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Further illusions: On key evolutionary mechanisms that could never fit with Modern Synthesis

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ABSTRACT

In light of illusions of the Modern Synthesis (MS) listed by Noble (2021a), MS's key concept, that gradual accumulation of gene mutations within microevolution leads to macroevolution, requires reexamination too. In this article, additional illusions of the MS are identified therein caused by the absence of system information and correct history. First, the MS lacks distinction among the two basic types of information: genome-defined system and gene-defined parts-information, as its treatment was based mostly on gene information. In contrast, it is argued here that system information is maintained by species-specific karyotype code, and macroevolution is based on the whole genome information package rather than on specific genes. Linking the origin of species with system information shows that the creation and accumulation of the latter in evolution is the fundamental question omitted from the MS. Second, modern evidence eliminates the MS's preferred theory that present evolutionary events can be linearly extrapolated to the past to reconstruct Life's history, wrongly assuming that most of the fossil record supports the gradual change while ignoring the true karyotype/genome patterns. Furthermore, stasis, as the most prominent pattern of the deep history of Life, remains a puzzle to the MS, but can be explained by the mechanism of karyotype-preservation-via-sex. Consequently, the concept of system-information is smoothly integrated into the two-phased evolutionary model that paleontology requires (Eldredge and Gould, 1972). Finally, research on genome-level causation of evolution, which does not fit the MS, is summarized. The availability of alternative concepts further illustrates that it is time to depart from the MS.

1. Introduction

In his recent article, Noble listed the four illusions of the Modern Synthesis (MS) that have been exposed by the development of science largely this century, some eighty years after their formulation (Noble, 2021a). They are: Natural Selection, Weissmann Barrier, Rejection of Darwin Gemmules, and Central Dogma. He ascribed these illusions to unintended errors of eminent scientists due to imprecise and misleading use of linguistic terms in interpreting evidence and theorizing about evolution. As a physiologist and a systems' biologist who is thinking deeply about evolution, he wants readers to change their view of how organisms work, away from MS's upward causality of "DNA brain" controlling every function of a cell, to a downward hierarchical causality of the wholeness of the cellular system, his principle of biological relativity. To uncover MS's illusions, he uses many arguments and concepts that the careful reader will find in this paper as well.

Noble's perspectives also reflect the general viewpoints promoted by the extended evolutionary synthesis (EES), the movement that was initiated in the 1950s by Wadington (1957), popularized in the 1980s by Gould and Eldredge (1993), and reconceptualized by Pigliucci (2007) and Muller (2007). Importantly, a fairly large disagreement seems to exist between MS and EES. While the EES movement insists the major theoretical themes, including current evo-devo research, are beyond the boundaries of the MS, and thus extended synthesis is urgently needed (Muller 2007; Laland et al., 2014), the MS holds that such efforts are unnecessary and unproductive, as "all is well" in current mainstream evolutionary studies, and the MS not only can, but has already

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addressed the issues the EES raises.

Nevertheless, many scholars from the Third Way of Evolution group (see the Third Way of Evolution website, https://www.thethirdwayofevolution.com), including James Shapiro, Denis Noble, Gerd Müller, Eva Jablonka, Evelyn Fox Keller, Stuart Newman, Keith Baverstock, John Dupre, John Torday, Michael Joyner, and others, starting from their favored subjects and viewpoints, have continuously promoted the twenty-first-century view on the basic evolutionary concepts. They emphasize more active rather than passive mechanisms of evolution, criticizing the gene-centric evolutionary explanations (e.g. selfish gene and junk DNA), illustrating the importance of epigenetic and other non-genetic inheritance in evolution, and highlighting the impact of diverse ways of transmission of genetic information (not all of it is vertically transmitted, and it is not only limited to germline) (Muller 2007; Pigliucci 2007; Baverstock 2021; Joyner 2015; Joyner and Prendergast, 2014). Coupled with the understanding of biological stochasticity, self-organization, and symbiogenesis, many have pushed the effort even further, asking for the "replacement" rather than "just the extension" of the MS (Shapiro, 2011; Noble 2013; Mazur, 2014).

Perhaps it is not quite plain to many, that the past two decades of post-genomic studies have not only promoted system-based research, but also fundamentally challenged the core concept of how biological inheritance works. Even the EES itself is constructed on a gene by gene information of the MS as its basic postulate, and natural selection as a general mechanism of accumulation of small changes (microevolution) which leads to speciation (macroevolution) over time.

As genes seem to be organized or even controlled by yet unforeseen principles beyond genes themselves, the research community should face the reality that missing heritability and multiple levels of genomic heterogeneity require system-based genomic theory. Such new genomic principles should reshape the evolutionary theory as well, as the current evolutionary concepts are based on our understanding of heredity (Heng 2009, 2019). One of Darwin's major contributions was that no one after him thought that evolution can be based on anything but heredity (cf. Gayon 1998). Similarly, with its postulate that species are the units of evolution, the MS correctly focused Darwinism on the problem of heredity in speciation. However, the MS's answer to this problem has not withstood the test of time and the advances of science require a new knowledge-based reformulation of the role of heredity in evolution. Since we show below that the gene-centrism of the MS can be called into question, it is worthwhile to consider some elements to work toward a possible future answer. What is needed is a paradigm shift in understanding heredity. In other words, the shift from gene-centric Genetics to genome-mediated Genomics is required as a basis for an evolutionary theory and Biology as science.

Here, we aim to question the basic inheritance concept that has enabled the MS to modernize Darwinism in the twentieth century. The main achievement of the Modern Synthesis is the addition of the gene-centric mechanism to Darwin's gradualist view of evolution. Specifically, it was assumed that the power of genes can explain both micro-and macroevolution via population dynamics. The MS also holds that individual genes define the phenotypic traits and that new genome systems (species) are created by accumulated gene changes (or that new gene content is the key to speciation). These assumptions seemed reasonable judged by evidence of the pre-genomic era, but now require revisitation.

Since the contemporary use in evolutionary theorizing of the basic assumptions of the MS is still widespread, their examination is needed from the standpoint of genome-based theory. For this reason, it is worthwhile to join Noble in enumerating MS illusions. Further, while it is true that experimental science is "the art of possible," this cannot be said for its underlying theories, especially if alternative theories exist with much better explanatory and predictive power. The pragmatic limits of the Mendelian and Population Genetics and early Molecular Biology were inappropriately used in the past as justification for the theoretical omissions. Now, eighty years later, when the practical limits constraining the MS at its inception are clearly no longer valid, the research community should be aware of the omissions in the evolutionary theory. Here we want to bring up the two important omissions of the MS: Absence of System Information and the Correct History.

The main illusion is the position that evolutionary theory can avoid dealing with system information. Modern Genomics made clear that Crick's Central Dogma and Jacob and Monod's Gene Regulation Theory insufficiently generalized or under interpreted information aspects of their evidence, due to the failure to treat their implications on evolutionary theory. The case is made here that modern Molecular Biology cannot be fitted within the confines of the MS anymore in this "information" century. For these reasons, recently uncovered system information properties of life forms require thorough theoretical treatment. The second omission of the correct history by Presentism[2] of the MS is made obvious not only by Evolutionary Genomics, but also by modern Paleontology. This is a serious challenge, since it can be argued that these two disciplines are the only ones able to provide direct evidence about deep evolutionary history. Despite the basic assumptions that the fossil record supports the pattern of gradual and directional changes, and that many presently observed fossil gaps will ultimately be filled, the facts point in a different direction. First, the majority of the fossil record displays a non-gradual pattern, and continuous fossil sequences are still the exception (Eldredge and Gould, 1972; Mayr 2001, Gould 2002, Jablonski, 2017; Hunt et al., 2015), suggesting that gradual evolution is not the general rule of evolution. Second, the fossils that represent the "missing links" between species are hard to find. If there are as many closely related populations between pairs of species as MS claimed, such links should be readily identifiable (Heng 2019). Currently, there are many different approaches available to correctly collect the facts about organismal evolution (Box 1). We find that most data, under careful examination, are at odds with MS predictions. We thus argue that the MS supposition that Microevolution plus time equals Macroevolution, besides facts of heredity, can no longer stand for the reason of MS getting Life's true historical pattern wrong. In this article, these illusions will be briefly examined through the lens of information flow and its relationship with evolution. In particular, by distinguishing the mechanisms of macro-and microevolution, the two-phased evolutionary model will be used to illustrate how karyotype coding is essential for system information creation, preservation, modification, and usage (Box 1).

2. Rationale, evidence, and system information-based framework

2.1. Information

2.1.1. Information and biology

The term information is frequently used in biology, but mostly without proper understanding. Everyone knows that DNA stores biological information, and information flows from it via genetic

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[2] "In literary and historical analysis, presentism is the anachronistic introduction of present-day ideas and perspectives into depictions or interpretations of the past" (https://en.wikipedia.org/wiki/Presentism_(literary_and_historical_analysis).

Box 1
Explanations of some concepts and terminology

1. **Karyotype code:** A newly identified organic code is defined by the unique order of genes and other regulatory or non-coding sequences along and among chromosomes. A common core karyotype and karyotype code are species-specific. Traditionally, a genetic code is defined by information flow between DNA and proteins via tRNA functioning as an adaptor (Barbieri, 2018). In contrast, karyotype coding needs an extended concept of code without adaptors, as within the karyotype code, information flow from a genomic basis to physiological regulatory networks is likely achieved by emergent properties, with the involvement of a coding network (Ye et al., 2019; Heng and Heng 2021; Noble 2021b).
2. **System Information:** Cell encoded genomic information is necessary for the completion of a life-cycle of species. In contrast to the genetic code defined as "Parts Information" (how to make protein from information stored within DNA), the karyotype code defines it as "System Information" (how to organize the interaction of parts formed in a network) when the totality of species-specific code is meant. System information includes a diverse type of genomic and non-genetic information (e.g. genetic, epigenetic, and physical information), all of which are coded by different organic codes. Even though different codes have their own function, they are ultimately coordinated by the genome system. More importantly, this species-specific information package is preserved by system inheritance via the karyotype constraint with the help of sexual reproduction (Heng 2009, 2019; Heng and Heng 2021). Note: "karyotype code" and the species-specific "system information" can be treated as equivalents in our discussions, even though system information can have wider meanings within a different context.
3. **Examples of empirical approaches to study the history of organismal evolution:** First, direct biological observations: As pointed out by Mayr, "Wherever we look at the living biota, whether at the level of the higher taxa or even at that of the species, discontinuities are overwhelmingly frequent" (Mayr 2001). Second, study the fossil record: "The discontinuities are even more striking in the fossil record" (Mayr 2001). Third, evolutionary genomic analyses: traditionally, karyotype analyses have demonstrated that the majority of plants and animals display different karyotypes. The current sequencing approach has confirmed this karyotype data. Moreover, the general pattern of whole-genome duplication followed by karyotype re-organization is observed in the majority of animals and plants. Fourth, watching evolution in action via experimentation: Barbara McClintock's genetic earthquake experiments with corn and our Genome Chaos experiments with cancer cells are some examples (Heng 2019).

code to protein and phenotype. As a result, most studies have focused on the genetic code from specific genes to specific proteins. Despite some interesting research that focuses on non-genetic information and their relationship with genetic regulation (Gatenby and Frieden, 2017; Frieden and Gatenby, 2019) that also links organic codes to evolution (Barbieri 1998, 2003; Lowenstein 1999), few have made any effort to define bioinformation beyond genes and especially on the question of how information and evolution shape each other (Barbieri 2018).

What started as the logical assumption that evolution needs inheritance, and that the gene is the answer to the needs of the MS, has turned into a glaring omission in this overwhelmingly important "Information Age" in the twenty-first century. Treatment of the role of system information in Biology is essentially missing from the MS.[3] Molecular Biology is directly responsible for a half a century delay of evolutionary Biology facing up to a basic treatment of information. Crick with "Central Dogma" (1958, 1970) and Jacob and Monod with their model of "Gene Regulation" (1961) came to the accurate, but incomplete conclusions about biological information implied by their results. The proximal accuracy of their interpretation of how information is stored in DNA, and how information flows from DNA to protein and phenotype has dominated Molecular Biology and allowed its enormous practical success in the second half of the last century. The omission of conclusions that could be drawn from their evidence allowed these pioneers to consign biological information to the present limbo of irrelevance for understanding evolution. The MS profited from being acceptable to a whole generation of Molecular Biologists. Jacob's "tinkering natural selection" metaphor (Jacob 1977) serves as an extreme example of unwarranted assignment to the natural selection of the MS of the genially understood Life's system information accumulation property. Needless to say, no theoretician found arguments for a notion that natural selection as an evolutionary force has "tinkering" properties, so the tinkering pattern of the creation of new system information by partially reusing the old one has not been the part of the MS, but in some form should be included in the future information-based theory of evolution. One can conjecture that these errors of judgment of the early Molecular Biologists were made due to their unshakable faith in the unlimited validity of Mendelian Genetics and by extension any and all conclusions of the MS based on it. Our essential complaint is that they accepted the fallacy of Mendelian genetics, that its experimental results under highly constricted artificial evolutionary conditions, specifically focusing on the connection of outliers (Heng 2019), define the limit of what is possible in Evolution. Further, it was known throughout the twentieth century that Mendelian Genetics is blind to fixed characters of species and characters differing among species, due to the impossibility of performing informative crosses (Amundson 2006), yet it is just these characters that are essential for the study of Evolution. We argue the evidence shows this concept of Genetics is obsolete, if the current understanding that Genetics equals Heredity is to be retained. To mention a few examples: The problem of missing heritability (Zuk et al., 2012; Heng 2010), the genes are "fuzzy" (not clearly defined functionally but endowed with arrays of potential from which appropriate instantiations can be selected by environments) (Heng 2019), and the wrong assertion, due to the blind spots, that saltational hybrid

[3] See, for instance, Mayr's most recent statement on the matter: "The genotype, the genetic program of every individual, codifies as Max Delbruck had put it, "the experience of billions of years of ancestors." Hence, every activity of an organism is controlled by two sets of causations, functional or proximate ones representing physicochemical factors, and ultimate or evolutionary causations, reflecting information provided by the genetic program" (Mayr 1997). It shows that one should disregard Mayr's speak of genetic programs and information (started in 1961 as a nod of the MS to the successes of Molecular Biology), since these terms were effectively reduced via individual genotype to the fundamental postulate of the MS that changes in gene frequencies cause evolution (this postulate is the textbook truism taught at university courses, *cf.* https://www.ndsu.edu/pubweb/∼mcclean/plsc431/popgen/popgen4.htm, or given in internet definitions, *cf.* https://www.nature.com/scitable/definition/speciation-183,/accessed Oct. 2021).

speciation is genetically impossible, which ignores that it happens in nature nevertheless (Crkvenjakov and Drmanac 2007).

2.1.2. Coding information

There is an idea in the literature that a new, specific kind of information emerged at the origin of the first cell, different from the kinds of information present in nonliving parts of the universe. This idea has been put forward by experts from fields as disparate as Physics (Feistel and Ebeling, 2011; 2016), Information Science (Battail 2014), and Semantic Biology (Barbieri 2003). Information specific to Biology is called symbolic, or semantic information. It is the essential basis of the functioning of every living creature that ever existed, including us. This kind of information is the basis of human civilization, language, science and computers, but is identical in its properties as in the simplest of organisms and is brought into existence by evolution. For instance, Shannon in his Information Theory (Shannon, 1948) did not discover universal properties of communication applicable to the nonliving world as well as to our human messages. He just uncovered very important aspects of the specific kind of biological information that enables Evolution. From the origin of Life, Shannon-type communication must take place between the genetic material and the rest of the cell for the latter to be viable.

The semantic/symbolic information carries the "meaning" aspect of the message in biology as well as human intentionality in ordinary communication, or computer science. Semantic information, or meaning, is always encoded in the material carrier of the message and does not increase or change if copied to the same or different adequate carrier. Therefore, due to encoding, codes underlay the essential distinctness of information Life processes. What Crick failed to realize and theorize about is that genetic code is not the first nor the only and the ultimate code brought about by evolution. Barbieri and others have since uncovered numerous additional codes within and outside DNA sequences (Barbieri 2017; Lowenstein 1999). One of us has proposed the karyotype code as a term for genome-specific coding to reflect its species rather than organismal properties (Heng et al., 2011; Ye et al. 2019; Heng and Heng 2021a) (Box 1).

Many types of inheritance can be linked to various organic codes (Heng and Heng 2021a): 1.) information contained in the sequence of genomic DNA, changeable by all kinds of mutations vertically or horizontally mediated (e.g. genomic changes mediated by cell to cell exchanges: Heng et al., 2016, Hamann et al., 2017; Javeed and Mukhopadhyay 2017; Raghuram et al., 2019, Mills et al., 2019, Ye et al., 2019b); 2.) information contained in the processing mechanisms which control and modify transcription and translation (e.g. liquid phase condensation affecting expression of phenotype: Hnisz et al., 2017; Shin et al., 2018); 3.) non-genomic information regulation mechanisms based on cellular structures like membranes (e.g. information dynamics by ion flows: Gatenby and Frieden 2017), protein complexes, epigenetic mechanisms, etc.; 4.) information mediated by dynamic cellular microenvironment contextualization in response to perturbation (Kontush et al., 2015; Sinkler et al., 2017; Wallace 2012; Wallace and Chalkia 2013; Heng 2015); and 5.) information contained in mechanisms responsible for switching among alternate cellular states or even imposing new ones, as in various phase transitions within or among cells as in development, cancer, regeneration, behavior etc. (Heng 2019; Heng and Heng 2021b).

2.1.3. Karyotype code

Karyotype code (Box 1) sits at the top of a hierarchical organization of all other cellular codes, integrating them into a functioning whole whether they have genomic DNA as a direct component of the material sender (as in the genetic code) or receiver of messages. Regarding codes contained in the sequence of genomic nucleic acids, Molecular Biology at its inception has chosen not to explicitly address the hierarchy of codes obvious from its results and to accept a reduction to Mendelian genetics as the basic conceptualization of information contained in these results. Obvious things of sequence organization, like the order of genes and various regulatory sequences extending to the fixity of structures of chromosomes underlying even the simplest mechanism of "gene regulation" such as lactose operon of *E. coli* (Jacob and Monod 1961) were ignored for the theoretical simplicity of the MS concept of a gene by gene control of phenotype. By the turn of the last century, it was suggested that genomic DNA is not the controller of the phenotype, but rather a major component of the read and write memory of the cellular software and hardware, which in turn control the dynamic phenotypic trajectory of the organism through its life-cycle (Shapiro 1997; Keller 2000). Maximizing the overlap of codes during evolutionary history by increasing their overlap/crowding as much as possible within a given sequence length is a straightforward way of increasing the information storage efficiency of this "memory" as required by the Shannon's coding theorem. For example, chromatin behavior and gene expression are defined by chromosome structure (Heng et al., 2004), and also proper expression of any particular gene depends on its correct placement within TAD (topologically associating domain), which is necessary for the correct 3D chromosomal looping in the nucleus (Dixon et al., 2016). A sequence code as important as TAD was undetectable by advanced Drosophila crosses, still held by some as a "perfect tool" of Mendelian Genetics to uncover "gene regulation." The additional methods required for the task demonstrate that modern genetics is broader than the Mendelian paradigm, and that the absence of evidence of the latter cannot be taken as evidence of the absence of evolutionary important, otherwise indicated, Heredity phenomena. This should not be taken as arguing that inheritance is just DNA coding, but instead that it consists of arrays of codes of the five kinds mentioned above which are organized and preserved by karyotype coding.

2.1.4. Macroevolutionary information

The correct theory has to answer how coding information is, 1. Created 2. Conserved 3. Modified and 4. Used in evolution in terms of twenty-first-century Molecular Biology (Heng and Heng 2021a). Regarding the karyotype coding change by modification of the sequence of genomic nucleic acids in evolution, views have drastically changed since the heyday of MS eighty years ago. Emphasis on the importance of undeniable point mutations of individual genes considered as supportive of Fisherian gradual evolution has been replaced by evidence of considerable chromosomal set reorganization at the genome system level, comprising a larger extent of sequence than contained in individual genes. McClintock's proposal of stress-induced genome reorganization (McClintock 1984) has now been explained and extended by Shapiro's natural genome engineering mutation theory (Shapiro 1997) making clear that larger phenotypic changes as seen in macroevolution are more likely to be brought about by genome-level changes that affect a plurality of genes. We have shown that the massive reorganization of the genome is the obligatory step in the evolution of the lethality of most cancers (Heng et al., 2006; Heng and Heng 2021b). The evidence of stress-induced karyotype change in somatic cells in cancer prompts the question of what induces similar order of magnitude change in chromosomes in speciation (Heng 2019). The mainstream theory has chosen to ignore pioneers like Goldschmidt (1940), McClintock (1942), White (1945), and Darlington (1958), among others, who emphasized the importance of coincidence of changes of cytological karyotype picture with speciation, while being otherwise stable in the germline of species member

organisms in microevolution. Some molecular biologists still fail to appreciate the importance of karyotype, because they consider genes as the only information carriers. For them, chromosomes are just scaffolds erected to hold and allow genes to function. Such views can not explain why in evolution of cancer the cellular crisis stage ensues with rapid phase transition to forced drastic karyotype changes we named Genome chaos (Heng 2007a, 2019; Liu et al. 2014). Our emerging knowledge of karyotype coded 3D chromatin organization in the nucleus illustrates that karyotype changes within species exert phenotypic effects through reorganization of the gene network, which is much more profound than the disruption or activation of specific gene sequences and shows how karyotype defines phenotype by controlling the transcriptional landscape (Stevens et al., 2013, 2014). Without seeing that sex (Heng 2007b; Gorelick and Heng 2011) and germline and soma separation mechanisms are specifically designed to repair and preserve the species karyotype unchanged through generations during the entire species' lifespan, one simply cannot account for the constancy of chromatin spatial organization of specific cells among different organisms within species. However, the cellular differentiation in each of these organisms is accomplished by species-specific complex deterministic changes of this spatial organization throughout development from zygote to a complex neuron or a simple fibroblast cells in adults (Payne et al., 2021, Takei et al., 2021a; 2021b). In speciation, conversely to its within species constancy, there is a necessity of thorough reorganization of this complex karyotype mediated chromatin differentiation dance. This is accomplished by the karyotype code change visualized by the cytological detection of the new karyotype.

2.1.5. Creation of macroevolutionary information

Nowadays, genome sequencing results complement the cytological results to allow the theory of speciation to require novelty information creation in rapid reorganization of the genomic sequence above gene level, which we call Genome Chaos (Heng 2007a, 2019; Liu et al., 2014). Genomic evidence is particularly well suited to uncover the Genome Chaos speciation trigger, consisting of the horizontal introduction of the entire genomic DNA of a different species into the host nucleus. Rare genome duplications or genome merging hybridization speciation cases were known before the genome sequencing era of this century, but the latter uncovered the abundance of examples in most branches of the tree, just as well recently as in the deep past. Moreover, stress-induced rapid genome reorganization via Genome Chaos, a powerful means for information self-creation, should play an important role in speciation—enough indeed to consider it a rule rather than an exception. For instance, the human genome incorporates Neanderthal and Denisovan DNA (Green et al., 2010; Reich et al., 2010) and hybridization speciation is a norm rather than the exception in such textbook icons of the MS as Darwin finches (Lamichhaney et al., 2018) and cichlid fish (Meier et al., 2017). In horizontally induced Genome Chaos speciation, coding information of two species is not simply added together but must be scrambled into the functioning whole in a single generation tested by the survival of progeny. In studying the genome in a new species in generations following the merger, it is obvious that before entering stability of stasis, significant portions of partner's DNAs are lost due to natural selection streamlining of duplicated information. However, the distinguishing functionality of the new species over its progenitor in a lineage is the result of a creation of new coding information that became an integrated part of the species-specific karyotype code in the first generation. This definite result of Genomics clashes with the presentism of Mendelian Genetics, which holds that genetic events cannot happen if they are not detected at experimentally or observationally measured frequencies. However, as indicated by Genomics, they do. Under normal conditions, there is an extremely rare chance of the success of macroevolutionary selection. The resulting organism needs to break the karyotype constraint by forming a new genome, meeting reproductive partners with the same or similar genomes to preserve the new system information, and surviving among individuals with parental genomes. Nevertheless, no matter how rare in human terms, the average rate of formation of macroevolutionary species, estimated to be on the order of 1–10 events per year in the entire biosphere, is sufficient to account for all species indicated to have ever existed by the fossil record (Sepkoski 1998). It should be pointed out that this speciation rate is probably much higher than that estimation, given that the vast majority of the newly formed species will go extinct before they can become long-lasting species with a robust population with a high enough chance to be fossilized (Heng 2019).

2.1.6. Maintenance and growth of macroevolutionary information

There are two aspects of the problem of maintenance of information contained in the codes created at speciation events. On the one hand, it can last maximally as long as species exist and then be extinguished at species extinction. On the other hand, at some point during its lifetime a species can be a participant in macroevolutionary speciation and pass a portion of, or the whole of, its code vertically to the next species in its higher taxon lineage. In the latter case, there is a growth of information in the lineage by accumulation in successive speciations.

Evolutionary stasis can be interpreted to be caused by the coding information package (karyotype code) formed at macroevolutionary speciation being stable during species lifespan, its coherence protected by the function of sex and/or strong purifying selection at karyotype level. Polymorphic variants and their populations within species are viable as long as they stay within the karyotype package's coherence limits (as long as the core genome is dominant in the population). In this case, a species' extinction after a stasis millions of years long is naturally seen as the result of the failure of a stable karyotype coding system to provide the fit of organisms carrying it to the necessarily time-changed external (mostly biotic) conditions anymore.

Vertical inheritance of coding information in the tree of Life ensures both partial, or complete maintenance of its speciation achieved gains and its accumulation in the particular lineage. This mode of accumulation would be vulnerable to a complete loss with the extinction of the lineage. However, horizontal inheritance mechanisms participating in some speciations involving more distantly related parents ensure the sharing of encoded functionalities between higher taxon lineages on the tree so that some hardly achieved informational gains are not lost with inevitable lineage extinctions. Some coding modules of the most important functionalities achieved in evolution, like photosynthesis, are passed among species from different lineages and preserved in recipients to provide them with a strong survival basis on which to build their own innovations. The exponential pattern of evolution lasting four billion years (cf. Benton 2016) shows that while some extinction losses of coding information were inevitable, like in mass extinctions, the exponential increase of system information with time was maintained overall.

2.2. Macroevolution

2.2.1. Presentism

We argue that the MS denies the importance of Macroevolution in Evolutionary History. This value judgment of the MS is based on the presentism fallacy, that Microevolution plus time equals Macroevolution. As mentioned above, Mendelian Genetics is objectively constrained to study genetic processes occurring within

given species only. Due to the near impossibility of crossing organisms from different species in nature, it cannot provide understanding about an alternative genetic process that might create speciation-mediated genetic differences abundantly observed by Genomics. Not recognizing, or dismissing, this fundamental difficulty, the MS made a virtue out of little more than a leap in faith by extrapolating the relevance of Population Genetics into the study of the origin of species and higher taxa. Genomics results have made this illusion bare for everyone to see. However, in the last century Paleontology posed the challenge to this extrapolation not on heredity grounds, but on the issue of timescale differences between processes of population and species change (Eldredge and Gould 1972; Mayr 2001; Jablonski 2000, 2017). This challenge, though refuted for a time, is now shown to have been correct by the Genomics results mentioned above. Our proposal of species stability being caused by its karyotype code explains stasis, the main feature of deep evolutionary history.

We turn to the role of historical facts in understanding Macroevolution. Evolution as a science must rely on the evidence of the deep past to understand real history, evidence of which is presently contributed only by the biology fields of Paleontology and Genomics. In view of these disciplines, the historical pattern of fossils and karyotype information are key. From the genomic point of view of history:

> "*the DNA record definitely does not support the slow accumulation of random gradual changes transmitted by restricted patterns of vertical descent" (Shapiro 2011).*

On the contrary, the distinctive karyotype changes (e.g. whole-genome duplication and translocations) are common historical events associated with macroevolution (Shapiro and Noble, 2021; Schubert 2007; Heng 2009; Murat et al., 2017; Simakov et al., 2020). From the point of view of fossils themselves, even though this issue has been a well-known challenge ever since Darwin's time, it is worth pointing out that the advanced analyses by modern paleontological techniques have only increased the questioning of gradualism. Recent systematic analyses have forcefully illustrated that in contrast to the general assumptions that fossil record supports the gradual and directional changes, a large majority of fossils display non-gradual patterns (Hunt et al., 2015), suggesting that there is no evidence to support the gradualism as a general pattern in evolution. Instead, the gaps between fossil species are a general rule (Heng 2019). Overall, the presently solidifying view of the fossil record does not support the MS view of evolutionary history.

The events and processes observed by us, humans, in the present or immediate past while being informative about Microevolution might be influencing the real evolution actors either indirectly (non-linearly), or not at all. As an example of a possible answer about that relation, see the evidence for the existence of "ephemeral" species alongside the long-lived (over a few million years, cf. Sepkoski 1998) ones, made visible by the order of magnitude improvement over the standard paleontological temporal resolution in an exceptional part of the fossil record (Crampton et al., 2020). In recent years, in a general trend, whole-genome sequencing of numerous animal and plant species illustrates that often the key evolutionary past events like genome duplications, genome mergers and symbioses are simultaneous with massive Genome Chaos, to re-organize karyotypes (Schubert 2007, 2021; Heng 2009, 2019; Hoang and Schubert 2017; Murat et al., 2017; Simakov et al., 2020; Mudd et al., 2020).

2.2.2. Macroevolutionary history of life

Current knowledge confirms Darwin's descent with modification principles, best symbolized by his tree of Life metaphor. However, Cladistics, a version of Systematics formulated after the MS, has made it possible to view the tree of Life (its degenerative branches trimmed off) as a history of additive accumulation of species-level novelties with time (Eldredge 1989). There is an approximate proportionality of the number of novelties and number of branches in successive horizontal time sections of the tree. Since the number of fossil species in the last 500 million years increased nearly exponentially with time (Benton 2016), the number of novelties carried by them must have followed. In other words, there is a progressive trend in Macroevolution toward increasing the functional repertoire of Life summed over all of its branches. Others have termed this now hardly deniable Macroevolutionary trend as an increase of complexity. However, despite Darwin, the MS has criticized notions of progress in evolution. The progressive novelty kinetics being roughly coincidental with the history of the planetary expansion of Life is not easily compatible with theories of non-biotic environmental factors being causative for the entire Macroevolutionary history, as favored by many followers of the MS. We have argued above for use of the basic notion of System Information in evolutionary discourse instead of the proxy terms of complexity and novelty.

2.2.3. The mode of macroevolution

Eldridge and Gould's (1972) theory of punctuated equilibrium has been initially seen as the most serious challenge to MS. Unfortunately, Gould could not identify the mechanism of punctuated evolution without access to the system information perspective on macroevolution (creation of new genomes by crisis, and preservation by sex and environmental constraint), which resulted in his eventual return to the MS (Gould 2002). The stasis question remains open to this day. Recent estimates suggest the pattern of morphological change during a species' lifespan in the record is that over half of all fossil species experience stasis (no change after their abrupt appearance in the record), one third follow a random walk pattern of change, while less than one-fifth exhibit the true MS pattern of gradual change (Hunt et al., 2015, Jablonski, 2017). Furthermore, based on the pattern of the sudden appearance of individual higher taxa in the record, it seems that the majority of the species which are progenitors of these long-living monophyletic species lineages follow a punctuated mode of evolution.

Both stasis and random walk mode on the scale of millions of years during a species' duration preclude microevolutionary change having the ability to constantly surface in and extrapolate to the macroevolutionary pattern. The MS has not faced up to this fact and to the problem of what causes the stasis. MS proponents agree that stasis is due to stabilizing selection but have advanced unconvincing explanations for various external selective factors, mainly climactic (Eldredge et al., 2005), since these factors do not exhibit the required stability necessary for acting on the majority of species in the record. As mentioned above, we argue for the possibility that stasis purifying selection is caused by the internal factor of karyotype code limiting the ability of species members to drastically change their karyotype and eliminate these individuals with altered genomes, regardless if environmentally or stochastically induced. The cause of stasis is the genomic constraint imposed in order to preserve system information. As indicated by the cancer evolutionary model (Heng and Heng 2021b), the evolution of a long-lived species in a lineage should be regarded as a two-phased evolutionary process, displaying a chain of successions between fast change and enduring constancy (Heng 2009, 2019).

2.2.4. Alternative frameworks to replace the MS

Pointing out the key limitations of the MS is the first and essential step to establishing a better evolutionary theory, as proposing a new paradigm is crucial to create competitive landscapes

for the new frameworks to be formulated, grow, and be accepted. In addition to many concepts proposed by The Third Way evolutionary biologists, we have introduced the Genome Architecture Theory (GAT). Compared to the MS, the GAT has obvious advantages in explaining evolutionary facts and observations. First, in evolutionary studies of cancer, the two-phase cancer evolution pattern was described which suggests the distinctive mechanisms of gene-mediated microevolution and karyotype-mediated macroevolution (Heng et al., 2006). This new relationship between cellular micro- and macro-cellular evolution also questions the role of natural selection in the latter (Heng et al., 2006; Heng 2015, 2019). Second, the inheritance was classified into gene-mediated "parts inheritance" and karyotype-mediated "system inheritance," plus non-genetic inheritance. The system inheritance is maintained by sexual reproduction, as meiotic pairing is a powerful system constraint functioning to preserve the species specificity of a given genome. This requires the re-thinking of how inheritance works in the evolutionary process. Third, all genomic and non-genomic inheritance is fuzzy, and the higher-level inheritance can constrain the inheritance at lower levels. Fourth, this information concept has been integrated into the evolutionary process. Specifically, karyotype coded system information has been introduced to organize the function of genes, the parts information, as well as the notion that evolution is all about information creation, preservation, modification, and usage (Heng and Heng 2021a) (Box 1). Starting with these new realizations, it is appropriate to reexamine many key assumptions in biology that relied on the correct understanding of the information underlying biological inheritance. This involves the recognition of a number of the paramount functions of the genome. The most important of which are: it serves as a system information package, is the macroevolutionary selection unit, and has the role of a key platform in displaying and preserving novelties/emergent properties (Heng 2019, p 383). By briefly introducing the GAT here, we hope that other alternative evolutionary theories can be comparatively discussed as well.

3. Conclusion

The evidence presented above can be divided into two groups. Genome structure findings are given in the form of evidence about cytological karyotype, and functional studies of supra-genic features of the organization of the genome. Further, comparative results of complete genome sequencing of different species diverged at various points of deep time allow conclusions about evolutionary history. Also, the summary of paleontological evidence is given about the true actors and pattern of evolution on the relevant record timescale of the last two billion years. The entirety of both lines of evidence leads to a single realization. The MS treatment of Heredity is outdated, as is its evidence base. Instead, the System Information is proposed as being responsible for hereditary phenomena. It is defined as the totality of materially encoded meaning available to organisms for their functions. The system information functions by supplying and organizing different organic codes including the genetic code in order to direct the making of phenotype. The primary mechanism of Heredity is the one creating, modifying, and preserving the system information on Darwin's tree of Life rather than just passing information from DNA to protein. Time-dependent expansion of planetary availability of system information is responsible for the increasing phenotypic richness (disparity and diversity) of the biosphere. In this view, Macroevolution is concerned with the creation and accumulation of System coding over the entire evolutionary history, and Microevolution likely involves the growth of populations and its associated selected gene frequency changes.

It is important to appreciate the need for new theoretical frameworks to explain the new facts produced by the advancement of scientific fronts, and then to form new concepts which unite those frameworks into a general theory. The history of the emerging genome theory, emerging in the last decades of the previous century and continuing to this day, still awaits review. However, along with key realizations from others, partially mentioned here, the eventual list (ordered chronologically) of contributions might also include: two-phased cancer evolution (Heng et al., 2006), the genomic definition of species (Crkvenjakov and Drmanac 1991; Heng 2009, 2019), the function of sex and karyotype change is the universal feature of speciation (Heng 2007b; Wilkins and Holliday 2009; Gorelick and Heng 2011), Genome Chaos as an evolved mechanism of system change (Heng 2007a, 2019; Liu et al., 2014), system theory of evolution by programming (Crkvenjakov and Drmanac 2007), the genome as an object in need of decoding (Heng et al., 2011; Heng 2019) and karyotype coding (Heng 2009; Ye et al., 2019; Heng and Heng 2021a). Taken together, this work finally provides some needed theoretical basis for the importance of the chromosomes in evolution suggested by some genome pioneers like McClintock, Goldschmidt and others in the last century. Recently, an increasing number of publications have addressed this issue (Shapiro and Noble, 2021a, 2021b).

By integrating many alternative frameworks, such as the theory of natural genetic engineering (Shapiro, 1977, 2011), the system and physiological theory of evolution (Noble, 2013, 2021a,b), non-genomic theories including the epigenomic theory (Jablonka and Lamb, 2005), the theory of organic codes including the "life code" (Barbieri, 1998, Liu, 2020), and the self-organization and complexity theory (Prigogine and Stengers, 1984); (Kauffman, 1995), a new landscape of evolutionary studies will soon emerge.

In closing, Genomics as a molecular science is the newest frontier of Molecular Biology, and its results impact the conceptual whole of its parent. At its inception, Molecular Biology subscribed to the absolute reliance on Mendelian Genetics and thus to the presentism of the MS interpretation of Evolution. Recent uncovering of new heredity phenomena by Genomics, beyond the gene concept of classical Genetics, indicates to us that Molecular Biology needs its own reconceptualized theory of Evolution, which will incorporate genome and species levels, entirely missing in MS. The new theory will show that Molecular Biology, rather than the science of gene control of phenotype, was and is a science of role of coding information in biological systems. Information as such needs to be finally integrated into the genome-based evolutionary theory. It is now becoming clear how information flow is shaped by evolution by identifying the key biological contributions of system information in the creation and preservation of codes, in contrast to the majority of current efforts that mainly focus on the usage of gene-level information and some non-genetic information. Such new appreciation also provides a strong answer to the claim of Intelligent Design that mechanisms of the evolutionary theory cannot sufficiently account for the generation of genetic information to prove the reality of evolution. Evolution is true, as shown by abundant evidence, but its proposed mechanisms need to be reassessed as science progresses.

Author statement

RC and HH drafted the manuscript. All authors have read and agreed to the published version of the manuscript.

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References

Amundson, R., 2006. The Changing Role of the Embryo in Evolutionary Thought: Roots of Evo-Devo. Cambridge University Press.
Barbieri, M., 1998. The organic codes: the basic mechanism of macroevolution. Riv Biol Biol Forum 91, 481–514.
Barbieri, M., 2003. The Organic Codes: an Introduction to Semantic Biology. Cambridge University Press, Cambridge.
Barbieri, M., 2017. How did the eukaryotes evolve? Biol. Theor. 12, 13–26.
Barbieri, M., 2018. What is code biology? Biosystems 164, 1–10. https://doi.org/10.1016/j.biosystems.2017.10.005.
Battail, G., 2014. Information and Life. Springer.
Baverstock, K., 2021. The gene: an appraisal. Prog. Biophys. Mol. Biol. 164, 46–62. https://doi.org/10.1016/j.pbiomolbio.2021.04.005.
Benton, M.J., 2016. Origins of biodiversity. PLoS Biol. https://doi.org/10.1371/journal.pbio.2000724.
Crampton, J.S., Cooper, R.A., Foote, M., Sadler, P.M., 2020. Ephemeral species in the fossil record? Synchronous coupling of macroevolutionary dynamics in mid-Paleozoic zooplankton. Paleobiology 46, 122–135.
Crick, F.H.C., 1958. On protein synthesis. Symp. Soc. Exp. Biol. 12, 138–163.
Crick, F.H.C., 1970. Central dogma of molecular biology. Nature 227, 561–563.
Crkvenjakov, R., Drmanac, R., 1991. Genomic Definition of Species. OSTI.GOV Technical Report. https://doi.org/10.2172/10159428.
Crkvenjakov, R., Drmanac, R., 2007. Biological Evolution as Natural Programming, Academie Serbe des Sciences et des Arts Bulletin, Tome CXXXVI, Sciences Naturelles. publ. No 45, pp. 1–108 (available on request as .pdf file from R.C. (rcrk@comcast.net)).
Darlington, C.D., 1958. Evolution of Genetic Systems. Oliver and Boyd, Edinburgh and London.
Dixon, J.R., Gorkin, D.U., Ren, B., 2016. Chromatin domains: the unit of chromosome organization. Mol. Cell. 62 (5), 668–680. https://doi.org/10.1016/j.molcel.2016.05.018.
Eldredge, N., 1989. Macroevolutionary Dynamics. McGraw-Hill, New York.
Eldredge, N., Gould, S.J., 1972. Punctuated equlibria: an alternative to phyletic gradualism. In: Schopf, T.J.M. (Ed.), Models in Paleobiology. Freeman Cooper, San Francisco, pp. 82–115.
Eldredge, N., Thompson, J.N., Brakefield, P.M., Gavrilets, S., Jablonski, D., Jackson, J.B.C., Lenski, R.E., Lieberman, B.S., MCPeak, M.A., Miller III, W., 2005. The dynamics of evolutionary stasis. Paleobiology 31 (2,Suppl. l), 133–145.
Feistel, R., Ebeling, W., 2011. In: Physics of Self-Organization and Evolution, first ed. Wiley, Weinheim, Germany.
Feistel, R., Ebeling, W., 2016. Entropy and the self-organization of information and value. Entropy 18, 193. https://doi.org/10.3390/e18050193. www.mdpi.com/journal/entropy.
Frieden, B.R., Gatenby, R., 2019. Ion-based cellular signal transmission, principles of minimum information loss, and evolution by natural selection. Int. J. Mol. Sci. 21 (1), 9. https://doi.org/10.3390/ijms21010009.
Gatenby, R.A., Frieden, B.R., 2017. Cellular information dynamics through transmembrane flow of ions. Sci. Rep. 7 (1), 15075. https://doi.org/10.1038/s41598-017-15182-2.
Gayon, J., 1998. Darwinism's Struggle for Survival: Heredity and Hypothesis of Naural Selection. Cambridge University Press.
Goldschmidt, R.B., 1940. The Material Basis of Evolution. Yale University Press, New Haven.
Gorelick, R., Heng, H.H., 2011. Sex reduces genetic variation: a multidisciplinary review. Evolution 65 (4), 1088–1098. https://doi.org/10.1111/j.1558-5646.2010.01173.x.
Gould, S.J., 2002. The Structure of Evolutionary Theory. Belknap Press of Harvard University Press, Cambridge, Mass.
Gould, S.J., Eldredge, N., 1993. Punctuated equilibrium comes of age. Nature 366 (6452), 223–227. https://doi.org/10.1038/366223a.
Green, R.E., Krause, J., Briggs, A.W., Maricic, T., Stenzel, U., Kircher, M., et al., 2010. A draft sequence of the neandertal genome. Science 328, 710–722.
Hamann, J.C., Surcel, A., Chen, et al., 2017. Entosis is induced by glucose starvation. Cell Rep. 20 (1), 201–210 https://doi.org/10.106/j.celrep.2017.06.037.
Heng, H.H., 2007a. Elimination of altered karyotypes by sexual reproduction preserves species identity. Genome 50 (5), 517e524. https://doi.org/10.1139/g07-039.
Heng, H.H., 2007b. Karyotype chaos, a form of non-clonal chromosome aberrations, plays a key role in cancer progression and drug resistance. In: FASEB Summer Meeting: Nuclear Structure and Cancer. Saxton reviver, Vermont.
Heng, H.H., 2009. The genome-centric concept: resynthesis of evolutionary theory. Bioessays 31 (5), 512–525. https://doi.org/10.1002/bies.200800182.
Heng, H.H., 2010. Missing heritability and stochastic genome alterations. Nat. Rev. Genet. 11 (11), 813. https://doi:10.1038/nrg2809-c3.
Heng, H.H., 2015. Debating Cancer: the Paradox in Cancer Research. World Scientific, Singapore.
Heng, H.H., 2019. Genome Chaos: Rethinking Genetics, Evolution, and Molecular Medicine. Academic Press Elsevier, Cambridge, MA, USA, ISBN 978-012-8136-35-5.
Heng, J., Heng, H.H., 2021a. Karyotype coding: the creation and maintenance of system information for complexity and biodiversity. Biosystems 208, 104476. https://doi.org/10.1016/j.biosystems.2021.104476.
Heng, J., Heng, H.H., 2021b. Genome chaos: creating new genomic information essential for cancer macroevolution Seminars in Cancer Biology. https://doi.org/10.1016/j.semcancer.2020.11.003.
Heng, H.H., Goetze, S., Ye, C.J., et al., 2004. Chromatin loops are selectively anchored using scaffold/matrix-attachment regions. J. Cell Sci. 117 (Pt 7), 999–1008. https://doi.org/10.1242/jcs.00976.
Heng, H.H., Stevens, J.B., Liu, G., et al., 2006. Stochastic cancer progression driven by nonclonal chromosome aberrations. J. Cell. Physiol 208 (2), 461–472. https://doi.org/10.1002/jcp.20685.
Heng, H.H., Liu, G., Stevens, J.B., et al., 2011. Decoding the genome beyond sequencing: the new phase of genomic research. Genomics 98 (4), 242–252.
Heng, H.H., Regan, S.M., Liu, G., Ye, C.J., 2016. Why it is crucial to analyze non clonal chromosome aberrations or NCCAs? Mol. Cytogenet. 9 15. https://doi.org/10.1186/s13039-016-0223-2.
Hnisz, D., Shrinivas, K., Young, R.A., Chakraborty, A.K., Sharp, P.A., 2017. A phase separation model for transcriptional control. Cell 169 (1), 13–23. https://doi.org/10.1016/j.cell.2017.02.007.
Hoang, P., Schubert, I., 2017. Reconstruction of chromosome rearrangements between the two most ancestral duckweed species Spirodela Polyrhiza and S.Intermedia. Chromosoma 126 (6), 729–739. https://doi.org/10.1007/s00412-017-0636-7.
Hunt, G., Hopkins, M.J., Lidgard, S., 2015. Simple versus complex models of trait evolution and stasis as a response to environmental change. Proc. Nat. Acad. Sci. U.S.A. 112, 4885–4890.
Jablonka, E., Lamb, M.J., 2005. Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic in the history of life. Bradford Books/The MIT Press, Cambridge.
Jablonski, D., 2000. Micro- and macroevolution: scale and hierarchy in evolutionary biology and paleobiology. Paleobiology 26 (4, Suppl. ment), 15–52.
Jablonski, D., 2017. Approaches to macroevolution: 1. General concepts and origin of variation. Evol. Biol. 44 (7), 1–24.
Jacob, F., 1977. Evolution and tinkering. Science 196, 1161.
Jacob, F., Monod, J., 1961. Genetic regulatory mechanisms in the synthesis of proteins. J. Mol. Biol. 3, 318–356.
Javeed, N., Mukhopadhyay, D., 2017. Exosomes and their role in the micro-/macro-environment: a comprehensive review. J. Biomed. Res. 31 (5), 386–394. https://doi.org/10.7555/JBR.30.20150162.
Joyner, M.J., 2015. Has Neo-Darwinism failed clinical medicine: does systems biology have to? Prog. Biophys. Mol. Biol. 117 (1), 107–112. https://doi.org/10.1016/j.pbiomolbio.2014.09.010.
Joyner, M.J., Prendergast, F.G., 2014. Chasing Mendel: five questions for personalized medicine. J. Physiol. 592 (11), 2381–2388.
Kauffman, S., 1995. At home in the universe. Oxford University Press, New York.
Keller, E.F., 2000. The Century of the Gene. Harvard University Press, Cambridge, Mass.
Kontush, A., Lindahl, M., Lhomme, M., Calabresi, L., Chapman, M.J., Davidson, W.S., 2015. Structure of HDL: particle subclasses and molecular components. Handb. Exp. Pharmacol. 224, 3–51. https://doi.org/10.1007/978-3-319-09665-0_1.
Laland, K., Uller, T., Feldman, M., Sterelny, K., Müller, G.B., Moczek, A., Jablonka, E., Odling-Smee, J., Wray, G.A., Hoekstra, H.E., Futuyma, D.J., Lenski, R.E., Mackay, T.F., Schluter, D., Strassmann, J.E., 2014. Does evolutionary theory need a rethink? Nature 514 (7521), 161–164.
Lamichhaney, S., Han, F., Webster, M.T., Andersson, L., Grant, B.R., Peter, R., Grant, P.R., 2018. Rapid hybrid speciation in Darwin's finches. Science 359, 224–228.
Liu, J., 2020. The “life code”: a theory that unifies the human life cycle and the origin of human tumors. Semin. Canc. Biol 60, 380–397.
Liu, G., Stevens, J., Horne, S., Abdallah, B.Y., Ye, K.J., Bremer, S.W., Ye, C.J., Chen, Heng, H., 2014. Genome chaos: survival strategy during crisis. Cell Cycle 13, 528–537.
Lowenstein, W.R., 1999. Touchstone of Life. Oxford University Press, Oxford.
Mayr, E., 1997. The establishment of evolutionary biology as a discrete biological discipline. Bioessays 19, 263–266. https://doi.org/10.1113/jphysiol.2014.272336.
Mayr, E., 2001. What Evolution Is. Basic Books, New York.

Mazur, S., 2014. Replace the Modern Synthesis (Neo-Darwinism): an Interview with Denis Noble. Huffpost, 05/09/2014 11:51 pm ET Updated Jul 09, 2014.
McClintock, B., 1942. The fusion of broken ends of chromosomes following nuclear fusion. Proc. Natl. Acad. Sci. U. S. A. 28 (11), 458–463.
McClintock, B., 1984. Significance of responses of the genome to challenge. Science 226, 792–801.
Meier, J.A., Marques, D.A., Mwaiko, S., Wagner, C.E., Excoiffer, L., Seehausen, O., 2017. Ancient hybridization fuels rapid cichlid fish adaptive radiations. Nat. Commun. 8, 14363.
Mills, J., Capece, M., Cocucci, E., Tessari, A., Palmieri, D., 2019. Cancer-derived extracellular vesicle-associated MicroRNAs in intercellular communication: one cell's trash is another cell's treasure. Int. J. Mol. Sci. 20 (24), 6109. https://doi.org/10.3390/ijms20246109.
Mudd, A.B., Bredeson, J.V., Baum, R., Hockemeyer, D., Rokhsar, D.S., 2020. Analysis of muntjac deer genome and chromatin architecture reveals rapid karyotype evolution. Commun. Biol. 3 (1), 480.
Muller, G.B., 2007. Evo-devo: extending the evolutionary synthesis. Nat. Rev. Genet. 8, 943–950.
Murat, F., Armero, A., Pont, C., Klopp, C., Salse, J., 2017. Reconstructing the genome of the most recent common ancestor of flowering plants. Nat. Genet. 49 (4), 490–496. https://doi.org/10.1038/ng.3813.
Noble, D., 2013. Physiology is rocking the foundations of evolutionary biology. Exp. Physiol. 98 (8), 1235–1243. https://doi.org/10.1113/expphysiol.2012.071134.
Noble, D., 2021a. The illusions of the modern synthesis. Biosemiotics 14, 5–24.
Noble, D., 2021b. Cellular Darwinism: regulatory networks, stochasticity, and selection in cancer development. Prog. Biophys. Mol. Biol. 165, 66–71. https://doi.org/10.1016/j.pbiomolbio.2021.06.007.
Payne, A.C., Chiang, Z.D., Reginato, P.L., Mangiameli, S.M., Murray, E.M., Yao, C.-C., Markoulaki, S., Earl, A.S., Labade, A.S., Jaenisch, R., Church, G.M., Boyden, E.S., Buenrostro, J.D., Chen, F., 2021. In situ genome sequencing resolves DNA sequence and structure in intact biological samples. Science 371. https://doi.org/10.1126/science.aay3446.
Pigliucci, M., 2007. Do we need an extended evolutionary synthesis? Evolution; Int. J. Org. Evol. 61 (12), 2743–2749. https://doi.org/10.1111/j.1558-5646.2007.00246.x.
Prigogine, I., Stengers, I., 1984. Order Our of Chaos: Man's New Dialogue with Nature. Bantam Books.
Raghuram, G.V., Chaudhary, S., Johari, S., Mittra, I., 2019. Illegitimate and repeated genomic integration of cell-free chromatin in the aetiology of somatic mosaicism, ageing, chronic diseases and cancer. Genes 10 (6), 407. https://doi.org/10.3390/genes10060407.
Reich, D., Green, R.E., Kircher, M., Krause, J., Patterson, N., Durand, E.Y., Viola, B., Briggs, A.W., Stenzel, U., Johnson, P.L., et al., 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468, 1053–1060.
Schubert, I., 2007. Chromosome evolution. Curr. Opin. Plant Biol. 10 (2), 109–115. https://doi.org/10.1016/j.pbi.2007.01.001.
Schubert, I., 2021. Boon and bane of DNA double-strand breaks. Int. J. Mol. Sci. 22 (10), 5171. https://doi.org/10.3390/ijms22105171.
Sepkoski, J., 1998. Rates of speciation in the fossil record. Phil. Trans. Roy. Soc. Lond. B353, 315–332.
Shannon, C.E., 1948. A mathematical theory of communication. Bell Syst. Tech. J. 27, 379–423, 623–656.
Shapiro, J.A., 1997. Genome organization, natural genetic engineering and adaptive mutation. Trends Genet. 13, 98–104.
Shapiro, J.A., 2011. Evolution: A View from the 21st Century. FT Press Science, Upper Saddle River, NJ, USA, p. 272 ([Google Scholar]).
Shapiro, J., Noble, D., 2021a. The value of treating cancer as an evolutionary disease. Prog. Biophys. Mol. Biol. https://doi.org/10.1016/j.pbiomolbio.2021.08.010. S0079-6107(21)00103-00106. Advance online publication.
Shapiro, J., Noble, D., 2021b. What prevents mainstream evolutionists teaching the whole truth about how genomes evolve? Prog. Biophys. Mol. Biol. https://doi.org/10.1016/j.pbiomolbio.2021.04.004. S0079-6107(21)00034-1. Advance online publication.
Shin, Y., Chang, Y.C., Lee, D.S.W., et al., 2018. Liquid nuclear condensates mechanically sense and restructure the genome [published correction appears in cell. 2019 mar 7. Cell 176 (6), 1518. https://doi.org/10.1016/j. cell.2018.10.057, 175 (6) 1481–1491, e13.
Simakov, O., Marlétaz, F., Yue, J.X., O'Connell, B., Jenkins, J., Brandt, A., Calef, R., Tung, C.H., Huang, T.K., Schmutz, J., Satoh, N., Yu, J.K., Putnam, N.H., Green, R.E., Rokhsar, D.S., 2020. Deeply conserved synteny resolves early events in vertebrate evolution. Nat. Ecol. Evol. 4 (6), 820–830. https://doi.org/10.1038/s41559-020-1156-.
Sinkler, C.A., Kalpage, H., Shay, J., et al., 2017. Tissue- and condition-specific isoforms of mammalian cytochrome c oxidase subunits: from function to human disease. Oxid. Med. Cell. Longev. 1534056. https://doi.org/10.1155/2017/1534056, 2017.
Stevens, J.B., Horne, S.D., Abdallah, B.Y., et al., 2013. Chromosomal instability and transcriptome dynamics in cancer. Cancer Metastasis Rev. 32 (3e4), 391–402. https://doi.org/10.1007/s10555-013-9428-6.
Stevens, J.B., Liu, G., Abdallah, B.Y., Bremer, S.W., Ye, C.J., Krawetz, S.A., Heng, H.H., 2014. Unstable genomes elevate transcriptome dynamics. Int. J. Cancer 134 (9), 2074–2087. https://doi.org/10.1002/ijc.28531.
Takei, Y., Yun, J., Zheng, S., Ollikainen, N., Pierson, N., White, J., Shah, S., Thomassie, J., Suo, S., Eng, C.-H.L., Guttman, M., Yuan, G.-C., Cai, L., 2021. Integrated spatial genomics reveals global architecture of single nuclei. Nature 590, 344–350.
Wadington, C.H., 1957. The Strategy of Genes. Allen and Unwin, New York.
Wallace, D.C., 2012. Mitochondria and cancer. Nat. Rev. Cancer 12 (10), 685–698. https://doi.org/10.1038/nrc3365.
Wallace, D.C., Chalkia, D., 2013. Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. Cold Spring Harb. Perspect. Biol. 5 (11), a021220. https://doi.org/10.1101/cshperspect.a021220.
White, M.J.D., 1945. Animal Cytology and Evolution. Cambridge University Press, 3rdEdition, 1973.
Wilkins, A.S., Holliday, R., 2009. The evolution of meiosis from mitosis. Genetics 181 (1), 3–12. https://doi.org/10.1534/genetics.108.099762.
Ye, C.J., Stilgenbauer, L., Moy, A., Liu, G., Heng, H.H., 2019a. What is karyotype coding and why is genomic topology important for cancer and evolution. Front. Genet. 10, 1082. https://doi.org/10.3389/fgene.2019.01082.
Ye, C.J., Sharpe, Z., Alemara, S., et al., 2019b. Micronuclei and genome chaos: changing the system inheritance. Genes 10 (5), 366. https://doi.org/10.3390/genes10050366.
Zuk, O., Hechter, E., Sunyaev, S.R., Lander, E.S., 2012. The mystery of missing heritability: genetic interactions create phantom heritability. Proc. Natl. Acad. Sci. U.S.A. 109 (4), 1193–1198.