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A degenerative process underlying hierarchic transitions in evolution[1,1]

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ABSTRACT

This paper describes an evolutionary process likely involved in hierarchic transitions in biological evolution at many levels, from genetics to social organization. It is related to the evolutionary process described as contingent neutral evolution (CNE). It involves a sequence of stages initiated by the spontaneous appearance of functional redundancy. This redundancy can be the result of gene duplication, symbiosis, cell-cell interactions, environmental supports, etc. The availability of redundant sources of biological functionality relaxes purifying selection and allows degenerative changes to accumulate in one or more of the duplicates, potentially degrading or otherwise fractionating its function. This degeneration will be effectively neutral so long as another maintains functional integrity. Sexual recombination can potentially sample different combinations of these sub functional alternatives, with the result that favorable synergistic interactions between independently degenerate duplicates will have a non-negligible probability of being uncovered. The expression of such a synergistic combinatorial effect will result in the irreversible degradation of any remaining autonomous functionality, thereby initiating selection to prevent breakup of co-dependency. This becomes relevant to the evolution of hierarchic transitions when two or more organisms reciprocally duplicate functions that each other requires. If the resulting relaxation of selection reliably persists for an extended evolutionary period it will tend to produce complementary degenerative effects in each organism, leading to their irreversible codependency and purifying selection to avoid loss of integrity of their higher order functional unity. This provides a partial inversion of Darwinian logic that explains how the potential costs of the loss of organism autonomy can be mitigated, enabling the incremental transition to a synergistic higher order unit of evolution.

1. Introduction

One of the most robust global evolutionary trends is the increase in hierarchic complexity of organism bodies (Maynard Smith and Szathmáry 1995). This hierarchic trend is not merely a reflection of the adaptive diversification and increased functional efficiency that is typically assumed to be a consequence of inter-individual competition and natural selection. Hierarchic transitions in evolution exemplify a divergence from the typical logic of natural selection, though not in conflict with it. Moreover, the resulting higher-order units are understood to be subject to selection at a higher level. Hierarchic evolutionary transitions raise many of the same questions that are addressed by theories attempting to explain the evolution of "altruistic" and prosocial behaviors. Both processes involve constraint on the autonomy of lower-level entities that enables higher-order collective relations to take precedence. There have been numerous theoretical mechanisms proposed to account for the stabilization of higher-order synergistic/cooperative units such as multi-celled organisms (e.g. Buss, 1987). At present there is no widely accepted theory for explaining how collections of formerly autonomous functional individuals could spontaneously sacrifice autonomy and fall into higher-order co-dependent relationships.

In this essay I review evidence that a generic process exhibited at all levels of biological organization significantly increases the probability that unprecedented higher-order functional synergies will emerge in evolution. The process is initiated by duplication of sources of functional determination that fractionates, redistributes, and reduces the constraints imposed by purifying natural selection. Relaxation of selection decreases the costs of degraded autonomy and increases the probability that the duplicate sources will serendipitously evolve toward complementary interactions and spontaneously facilitate higher-order synergistic functional interactions. This increase in probability is because redundancy decreases the otherwise high probability that degraded functional components will be eliminated by natural selection. I

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survey a number of major hierarchic evolutionary transitions and show how this common mechanism is likely involved in each.

2. Hierarchic trends in evolutionary theory: a brief history

The popular image of biological evolution is often characterized as a process that tends to produce increasing complexification over time. However, the idea that there is a progressive hierarchic directionality implicit in the evolutionary process is widely criticized by biologists and evolutionary theorists. It is undeniable that over the vast span of geological time there has been an increase in the hierarchic complexity of organism forms on the earth. Indeed, complex multi-celled organisms were comparatively late to evolve, most of which only appeared within the last half billion years of the 3.8 billion years since life first appeared. And only within the last two million years—and possibly much less—have creatures with brains capable of language and complex symbolically-mediated social organizations appeared. Prior to each of these hierarchic transitions organism functions and organizations were simpler. The reasonable implication, often drawn from these examples, is that there must be some tendency implicit in the evolutionary process that is responsible for this progressive increase in complexity. But if there is such a tendency why are these major transitions comparatively rare exceptional cases and not the rule? And why are the vast majority of living forms unicellular?

There are many examples of evolutionary theorists who have argued that there is an intrinsic hierarchic tendency in the evolutionary process. It is a view of the history of life that long preceded Darwin's (1859) *Origin of Species*. In fact, Charles' grandfather, Erasmus Darwin, offered a hierarchic conception of evolution in a number of poems throughout his life. In his poem *The Temple of Nature* (1803, published posthumously) he describes a continuous progression from micro-organisms to complex human societies. Following a similar insight, Jean Baptiste de Lamarck (1809) also viewed the living process as ultimately progressive. In many respects, his commitment to scientific materialism led him to invert the then influential "great chain of being" conception of life. His alternative was a hierarchic progression from micro-organisms to humans. He referred to the principle behind this process as *le pouvoir de la vie* (the power of life) and more specifically as *la force qui tend sans cesse à composer l'organisation* (the force that constantly tends to produce organization). Lamarck argued that living processes progressively complexify from generation to generation as they "strive" to adapt to their changing environments. Assuming that the results of adaptation were then passed down to offspring, these effects could thereby compound over generations producing increasingly complex bodies and mental functions.

Two contemporaries of Charles Darwin, Herbert Spencer and Ernst Haeckel, each developed evolutionary theories that were also explicitly progressive, though based on different hypothetical mechanisms. Darwin was influenced by both, and considered these mechanisms as possible hypotheses able to account for the patterns of "descent with modification." But he was also wary of assuming that either theory was strictly necessary for an explanation of evolution, and was skeptical of progressive assumptions in general.

Spencer (1864, 1867) followed Lamarck in arguing that the law of use and disuse would tend lineages of organisms toward increased complexity. He emphasized the importance of "the struggle for existence" and competition (captured in his phrase "survival of the fittest"—later adopted by Darwin) as a critical driving force behind progressive complexification, both in biology and in sociology.

The naturalist and embryologist Ernst Haeckel (1866) championed Darwin's *Origin* in Germany in the decades following its publication, but he argued that an additional mechanism, besides natural selection, explained patterns of progressive complexification in evolution. He called it the "biogenetic law" by which adaptive complexity would inevitably increase over time. Like the previous accounts it was based on an accretive process, where earlier adaptations could be progressively honed and to which new adaptations could be added. The biogenetic law, often summarized with the phrase "ontogeny recapitulates phylogeny" assumed that progressive evolution was a consequence of additive processes in development in which new adaptations are preferentially generated and added toward the end of development. If these changes proved beneficial these added modifications would be inherited in subsequent generations and thus developmental processes would tend to become more complex over evolutionary time.

Charles Darwin was receptive to these alternatives, but ultimately focused on natural selection as the primary if not the sole influence on the evolution of organism complexity. Darwin reasoned that if variations occurred due to "random" processes there should be no preferred direction to evolution, except for local adaptive improvement. Improvement can be considered an incrementally progressive source of novelty, but it does not distinguish descent with modification from major hierarchic changes in body organization. This led many early 20th Century evolutionary biologists to turn their attention to the effects of mutation.

There were several variants of progressive evolution theories produced throughout the 20th Century as well. These include Leo Berg's (1922) *Nomogenesis, or Evolution Determined by Law*, Conwy Lloyd (1923) Morgan's *Emergent Evolution*, and Pierre Teilhard de Chardin's (1961) *Phenomenon of Man,* among others.

Most evolutionary theorists of the late 20th Century, however, accepted some version of a view articulated by Steven Jay Gould. In his 1996 book *Full House* he argues that the apparent complexification of organism forms over the past few billion years is the result of a bias in what might be described as the statistics of random evolutionary change. He describes the evolutionary tendency toward an increase in hierarchic complexity as the result of a "drunkards walk" through complexity space in which organism forms can always develop toward greater complexity but no simpler than the simplest forms already in existence. The increase in complexity was thereby presumed to be a statistical bias, not an intrinsic tendency of life. Explaining the appearance of increased complexity in terms of statistical bias was also examined by Brooks and Wiley in their 1988 book with the enigmatic title *Evolution as Entropy* in which they compared evolutionary diversification and complexification to entropy increase. Thus, just by virtue of an otherwise undirected tendency for organism adaptations to diverge from ancestral forms there should be a statistical bias toward increased diversity. This would inevitably include diversity in hierarchic complexity of physiological organization.

In many respects the first theories to suggest an unambiguously hierarchic process of evolutionary change were efforts to explain the complexity of eukaryotic cells due to endosymbiosis. In 1883, Andreas Schimper described the process in a footnote. He reasoned "If it can be conclusively confirmed that plastids do not arise de novo in egg cells, the relationship between plastids and the organisms within which they are contained would be somewhat reminiscent of a symbiosis. Green plants may in fact owe their origin to the unification of a colorless organism with one uniformly tinged with chlorophyll" [Schimper (1883), pp. 112–113). The idea was explicitly developed by Konstantin Mereschkowsky (1905) who argued that symbiosis is the major driving force of evolution. By 1927 Ivan Wallin made this the thesis of the book *Symbionticism and the Origin of Species*. In that text it was explicitly argued that mitochondria had a bacterial origin and suggested that many progressive processes in evolution could be attributed to this mechanism. But it wasn't until the 1960s and '70s with the discovery that mitochondria and chloroplasts each contained their own DNA that the endosymbiotic theory gained mainstream attention as a significant process in evolution. The biologist Lynn Margulis (1970) marshaled extensive morphological and physiological data supporting endosymbiotic theories explaining the possible origin of many eukaryotic cell components, including mitochondria and chloroplasts, and by the early

1980s there was almost unanimous acceptance that at least those organelles were of bacterial origin.

In general, endosymbiotic theories argued that combinatorial codependence between previously autonomous living units (i.e. prokaryotes and Archaea) gave rise to higher-order organismic units. For this to happen, lower-order components had to sacrifice some aspect of their autonomy and become part of a synergistic higher-order collective entity. Thus, Margulis demonstrated that many organelles and molecular complexes within eukaryotic cells exhibited morphological traits only found in bacteria and plasmids. This was later corroborated in the case of mitochondria and chloroplasts when it was shown that their DNA sequences unambiguous placed them in the bacterial clade.

But acceptance of this mechanism for evolutionary change required an expansion of Darwinian theory to accommodate these transitions. It also contributed to the long-running debate over whether competitive or cooperative processes were more important for driving the evolutionary process. But by the time that John Maynard Smith and Eörs Szathmáry published their (1995) book *The Major Transitions in Evolution*, evolutionary biologists were ready to reconsider the possibility that major hierarchic transitions might reflect a distinct evolutionary mechanism from natural selection, though not one that contradicted natural selection.

3. Major transitions and the problem of cooperation

Maynard Smith and Szathmáry (1995) argued that endosymbiotic transitions were variants of a more general pattern of major evolutionary transitions. They proposed eight major transitions, including such transitions as led to the evolution of eukaryotic cells, multicellularity, insect eusociality, and human language. They further argued that these transitions each reflect a common Darwinian challenge: explaining the origin of altruistic and cooperative relationships in the context of the ubiquity of inter-organism competition characteristic of natural selection.

Though Darwin also recognized that cooperative behavior was problematic for natural selection theory, it was not until the 1960s that the issue received theoretically sophisticated treatment. This was initiated by the critiques of group cooperation theories by George C. Williams (1966) and by the development of inclusive fitness theory by W. D. Hamilton (1964a & b) and others, which led to renewed debates about the evolutionary basis for altruistic behaviors in general. Since then, competing theories have alternatively gained and lost footing. As will be discussed in more detail below, the major views have tended to fall into two general categories: group selection theories and kin selection theories. Both of these general approaches are ultimately dependent on a logic of convergent reproductive "interest" within as opposed to between groups of individuals. Other theoretical perspectives that complicate this simple dichotomy also invoke mechanisms that promote convergent versus divergent reproductive interest. They include reciprocal altruistic theories that explain this shared interest in terms of the relative closure of altruistic interactions within versus between groups; non-zero sum theories that focus on the way that collective action can provide access to resources not available to individuals and which thereby provide an advantage that outweighs the costs of sharing that resource; and top-down theories (e.g. "management theory" or "reverse dominance" theory) that explore the advantages accruing to groups that include dominant individuals or shared tendencies to suppress non-cooperative behaviors of individuals trying to benefit from the cooperative behaviors without themselves contributing (e.g.so-called "cheaters" and "free-riders").

Group selection theories generally depend on being able to show that success or failure at inter-group competition can overshadow the reproductive advantages that might result from inter-individual competition within a group. When this is the case, selection can favor intra-group cooperation and suppress intra-group competition. For example, kin selection theories grew from the recognition that the most extreme levels of reproductive cooperation were found in eusocial insects like ants, hive bees, and termites, and that this correlated with extreme asymmetric degrees of genetic relatedness within these social groups (e.g. colonies). Because of the relatively high genetic relatedness of kin, individuals have a high probability of passing down genes they each share. This probability of gene reproduction by proxy can minimize the fitness costs of sacrificing reproduction to support kin reproduction (e.g. the reproduction of the colony's queen). Over the course of recent years evidence has mounted to support the plausibility of each of these general mechanisms, and the arguments have therefore tended to be about which is more relevant to a specific case.

As I will argue below, all these theories for the evolution of cooperative behavior tend to be supported by arguments showing that the cooperative adaptations can become evolutionary stable strategies if there are processes that maximize the reproductive advantages due to cooperating and minimize the reproductive advantages that could be gained by not cooperating. Instead of exploring the many ways that theorists have discovered that this condition can be stabilized either by group-level effects or by asymmetries in genetic relatedness, however, I want to focus on an assumption common to all such approaches.

These theories all are efforts to answer the question: "How do higher-order cooperative units preserve their unity and prevent lower-order components from re-expressing their autonomy?" In this respect there is an *ex post facto* aspect to these accounts. They account for the selective advantages and the stability of these relations, but are less informative concerning the transition from the predominance of non-cooperation to the predominance of cooperation.

A recent theoretical effort, focused on the evolution of novel synergistic adaptations in evolution has been developed by the complex systems theorist Peter Corning (e.g. 1981, 2005). He argues that the major driver of biological evolution can best be characterized as "synergistic selection." The basic premise of synergistic selection theory is that synergistic functional organization distributed among component structures tends to be more resilient, efficient, and stable than the same function produced in a non-synergistic way. Much of the evidence for this is provided by surveying the near ubiquity and diversity of synergistic functional relationships, both among the subsystems of complex organisms and between different organisms in their interdependent ecosystemic relationships.

The synergism hypothesis is supported by the remarkable robusticity and metastability of large multi-celled organisms with their complex interdependent organ systems, diversity of cell phenotypes, and capacity to adapt to a wide range of conditions inaccessible to microorganisms. It is also supported by the fact that cooperative group behaviors can provide access to resources that are inaccessible to organisms that do not cooperate (i.e. non-zero sum effects). Synergistic relations thus produce hierarchically more complex organisms with the ability to exploit niches that are unavailable to simpler organisms.

But demonstrating that synergistic organization is more efficient and reproductively advantageous, does not explain how it arose during the course of evolution. It is not obvious that selection should favor the evolution of synergies, especially if there are also costs. Moreover, if synergistic adaptations were invariably more efficient and flexible than their non-synergistic analogues, one would expect that hierarchic transitions in evolution would be the rule, not the extreme exception. But, despite over three billion years of biological evolution, the major examples of major hierarchic transitions can be numbered on one's fingers. This suggests that there are barriers to realizing the advantages provided by synergistic adaptations, and that the transition from autonomous to cooperative adaptations is not aided by any simple selective advantage. And, as mentioned above, complex multi-celled organisms have not replaced or become more prolific than their simpler single-celled cousins, nor even when compared to their even more distant bacterial ancestors. In fact, the ratios vastly favor the simpler over the

more complex forms (in terms of the diversity of forms, though not in biomass). This casts doubt on the assumption that increasing synergistic complexity is inevitably selectively advantageous. And again, it provides little in the way of an explanation for how such transitions are achieved.

An additional problem is that higher-order functional organization involving formerly autonomous functional subunits often requires that lower order units must sacrifice autonomous functioning in order to converge on a collective function that is selectively advantageous. But the evolutionary costs of loss of autonomy are high. This quite serious cost leaves open the question of how such distributed changes could ever converge toward a synergistic function, since there is no evolutionary foresight to predict the relative advantage of cooperation.

This barrier to cooperation has led some to invoke "hopeful monster" mutations (Goldschmidt 1940) that are imagined to achieve a synergistic or cooperative result in a single "leap" (Dietrich 2003, Gould 1977, Theissen 2006). Additionally, this requires that the lucky mutation to be shared by a significant fraction of the immediate cell group or organism colony (as might occur within a clade derived from a mutant common ancestor). By such an improbable shared coincidence, a serendipitous synergy might be able to emerge with minimal evolutionary cost in a localized social group. This may be one reason why the most complete and stable hierarchic transitions tend to involve a single kin lineage such as in highly related colonies of ants, bees, or termites and in multi-celled organisms that develop from a single fertilized egg cell. In this way shared genetics can provide a contextual bias favoring cooperation over competition for a localized group, though it doesn't resolve the issue of loss of autonomy or defense against free-riders.

4. Duplication–degeneration–complementation

A hint of an alternative approach emerged some decades ago, but it was not recognized as relevant to the conundrum about the evolution of cooperative complexity. In his book *Evolution by Gene Duplication* Susumo Ohno (1970) saw gene duplication as a mechanism for the creation of "new" genes that could eventually take on novel functions. This was motivated by the discovery of whole genome duplication in a number of species (e.g. in plants like domestic wheat and animals like vertebrates). In the half century since these initial speculations, the evidence for the role of gene duplication as a major factor in evolution has become overwhelming. Evolutionary gene duplication has resulted in novel gene functions, fractionation of prior gene functions, redistribution of the timing and body location of gene expression, the generation of entire families of genes with related functions, and whole genome duplications.

Beginning in the late 1990s a number of molecular biologists recognized a common pattern reflected in these genetic effects. Though the process was described in slightly different terms, the commonalities were obvious. For example, in an influential article by Arnold Stolzfus (1999)he described the process as Contingent Neutral Evolution (CNE). Because duplicates are redundant in their effects they do not necessarily produce functional problems, unless, for example, excess "dosage" effects are harmful. So, gene duplication can be relatively neutral with respect to selection. But this redundancy can also provide some protection against the effects of mutational damage, since mutations that reduce functionality of one duplicate will minimally influence viability so long as another functioning duplicate persists alongside the degenerate duplicate. Although this logic was implicit even in Ohno's account, Stolzfus realized that this logic could be generalized to many other molecular relationships. To make his point he chose molecular examples that appeared to exhibit extremes of superfluous complexity, including the eukaryotic spliceosome which edits out noncoding intron sequences in mRNA and involves five snRNAs and often dozens of proteins, RNA pan-editing in kinetoplastid mitochondria, and the scrambling of gene pieces in the germline nuclei of ciliates. All appear to be gratuitously complex beyond what is needed for the functions they perform.

In that same year Allan Force and colleagues (Force et al. 1999) also published an article in which they described the same process of gene duplication and subfunctionalization. They distinguished three phases of this process which they designated Duplication, Degeneration, and Complementation (DDC). In hindsight, both were foreshadowed in the pioneering book *The Major Transitions in Evolution* published a few years earlier (1995) by John Maynard Smith and Eörs Szathmáry in which they described a neutral ratchet-like effect as "contingent irreversibility" and suggested that it may have contributed to hierarchic complexification. But what distinguished the CNE and DDC approaches was their focus on the role of the degenerative effects that tended to follow from the way duplication relaxes the influence of purifying selection.

Since these original insights many more examples of complex cellular molecular machines have been found to exemplify structures best explained in this way. Summarizing a decade of findings that support these hypotheses Gray and colleagues (Gray, et al. 2010) described it as producing "irremediable complexity" and analogous to "runaway bureaucracy." However, this negative characterization misses the positive consequences of such increases of complexity, including most importantly an increase in optional ways to flexibly respond to changing conditions.

Unaware of the CNE and DDC approaches to molecular evolution at the time, I also began to reconsider the importance of degenerative processes in evolution, but at the whole organism level. This was initially motivated by my critical reconsideration of three related variants on Darwin's logic: the Baldwin effect, Waddington's concept of genetic assimilation, and what would later come to be called niche construction. Although each was often described as a positive source of adaptive innovation, I began to suspect that their likely degenerative consequences were being overlooked and under-appreciated.

In a series of papers, I explored the implications of this possibility. They included essays reconsidering the logic of the of Baldwin effect (Deacon, 1997); critiquing the tendency to confuse the Baldwin effect with genetic assimilation (Deacon, 2009); exploring the evolution of vitamin C dependency in primates (Wiles et al. 2005; Deacon 2009); explaining the shift from innate to socially inherited song structure in a domesticated songbird (Deacon 2009, 2010); arguing that human language competence was partly the result of neurological dedifferentiation (Deacon 2009, 2012) and reframing the evolution of prosocial behavior in terms of social addiction (Hui & Deacon 2009). Only after discovering that related processes had been also described in molecular biology, however, did it dawn on me that there might be a more general logic underlying these and many more evolutionary processes.

In particular, it became apparent that a slight variation of the CNE and DDC logic was relevant to the evolution of many of the "major transitions in evolution." The critical feature shared by within-organism complexification and hierarchic transitions is that duplication and its protected degenerative effects can also occur at both the intra- and supra-organismic levels; e.g. between an organism and its environment or between different organisms.

In the sections that follow I describe several well-known examples where interrelationships established between functional elements at one level interact to create a higher-order synergistic function or a higher–order form of organism. I will argue that in each case a process involving four phases of evolutionary change has been responsible for the transition from lower-order autonomous functional units to an integrated higher-order synergistic unit. These phases include (1) duplication of some functional unit leading to (2) redundancy of function and relaxation (or masking) of selection on the duplicates that allows (3) partial degeneration of functional specificity in one or both that (4) increases the probability of exposing functionally synergistic interactions between the differently degenerated components and which can be-

come subjected to selection for their synergistic function and thereby preserved within a lineage.

In this review I begin with the simplest form of this process: structural gene duplication. Exploring the way that gene duplication events can lead to the evolution of gene "families" exhibiting synergistic functional interdependencies. This will serve as the model for each higher-order transition. Expanding from this archetypical exemplar, I discuss examples of regulatory gene duplication, as well as exogenous functional duplication effects that relax selection on genetic information, resulting in mutualism and symbiosis. I next trace analogous processes involved in two of the major hierarchic transitions in evolution: the endosymbiosis producing the eukaryotic cell and the evolution of multicellularity in fungi, plants, and animals. Finally, I explore some possible applications of the theory to the evolution of social cooperation (including eusociality), the effects of domestication, and some of the unprecedented products of human evolution. I conclude by considering the common extra-Darwinian processes involved in each of these cases, show how this can be integrated with standard Darwinian logic to provide a more complex evolutionary theory in which hierarchic transitions are not exceptions but are an expected process.

5. Gene duplication

Gene duplication is a common feature of genome evolution (Ohno, 1970; Ohta, 1994). It is probably the major source of new genes in the course of evolution. It is also a major means by which cooperative protein complexes arise in evolution (Orgel, 1977; Zhang, 2003). Thus, multiple occurrences of gene duplication over the course of evolution have produced large "families" of structurally and functionally related genes. Indeed, most genes can be recognized as members of larger families of genes derived from a common ancestral gene (Walsh, 1995; Zhang, 2003).

During gene duplication, a length of DNA is literally copied and spliced into the chromosome nearby, possibly as a result of uneven crossover events during meiotic replication, viral gene insertion and excision, retrotransposon action, or some other intrinsic or extrinsic mechanism that modifies chromosomal repair and gene modification. The result of such events is that a nucleotide sequence may be duplicated that contains a full or partial coding region for the production of a functional protein either with an intact promotor or under the influence of some other gene's regulatory influence. A possible functional consequence is that there is now two ways of producing the same or similar phenotypic effect, though the timing and conditions of expression may vary due to its new genetic context.

This redundancy can be deleterious if it results in overproduction of a gene product whose functionality depends on strict quantitative regulation. Selection against such effects can favor additional regulatory changes or functional inactivation of a duplicate. But duplication can also reduce the intensity of selection maintaining either or both of the duplicate genes' functions. Thus, if one of two duplicated genes acquires a mutation that alters its protein product in a way that modifies or degrades its function or causes it to be expressed at a different time or body location, this mutation doesn't necessarily impact the reproduction of the organism so long as the other copy remains intact and the modification isn't itself damaging. Moreover, the now mutated gene may continue to acquire mutational changes without negatively impacting later generations of organisms that inherit it, so long as this slightly modified phenotypic contribution remains non-deleterious. Such mutations will thus be effectively or nearly neutral.

The typical consequence of this sort of neutrality with respect to selection can be described as a "random walk" away from the original function. The result is typically the accumulation of arbitrary sequence changes at the genetic level and a progressively dedifferentiated or otherwise altered contribution to the phenotype. Presumably, persistent relaxation of selection can eventually lead to accumulation of a very large number of mutations, or of mutations that stop the translation of its sequence information, and may ultimately result in complete loss of function, producing a pseudogene.

But degradation to pseudogene status is not inevitable for gene duplicates. Gene duplication involves an already functional segment of DNA. Typically, point mutations that produce slight degradations of its sequence may only incrementally alter the structure of the protein it codes for. So long as the changes do not involve an essential binding site, stop codon, or some other critical structure, its functional links to other molecular components is likely to degrade in non-catastrophic ways. This may result in a progressive loss of the specificity of protein function, with some functional associations being lost while other related interactions maintained. Whereas the initial evolution of protein function may involve structural compromises to accommodate its multiple associations to other molecules, multiple variant forms may provide a "have your cake and eat it too" option, with each variant form able to evolve greater specificity for one or another of these subfunctional capacities. In other words, the duplication, relaxation of selection, and random walk can provide a kind of exploration of the space of possible synergistic relationships that lie, in effect, in the "function space" just adjacent to an existing function. This is a recipe for increasing functional complexity (e.g., see Lynch and Conery, 2003).

If the prevalence of gene duplication in animal and plant genomes is any indication, the probability that a given duplication will achieve functional integration is far from zero. Gene families, consisting of large numbers of paralogous genes (e.g., derived by duplication from a common ancestral gene), are widespread in complex organisms and are often responsible for similar or even synergistic phenotypic functions. One incidental advantage for genomic research has been that identification of a functional correlate of one genetic sequence often provides a probe sequence that can be used for searching out other members of its family that have related functions.

6. The hemoglobin family

To illustrate this, I describe two well-known examples. The first is the globin gene family, and specifically the hemoglobins. The hemoglobin protein complex contained in red blood cells in adult mammals comprises two varieties of the hemoglobin protein—alpha and beta hemoglobin—each coded by a distinct gene. The structure of the protein makes it possible to bind a special molecular formation (a porphyrin ring) within which an iron atom is suspended. It is this iron atom that provides the oxygen-binding capacity. Two alpha and two beta hemoglobin proteins fit together to form a tetrahedral complex made possible due to the complementary shapes of the molecular surfaces forming the interior of the tetramer. The two forms of adult hemoglobin arose from a hemoglobin gene duplication event. The alpha and beta hemoglobin duplicates each acquired independent changes in shape but minimal changes in oxygen binding capacity in their separate divergence from the original "ancestral" hemoglobin gene. Changes that increased the stability of tetrameric binding appear to have been favored by natural selection with respect to one another, probably because of the superior oxygen transport capacity of the tetrahedral form. In other words, in their random walks through different three-dimensional configurations, the duplicates retained their oxygen-binding function while effectively "sampling" functional consequences of this secondary feature of molecular shape. The combinatorial "sampling" was made possible due to sexual reproduction, enabling different combinations of differently altered alpha and beta hemoglobin genotypes to get "mixed" differently in successive generations. The functional superiority of the tetrameric form when serendipitously "discovered" in this way allowed the current alpha and beta forms to outcompete the others and thereby their functional co-dependence became stabilized by purifying selection.

This particular combination of alpha and beta hemoglobins is not, however, present at all stages of the mammalian life cycle. In the fetus of a placental mammal, additional variant beta-hemoglobin forms are expressed, three of which are termed gamma, delta, and epsilon hemoglobin. These variants of beta are expressed at different stages of gestation and are each coded by a different variant duplicate of the beta form of the gene, with the entire gene family present along a contiguous segment of chromosome 11.

These beta-hemoglobin duplication events, which occurred during placental mammal evolution, have also given rise to two pseudo–beta hemoglobin genes, which no longer produce a corresponding protein. In effect, these variants acquired mutations that inactivated gene translation in their random walk away from the original sequence. The remaining four beta-hemoglobin genes are expressed at slightly different times during development in the order epsilon-gamma-delta-beta. The functional value of this is probably related to the fetus's need to acquire oxygen from mother's hemoglobin and yet still transfer it from its own blood to the myoglobin in its various somatic cells. So in order to be able to "steal" oxygen from maternal hemoglobin, fetal hemoglobin requires a slightly higher oxygen binding affinity than mother's hemoglobin. It then must diffuse oxygen out of its own hemoglobin into its tissues, which ideally requires yet a higher oxygen-binding affinity than its own hemoglobin. Between these values there is an optimal balance, but this changes as the fetus and placenta grow and change and the corresponding oxygen needs change. The result is that these different beta-hemoglobin variants expressed during different phases of gestation allows the fetus to progressively adapt to this challenge, until at birth the beta-hemoglobin becomes the predominant form produced.

So in this case, analogous to the shape complementarities "discovered" consequent to alpha/beta duplication, these parallel random walks of beta-hemoglobin gene duplicates led to synergies of timing and molecular affinities, as certain variant mutations, which modified the different redundant genes' oxygen-binding properties, became subject to selection with respect to each other in the context of internal gestation. The duplication and differentiation enabled not only the slight variation of protein function but also differences in the timing of expression of each. The result was the evolution of a distributed multicomponent synergistic functional relationship and the emergence of a novel mode of reproduction.

7. Duplication and variation of regulatory genes

Perhaps the most dramatic example of the duplication, relaxation of selection, random walk degradation, and functional complementation effect is demonstrated by duplication of genes that code for proteins that bind to DNA and regulate the expression of yet other genes. This general class of genes is often referred to as regulatory genes. One consequence of this hierarchic recursive genetic relationship is that the expression of one gene can influence the expression of many other genes in concert. So, the functional divergence and interaction effects that result from duplication of such regulatory genes can be global and systemic.

The classic example of regulatory gene duplication effects involves a family of genes containing a nucleotide sequence coding for a DNA binding domain called the homeodomain. One class of such genes, called homeobox genes, are responsible for the large-scale segmental organization of animal body plans. In the fruit fly, they are called HOM genes (for homeobox) and their homologues in mammals are called Hox genes (and collectively such genes are referred to a homeotic genes). These underwent a number of duplications in the common ancestry of a number of multi-celled animal lineages, including individual gene duplications producing a family of linked Hox genes (in the common ancestor of insects and vertebrates) and duplications of the entire Hox gene family (the result of whole genome duplications) in different vertebrate lineages.

Because these genes affect coordinated expression of large suites of other genes (many of which also have further regulatory functions), they play a role in producing slightly variant forms of whole body structures in these animals. This was first demonstrated by recognizing that mutations of these genes produce systematic variations of body segmentation in flies, causing out-of-place expression of structures that normally are segment-specific, such as legs expressed where antennae are normally produced.

The discovery that the theme-and-variation logic of the different insect body segments was correlated with the expression of a different HOM gene duplicate in that segment revolutionized the study of development and served as the keystone insight solidifying the value of the "evodevo" paradigm. But the fact that homeotic gene duplication expresses itself as organ duplication demonstrates that the logic of duplication, masking, divergence, and complementation is general. It can play a role in promoting the evolution of synergistic interactions between different body parts.

In arthropods such as centipedes, for example, the corresponding organs (e.g., legs) of adjacent segments are highly similar, but since adjacent legs serve almost identical functions they can also partially mask selection on the functional specificity of one another. This reduction of the effects of stabilizing selection can lead to drift of features on one segment away from those on another. The structural–functional redundancy provided by adjacent segments minimizes the probability of catastrophic loss of function, and also increases the likelihood that complementary functions might develop on other segments. In various arthropods, such as grasshoppers, spiders, lobsters, flies, and so forth, the different appendages with jointed leg-like form have evolved into specialized antennae, spinnerets, claws, and many other structures sharing the same mechanical architecture, but modified to serve quite distinct functions.

In each of these cases, and despite their different levels of function, the redundancy of function that results from duplications significantly reduces the improbability of evolving synergistic functional linkages between independent structures. Because they share a common ancestral function, randomly varying duplicated features of an organism are able to effectively "explore" related dimensions of the original function. Their underlying commonalities also increase the probability that variant duplicates will fractionate the original function, each assuming greater roles with one but not another aspect of the original. This redistribution of functional contributions can result in increased flexibility, including expression patterns that vary in response to changing physiological or environmental conditions.

This interplay between duplicated genetic and epigenetic factors borrows features from both Baldwinian and Waddingtonian mechanisms, and yet it does not involve, even superficially, a Lamarckian logic. Duplication reduces the constraining influence of natural selection on a particular structure or function. This is analogous to the way acquired adaptations produce what Baldwin thought of as protection from selective elimination. But unlike Baldwin's hypothesized effect, relaxation of selection more often contributes to the evolution of increased genetic and functional variation rather that a shift from more plastic to more ineluctable functional expression. The way that the resulting functional interactions exploit combinatorial relationships that were previously hidden (or inaccessible because intense selection prevented variation) is analogous to Waddington's logic of canalization, in which epigenetic interdependencies can emerge to become selected in their own right. Like Waddington's notion of a "phenocopy" a novel functional capacity that emerges from complementary combinatorial relationships can become selectively favored for the synergy that results. Together these effects not only "explore" adjacent functional possibilities and "stabilize" novel higher-order synergistic relationships, but they provide an evolutionary cycle that can generate progressively more complex forms of adaptation, as each stabilized synergistic relationship can supply the substrates for new duplication effects.

8. Extrinsic duplication of function: the ascorbic acid example

This interplay between aspects of Baldwinian and Waddingtonian mechanisms suggest an even more general application of this principle. For example, redundancy and masking effects can be generated extrinsically, and maintained irrespective of specific genetic inheritance. In this case, however, reduced selection on the intrinsic function that is thereby provided with redundant support from outside will allow the intrinsic capacity to degrade. With no internal functional redundancy selection can be redistributed fractionally across highly diverse, and previously independent, genetic loci and epigenetic mechanisms.

A classic example that bridges between genetic and environmental duplication-masking effects is the evolution of ascorbic acid (vitamin C) dependency in anthropoid primates. It has long been known that monkeys and apes, including humans, are among some of the very few mammals that must obtain ascorbic acid from dietary sources (Chatterjee, 1973). In contrast, most mammals synthesize their own ascorbic acid. This is the case for rats. In 1994, a group of Japanese researchers (Nishikimi et al., 1994) sequenced the gene on chromosome 8 of the rat that codes for the Ninal catalyst in the metabolic pathway that endogenously produces ascorbic acid (called l-gulano-lactone oxidase, abbreviated GULO). They then used the sequence from this gene to probe the genomes of other species.

One of the first species they probed was *Homo sapiens*. What they found was surprising. Although humans are unable to synthesize their own ascorbic acid, the human genome includes a pseudogene that is homologous to the rat GULO. The GULO pseudogene in humans has accumulated considerable mutational damage, including the deletion of large coding regions (exons), the random insertion of "stop" codons, and a frame-shift mutation that completely shuts down expression. This is evidence that it has long been freed from the stabilizing influence of natural selection. So, what masked its functionality and allowed it to degrade to this extent?

Although phylogenetic analysis of the variants of the GULO pseudogene in other anthropoid primates is still incomplete, it is likely that all share a GULO pseudogene with divergent mutations. A reasonable estimate of the date in the evolution of primates when this gene began to accumulate damaging mutations is suggested by the comparative fossil evidence. Changes in eyes and teeth of fossil primates suggest that a shift to diurnal foraging and a shift from insectivory to frugivory took place before at least 35 million years ago (and possibly earlier) in the lineage leading to anthropoids. The evolutionary implication is that at this point regular foraging on fruit introduced a semi-reliable extrinsic source of ascorbic acid into the diet. Under these conditions, there would be no selective disadvantage of inheriting or transmitting a non-functional variant of the GULO gene. Selection would be masked by an acquired behavioral adaptation and by the ascorbic acid rich niche that was thereby created. But the eventual complete loss of function of the GULO gene would lead to the equivalent of an evolutionary addiction to foods providing ascorbic acid.

This example of extrinsic ascorbic acid dependency provides us with an opportunity to look at some of the secondary consequences of this degradation. The reduction of purifying selection maintaining this enzyme in turn would have unmasked selection on a variety of other traits that help guarantee the availability of this now essential nutrient. Thus, the behavioral flexibility that initially allowed primates to regularly forage on fruit eventually "addicted" anthropoid primates to a dietary niche in which fruit acquisition and digestion were critical. Degradation of this gene and its function would have unmasked selection on many diverse traits that coincidentally supported this "addiction." These likely included the capacity to judge the ripeness of fruit (e.g., by the evolution of three-color vision), forage on the outer limbs of trees (e.g. by arboreal locomotor adaptations), find the sugar-rich and slightly acidic content of fruit attractive (e.g. taste receptor changes), and metabolize the sugars and tolerate the ethanol that over-ripe fruits contain (e.g. by changes in liver enzymes). All of these could be considered part of an adaptive suite for guaranteeing the supply of ascorbic acid.

9. Major hierarchic transition I: endosymbiosis

Probably the best-studied major hierarchic transitions in evolution involve the evolution of eukaryotic cells and the evolution of multicellularity. Though there are still many details to be discerned, advances in molecular and cell biology make it possible to approximately trace stages of duplication, relaxed selection, degeneration, and functional complementation leading to the hierarchic transitions in each case. In what follows, I will argue that this generic sequence of phases in the evolutionary process comprises a trajectory that is common to each of these major biological transitions.

First, consider the well-studied examples of endosymbiosis in the evolution of the eukaryotic cell discussed above. Though there are many details remaining to be uncovered there are two major events that are all but certain: the dozens of mitochondria in animal and plant cells and the chloroplasts in plant cells were once free-living monera: i.e. bacteria. Though the ancient origin of these endosymbiotic transitions has obscured many relevant details, a common feature of both is significant genetic simplification. In comparison to their closest free-living genetic precursors, it is estimated that mitochondria have lost as much as 99% of the functional genes typically present in their bacterial ancestors and chloroplasts have lost as much as 98% (Martin et al. 2015). This includes lateral transfer of genes to the cell nucleus in each case and use of proteins produced by nuclear genes. It is also generally accepted that the ancestor to the host cell was derived from the third major cellular clade, the Archaea, and was likely capable of anaerobic metabolism. The genetic support for this metabolic machinery appears also to have been lost in the process of symbiogenesis of eukaryotes. Thus, the evolution of eukaryotes involved a complementary degradation and loss of genetic control from both the host and the endosymbionts.

This transition shares several features in common with the genetic and functional degradation of ascorbic acid biosynthesis in primate evolution as well as with gene duplication in general. Both examples of endosymbiosis involve the degradation and reorganizational effects that characterize extrinsic duplication of function. In the case of mitochondria and chloroplasts, redundancy of molecular functions previously provided by the host genome, and vice versa, begins as an extrinsic duplication of functions regulated by each previously autonomous genome. Exactly which functions were duplicated and in what order is difficult to discern so long after the fact, though almost certainly the distinctive metabolic contributions of oxidative metabolism with its orders of magnitude increase in energy generation and of photosynthesis with the autonomy it provides were critical to the early stages of these mutual degradation processes. Although the most common scenarios for explaining these transitions hypothesize either the invasion of the host cell by bacterial parasites that eventually become innocuous passengers or else the ingestion of bacteria e.g. as a form of nutrient for the "host" cell but which ends up not being fully assimilated.

Comparison with the duplication-degradation-synergy examples described above, offers a third kind of scenario: an incremental transition from a mixed co-dependent community of free-living cells to the eventual fusion of two types into a single complex form.

Consider the following somewhat fanciful scenario: A major catastrophic ecosystemic event in the early evolution of life on earth was the oxygen "poisoning" of the sea and atmosphere by the photosynthetic activity of free-living cyanobacteria. This is often caricatured as a "poisoning" event because free oxygen is toxic to most anaerobic microorganisms, which were likely the predominant forms prior to the evolution of photosynthesis. In this context, anaerobic bacteria able to co-exist in mixed colonies (e.g. as in bacterial mats) with oxygen metab-

olizing forms would have provided the anaerobic forms some degree of protection from high oxygen concentrations. It may also have provided a source of nutrients, either in the form of waste products produced by the other bacterial lineage or even the oxygen-using bacteria themselves. As in the case of ascorbic acid dependency, however, long-term reliable association between these organism lineages would have partially shielded each from otherwise deleterious conditions. This could have masked selection on intrinsically maintained means to achieve these protections.

Under these reliable circumstances intense purifying selection affecting genes in each component lineage would have been relaxed and degradation of these duplicated functions in different organisms along with their supportive genetics would have ensued. But regular copresence is not guaranteed. As in the case of the degradation of the endogenous production of ascorbic acid, once there is considerable degradation of genetic support due to extrinsic duplication, selection becomes shifted onto any intrinsic influence that increases the probability of maintaining access to this extrinsic factor. In the case of ascorbic acid synthesis this involved changes in vision, taste, digestion, etc. But in the case of early bacterial, co-location can also be accomplished by endosymbiosis. Once such guaranteed linkage is achieved the symbiogenic process can proceed analogous to what occurs in the case of gene duplication, though in this case within separate structural-functional partitions.

10. Major hierarchic transition II: multicellularity

In an insightful monograph\, somewhat cryptically titled *The Evolution of Individuality*, Leo Bus (1987) provided a general theory to account for the evolution of the three major kingdoms of multicellular organisms: fungi, plants, and animals. He identified a common problem of multicellularity that required a solution: how each kingdom defends against the problem of the re-emergence of lower-level cellular autonomy.

In many respects he identified a biological analogue to what the social philosopher John Rawls (1971) described as the essential guarantor of social justice at the human level. Rawls argued that social cohesion and equality is best maintained by what he called a "veil of ignorance." In other words, a situation in which individuals cannot determine in advance their eventual station or rank in the social milieu. As a result, collectively, people will tend to set things up so that there is an equal chance of being in an advantaged social position.

For individual cells within a multicellular organism the analogous advantageous condition is being a germ line cell with the potential for unlimited reproduction rather than a somatic cell with a terminal cell lineage. A cell lineage that could favorably bias its tendency to become part of the germ line would ultimately threaten the shared reproductive success of the whole, and thus undermine the possible evolution of higher-level functional organization. Bus describes how each of these three multicellular kingdoms have evolved distinct means for preventing this sort of "backsliding" that could undermine the unity and coherence of the larger organism. In each case, individual cells are prevented from intrinsically determining the ultimate "fate" of their lineage. Briefly, this is accomplished in fungi by preventing genetic determination of distinct tissue types, in plants by eliminating mobility of cells, and in animals by determination of cell lineage fates by maternal factors prior to cell-specific gene expression. These mechanisms also each have analogues in cooperative social processes as well, such as in eusocial animals and even human prosocial conventions (though with less reliability).

These mechanisms for maintaining higher-order cooperative functionality and preventing loss of organism coherence, do not however explain how these collective adaptations initially arose. They only make sense once higher-order collective adaptations are established and are costly if allowed to degrade. So, except for invoking shared lucky accidents that assume the loss of cell-lineage autonomy and the appearance of collective functional advantage all at once, the transition from autonomous single-cell forms to higher-order multicellular forms is difficult to explain.

Here again, the effect of functional duplication, degradation, and synergistic interaction can provide insight into these transitions. In multi-celled organisms an important source of extra-genomic redundant information is geometrical. This is because both extracellular signaling and cell-cell contact can provide critical regulatory information. As a result, the relative position within a structured collection of cells can provide information concerning location-specific differentiation of molecular, structural, and functional phenotypes that can contribute to synergistic interactions with alternatively differentiated cells elsewhere in the body.

A recent study by Felipe Veloso (2017) unambiguously demonstrates that the development of multicellular animals depends on a shift of control from intracellular genetic constraints to extra-cellular relational constraints that emerge at the organism level. Using an ingenious analysis of correlations between chromosomal level regulation of gene expression patterns and cell phenotypes in human, mouse, and fly cell lineages he finds that gene-gene interactions do not fully account for cell phenotype distinctions. This indicates that the gene expression patterns that determine cell phenotypes must in part be regulated by extra-genomic sources of constraint. The author compares these distinct sources of developmental control to the genetically self-organized epigenetic landscape of Conrad Waddington (1957) on the one hand, and the extra-cellular epigenetic factors theorized by David Nanney (1958), on the other. He argues that these distinct sources of intra- and extra-genomic constraint have become functionally codependent via their recursive interactions across extracellular space and developmental time within the developing multi-celled organism. In this way extracellular interactions change gene regulation within local cell lineages which in turn modulates cell-proliferation and molecular signaling which in turn changes the extracellular context which further changes gene expression, and so forth.

Recognizing the necessity of such a regulatory "strange loop" coupling intra- and extra-cellular self-organizing processes provides an important corrective for the commonly expressed belief that gene-gene interaction effects are sufficient to determine the distinct cell phenotypes and their spatial distributions and functional interdependencies in the mature multicellular body.

Analogous to the different hierarchic transitions described in previous sections, this creates a context where functional redundancy can lead to higher-order synergies and complexity via lower-level degeneracy. Offloading aspects of gene regulation onto the extracellular environment (which constitutes the higher-order organism) frees up intracellular mechanisms so that they might be recruited for new complementary functions and thus more complex and diverse cell phenotypes.

This suggests an analogous evolutionary hypothesis for the transition to multicellularity. Simple clustering of otherwise autonomous cells derived from a common progenitor increases the probability of producing conditions in which intercellular interactions can come to redundantly influence intracellular genetic processes. To the extent that this extracellular redundancy enables subsequent degeneration of intracellular genetically based regulation, previously autonomous cells would become increasingly dependent on their multicellular environment, while at the same time increasing the probability that different cell lineages will develop complementary functions.

Veloso further argues that the evolution of this higher-order level of whole organism "telos" is possible precisely because these two sources of developmental constraint derive from otherwise completely independent self-organizing processes. The physical-chemical independence of the mechanisms involved in intracellular genetic and extracellular geometric constraints is a critical factor making them capable of providing redundant information. If this were not the case the intercellular ge-

netic constraints could not degrade without loss of critical functions. In addition, he argues that offloading regulatory work that each cell once produced intrinsically to an extrinsic locus increases the free energy available for cells to evolve additional synergistic complexity.

Particularly complex (and also counterintuitive) extra-genomic geometrical influences can emerge from "self-organizing" cell interaction dynamics. A classic example of a self-organized developmental process is the mathematically regular Fibonacci spirals observed in pinecones, sunflowers, celery stalks, and a myriad of other plants. This complex and highly regular pattern contributes to optimal spacing around a stalk and to scalable self-similar growth patterns over many orders of magnitude in size. However, its characteristic pattern of interlocking spirals of adjacent Fibonacci numbers (e.g., 3–5, 5–8, 8–13, 13–21, 21–33, …) is not explicitly coded in the genome. It is a self-organizing effect that emerges from cell–cell interactions in response to differential sensitivity to growth hormone expression. Only this hormonal regulatory response is passed from generation to generation by genetic inheritance. So again, the self-organization of this distinctive and highly regular morphology emerges from the multi-level interaction of extracellular gradients, cell proliferation, and context-sensitive gene regulation. Indeed, many of the form-generating processes of embryogenesis involve the self-organizing consequences of the way gene expression is affected by recurrent cell–cell interactions, physical forces incidental to growth and cell proliferation, and the emergent geometry of molecular diffusion that results (e.g., Newman 2016).

In animals the effects of cell-cell interaction play a major role in determining morphogenesis and tissue-specific cell types. Thus, the regulatory gene effects, discussed above, are only half of the story. The global geometry of whole organism level cell-cell contacts and molecular diffusion relationships play an indispensable organization role. During the early stages of embryo formation overlapping concentration gradients provide positional information that regulate the expression of genetic information in the cells at that locale. For example, the early anterior-posterior segmentation of Drosophila embryos is determined by extracellular gene expression gradients that are successively superimposed on each other to produce progressively more differentiated cell lineage subdivisions. The initial patterning begins with material gene expression along an anterior-posterior gradient. This gradient creates the spatial context for the expression of gap genes that establish a discontinuity between anterior and posterior cell lineage domains. This is followed by pair rule and polarity gene expression patterns that create regular striped segmental domains within which the sequence of homeobox genes becomes serially organized.

This general logic is further elaborated in vertebrate embryonic development, where multiple duplications of the entire Hox gene series enables nested levels of the same theme and variation logic. For example, this segmentation logic is roughly recapitulated in the formation of the tetrapod limb, where a medial-lateral gradient of Hox gene expression in concert with other gradient effects determines finger/toe order (e.g. see Zhu et al., 2010 and Sheth et al., 2012).

A particularly complex example of this hierarchically nested pattern of extra-/intra-cellular regulatory effects is exhibited in mammal brain development. For example, diffusion gradients of gene products (e.g., Shh, Wnt, Bmp, and Pax6) and growth factors (e.g., fgf7 and fgf8) emanating from different positions near the edges of the developing primordial cerebral cortex creates a two-dimensional matrix of concentrations that determines the relative location of cells that will distinguish later-developing cortical areas (O'Leary et al., 2013). But in addition, and unlike the local cell-cell interactions mediated by contact and molecular diffusion in most other tissues, neuronal cell-cell interactions during development can exhibit complex "action-at-a-distance" effects. This more complex extracellular influence is due to axon extension and synaptic contacts that extend across considerable intercellular distances within the nervous system. This makes possible the detailed topography of neural circuitry and the intricate functional specificity of different brain regions. These highly differentiated localized systems of distinct cell types and connection patterns are fine-tuned by selectively eliminating or preserving neurons and connections via activity dependent competitive interactions correlated with extrinsic sensory information. Consequently, manipulations of a developing animal's sensory experience can ultimately influence connectivity, neuronal cell phenotype, and gene expression in the brain. So brain development adds two additional layers of higher-order regulatory effects over and above those characteristic of other tissues.

From an evolutionary point of view these findings are consistent with the redundancy-degeneration-synergy logic proposed for the simpler hierarchic transitions discussed above. The evolution of the functional synergies between cell phenotypes emerges as a necessary correlate of this codependence of intrinsic and extrinsic sources of redundant information. This suggests that the subordination of cell functions to the requirements of their collective synergy emerged as lower-level functional autonomy degraded in the context of redundant higher-order influences. In this way the evolution of the complex forms exhibited by multicellular bodies—including animal brains—also appears to be a consequence of an analogous duplication-degradation process that ultimately shifts phenotypic control to the higher-order synergy that constitutes the multicellular organism.

11. Eusociality from the Duplication-Degeneration-Complementation perspective

For Darwin one of the most troubling apparent counterexamples to his theory of natural selection was the eusocial reproductive organization of ant and bee colonies. He intuited that their atypical reproductive specialization involved familial support and demonstrated the importance of reproduction over individual survival in evolution. But it was unclear to him how the distinctive traits of workers could be passed on to future generations if they never reproduced. The altruists' failure to reproduce for themselves would seem to have limited the ability for this trait to evolve in the first place.

As noted above, in the 1960s William Hamilton proposed an ingenious solution to this apparent paradox. He reasoned that individuals might "give up" their capacity to reproduce in order to aid the reproduction of another (e.g. the queen) if this indirectly increased the probability of passing on that individual's genes due to common inheritance. Hamilton noticed that this hyper-altruistic social adaptation in ants and bees was correlated with another atypical feature of their reproduction: haplo-diploidy, in which males are haploid and females are diploid. This major asymmetry in male/female inheritance results in the fact that daughters can be far more genetically similar to each other than they would be to their own offspring. Thus, Hamilton argued that aiding their mother's reproduction rather than reproducing on their own would be more likely to preserve more of their traits in future generations. This could be considerably amplified by the efficiency of scale that a colony could provide. This focus on genetic relatedness led to a whole domain of theories attempting to explain the evolution of such altruistic behavior: kin selection theories and a focus on evolution at the genetic level. This approach was further supported by the discovery that the few diplo-diploid species that exhibited eusociality, like termites and naked mole rats, was correlated with unusually high levels of inbreeding, which likewise produced an elevated probability of indirect genetic transmission (inclusive fitness).

Despite its elegance, it eventually became clear that kin selection theories were not complete explanations for the evolution of altruism in general, not even reproductive altruism. It was initially thought that kin selection theories would replace group selection theories, which had argued for prosocial adaptations that aided survival of lineages by virtue of preserving the breeding group at a cost to individual fitness. But it eventually became clear that there were many intergroup competitive relationships and intra-group genetic relationships that could promote

the evolution of within-group prosocial (and possibly even eusocial) adaptations. Even some of the most ardent supporters of kin selection theory have come to believe that group selection effects have made a significant contribution to the evolution of prosocial and altruistic traits (e.g. E. O. Wilson 2012), and that these two evolutionary "mechanisms" may complement one another.

One feature that both alternative accounts share is their focus on conditions that promote the indirect transmission of traits influencing prosociality, whether due to genetic factors alone (e.g., haplo-diploidy or high levels of inbreeding) or due to behaviors that result in asymmetries of relatedness within versus between groups. These conditions share many analogous features with the sorts of mechanisms that preserve multicellularity in fungi, plants, and animals (discussed above). Similarly, their primary contribution is to minimize the probability of regression back to individual autonomy.

As in the case of multicellularity, this begs the question of how these conditions were initially established during their evolution. Group selection approaches often hypothesize that demographic isolating conditions might initially promote the evolution of intra-group prosociality. Kin selection approaches alternatively often hypothesize that specialized reproductive adaptations such as the evolution of haplo-diploidy for controlling sex ratio of offspring might be exapted to promote colonial reproduction. But following the logic of duplication effects that we have explored above, there may be a third type of mechanism that could predispose the evolution of prosocial and altruistic adaptations.

This was first suggested in Hui and Deacon (2009) and described as a form of "social addiction." Both kin selection and group selection approaches have demonstrated a number of ways that altruism can be maintained across generations despite being faced with "cheating" and "freeloading" strategies (i.e. those that take advantage of cooperation but don't bear the costs of cooperating). But this means that these social behaviors must have evolved as a consequence of a prior rise in the probability of altruistic or other cooperative behaviors. This again begs the question: How did these altruistic and pro-social behaviors arise in the first place, given the costs of sacrificing autonomy? The social addiction hypothesis explains this in terms of a prior degeneration of autonomous capacities to forage, defend against predation, battle for next sites, etc., due to prolonged relaxed selection in a context where these are available in excess. But if this degeneration reaches a point of irreversible loss, maintenance of co-dependence becomes necessary. Social cooperation is no longer optional and any threat to social cohesion becomes a threat to everyone's survival. So analogous to the examples discussed above a similar process involving relaxation of selection, degradation of adaptive autonomy, and convergence onto synergistic adaptive functions may also be relevant to the evolution of social cooperation.

In the case of insect eusociality comparison to the duplication-masking-degeneracy effects that enabled multicellularity offers an interesting parallel. In the case of honey bees, for example, the regulation of gene expression that determines whether a female will become an infertile worker or a fertile queen is controlled by hormones provided to larvae by other workers (in what is called "royal jelly"). So not only is this an extra-genomic influence, it is also extra-somatic. Determination of when workers will begin producing this hormone-enriched diet is in turn regulated by the state of the queen, which may be directly signaled or indirectly indicated by changes in her reproductive output (e.g. with respect to the sex ratio of eggs). In this way, eusociality may also have evolved in the context of redundant effects of communication via social hormones that enabled degradation of intra-individual regulation of reproductive body types.

In Hui and Deacon (2009) we speculate that the presence of relaxed selection conditions that enable groups to form with minimal competition for resources and reproduction—such as in response to an overabundant resource (e.g., for feeding or nesting) that persists or recurs over generations—will enable the degradation of any adaptation that is thereby no longer under purifying selection. It should, for example, minimize any advantages gained by competition, thus degrading competitive adaptations. In parallel, any advantages that are gained by proximity, such as information about resource location or avoiding danger that can be incidentally acquired by observing neighbors, will also selectively favor maintaining proximity. So, to the extent that social proximity provides redundant functions to those important for more autonomous adaptation, those capacities will tend to degrade, analogous to the ascorbic acid example discussed above. But as in the case of loss of endogenous ascorbic acid synthesis, degradation of functions due to this socially supplied redundancy will tend to produce a degree of dependency on the social group. If maintaining this group-derived function becomes a necessity (as in the ascorbic acid analogue) it will selectively favor adaptations that help to prevent loss of group cohesion. This is what motivates calling this a form of social addiction (despite the misleading negative connotations of 'addiction') and is where various group selection theories also overlap with this analysis. Once there is a serious individual disadvantage to group breakdown selection should favor the evolution of prosocial behaviors that promote the maintenance of group cohesion and cooperation, e.g. via behaviors that minimize the re-emergence of selfish or cheating behaviors. The difference is that from the point of view of this social addiction theory a mechanism is described whereby social co-dependence initially arises due to degenerative processes and creates conditions favoring the evolution of prosocial behaviors.

12. Language

The last and highest-order evolutionary transition described by Maynard Smith and Szathmáry is the evolution of language. They consider it to be almost as significant a transition as the initial emergence of the genetic code. Language provides a critical tool for negotiating social cooperation and regulating prosocial behavior, as well as sharing and transmitting adaptive information from individual to individual and down the generations.

So, it follows that this approach to the evolution of hierarchic transitions should also be relevant for explaining the evolution of human sociality and in particular to the evolution of language. One's language capacity can only be acquired in the context of extensive social communication. Outside of a community of speakers of a common language the sound units we call words have no intrinsic meaning or function. And children deprived of social contact early in life will also be deprived of normal language capacities, rendering many of the advantages of human social life inaccessible to them. We are thus in effect "addicted" to language and the social milieu where language is a critical resource for gaining access to the advantages of collective action.

I believe that the evolution of the human capacity to acquire and use language can be understood to be partly explained as an analogous hierarchic transition process. In a series of recent papers (e.g., Deacon 2009, 2010 & 2012) I have examined a songbird parallel to evolutionary processes that have likely played a role in the evolution of the human language capacity. This involves relaxation of selection as a result of domestication and the consequences for the acquisition, transmission, and neurological production of birdsong.

In a recent series of studies comparing the singing behavior of a wild finch (White-Rump Munia) to a long-domesticated breed of the same species (Bengalese Finch, domesticated in Japan for about 250 years) it was found that the singing behavior of the domesticated birds were less innately constrained and more influenced by the experience of listening to others (Okanoya, 2004). This difference had apparently "evolved" despite the lack of any breeding for singing behavior (only breeding for coloration). I hypothesized that being shielded from natural and sexual selection in captivity has incidentally resulted in increased song complexity, greater involvement of social learning in song development, and more diverse neural control of singing behaviors, as compared to its

wild cousin. Since it is generally believed that complexity of singing behavior in songbirds is a consequence of sexual selection for male display (Catchpole and Slater 1996; Darwin, 1871; Zahavi and Zahavi, 1997), this result appears paradoxical. How could an increase in the complexity of both song structure and of neural systems for producing song have evolved in the absence of overt selection acting on these traits?

I have argued that prolonged domestication relaxed selection that in the wild had maintained highly canalized control over song structure and production (Deacon, 2010). Relaxing these environmental pressures and eliminating the role of sexual selection led to spontaneous degradation of previously strong genetic constraints which opened the door to increased epigenetic variability and conditionality. In this way the diminution of bottom-up constraints would have allowed a wider range of neural substrates and sensory experiences to influence singing behavior. More importantly, this relaxation-degradation effect and the upward shift of epigenetic control that it produces, can under certain circumstances also lead to an increase in complexity of both brain and behavior.

While it is not difficult to imagine how domestication might produce increased behavioral variability, it is less obvious how the effects of drift could explain this increase in the complexity of neural control. Relaxation of selection can be expected to produce progressive de-specialization of the circuits that contribute tight constraints on motor patterning that specify song structure. With the relaxation of inherited context independent biases, other previously inhibited or ineffectual influences, contributed by other brain systems—such as the trace of early auditory experience—could begin to play a larger role in biasing song formation. This pattern of redistributed control of function among brain systems is loosely analogous to the redistribution of the control over ascorbic maintenance that resulted from degradation of its genetic basis in the sense that degradation of this highly constrained mechanism opened the door to many other contributions from diverse and previously irrelevant mechanisms.

So how does this compare to human language adaptations?

Not only does language require vocal flexibility and decoupling of specific vocalizations from specific cognitive-emotional states, but it also requires coupling with auditory analysis and memory and with motor skill learning systems. In this respect, the functional linkage of these otherwise largely independently functioning neural subsystems in the evolution of the human brain is also paralleled by the effects of relaxed selection on the brain systems controlling song in the Bengalese Finch. The neuroanatomical contrast between song-learners' brains and songbirds with highly canalized innate songs is strikingly analogous to the neuroanatomical differences in the substrates for innate human stereotypic calls (like laughter and sobbing) and language. In humans, these stereotypic calls are largely subcortical in their origin and do not get transmitted socially. But in both socially transmitted birdsong and language there is extensive involvement of a diverse and interconnected group of forebrain structures that are not involved in the production of innate calls. Moreover, these many neural functional interactions play a critical role in the social transmission of these modes of communication. Though the similarities end there, and provide no insight into the deep semiotic and functional differences between birdsong and language, the possible role of relaxation-degradation in favoring the evolution of higher-order synergistic interactions suggests that we should begin considering possible ways that relaxed sexual and natural selection may have played a role in human language evolution.

The most obvious place to look for evidence of relaxed selection in human prehistory is associated with the development of stone tool technologies. The use of stone tools to gain access to scavenged meat beginning at rough 2.5 million years ago appears to have had two obvious relaxation effects. First it appears to have contributed to relaxation of selection on the masticatory adaptations of the australopithecine skull, jaw, teeth, and even musculature. Within about a half million years of the first fitful appearance of stone tools in the fossil record there is a significant reduction of all these adaptations, which were probably evolved for processing fibrous vegetable foods. This includes degradation of a gene for a particular myosin protein associated with jaw muscles. Second, in parallel with the reliable and ubiquitous association of stone tools with early members of the genus *Homo,* as it spread throughout the Old World, there was a significant reduction in sexual dimorphism, along with increasing stature. This almost certainly indicates that there was also a major change in social structure away from intense male-male sexual competition to a more cooperative less polygynous social organization. It is during this transition that the first significant increases in relative brain size also appears in the hominid lineage.

It is tempting to interpret these changes as the expected consequences of the relaxation of selection on a range of adaptations associated with more or less autonomous foraging and the development of cooperative foraging, with a correlated reduction of sexual selection. Though these correlated changes do not serve as direct evidence for a hierarchic transition as described in the examples described above, and the neuroanatomical changes in human brain function are only superficially analogous to changes in the finch example, the parallels are striking.

13. Conclusions and implications

The thrust of this analysis has been to extend the Duplication-Degeneration-Complementation (DDC) perspective and its analogues to also account for hierarchic transitions between levels of biological individuation. I have called the class of processes that include DDC and CNE, as well as those described above, *inverse Darwinism*. While they retain Darwin's focus on the effects of reproduction (duplication-multiplication) and variation (degeneration), they invert the Malthusian implications that follow at the ecological level. Inverse Darwinism is common in contexts of resource over-abundance, such as within a growing organism or where some essential resource is supplied extrinsically *ad libitum*.

Inverse Darwinism ultimately exemplifies an epigenetic parsimony principle: *extragenetic biases and constraints that are reliably present across generations (whether expressed by other cells in the body, other organisms in the local environment, reliable environmental constraints, or highly probable self-organizing dynamics) will tend to relax selection maintaining corresponding genetically inherited information, allowing it to degrade, and thereby increasing the probability of dependence on this extragenetic influence.* As a result, control of any correlated trait will tend to get "offloaded" onto this reliable and less costly redundant source. This becomes relevant to the evolution of hierarchic transitions of organism individuation when organisms reciprocally duplicate functions that each other needs. If this relationship reliably persists for an extended evolutionary period it will tend to produce complementary degenerative effects in each organism which if allowed to continue can result in irreversible codependency. Irreversible codependency is the defining property that characterizes each distinct level of organismic hierarchy from molecular synergies to obligate endosymbiosis to eusociality and beyond.

Inverse Darwinism provides a plausible alternative explanation for such hierarchic transitions in evolution as incidental consequences of relaxation of selection, not the effects of selection favoring higher order functions (such as in so-called "synergistic selection" theories). It is also distinct from multilevel selection theories, which focus on selection for adaptations that stabilize higher order codependencies, e.g., by suppressing "free riders" and "punishing" non-reciprocators. An inverse Darwinian approach complements multilevel selection theories by focusing instead on factors that allow codependency relations to emerge and become obligate due to irreversible degradation. As codependency becomes increasingly irreversible there will be increased selection against any internal or external threats to its dissolution. So the longer that reliable duplicate extra-genomic influences persist they become in-

creasingly likely to take over functions that have thereby been allowed to degrade.

The difficulty of explaining the evolution of cooperative and synergistic relationships has posed a challenge for natural selection theory since Darwin's time, as has the enigmatic trend toward increasing hierarchic complexity in evolution. The inverse Darwinian perspective fills in a gap in multilevel selection theories by explaining why codependent effects tend to accumulate in evolution, including hierarchic codependencies. In many respects, inverse Darwinism more fully explains the 'devo' in evodevo theory, by identifying the necessary productive complement to Darwin's selection logic.

Uncited references

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Declaration of competing interest

I assert that there is no conflict of interest.

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