affect multiple characteristics. Many genes (e.g. *AAT1* α1-antitrypsin) show several distinct forms of AP involving different mechanisms, reflecting the presence of multiplex constraint.

Organizational constraint: Where the optimization of biological function is constrained (Acerenza, 2016). This can result either from the highly integrated nature of biological systems, such that improving one aspect causes deterioration of another (interconnection constraint); or because evolution of a given trait is not possible (impossibility constraint).

Programmed aging: Senescence caused by a relatively ordered series of biological processes that promotes fitness via inclusive fitness or group fitness. Programmed aging is thought to occur only in certain species, largely those with colonial lifestyles (e.g. colonial microbes) (Galimov and Gems, 2021; Lohr et al., 2019).

Programmatic aging: Where complex, wild-type biological processes contributes to senescence, but where senescence does not necessarily contribute to fitness (cf. quasi-programs, costly programs). Programmed aging is a subset of programmatic aging.

Programmatic molecular damage (new term): Where molecular damage occurs as a consequence of biological constraint, such that program action increases levels of molecular damage.

Quasi-program: A cause of senescence entailing a relatively ordered series of biological processes that does not promote fitness; quasi-programs may occur e.g. due to futile run-on of wild-type programs that promote fitness earlier in life (Blagosklonny, 2006) (cf. programmatic aging).

Reproductive death: A form of suicidal reproductive effort found in some semelparous species (e.g. Pacific salmon, monocarpic plants). Here, reproductive maturity triggers the rapid development of lethal pathologies and fast senescence coupled to reproductive success (Finch, 1990) (chapter 2).

Run-on: Futile continuation of gene function or processes in later life, leading to pathology (de la Guardia et al., 2016) (cf. quasi-program).

Selective constraint: Where a trait is under opposing forces of selection due to different ecological determinants (Acerenza, 2016). For example, male túngara frogs (*Engystomops pustulosus*) croak in order to attract females, which also attracts a predator, the fringe-lipped bat (*Trachops cirrhosus*) (Tuttle and Ryan, 1981).

Semelparous: Organisms with a single reproductive episode before death. Also sometimes used to denote semelparity with reproductive death.

Senescence: The overall process of deterioration with age or the resulting pathological condition (not to be confused with *cellular senescence* sensu Hayflick, which is a particular form of cell cycle arrest affecting some vertebrate cell types). Although *aging* has several meanings, in the biological context it is usually synonymous with senescence.

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Sexual dimorphism constraint (new term): Where selection for a trait in one sex leads to its expression in the other. Examples in humans include male nipples and, potentially, female longevity (Gems, 2014; Gould, 1991).

Signaling constraint (new term): Where a given signaling molecule (e.g. hormone or growth factor, receptor, signaling kinase, transcription factor) acts in diverse contexts (cell types, tissues, organs), such that optimization of function in all contexts is not possible. For example, mTOR integrates diverse stimuli (e.g. growth factors, insulin, nutritional status, stress) and interacts with diverse proteins to control various cellular processes (Kim and Guan, 2019).

Synchronous constraint (new term): A form of biological constraint where the opposing forces of natural selection, or the interconnectedness of traits that give rise to the constraint, exert their effects simultaneously.

Synchronous trade-off (new term): A form of trade-off where costs and benefits are experienced simultaneously, that arises from synchronous constraint.

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Supplementary Table 1: Examples of antagonistic pleiotropy, spandrels and biological constraint

Example[1]	Possible type of constraint	Possible pathogenetic mechanism	Sources	Notes[2]
Antagonistic pleiotropy, spandrels				
AAT1 α1-antitrypsin inhibits neutrophil elastase, aiding migration of neutrophils through tissue, which supports immunity but causes tissue damage (e.g. destruction of elastin) that promotes COPD.[3]	Mixed (including interconnection)	Costly program, firehose type, hyperfunction.	(Sapey et al., 2014; Stoller and Aboussouan, 2012; Voynow and Shinbashi, 2021)	Elastin in extracellular matrix destroyed by neutrophil elastase is not replaced.
AAT1 Z allele protects against myocardial infarction (heterozygote) and promotes longevity, but increases risk of COPD.[3]	Interconnection	The M ("wild-type") allele is hypofunctional with respect to correcting hypertension.	(Dahl et al., 2003; Listì et al., 2007; Tanash et al., 2020)	Elastase also reduces hypertension, perhaps by breaking down elastic tissue in the arterial wall and altering vessel distensibility. This reduces myocardial infarction.
AAT1 Z allele protects against myocardial infarction (heterozygote) and promotes longevity, but increases risk of COPD.[3]	Interconnection	The M allele C-36 promotes an atherogenic quasi-program, hyperfunction	(Dahl et al., 2003; Dichtl et al., 2000; Tanash et al., 2020)	Cleavage of AAT generates the C-36 peptide which stimulates inflammatory processes that promote atherogenesis.
ADRB2 beta-2 adrenergic receptor *Arg16Gly, Gln27Glu* polymorphisms improve early life cognition but increase late-life disease (hypertension, myocardial infarction, cancer).[3]	Interconnection	Unclear. Constraint on diverse functions of ADRB2 leads to hyperfunction or hypofunction.	(Bao et al., 2005; Bochdanovits et al., 2009; Cagliani et al., 2009; Kulminski et al., 2010)	ADRB2 plays multiple roles in different organs and tissues, making interpretation of AP difficult.
ALOX15 G SNP increases bone mineral density before menopause but promotes osteoporosis after menopause (femoral neck).[3]	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Cheung et al., 2008)	ALOX15, arachidonate 15-lipoxygenase.
APOE4 allele confers female reproductive advantage, but increases risk of Alzheimer's disease and cardiovascular disease.	Interconnection	Unclear.	(Corbo et al., 2004; Jasienska et al., 2015; van Exel et al., 2017)	*APOE4* allele increases luteal progesterone, increasing fertility (Jasienska et al., 2015).
APOE4 allele increases aspects of cognitive performance in early life, but increases risk of Alzheimer's disease and cardiovascular disease.	Interconnection	Unclear.	(Alexander et al., 2007; Jochemsen et al., 2012; Rusted et al., 2013; Wright et al., 2003; Yu et al., 2000)	*APOE4* allele improves performance in tests of memory (including visual working memory in later life)(Lu et al., 2021), attention, verbal fluency, and mental arithmetic.
AR (androgen receptor) variants from alleles with shorter CAG repeat length have higher androgen sensitivity. In young men, this increases reproductive fitness (increased sperm viability, enhanced traits attractive to females), but in later life increases prostate cancer.[3]	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, leading to benign prostatic hyperplasia, hyperfunction.	(Butovskaya et al., 2015; Dowsing et al., 1999; Ingles et al., 1997)	
AR variants from alleles with longer CAG repeat length reduce prostate cancer, but longer polyglutamine tracts can cause neurodegeneration (Kennedy's disease).[3]	Interconnection, molecular constraint	Programmatic molecular damage.	(La Spada et al., 1991)	
AR variants from alleles with shorter CAG repeat length reduce risk of breast cancer, but increase risk of ovarian cancer.[3]	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Levine and Boyd, 2001; Rebbeck et al., 1999)	
AR with shorter CAG repeat length increases reproductive fitness in men but increases ovarian cancer in women.[3]	Interconnection, sexual dimorphism constraint, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.		
BRCA1/2 mutation can increase female fertility under natural fertility conditions, and ovarian and breast cancer.	Interconnection	Run-on or triggered quasi-program, hyperfunction (hypofunction).	(Smith et al., 2012)	Loss of a tumor suppressor gene leading to hyperproliferation is hypofunction leading to hyperfunction.

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BRCA1/2 mutation promotes breast development, but also ovarian and breast cancer.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction (hypofunction).	(Crespi and Summers, 2006)	Tentative.
CFTR mutation increases fertility (heterozygote) but causes cystic fibrosis (homozygote).	Allele dosage	Hypofunction.	(Knudson et al., 1967)	Trans-membrane chloride channel defect. Overdominance.
CFTR mutation increases cholera resistance (heterozygote) but causes cystic fibrosis (homozygote).	Mixed (including allele dosage)	Hypofunction.	(Gabriel et al., 1994; Meindl, 1987)	Suggested by findings with mice, and human cell culture.
CFTR mutation increases resistance resistance to influenza and other myxo- and paramyxoviruses (heterozygote) but causes cystic fibrosis (homozygote).	Mixed (including allele dosage)	Hypofunction.	(Shier, 1979)	Suggested by cell culture work.
FRM1 mutation increases female fertility (heterozygote) but causes mental retardation in hemizygous males (fragile X syndrome).[3]	Allele dosage	Hypofunction.	(Vogel et al., 1990)	Overdominance.
G6PD mutation protects against malaria (heterozygote) but causes hemolytic anemia (homozygote/hemizygote).	Mixed (including allele dosage)	Hypofunction.	(Clark et al., 2009; Guindo et al., 2007)	Glucose-6-phosphate dehydrogenase deficiency.
GHR (growth hormone receptor) mutation increases resistance to cancer, diabetes, but causes Laron syndrome (including dwarfism).	Interconnection	Hypofunction.	(Guevara-Aguirre et al., 2011)	Wild-type GHR is hyperfunctional in later life, contributing to cancer and diabetes.
GROW1/GDF1 variant promotes joint and bone development and osteoarthritis.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Capellini et al., 2017)	
HBB β-globin mutation protects against falciparum malaria (heterozygote), but causes sickle cell anemia (homozygote).	Mixed (including allele dosage)	Hypofunction.		Overdominance. Wild-type HBB is hyperfunctional insofar as it increases susceptibility to malaria.
HBB mutation protects against malaria (heterozygote) but causes β-thalassemia (homozygote).	Mixed (including allele dosage)	Hypofunction.	(Haldane, 1949)	Overdominance.
HEXA mutation may increase resistance to tuberculosis, and does cause Tay Sachs disease.[3]	Mixed	Hypofunction.	(Diamond, 1988)	HEXA encodes the alpha-subunit of the lysosomal enzyme beta-N-acetylhexosaminidase. Tentative.
HFE (high Fe^{2+} protein) mutation improves dietary iron uptake and protects against typhoid fever and tuberculosis (heterozygote) but causes hemachromatosis, including liver damage (homozygote).	Mixed (including allele dosage)	Hyperfunction.	(Weinberg, 2008)	Overdominance.
Htt (Huntingtin). High CAG number *Htt* alleles increase fertility but cause Huntington's disease.[3]	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Shokeir, 1975; Walker et al., 1983)	Increased fertility may be due to altered behavior, reflecting cognitive changes.
Htt. High CAG number *Htt* alleles reduce incidence of various forms of cancer but cause Huntington's disease.[3]	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Eskenazi et al., 2007; McNulty et al., 2018; Sorenson et al., 1999)	High CAG number *Htt* alleles increase apoptosis, perhaps by increasing levels of the pro-apoptotic and anti-cancer protein p53. This may contribute to increased neuronal apoptosis, and neurodegeneration.
ORL1 (lectin-like low-density lipoprotein receptor 1) promotes immune defense by binding bacterial cell wall proteins, but also promotes atherosclerosis and cardiovascular disease by binding oxidized low density lipoprotein in endothelial cells.	Mixed	Quasi-program, hyperfunction.	(Predazzi et al., 2013)	
PAH (phenylalanine hydroxylase) mutation provides protection against mold-induced miscarriage (heterozygote), but causes phenylketonuria (homozygote).	Mixed (including allele dosage)	Hypofunction.	(Woolf, 1986)	Resistance to ochratoxin A, an N-acyl derivative of phenylalanine, and mycotoxin produced by some *Aspergillus* and *Penicillium* species. Overdominance. Tentative.
PTPN11 mutation protects against leukemia but increases hepatocellular carcinoma (mouse).[3]	Interconnection	Quasi-program, hyperfunction.	(Bard-Chapeau et al., 2011)	*PTPN11* (proto-oncogene) encodes the shp2 protein.

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TNFRSF11B expression at higher levels increases bone mineral density but also risk of several epithelial cancers, and affects tumor angiogenesis.[3]	Interconnection	Quasi-program, hyperfunction.	(Ito et al., 2003; Samelson et al., 2008)	*TNFRSF11B* encodes the cytokine receptor protein osteoprogesterin.
SPATA31 higher copy number improves sensing of UV-induced DNA damage and sun damage resistance but increases cellular senescence and, perhaps, aging.	Interconnection	Hyperfunction?	(Bekpen et al., 2018)	Spermatogenesis-associated protein 31.
TP53 (p53) variants affect female fertility, longevity and cancer risk.	Interconnection	Hyperfunction (hypofunction).	(Kang et al., 2009; Olivier et al., 2010; Ørsted et al., 2007)	Loss of a tumor suppressor gene leading to hyperproliferation is hypofunction leading to hyperfunction.
Multiple loci protect against Crohn's disease and ulcerative colitis but promote type 1 diabetes.	Interconnection	Unknown	(Wang et al., 2010)	
Positive selection drives clonal expansion of cells with tumor suppressor mutations (*TP53, NOTCH1*) among healthy oesophageal cells due to increased resistance to stomach acidity.	Interconnection	Hyperfunction (hypofunction).	(Martincorena et al., 2018; Yokoyama et al., 2019)	Loss of a tumor suppressor gene leading to hyperproliferation is hypofunction leading to hyperfunction.
Uricase loss protects against neurodegeneration (vascular dementia, Alzheimer's disease, Parkinson's disease) but causes gout (especially in older men).	Interconnection	Hypofunction, leading to programmatic molecular damage.	(Hong et al., 2015; Lu et al., 2016; Pakpoor et al., 2015; Weisskopf et al., 2007)	Most mammals possess uricase, but it has been lost among higher primates, possibly to protect brain longevity.
Chromosomal regions 6p22-p24 and 11q21-22 increased fertility but increase risk of schizophrenia.	Interconnection	Unknown.	(Srinivasan and Padmavati, 1997)	
Tumor suppressor mutations provide benefits in extreme cold and at high altitudes (e.g. by reducing apoptosis) increase cancer risk (e.g. Inuit, Tibetans, Scandinavians).	Interconnection	Quasi-program, hyperfunction.	(Voskarides, 2018; Voskarides, 2019)	Cancer-cold hypothesis.
GHR mutation increases lifespan but causes dwarfism (mouse).	Interconnection	Hypofunction.	(Coschigano et al., 2000)	*GHR*, growth hormone receptor.
Prop1 mutation increases lifespan but causes combined pituitary hormone deficiency (mouse).	Interconnection	Hypofunction.	(Brown-Borg et al., 1996)	*Prop1*, prophet of *pit-1*, transcription factor promoting anterior pituitary development.
Region of chromosome 17 specifies negative correlation between dimensions of two bones in the skull (in the zygomatic arch) due to developmental constraint (mouse).	Interconnection, synchronous developmental	No clear fitness cost.	(Percival et al., 2018)	
oca2 mutation increases brain norepinephrine levels but causes albinism (*Astyanax mexicanus* fish).	Interconnection	(Hypofunction). Within caves, albinism is not a fitness cost.	(Bilandžija et al., 2018)	Mexican tetra (blind cave fish). Loss of melanin synthesis increases tyrosine availability for catecholamine synthesis (e.g. norepinephrine).
Xmrk oncogene increases melanin pigmentation pattern promoting male mating success, but causes melanoma in males (*Xiphophorus cortezi* fish).[3]	Mixed, selective (sexual selection) and organizational	Run-on type quasi-program, hyperfunction.	(Fernandez and Bowser, 2010; Fernandez and Morris, 2008)	*Xmrk* (*Xiphophorus* melanoma receptor kinase), constitutively active form of epidermal growth factor receptor causing melanocyte hyperproliferation and melanoma.
Xmrk increases male size but causes melanoma in males (*X. cortezi*).[3]	Selective: S. vs N. (sexual selection vs natural selection)	Run-on type quasi-program, hyperfunction.	(Fernandez and Bowser, 2010; Fernandez and Morris, 2008)	
Xmrk increases melanin pattern promoting male mating success, but causes melanoma in females (*X. cortezi*).[3]	Interconnection, sexual dimorphism	Run-on type quasi-program, hyperfunction.	(Fernandez and Bowser, 2010; Fernandez and Morris, 2008)	
Xmrk causes more melanoma in homozygotes than heterozygotes (*X. cortezi*).[3]	Interconnection, gene dosage	Run-on type quasi-program, hyperfunction.	(Fernandez and Bowser, 2010; Fernandez and Morris, 2008)	
daf-2 mutation strongly increases lifespan but increases larval diapause thereby reducing fertility, and reduces population growth and survival under some conditions (*C. elegans*).	Interconnection, asynchronous developmental	Hypofunction.	(Jenkins et al., 2004; Riddle et al., 1981; Van Voorhies et al., 2005)	
tra-3(e2333) increases brood size by extending spermatogenesis but reduces fitness by delaying onset of fertilization (*C. elegans*).	Interconnection, asynchronous developmental	Hyperfunction, leading to hypofunction.	(Hodgkin and Barnes, 1991)	Protandry in *C. elegans* enables rapid reproduction and resource colonization but causes early cessation of reproduction.

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RPM1 polymorphism increases plant pathogen resistance but reduces growth rate (*Arabidopsis thaliana*).	Mixed	Hypofunction.	(Tian et al., 2003)	*RPM1*, Resistance to *Pseudomonas syringae pv. maculicola* 1.
Chromosome rearrangement can increase mitotic rates but impair sexual reproduction (meiosis) (*Schizosaccharomyces pombe*).	Interconnection	Hypofunction.	(Avelar et al., 2013)	
Loss of *rpoS*, encoding σ^S subunit of RNA polymerase, increases growth under nutrient-replete conditions, but reduces resistance to starvation (*Escherichia coli*).	Interconnection	Hypofunction.	(Nyström, 2004)	Different σ factors compete for access to limited amounts of RNA polymerase holoenzyme, creating trade-offs between them.
Spandrels				
The clitoris (female mammals).	Interconnection, sexual dimorphism	None.	(Gould, 1991)	
The chin (humans).	Architectural constraint	None.	(Gould and Lewontin, 1979; Williams, 1992)	The chin appears to be a futile product of human jaw evolution, left over after the more massive dental arcades of our hominin ancestors shrank to their modern size.
Dihydrotestosterone promotes seminal fluid production by the prostate gland throughout adulthood, but promotes benign prostatic hyperplasia, and prostate cancer in later life (human, chimpanzee).	Interconnection, synchronous developmental	Quasi-program, hyperfunction.	(Untergasser et al., 2005)	
Genes altering joint morphology to facilitate bipedalism in later life promote osteoarthritis (humans).	Interconnection, asynchronous, developmental	Unknown.	(Aubourg et al., 2021)	
IGF-1 at high levels in youth promote health but in late life increase risk of mortality, dementia, vascular disease, diabetes, osteoporosis, and cancer (humans).	Interconnection, asynchronous, developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Zhang et al., 2021)	
Presbyopia (humans).	None	Run-on quasi-program, hyperfunction.	(Strenk et al., 2005)	Late life run-on of lens growth leads to increase in lens thickness, impairing vision.
TGFβ1 in seminal fluid protects sperm within the female by suppressing female immunity, but in the male causes fibroblast to myofibroblast transdifferentiation within the prostate, leading to epithelial cell hypertrophy (male humans).	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Untergasser et al., 2005)	
Male nipples (mammals).	Interconnection, sexual dimorphism	None.	(Gould, 1991)	
In male babirusas (a form of wild pig) tusk-like protruding canines point backwards over the snout, whose continued growth can pierce the cranium (genus *Babyrousa*).	None	Run-on quasi-program, hyperfunction.	(Macdonald, 2018)	As a run-on quasi-program, not resulting from constraint, this is an example of a constraint-independent spandrel.
Pandas have evolved a functional false thumb from the radial sesamoid bone of the wrist. There is also a non-adaptive expansion of the equivalent bone in the foot (the tibial sesamoid).	Interconnection, synchronous, developmental	None.	(Gould, 1992)	Evolution appears to have acted on mechanisms affecting equivalent growth fields in hand and foot development.
Pseudo-penis of the female spotted hyena (*Crocuta crocuta*).	Interconnection, synchronous developmental	None.	(Frank, 1997; Gould, 1997)	Selection for androgen-mediated bellicosity in female hyenas led to clitoral hypertrophy.
Synaptic pruning promotes neurodegeneration (mammals).	None	Run-on quasi-program, hyperfunction.	(De Magalhaes and Sandberg, 2005)	Synaptic pruning in the brain promotes cognitive development, but then runs on in later life, leading to age-related cognitive decline (hypothetical).
mTOR promotes cell growth but in cells that have exited the cell cycle, promotes geroconversion (hypertrophic and hypersecretory states of senescent cells) (mammals).	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Blagosklonny, 2014)	

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mTOR promotes growth but in later life promotes multiple diseases of aging (mammals).	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Blagosklonny, 2008b; Tsang et al., 2007)	E.g. cardiomyocyte hypertrophy contributing to cardiac hypertrophy; hypertrophy and hypersecretion in "senescent" cells.
Snail umbilicus.	Architectural constraint.	None.	(Gould, 1997)	Snails that grow by coiling a tube around a central axis generate a cylindrical space, the umbilicus. A few species use this as a brooding chamber to protect the eggs (exaptation).
Biological constraints				
Aβ functions as an antimicrobial but promotes Alzheimer's disease.	Mixed, interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Moir and Tanzi, 2019; Soscia et al., 2010)	
Aβ regulates cholesterol transport but promotes Alzheimer's disease.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Igbavboa et al., 2009; Yao and Papadopoulos, 2002)	
Aβ (β amyloid) provides protection against oxidative stress but promotes Alzheimer's disease.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Baruch-Suchodolsky and Fischer, 2009; Zou et al., 2002)	
Aβ functions as a transcription factor but promotes Alzheimer's disease.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Bailey et al., 2011; Maloney and Lahiri, 2011)	
Angiotensin II receptor promotes organ development and function, and also cardiovascular disease (e.g. hypertension, atherosclerosis, cardiac hypertrophy), heart failure, diabetes, chronic kidney disease, dementia, osteoporosis, and cancer.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Kamo et al., 2015)	
Autism is associated with improvements in some aspects of cognitive function.	Interconnection	Hypofunction?	(Crespi, 2016)	
Bipolar disorder is associated with increased creativity.	Interconnection	Costly program?	(Redfield Jamison, 1993)	
Bone breakdown by osteoclasts during lactation releases Ca^{2+} for milk production but promotes osteoporosis, especially after menopause.	Interconnection, asynchronous developmental	Costly program, triggered quasi-program, hyperfunction.	(Speakman, 2008)	
General resistance to cell death may protect against Alzheimer's disease but increase cancer risk.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Li et al., 2014; Staropoli, 2008)	Individuals with AD have reduced cancer risk and vice versa (Ma et al., 2014; Shi et al., 2015; Zhang et al., 2015).
Cellular senescence is a tumor suppressor mechanism but senescent cell accumulation promotes cancer.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Campisi, 1997)	
High levels of C-reactive protein, a marker of inflammation (immune defense), is associated with memory impairment in non-demented elderly.	Mixed	Costly program/quasi-program, hyperfunction.	(Silverman et al., 2009)	
Diarrhea may help clear intestinal infections (e.g. *Shigella*, a cause of dysentery) but chronic diarrhea can cause dehydration and infant death.	Mixed	Costly program, hyperfunction.	(DuPont and Hornick, 1973; Tsai et al., 2017)	Tentative.
Fever protects against infection, but is temporarily disabling and can cause febrile seizures in children.	Mixed	Costly program, hyperfunction.	(Nesse and Williams, 1994)	Effects of fever are largely benign.
Fibroblast "senescence" promotes wound healing but SASP promotes multiple diseases of aging.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Demaria et al., 2014)	

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Gastric acidity protects against infection but increases risk of gastric and duodenal ulcers.	Mixed	Costly program, hyperfunction.	(Albin, 1988; Rotter and Diamond, 1987)	
Gay men have fewer offspring, but their relatives show increased fecundity.	Sexual dimorphism constraint	Hypofunction.	(Camperio-Ciani et al., 2004; King et al., 2005)	
Immune responses protect against pathogens, but can cause autoimmune diseases (e.g. lupus erythematosus, rheumatoid arthritis).	Mixed	Costly program/quasi-program, hyperfunction.		
Inflammatory responses to bacterial infection help clear infection but if over-induced (e.g. during sepsis) the resulting cytokine storm can cause fatal immune suppression.	Mixed	Costly program/quasi-program, hyperfunction.	(Nedeva et al., 2019)	
Innate immunity protects against infection but can increase miscarriage rate by causing rejection of fetus.	Mixed	Costly program/quasi-program, hyperfunction.	(Van Bodegom et al., 2007)	
Elevated insulin reduces hyperglycemia but promotes diabetic retinopathy by increasing neovascularization.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Blagosklonny, 2013)	Insulin stimulates mTOR, which activates VEGF and angiogenesis.
Low iron protects against bacterial and protozoan pathogens (e.g. malaria) and cancer, but causes anemia.	Mixed	Hypofunction.	(Weinberg, 1984)	
Absence of iterogametogenesis due to gametogenic program design leads to exhaustion of oocyte stocks, menopause and loss of fertility.	Impossibility, unreachable	Hypofunction.	(Austad, 1994)	
NADPH oxidases (Nox, Duox enzymes) generate ROS for diverse functions (innate immunity, signal transduction, biochemical reactions) which also contributes to inflammaging, and resultant diseases (mammals).	Mixed, interconnection	Costly program/quasi-program, hyperfunction. Programmatic molecular damage.	(Lambeth, 2007)	
Pain perception conditions avoidance of noxious stimuli, but untreatable, chronic illness can produce futile chronic pain.	Interconnection	Costly program/quasi-program, hyperfunction.		
Aggregation and adhesion of platelets promotes blood clotting and wound healing, but also thrombosis (e.g. stroke, myocardial infarction, pulmonary embolism).	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Blagosklonny, 2006)	
ROS production as part of oxidative burst by phagocytes (e.g. neutrophils, macrophages) effects antimicrobial defense, but contributes to inflammaging, and resultant diseases.	Mixed	Costly program/quasi-program, hyperfunction. Programmatic molecular damage.	(Lambeth, 2007)	
The shelterin complex prevents telomere end joining and aneuploidy, but impedes telomeric DNA repair, increasing DNA damage and telomere shortening.	Interconnection	Hypofunction, programmatic molecular damage.	(Fumagalli et al., 2012)	
Skin pigmentation protects against solar radiation injury but also reduces vitamin D synthesis.	Interconnection	Hypofunction.		
mTOR reduces cellular overgrowth by promoting signal resistance in growth factor receptors, also causing insulin resistance, and age-related loss of stem cell function.	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Blagosklonny, 2006; Blagosklonny, 2008a)	
Cessation of successional tooth development (elephant).	Impossibility, unreachable	Hypofunction	(Lee et al., 2012) (This study)	
Wnt/β-catenin signaling promotes normal development but also muscle stem cell exhaustion during aging (mouse).	Interconnection, asynchronous developmental?	Run-on and/or triggered quasi-program, hyperfunction.	(Brack et al., 2007; Naito et al., 2012)	Wnt hyperfunction promotes switch from myogenic to fibrogenic lineage.
Males are brightly colored to attract females, which also attracts predators (guppy, *Poecilia reticulata*).	Selection	Predation.	(Endler, 1980)	The predator here is the pike cichlid (*Crenicichla alta*).
Males croak to attract females, which also attracts predators (túngara frog, *Engystomops pustulosus*).	Selection	Predation.	(Tuttle and Ryan, 1981)	The predator here is the fringe-lipped bat (*Trachops cirrhosus*).

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Sex peptides in seminal fluid increase egg production but reduce female lifespan (*Drosophila melanogaster*).	Interconnection	Costly program?	(Wigby and Chapman, 2005)	
Loss of the flagellum during cell division (unicellular algae).	Mixed	Predation.	(Michod, 2007)	The function of the flagellum requires the centriole. The latter is lost during cell division, increasing vulnerability to predation. This creates a trade-off between survival (aided by flagellar locomotion) and reproduction.
Increasing ATP production rate reduces yield and vice versa (general biology).	Interconnection	Hypofunction.	(Pfeiffer et al., 2001)	
Increasing enzyme specificity can reduce speed and vice versa (general biology).	Interconnection	Hypofunction.	(Tawfik, 2014)	
Protein occupancy constraint generates trade-offs between reproductive and stress resistance functions (general biology, particularly bacteria).	Interconnection	Hypofunction, programmatic molecular damage.	(Acerenza, 2016)	Constraint on space for proteins promoting growth (e.g. ribosomal) and survival (e.g. molecular chaperones) leads to trade-offs between growth and stress resistance.

For AP examples, mutation, spandrel and constraint are described. For spandrel examples, only spandrel and constraint are described. For constraint examples, constraint alone is described. For some examples, operative constraints and pathogenetic mechanisms are suggested hypotheses to varying degrees. Many examples presented offer food for further thought, and a testing ground for the ideas framework presented in this report.

[1]Human, unless otherwise stated.
[2]Established examples unless otherwise stated.
[3]Explored in detail in Supplementary Discussion.

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Supplementary Discussion

Detailed discussion of five examples of antagonistic pleiotropy

Here we consider, for selected examples of AP, the possible constraint that underlies it, and the type of programmatic mechanism involved. For a full list of examples, see Supplementary Table 1.

***AAT1* (α1-antitrypsin)**. This gene exhibits at least three modes of AP, arising from multiplex constraint.

Elastase degradation of elastin aids migration of neutrophils through tissue to sites of infection, thus aiding in protection against infection but causing tissue injury in the process. This exemplifies the firehose principle, where acute responses to immediate danger lead to long-term collateral tissue injury. Thus, elastase function is subject to constraint: it is not possible to both optimize tissue migration capacity and minimize collateral tissue injury. This is an organizational constraint of the interconnection type.

Firehose-type detriments involve programmatic injury, including programmatic molecular damage. Injury caused by phagocyte tissue invasion and degranulation is the detrimental component of a costly program. Mechanistically, injury is caused by elastase hyperfunction.

AAT inhibits elastase, which otherwise breaks down elastin. The *AAT1* M allele is viewed as wild type, and MM homozygotes have normal plasma AAT levels. The Z allele, causes a Glu^{342} to Lys substitution, and ZZ homozygotes show a 84% drop in plasma AAT. In MZ heterozygotes a 17% drop is seen (Listì et al., 2007). ZZ increases risk of chronic obstructive disease (COPD) and emphysema, due to increased neutrophil elastase and the resulting increase in tissue injury.

But there is evidence from a Sicilian population that Z allele frequency increases with age, from 3.1% in young controls to 13.3% in centenarians (Listì et al., 2007), suggesting that the Z allele protects against aging. This could reflect protection against cardiovascular disease by the Z allele. The Z allele was less frequent in young patients affected by acute myocardial infarction (Listì et al., 2007). The ZZ and MZ were also found to be associated with lower blood pressure in coronary artery disease patients, and MZ with reduced risk of ischemic cerebrovascular disease and coronary artery disease (Dahl et al., 2003; Tanash et al., 2020). It has been suggested that neutrophil elastase breaks down elastic tissue in the arterial wall, altering the distensibility of the vessel wall in a way that reduces blood pressure and cardiac load (Dahl et al., 2003).

Thus, elevated levels of neutrophil elastase can increase risk of COPD and emphysema but, potentially, reduce risk of cardiovascular disease and, in Sicilian populations

at least, increase lifespan. This is a second example of AP exhibited by *AAT1*. Again, elastase function is subject to constraint: it is not possible to both maximize benefits in terms of protective reductions in hypertension, and minimize collateral tissue injury from neutrophil migration in the lung. This is an organizational constraint of the interconnection type. The harm to cardiovascular health arising from wild-type *AAT1* is, according to the Dahl et al. hypothesis, deficiency in a corrective mechanism that reduces hypertension, i.e. hypofunction.

A third possible form of AP relates to the interaction between AAT and elastase. This results in suicide cleavage of AAT and release of a C-terminal 36 amino acid fragment (C-36). There is evidence that C-36 has proinflammatory properties and promotes atherogenesis (Dichtl et al., 2000). Thus, the *AAT1 Z* allele, by reducing AAT levels, could reduce atherosclerosis and risk of acute myocardial infarction. In this form of AP, AAT rather than elastase is subject to constraint. It is not possible to both maximize the benefits of inhibiting elastase and the collateral injury that it causes, and minimize the atherogenesis-promoting properties of C-36. This is an organizational constraint of the interconnection type. Mechanistically, injury is caused by AAT (specifically C-36) hyperfunction. The promotion of atherosclerosis by C-36 involves a quasi-program.

***AR* (androgen receptor)**. This gene exhibits at least four modes of AP, arising from multiplex constraint.

The AR responds to androgenic hormones, particularly testosterone and dihydrotestosterone. The AR gene has variable numbers of CAG repeats. AR encoded by alleles with fewer repeats are more responsive to androgens.

In men, shorter CAG repeats increases reproductive fitness in young adults (increased sperm viability, enhanced attractiveness to females)(Butovskaya et al., 2015; Dowsing et al., 1999), but in later life promotes benign prostatic hyperplasia (BPH) and prostate cancer (Ingles et al., 1997). If BPH or prostate cancer are androgen-dependent, triggered quasi-programs, then androgen and AR function is subject to asynchronous developmental constraint, since androgens have different effects on the prostate gland in early and late adulthood. In later life, AR is hyperfunctional, and BPH, which increases prostate cancer risk, is the result of a quasi-program.

A second form of AP relates to Kennedy's disease (spinal and bulbar muscular atrophy), a neurodegenerative disease affecting the brainstem and spinal cord. *AR* is X-linked, hence this conditions occurs largely in men. The CAG repeats in *AR* encode polyglutamine tracts which can have a toxic gain-of-function effect, as in as in Huntington's disease. Shorter CAG tracts reduce risk of Kennedy's disease (La Spada et al., 1991), but increase BPH and risk of prostate cancer (Ingles et al., 1997). Here the constraint involves two different activities of the AR protein: aggregation to promote Kennedy's disease, and hyperfunction to promote BPH. This is an example of *molecular constraint*, i.e. the constraint occurs due to properties of

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the AR protein itself, rather than of the system the protein affects. Although Kennedy's disease is caused by the AR protein (by its aggregation), this is unrelated to receptor function, so it is not a consequence of hyperfunction. Rather, this is an example of molecular constraint-derived, programmatic molecular damage.

A third form of AP relates to AR action in women. Shorter CAG repeat length reduces breast cancer risk (Rebbeck et al., 1999), but increases ovarian cancer risk (Levine and Boyd, 2001). Androgens inhibit proliferation of mammary epithelia but stimulate that of ovarian epithelia. Here constraint occurs due to differences between tissues in their response to androgens. The promotion of ovarian cancer by short CAG repeat *AR* alleles is likely due to AR hyperfunction, and an androgenic quasi-program in ovarian epithelia (cf AR hyperfunction in the prostate).

A fourth form of AP relates to the likely existence of sexual antagonism in selection for *AR* alleles. For example, shorter CAG length increases male reproductive fitness but also increases ovarian cancer. Here a sexual dimorphism constraint is operative. The programmatic mechanisms involves are as described above.

***ADRB2* (beta-2 adrenergic receptor)**. ADRB2 is a receptor for both the hormone epinephrine and the neurotransmitter norepinephrine. ADRB2 is expressed in smooth muscle of the airways and blood vessels and in the CNS. Adrenergic activation of ADRB2 regulates vasomotor tone and blood pressure, but ADRB also has pulmonary and endocrine functions, and in the CNS. Unsurprisingly, *ADRB2* is highly pleiotropic. In a complex fashion *ADRB2* genotype affects risk of heart disease, hypertension, obesity, COPD, diabetes, asthma, Alzheimer's disease and cancer (Bao et al., 2005; Cagliani et al., 2009; Kulminski et al., 2010). Arg16Gly, Gln27Glu variants improve cognition in the young but reduce it in later life (Bochdanovits et al., 2009), and reduce hypertension in the young but increase it in later life (Bao et al., 2005). They also show opposite effects on longevity in young old and oldest old ages (Kulminski et al., 2010).

ADRB2 has numerous functions, making AP in this case difficult to interpret. Beta-2 adrenergic signaling promotes memory and learning. Adrenergic activation of ADRB2 regulates vasomotor tone and blood pressure. ADRB2 stimulates fibroblast and endothelial cell proliferation, and has been linked to inhibition of cellular immunity in cancer (Kulminski et al., 2010). Plausibly, the multiple functions of ADRB2 creates multiplex constraint, such that ADRB2 optimization requires functional compromises that lead to hyperfunction and quasi-programs, or to hypofunction.

***Htt* (Huntingtin)**. This gene was initially viewed as an example of a late-acting deleterious mutation without linked benefits, but there is evidence that it exhibits at least two modes of AP.

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Huntingtin is a protein of unknown function expressed in many tissues, particularly the brain. The gene contains a series of CAG repeats, encoding a string of glutamine (Q) residues. The number of CAG repeats is variable, in most cases 6-35. Rare alleles with more than 35 repeats (up to ~250 repeats) cause Huntington's disease (HD) because long polyQ tracts promote protein aggregation, which disrupts neuronal function. This severe and fatal neurodegenerative disease has an age of onset typically between 30 and 50 years, and disease-causing alleles are genetically dominant.

The disease-causing *Htt* allele was found to increase fertility by some studies (Shokeir, 1975; Walker et al., 1983) though not all (Kishimoto et al., 1959; Reed and Neel, 1959). How this occurs is unclear, but one possibility is that it is due to behavioral alterations attributable to early stages of neurodegeneration. Disease-causing *Htt* alleles causes increased incidence of hypersexuality (including paraphilias), which has been suggested as an explanation for increased offspring number (Dewhurst et al., 1970), but concrete evidence for this is lacking. There is evidence that the alleles cause bearers to continue to have children at later ages when childbearing in unaffected individuals is more constrained (Shokeir, 1975; Walker et al., 1983), possibly reflecting impairment of judgement. The great American folk singer Woodie Guthrie married 3 times and had 8 children before dying of HD at the age of 55.

As far as cognition and behavior are concerned, drawing a clear line between illness and health is sometimes difficult. Mild (fruste) forms of a variety of neurological and psychiatric disorders can give rise to cognitive and performance enhancement, including manic depression, autism, Tourette syndrome, and even neurosyphilis (Crespi, 2016; Kramer, 1993; Redfield Jamison, 1993; Sacks, 2011). In such cases, a mild functional defect leads to enhanced performance and fitness (here increased fertility), while a more severe functional defect leads to disease.

If disease-causing *Htt* alleles conform to this description, then HD can be understood as the result of an unusual form of hyperfunction in which a program involving a mild and beneficial defect later becomes a pathogenic quasi-program. If correct, this suggests that it is the aggregation-promoting properties of the polyQ tract in Huntingtin rather than an activity arising from Huntingtin function that provides the fitness benefits of disease-causing *Htt* alleles. One possibility is that in its early stages, polyQ aggregation triggers cellular responses (e.g. the UPR) which give rise to some benefits, i.e. a hormetic effect. Another is that mild disturbance of neuronal function, and even subtle neurodegeneration results in functional enhancements. The constraint operative here is of the asynchronous developmental type, leading to a neurodegenerative quasi-program.

In a second form of AP, disease-causing *Htt* alleles increase resistance to many forms of cancer (not including cancer of the buccal cavity and pharynx) (McNulty et al., 2018; Sorenson et al., 1999). This may be due to increased levels of apoptosis, perhaps due to increased levels of the pro-apoptotic and anti-cancer protein p53 (Eskenazi et al., 2007;

Sorenson et al., 1999). According to this view in HD patients increased apoptosis protects against cancer but promotes neuronal apoptosis and neurodegeneration. The possible constraint here relates to p53 and apoptosis, which protect against cancer but cause cell death. Higher levels of apoptosis provide early life benefit (cancer protection) but long term harm (neurodegeneration). This is an interconnection constraint of the asynchronous developmental type.

There is evidence of purifying (negative) selection at the *Htt* locus (Peng et al., 2007), which is at least consistent with AP at the *Htt* locus (Byars and Voskarides, 2020).

***Xmrk* (*Xiphophorus* melanoma receptor kinase)**. This is a particularly informative case. This gene appears to exhibit at least 4 modes of AP, arising from multiplex constraint.

Xiphophorus is a genus of fish (platyfishes and swordtails), e.g. *X. cortezi*. *Xmrk* is a paralog of the *egfr-b* protooncogene (epidermal growth factor receptor). It contains two activating DNA alterations that make it able to signal without ligand binding, i.e. is constitutively active, and an oncogene. *Xmrk* is present in some but not all individuals, and is genetically dominant. *Xmrk* causes the spotted caudal (Sc) melanin pattern on the surface of male *X. cortezi*, which is attractive to females (Fernandez and Morris, 2008). It also causes melanoma, which develops due to invasion of melanocytes into the underlying muscle.

Xmrk exhibits AP, promoting fitness by increasing male reproductive success, but shortening lifespan by causing cancer. Because *Xmrk* is an oncogene, fish that lack it have been referred to as wild type (Fernandez and Bowser, 2010). However, this is an example of the disruption paradigm-generated fallacy that if a gene causes disease, then it is mutant. *Xmrk* promotes reproductive fitness, has existed in the *Xiphophorus* genus for millions of years, and has experienced purifying selection (Fernandez and Bowser, 2010); hence *X. cortezi* individuals with or without *Xmrk* are both wild type. Also, the melanoma here is of an unusual sort, not involving somatic mutation but rather hyperproliferation of wild-type, oncogene-containing melanocytes: it is wild-type cancer. AP arises due to constraint on both maximizing male reproductive fitness and minimizing risk to male health from melanoma. This is an example of a mixed constraint: that is selective (here sexual selection) and organizational (increased melanocyte proliferation). Male *X. cortezi* with *Xmrk* experience disease due to hyperfunction in the form of a run-on-type quasi-program. Those without *Xmrk* may experience reduced reproductive fitness due to being sexually drab and lacking in decoration, a form of hypofunction.

A second possible form of AP is suggested by possible effects of *Xmrk* on body size. Male *X. cortezi* with *Xmrk* grow larger, which not only further increases attractiveness to females, but also reduces predation (Fernandez and Bowser, 2010). Thus, *Xmrk* increases mortality by causing melanoma as a cost of a sexually selected trait, but also reduces mortality from predation. Here there exists constraint between benefits of sexual selection and natural

selection, another form of biological constraint (*S. vs N. selective constraint*). Sexually selected traits often generate costs in terms of natural selection (Zuk and Kolluru, 1998).

The presence of two further forms of AP are suggested by the fact that *Xmrk* has not evolved to fixation in any *Xiphophorus* species or population, implying the presence of balancing selection. One possibility stems from the fact that *Xmrk* can also cause melanoma in females, suggesting possible antagonistic selection: for *Xmrk* in males and against it in females (Fernandez and Morris, 2008). This would be an example of AP arising from sexual dimorphism constraint. Another, theoretical possibility is that *Xmrk* exhibits overdominance, promoting fitness more in heterozygotes, an example of AP arising from allele dosage constraint.

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