



Beyond the modern synthesis: A framework for a more inclusive biological synthesis

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ABSTRACT

Many theorists in recent years have been calling for evolutionary biology **to move beyond the Modern Synthesis** – the paradigm that has long provided the theoretical backbone for the discipline. Terms like “postmodern synthesis,” “integrative synthesis,” and “extended evolutionary synthesis” have been invoked by various critics in connection with the **many recent developments that pose deep challenges – even contradictions – to the traditional model and underscore the need for an update, or a makeover.** However, none of these critics, to this author’s knowledge, has to date offered an explicit alternative that could provide a unifying theoretical paradigm for our vastly increased knowledge about living systems and the history of life on Earth (but see Noble 2015, 2017). **This paper briefly summarizes the case against the Modern Synthesis** and its many amendments over the years, and a new paradigm is proposed, called an “Inclusive Biological Synthesis,” which, it is argued, can provide a more general framework for the biological sciences. The focus of this framework is the fundamental nature of life as a contingent dynamic process – an always at-risk “survival enterprise.” The ongoing, inescapable challenge of earning a living in a given environmental context – biological survival and reproduction – presents an existential problem to which all biological phenomena can be related and comprehended. They and their “parts” can be analyzed in relation to ethologist Niko Tinbergen’s four key questions. Some basic properties and guiding assumptions related to this alternative paradigm are also identified.

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1. Introduction

There is a growing constituency among biologists and other evolutionary theorists these days in favor of the once heretical idea that the time has come to **move decisively beyond the Modern Synthesis in evolutionary biology.** Much of what has been learned by the biological sciences in recent decades goes far beyond and sometimes even contradicts the narrow and constricting assumptions and expansive claims associated with what has long been viewed as the theoretical backbone of the discipline. Here it is contended that this venerable framework is **outdated and should be replaced** with a new paradigm – in the strict sense first proposed by Thomas Kuhn (1962) – one that can accommodate our vastly increased understanding of the evolutionary process.

There are, of course, many traditionalists who remain deeply committed to the reductionist, gene-centered, “neo-Darwinian” paradigm where, as biologist John H. Campbell put it, “changes in

the frequency of alleles by natural selection are evolution” (Campbell, 1994:86). Or as Richard Dawkins expressed it in his popular book *The Selfish Gene*, “We are survival machines – robot vehicles blindly programmed to preserve the selfish molecules known as genes” (Dawkins, 1989/1976:ix). In a recent defense of the Modern Synthesis by a group of prominent biologists (Wray et al., 2014), it was asserted that “we could not agree more” about the importance of recent developments, “but we do not think these processes deserve special attention.” They are already “well integrated” into evolutionary biology, these authors claim.

Here it is argued – to the contrary – that the Modern Synthesis obscures and sometimes seriously misrepresents the underlying causal dynamics in living systems, and in evolution. It has become an obstacle to our continued progress in understanding the evolutionary process. While genes (DNA) and genetic influences have obviously played a vitally important role in the history of life on Earth, and will continue to do so, they are by and large the servants of living organisms rather than the masters. Indeed, very often they are followers of evolutionary changes, not the other way around. Natural selection, furthermore, is not a concrete causal

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agency. It is a metaphor — an open-ended “umbrella category” that sometimes masks the causal dynamics in evolution (see below). Once upon a time, the Modern Synthesis played a unifying role in the biological sciences. Now it has become a divider. It has outlived its usefulness. A fundamental paradigm shift is required.

Here the elements of the Modern Synthesis will be briefly described and some of the major problems and objections that have arisen over time will be briefly discussed, along with a summary of the case for making a change. Some key elements of an alternative paradigm will then be proposed — one where the Modern Synthesis is reformulated and subsumed rather than being completely rejected. I refer to it as an “Inclusive Biological Synthesis.”

2. Unpacking the modern synthesis

The term “Modern Synthesis” was coined by the biologist Julian Huxley in his popular 1942 book, *Evolution: The Modern Synthesis*. Huxley was referring to a combination of Darwin (1968/1859) basic principles of variation, heredity, and natural selection coupled with a Mendelian, gene-centered focus and the claim that genetic mutations (along with sexual recombination) are the primary sources of novelty in biological evolution. Although there were some significant differences among the various “architects” of the Modern Synthesis, including August Weismann (1892), Fisher (1999/1930), Sewall Wright (1931, 1932), J.B.S. Haldane (1932), Theodosius Dobzhansky (1937), Ernst Mayr (1942), and others, the general consensus was that evolution can be defined in terms of changes in the genetic composition of an interbreeding population of organisms.

Other elements of the original synthesis included the assertion that genetic mutations are essentially “random” (or undirected) and that there can only be a one-way flow of information from the germ plasm to the phenotype — the so called Weismann Barrier or, later, the Nobel geneticist Francis Crick (1970) “Central Dogma.” This was undergirded theoretically by the pioneering mathematical work in the then new science of population genetics, along with a growing volume of laboratory and field research which, among other things, reduced the concept of natural selection to a mathematical “selection coefficient” and used numerical changes in gene frequencies in a population of conspecifics to define and quantify evolutionary change.

Over the next several decades, many significant elaborations, qualifiers, and amendments were added to this basic vision, including the discoveries related to genetic drift, heterosis, linkage effects, mutational biases, polyploidy, the effect of geographic isolation and population structures — such as the “founder effect” (Mayr, 2001) — the discovery of the genetic code and other major advances in molecular biology, along with the development of inclusive fitness theory to explain seemingly “altruistic” phenomena (Hamilton, 1964), the game changing but controversial introduction of sociobiology by Edward Wilson (1975), and more. (For an authoritative but accessible textbook covering the history of evolutionary biology during the twentieth century, see Ridley, 2003).

However, none of these developments appeared to threaten the core assumptions of the Modern Synthesis: heritable genetic variation, ecological competition, and differential (genic) survival and reproduction via natural selection. Thus, for example, Conrad Waddington (1942, 1952) work on “genetic assimilation” was portrayed as merely a Darwinized version of Lamarck and Elliot (1984/1809) theory of acquired characters. Likewise, the “punctuated equilibrium” theory proposed by paleontologists Eldredge and Gould (1972), which holds that macro-evolution is often characterized by long periods of stasis followed by abrupt transitions rather than by steady incremental changes, challenged the neo-

Darwinian assumption of “gradualism” but not the basic paradigm (See also Valentine and Campbell, 1975). In the same vein, the “neutral theory” of Kimura (1968) and King and Jukes (1969), which revealed that much evolutionary change at the molecular level is initiated by “genetic drift,” challenged the hegemony of natural selection but not the basic model itself.

3. Growing challenges to the modern synthesis

The first serious theoretical challenge to the Modern Synthesis (setting aside the creationists and other anti-Darwinists) came with the growing evidence, championed especially by biologist Lynn Margulis (1970, 1993, 1998; Margulis and Fester, 1991), that symbiosis — cooperative relationships between organisms of different species with complementary capabilities — is a widespread phenomenon in the natural world, and that “symbiogenesis” has played a major causal role in shaping the evolutionary trajectory (Margulis, 1993; Margulis and Sagan, 2002; Sapp, 1994, 2004, 2009; Gontier, 2007; Carrapiço, 2010; Archibald, 2014; c.f., Aanen and Eggleton, 2017). Among other things, this theory shifted the locus of innovation away from “random” changes in genes, genomes, and “classical” natural selection to the behavioural actions of the phenotypes, and their functional consequences.

Indeed, we now know that most plants and animals, including humans, engage in a great variety of symbiotic partnerships with other species (Gilbert et al., 2012). Herbivory, for example, depends entirely upon it. Another example is the “microbiome” in human-kind. The total number of symbiotic microbes that inhabit our bodies may be even greater than the number of our own somatic cells (albeit far smaller in size). Various kinds of bacteria, fungi, viruses, and protozoa perform many functions for us, from helping to digest our food to defending against pathogens and producing several vitamins (Turnbaugh et al., 2007; Salvucci, 2016).

An even greater challenge to the Modern Synthesis arose with the discovery that single celled prokaryotes are profligate sharers of genetic material via “horizontal” (or lateral) gene transmission and do not strictly follow the pattern of competition and Mendelian “vertical” inheritance from parent to offspring, as assumed under the Modern Synthesis (Sapp, 2009; Koonin, 2011; Crisp et al., 2015). As molecular biologist Eugene Koonin (2009) concluded, all the central tenets of the Modern Synthesis break down with prokaryotes and the findings of comparative genomics. The prokaryote world can best be described as a single, vast, interconnected gene pool, he argued.

Thus, cooperative phenomena of various kinds, which are portrayed as being highly constrained and problematic under the predominately competitive assumptions of the Modern Synthesis, are now seen to play an important causal role in living systems, and in evolution. Biologist Richard Michod (1999) asserts that “cooperation is now seen as the primary creative force behind ever greater levels of complexity and organization in all of biology.” Martin Nowak (2006) calls cooperation “the master architect of evolution.” However, it is not cooperation per se that has been the “creative force” or the “architect”. Rather, it is the unique combined effects (the synergies) produced by cooperation. Beneficial Synergies of various kinds have been a prodigious source of evolutionary novelties and the underlying cause of cooperation and increased complexity in evolution over time. (Corning, 2005, 2018).

The rise of evolutionary developmental biology (evo-devo in short) has also produced serious challenges to the Modern Synthesis, including the discovery that there are many deep homologies and highly conserved structural gene complexes in the genome (some of which are universal in living systems), and especially the extensive work on morphological development and “phenotypic plasticity” (Müller and Newman, 2003; West-

Eberhard, 2003; 2005a, 2005b; Koonin, 2011; Bateson and Gluckman, 2011).

There is also the burgeoning evidence that the genome is in fact a “two-way read-write system,” as the microbiologist James Shapiro (2011, 2013) characterizes it. The extensive and rapidly increasing evidence of epigenetic inheritance (changes in the phenotype that are transmitted to the germ plasm in the next generation) also falsifies the Weismann Barrier, a pillar of the Modern Synthesis (see Jablonka, 2013; Jablonka and Raz, 2009; Jablonka and Lamb, 2014; Noble, 2013, 2015, 2017; 2018; Walsh, 2015; Huneman and Walsh, 2017).

Recent progress in microbiology has shown that an overwhelming majority of DNA changes in the genome are the result of what Shapiro (2011) calls “natural genetic engineering” and the influence of internal regulatory and control networks, not random mutations and incremental “additive” selection. In fact, rapid genome alteration and restructuring can be achieved by a variety of mobile DNA “modules” – transposons (McClintock and Moore, 1987), integrons, CRISPRs, retrotransposons, variable antigen determinants, and more (Craig, 2002, 2015; Sapp, 2009; Shapiro, 2011, 2013; Koonin, 2011, 2016; Noble, 2017). As Shapiro (2011:2) emphasizes, “The capacity of living organisms to alter their own heredity is undeniable. Our current ideas about evolution have to incorporate this basic fact of life.”

It is now also apparent that individual cells have a great variety of internal regulatory and control capabilities that can significantly influence cell development and the phenotype and may even provide feedback that modifies the genome and affects subsequent generations (Pan and Zhang, 2009; Gladyshev and Arkhipova, 2011; Koonin, 2011; Shapiro, 2011; Noble, 2006, 2011, 2017, 2018). Particularly significant are the discoveries related to the influence of exosomes, which resemble Darwin’s speculative ideas of internal migratory “gemmules” and pangenesis in reproduction, as Noble (2019a) points out. Exosomes also violate the Weismann Barrier.

A further challenge to a gene-centered model of evolution is our growing appreciation of the fact that what was long considered to be irrelevant “junk DNA” – because it was non-coding and presumably not subject to natural selection – in fact plays an important role in shaping epigenetic development and gene regulation. Equally significant, these non-coding molecules are agents for generating adaptive new configurations in the genome (Adelman and Egan, 2017; Mattick, 2018).

It has long been appreciated that “microevolution” at the level of individual traits may have a very different pattern of causation from “macroevolution” – systematic changes in populations, species, and lineages over time (Mayr, 2001). However, this categorical distinction can be breached by hybridization between species, what the pioneering botanist and evolutionary biologist G. Ledyard Stebbins (1951) called “catastrophic evolution.” We now know that hybridization is ubiquitous – both in plants and in animals – and that it plays a significant role in creating new species. One recently documented example involved the creation of a new ground finch in the Galapagos islands within three generations following matings between two different species (Lamichhaney et al., 2018).

4. Evolution “on purpose”: behaviour and evolution

Finally, and perhaps most significant theoretically, there has been a growing recognition that the “purposeful” (teleonomic) behaviour of living organisms themselves has had a major influence in shaping the trajectory of evolution over time. In the terminology of cybernetics and control systems engineering, living organisms are value-driven decision systems. Indeed, we now recognize that even plants can be sophisticated decision makers. The marine alga *Fucus*, for example, can sense at least 17 environmental conditions,

and this information is then either summed or integrated synergistically in making choices, according to Gilroy and Trewavas (2001; also Trewavas, 2014).

Some contemporary theorists have adopted the concept of “agency” to characterize this defining biological characteristic (e.g., Walsh, 2015). Others have adopted Humberto Maturana and Francisco Varela’s concept of “autopoiesis” (e.g., Capra and Luisi, 2014). However, the basic idea of the organism as a self-organized and self-directed agent can be traced back at least to Lamarck, who first proposed that changes in an animal’s “habits”, stimulated by environmental changes, have been a primary source of evolutionary change over time. Lamarck and Elliot (1984/1809:114) wrote: “It is not the organs ... of an animal’s body that have given rise to its special habits and faculties; but it is, on the contrary, its habits, mode of life and environment that have over the course of time controlled ... the faculties which it possesses.” Lamarck used the long necks of giraffes as an illustration. He proposed that this trait resulted from the way giraffes on the African savanna had stretched their necks over time to feed on the leaves of the acacia trees. (Even Darwin was open to Lamarck’s idea and mentioned it no less than 12 times in *The Origin of Species*, 1968/1859. Conversely, late in life Lamarck embraced a precursor of Darwin’s natural selection idea. See Corning 2018:70).

A “Darwinized” version of Lamarck’s insight, called “Organic Selection Theory” made a brief appearance at the end of the 19th century (the basic idea was that purposeful behavioural changes could alter the selective context for natural selection), but this was soon overwhelmed and supplanted by “mutation theory” and the later work that led to the Modern Synthesis (see Corning, 2014).

Organic Selection Theory and the idea of behaviour as an influence in evolutionary change was tentatively reintroduced by the palaeontologist George Gaylord Simpson (1953) under the neologism of the Baldwin Effect. However, he portrayed it as being of only minor significance in evolution. A turning point came with an important set of conferences and an edited volume called *Behavior and Evolution* (Roe and Simpson, 1958). One of the conference attendees, Ernst Mayr (1960), in a landmark follow-up essay on the subject, concluded: “It is now quite evident that ... the evolutionary changes that result from adaptive shifts are often initiated by a change in behaviour, to be followed secondarily by a change in structure ... Changes of evolutionary significance are rarely, except on the cellular level, the direct results of mutation pressure ... The selection pressure in favor of the structural modification is greatly increased by a shift to a new ecological niche, by the acquisition of a new habit, or by both.” Mayr characterized these (Lamarckian) behavioural innovations as the “pacemakers” of evolution.

An important variation on this general theme is the recent work on “Niche Construction Theory” (Laland et al., 1999; Odling-Smee et al., 2003). Here the focus is on how living organisms very often modify their environments in ways that induce evolutionary changes in their own and other species – from beaver dams to underground mole rat burrows, the changes that earthworms make to the soil, and, most dramatic, how photosynthetic cyanobacteria transformed the Earth’s atmosphere and created a hospitable environment for aerobic organisms. In other words, behavioural changes do not just alter the actors’ costumes or the stage props, they can change the plot and change the outcome of the play. Biologist Patrick Bateson (2004) called behaviour an “adaptability driver” in evolution.

It should also be noted that many other theorists have drawn attention to the role of behaviour in evolution over the years, notably including Conrad Waddington, Jacques Monod, Lynn Margulis, Jan Sapp, Henry Plotkin, Eva Jablonka, Bruce Weber, David Depew, Terrence Deacon, Denis Noble, Kevin Laland, John Odling-Smee, Denis Walsh, Peter Richerson, and this author, among

others. Equally important, the idea of “purposeful” adaptive changes has now been extended to the genome and to ontogeny, as was noted above (see Goodman, 1998; Shapiro, 2011; Noble, 2017). Teleonomy (evolved purposiveness) is thus a core property of living systems at all levels and influences evolution in innumerable ways (see Corning, 2014, 2018, 2019).

5. Voices for change

Objections to the Modern Synthesis from within the biological “fraternity” itself go back at least to Conrad Waddington in the 1950s. “The whole real guts of evolution – which is how do you come to have horses, and tigers, and things – is outside the mathematical theory,” he complained in a review (quoted in D.E. Rosen, 1978). As Waddington observed, it requires an act of faith to believe that highly complex (purposive) organisms could have evolved exclusively via the narrow pathway of random (mostly deleterious) mutations and the differential survival of gradual, incremental phenotypic changes over time. Waddington (1957, 1961) also called for extending the Modern Synthesis to include developmental influences. (He also coined the term “epigenetics”).

As the evidence has accumulated in recent decades that major sources of evolutionary causation and change do in fact lie outside and may even contradict the tenets of Modern Synthesis, the number of voices calling for a paradigm change has increased. One critic described the state of evolutionary biology as “an interpretive mess” (Smocovitis, 1996: 43). Carl Woese (2004) saw the discipline as being at a “crossroads”. He concluded that the molecular paradigm is no longer a reliable guide, and he urged the development of a “new and inspiring vision of the living world that could address the major contemporary problems in biology.” Rose and Oakley (2007) detailed how several new disciplines have been undermining the assumptions of the Modern Synthesis, leading to the “Balkanization” of biology. They seek a new “postmodern synthesis” – a term that was also adopted by Eugene Koonin (2011). Michael Wade (2011) speaks of creating a “Neo-Modern Synthesis,” while the physiologist and systems biologist Denis Noble (2011, 2013, 2015, 2017, 2018) argues that many of the recent developments in physiology and related disciplines falsify the assumptions in the Modern Synthesis, and that it provides no useful guidance for developmental biology and physiology. He calls for replacing it with a more “Integrative Synthesis.” (See also Huneman and Walsh, 2017).

Perhaps the most extensive and systematic effort to move beyond the Modern Synthesis is the work on what has been called an Extended Evolutionary Synthesis (EES) by Massimo Pigliucci, Gerd Müller and a number of their colleagues (Pigliucci and Müller, 2010; Laland et al., 2014, 2015; see also Danchin et al., 2011; Wade, 2011; Laubichler and Renn, 2015). Rather than replace the underlying principles and assumptions of the Modern Synthesis, these theorists would modify and supplement them to accommodate the recent work in developmental biology, epigenetic inheritance, genomics, multi-level selection, Niche Construction Theory, and the like. In their view, these constructive processes “share the responsibility for the direction and rate of evolution” with the classical model (Laland et al., 2015). Indeed, some EES supporters are currently testing a number of “predictions” that, they argue, go beyond and even diverge from the Modern Synthesis (Laland et al., 2014, 2015).

This is an important step forward, but a growing number of theorists believe that the combined weight of the many theoretical and research developments – and contradictions – cited above, as well as others, compels us to go further. The Modern Synthesis needs to be reformulated and subsumed within a more inclusive and better focused theoretical paradigm.

6. What is the question?

The place to start, perhaps, is to step back and ask what is the underlying theoretical question (or questions) that evolutionary biology seeks to address? What is it trying to explain? For Darwin in the 1850s, the challenges were to convince the world that evolution had in fact occurred (it was very much a minority view at the time), and that it was not the result of an externally imposed teleology, or an Aristotelian entelechy. Rather, it involved a naturalistic process in which biological variations of many kinds are subject to testing and differential survival and reproduction in a highly competitive natural world – i.e., natural selection. Beginning with the very origins of life on Earth, Darwin claimed, this competitive dynamic has resulted over time in the great diversity and complexity of living forms that can be observed all around us today. In effect, Darwin was proposing what is, in essence, an entrepreneurial, “economic” theory to explain biological evolution. Natural selection was conceived by Darwin as a way of characterizing this functionally based, competitive, “trial-and-success” process (as Theodosius Dobzhansky called it).

The Modern Synthesis, likewise, sought to address these same underlying theoretical questions. Indeed, in the early part of the twentieth century there was still strong opposition to Darwin’s theory, and especially the concept of natural selection. However, the architects of the Modern Synthesis shifted the theoretical frame – the “target” of natural selection and evolution – from Darwin’s focus on organisms and their adaptive “traits” to variations in the genes that were presumed to exert tight (deterministic) control over the expression, and reproduction, of the phenotypes and their traits. The important mathematical work in population genetics in that era also lent rigor and testability to this paradigm. It was immensely productive but also mechanistic and highly constricted.

A related problem has been a tendency for biologists (then and now) to reify the concept of natural selection and portray it as a kind of external selecting “agency”, “mechanism”, “force”, or “driver” out there in the environment somewhere that actively chooses among genetic alternatives (analogous to the practice of “artificial selection” in animal and plant breeding, which was, in fact, the inspiration for Darwin’s term). There has also been much talk about how the environment exerts various kinds of “selection pressures” (see the Mayr quote above, for example).

The basic problem with these euphemisms is that they mask the underlying causal dynamics. In fact, natural selection does not *do* anything. Nothing is ever actively “selected” (with the limited exceptions of sexual selection in reproduction, some predator-prey interactions, and the like). The term “natural selection” is actually a metaphor – a placeholder for whatever specific factors – internal, external, or both – are responsible for causing differential survival in a given environmental context. Moreover, it is now abundantly evident that natural selection is not just focused on individual alleles but also on gene complexes, whole genomes, phenotypes, symbiotic partnerships, social groups, interbreeding populations, even entire ecosystems – in other words, any defined, functionally interdependent “unit” of differential survival and reproduction – any biological “system”. Accordingly, what has been called “multilevel selection” (e.g., D.S. Wilson, 1997a; 1997b) should not, technically, be focused on genes but should refer to any functional “unit” in the natural world – even, say, a symbiotic partnership like lichens.

The “locus” of natural selection in every case is the relationships and interactions within and between living systems and their environments, inclusive of other organisms. A striking example can be seen in new report on blue whales (Goldbogen et al., 2019). Their huge size is a combined product of a very efficient physiological trait (filter feeding) and an abundance of concentrated small prey

that can be efficiently harvested (an ecological opportunity). As [Laland et al. \(2013\)](#) have stressed, the role of “reciprocal causation” in evolution has been greatly underrated. The organism–environment relationship is the key, and there can be many – often conflicting – sources of evolutionary continuity and change in the natural world.

To use a hypothetical example, imagine that a particular species of birds may be increasing in numbers relative to an adjacent competitor species, because they have bigger, stronger beaks that aid them in their feeding behaviours (positive individual selection). Yet, at the same time, their absolute numbers are gradually declining, because all of the bird species in the region are being impacted by expanding human populations and shrinking ecosystems (ecological or population selection). Needless to say, humankind has become an increasingly important cause of natural selection over time, in many different ways. Ecologist Menno [Schilthuizen \(2018:7\)](#) argues that today “human actions are the world’s single most influential ecological force.” (See also [Kolbert, 2014](#)).

Likewise, consider how the massive asteroid “Chicxulub” impacted the Earth some 66 million years ago, producing a huge “extinction event” that wiped out the dinosaurs and about three-quarters of all the other living species at that time. Darwin himself admitted (in a letter in 1876, quoted in [Noble, 2019b](#)) that he did not “give sufficient weight” in his writings to such things as “the direct action of the environment, i.e. food, climate, etc.” If such direct actions are *not* treated as causes of natural selection (as Darwin himself seemed to do), then many of the most important influences that shape “differential survival” and evolution over time must be arbitrarily excluded.

In other words, the incremental, gene-centered, statistically-oriented Modern Synthesis framework has tended to constrict and distort our perspective on the manifold sources of causation and the multi-level dynamics of the evolutionary process and to compartmentalize and greatly limit the factors that can be counted as causes of natural selection (see also [Noble, 2017](#)). It is like looking into a very large room through a small keyhole. We can see only a small portion of what is inside. But if we adopt a more inclusive paradigm, we might then be able to view the entire room.

7. A summary of the case

To summarize the case against the Modern Synthesis:

- Most variation in living systems is not strictly random (it is “harnessed” in various ways, as Noble puts it); purely random mutations are of relatively limited significance in evolution.
- There are a great many different sources of variation/innovation at various levels of biological organization; some of it is even highly “intentional” (teleonomic).
- The life experience of an organism often provides “feedback” that can re-shape the evolutionary process in various ways.
- Natural selection is not a concrete mechanism; it is an “umbrella term” for whatever specific factors (internal, external or both) determine differential survival and reproduction in a given context.
- Evolution is not focused on the genes. It is a global process that has many “levels” and functional “units” and encompasses an admixture of change and enduring continuities over time.
- Cooperation and competition have been of co-equal importance in shaping the course of evolution.
- “Teleonomy” – purposeful means-ends processes and behaviours – is at once a major product of evolution and a significant cause of evolutionary change, as described in Section Four above and in some depth in [Corning \(2018, 2019\)](#). As [Walsh \(2015:209\)](#) puts it, living organisms also “enact” evolution.

8. Reformulating the modern synthesis

What I propose to call an “Inclusive Biological Synthesis” starts by re-defining the underlying theoretical question. As Darwin well understood (and famously expressed it) the fundamental challenge for life on Earth is “the struggle for existence.” Life is a contingent dynamic process, an always at-risk “survival enterprise.” The ongoing, inescapable problem of earning a living in any given environmental context presents an existential challenge to which all biological phenomena can be related and comprehended. All living organisms, and virtually all of their “parts”, are evolved designs for survival (though certainly not without flaws). They are open thermodynamic systems, and dynamic kinetic systems (see [Pross, 2016, 2018](#)), that are sustained by inputs/throughputs of energy and “control information” ([Corning, 2007](#)), as well as a variety of other materials. To modify a famous line from Dobzhansky, nothing in biology makes sense except in light of the challenge of survival and reproduction (see [Box 1](#)).

The basic unit of analysis in this alternative paradigm is not the genes but interdependent living “systems” and their parts – along with their external dependencies (R. [Rosen, 1970, 1991](#); [Bateson, 2004, 2005](#); [Corning, 2005, 2018](#); [Noble, 2006, 2017](#); [Capra and Luisi, 2014](#); [Walsh, 2015](#)). Some theorists (e.g., [Gilbert et al., 2012](#)) have adopted the term “holobiont” to characterize this frame shift. A living system represents a “combination of labor” with an overarching vocation, a means-ends teleonomy. To repeat, a living organism is a value-driven decision system, a cybernetic system. Denis [Noble \(2006, 2015, 2017\)](#) characterizes it as a complex “network” and describes the genes as being like a library of “templates” rather than an active causal agency, while the genome as a whole acts as a purposeful dynamic system.

This theoretical frame shift also redirects our focus away from issues related to genes and micro-evolution to a much broader and more “inclusive” set of questions and theoretical concerns that span the many other research domains that are involved these days in exploring various aspects of life on Earth. Among others, these substantive domains include: (1) the origins of life; (2) the nature and functioning of living organisms as goal-oriented systems (their basic properties and their dynamics); (3) ontogeny and the dynamics of development; (4) the sources of continuity, stability, and heredity; (5) the sources of change and evolution over time, including such important trends as increasing complexity and the “major transitions” in evolution ([Maynard Smith and Szathmáry, 1995](#); [Corning and Szathmáry, 2015](#); [Corning, 2018](#)); (6) discontinuities and “terminations” in evolution; (7) hierarchies and levels of organization and selection in the natural world; (8) the distinctive roles of competition and cooperation (and functional synergy) in nature, and in evolution; (9) human evolution and its impact (past, present, and future); and (10) the life-and-death challenge of global climate change.

It perhaps goes without saying that this paradigm shift also allows for the incorporation and utilization of the new discoveries about biological and evolutionary causation in recent decades without creating any theoretical angst or apparent contradictions. In the introduction to the edited volume on the Extended Evolutionary Synthesis, the editors, Massimo Pigliucci and Gerd Müller (2010:12), note that the current “shift of emphasis from statistical correlation to mechanistic causation arguably represents the most critical change in evolutionary theory today.” Equally important, it should be added, is a shift of focus from the genes as the basic unit of analysis (and evolution) to living systems and their parts (including the genes, of course). In an important sense, this paradigm shift also brings us back to Darwin’s Darwinism.

BOX 1**The Inclusive Biological Synthesis:****Some Properties & Assumptions.**

- Biological evolution can be defined as a dynamic, cumulative historical process – characterized by both continuities and change – which is embedded in an evolving, physical and biotic environment.
- Living organisms are open systems that interact with their environments in many different ways, including especially the acquisition, utilization, and dissipation of energy, information, and other materials.
- Living organisms are also “purposeful” agents (with an internal, self-organized teleonomy) that can actively influence and sometimes may even control their own evolutionary trajectories.
- There are many different levels and domains of causation involved in evolutionary continuity and change, from molecular to genomic, physiological, developmental, behavioural, social, ecological and more. Genes are not privileged in evolutionary innovation and are often followers in evolutionary change.
- Natural selection is not a discreet causal agency – a “mechanism” or a “force” – but a metaphor for an open-ended “umbrella category” that refers to whatever specific causal influences are responsible for differential survival and reproduction of a given survival unit in a given context.
- Living organisms exhibit a number of distinctive properties that are often downplayed or ignored in the traditional gene-centered evolutionary paradigm, including systemic processes and dynamics, multi-level causation (and selection), both top-down and bottom-up causal dynamics, internal organismic innovation and adaptive change (“natural genetic engineering”), non-linear, discontinuous, even “saltational” evolutionary changes, reciprocal and iterative causal dynamics, co-evolution, “bioeconomic” cost-benefit constraints, and more.
- Cooperative – synergistic – phenomena have played an important role in the evolution of biological complexity (at all levels) over time, on an equal footing with competitive phenomena.
- The Inclusive Biological Synthesis does not purport to provide a definitive theoretical explanation; it represents a framework for an open-ended work-in-progress that is focused on a common set of questions regarding the ongoing biological challenge of survival and reproduction.

and the “why” questions, or proximate and ultimate causation (see [Corning, 2019](#)). (Nathalie Gontier, in a personal communication, provided a reminder that Tinbergen’s contribution was presaged by a major essay on causation in biology authored by [Mayr, 1961](#)).

Tinbergen’s primary concern was the study of animal behaviour, but he believed his four questions could be applied to any biological phenomenon, and he called for an integration of the many specialized research efforts that focus on only one or two of them. As Tinbergen expressed it, there must be a “fusing of many sciences, all concerned with one aspect of behaviour, into one coherent science.” (For the record, Julian Huxley made a similar plea in his eponymous 1942 book).

In a recent “appreciation and update,” of Tinbergen’s classic article, [Bateson and Laland \(2013\)](#) pointed to some of the many changes that have occurred in the biological sciences during the intervening 50 years and suggested that a somewhat more “nuanced” rendering of Tinbergen’s four questions is in order. They noted, for example, that the current utility of a trait may not equate to its original function, and that functionality may not necessarily be a product of “classical” natural selection. Phenotypic behavioural traditions might also play a role, for example. They also stressed that the process of development may start even before conception, that significant parental influences over ontogeny can occur even in the placenta, and that there can be legacy effects (genetic and behavioural) between generations. Bateson and Laland also noted that living systems may have multiple levels of organization, and that Tinbergen’s four questions may need to be asked at each level.

There are, as well, some new questions that should be added to Tinbergen’s list, including some that were considered completely out of bounds two generations ago. For instance, how is a given trait inherited? We now know that it may not necessarily be transmitted via the genome but via behavioural and cultural traditions, or what has been termed “inclusive inheritance.” ([Jablonka and Lamb, 2014](#); [Laland et al., 2015](#); [Noble, 2017, 2018](#)). Likewise, to what degree do ecological-environmental influences and life experiences shape ontogeny, development, and the phenotype? To what extent do these “plastic” influences reciprocate and affect the genotype over time? And does a given case of phenotypic plasticity represent a teleonomic adaptation, or could it be a fortuitous “spandrel”, after [Gould and Lewontin \(1979\)](#) famous architectural metaphor?

Finally, there are some questions and research domains that could be added to the current mix. One example is the causal role of teleonomy and intentional behaviours – or “agency” if you prefer – in shaping the trajectory of evolution over time ([Corning, 2005, 2014, 2018; 2019](#); [Capra and Luisi, 2014](#); [Walsh, 2015](#)). Another domain might focus on the economics of living systems – the costs and benefits (and economic constraints) associated with earning a living in “the economy of nature” – to use Darwin’s term. Much relevant work on this subject can be found in such sub-disciplines as behavioural ecology and bioeconomics, along with the theory and research related to the role of synergistic functional innovations in evolution ([Corning, 2005, 2018](#)), and the important field of complexity economics ([Arthur, 2015](#)).

10. Conclusion: a unifying theoretical framework?

I contend that the contingent nature of all living systems and the ongoing challenge of survival and reproduction provides a “common denominator” – a unifying theoretical perspective for the biological sciences. In addition, an updated (and enhanced) version of Tinbergen’s four key questions provides a common research agenda that, unlike the Modern Synthesis, can lead in time to a more comprehensive synthesis among the biological sciences.

To be clear, for the immediate future the Inclusive Biological Synthesis framework would serve primarily as an umbrella for the

9. Tinbergen’s four questions

In 1963, Niko Tinbergen, one of the founding fathers of ethology, published an article about what he described as the “four major problems,” or questions that should be posed with respect to any given biological trait ([Tinbergen, 1963](#)). He labeled them “survival value,” “ontogeny,” “evolution,” and “causation” (or the mechanics). The questions were: What purpose does the trait serve (its current function)? How does it develop during an organism’s lifetime? How did it evolve over time? And how does it work? These four questions encompass what today would be called both the “how” questions

ongoing, widely diversified research enterprise in the biological sciences; it is still very much a work in progress. However, it would also serve to focus our minds on asking the right questions, and it would encourage the ultimate “fusing” (as Tinbergen called it) of our knowledge about this all-important subject into a definitive, unifying synthesis.

I venture to predict that this ultimate “fusion” – or “integration”, in Noble’s term – will lead us to conclude that the most fundamental property of living organisms is their evolved, and still evolving purposiveness, or teleonomy (Monod and Wainhouse, 1971; Corning, 2019). In humankind, moreover, the evolutionary process has achieved the power to control the very destiny of life on Earth – for better or worse. The classic distinction between natural selection and artificial selection has been obliterated. In this era of climate change and a growing threat to humans and many other species, a more inclusive biological synthesis should therefore become an urgent priority. We must focus now on the intensifying “struggle for existence.” To quote Dobzhansky once again, “the future is not vouchsafed by any law of nature, but it can be striven for.”

11. Author’s statement, “beyond the modern synthesis” (Corning)

I am quite satisfied with the reviewers’ comments and have undertaken to fully respond. Along with the other minor revisions and added references, the paper should now be ready to publish as submitted herewith. Peter Corning.

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References

- Bateson, P.P.G., 2005. The return of the whole organism. *J. Biosci.* 30, 31–39. <https://doi.org/10.1007/BF02705148>.
- Corning, P.A., 2005. *Holistic Darwinism: Synergy, Cybernetics, and the Bioeconomics of Evolution*. University of Chicago Press, Chicago.
- Margulis, L., 1970. *Origin of Eukaryotic Cells*. Yale University Press, New Haven, CT.
- Aanen, D.K., Eggleston, P., 2017. Symbiogenesis: beyond the endosymbiosis theory. *J. Theor. Biol.* 434, 99–103. <https://doi.org/10.1016/j.jtbi.2017.08.001>.
- Adelman, K., Egan, E., 2017. Non-coding RNA: more uses for genomic junk. *Nature* 543 (7644), 183–185. <https://doi.org/10.1038/543183a>. <http://www.ncbi.nlm.nih.gov/pubmed/28277509>.
- Archibald, J., 2014. *One Plus One Equals One: Symbiosis and the Evolution of Complex Life*. Oxford University Press, Oxford, UK.
- Arthur, W.B., 2015. *Complexity and the Economy*. Oxford Economic Press, Oxford, UK.
- Bateson, P.P.G., 2004. The active role of behaviour in evolution. *Biol. Philos.* 19, 283–298. <https://doi.org/10.1023/B:BIOP.0000024468.12161.83>.
- Bateson, P.P.G., Gluckman, P., 2011. *Plasticity, Robustness, Development, and Evolution*. Cambridge University Press, Cambridge, UK.
- Bateson, P.P.G., Laland, K.N., 2013. Tinbergen’s four questions: an appreciation and an update. *Trends Ecol. Evol.* 28 (12), 712–718. <https://doi.org/10.1016/j.tree.2013.09.013>.
- Campbell, J.H., 1994. Organisms create evolution. In: Campbell, J.H., Schopf, J.W. (Eds.), *Creative Evolution? Jones & Bartlett*, Boston, pp. 85–102.
- Capra, F., Luisi, P.L., 2014. *The Systems View of Life: A Unifying Vision*. Cambridge University Press, Cambridge, UK.
- Carrapico, F., 2010. How symbiogenic is evolution? *Theor. Biosci.* 129, 135–139. <https://doi.org/10.1007/s12064-010-0100-1>.
- Corning, P.A., 2007. Control information theory: the ‘missing link’ in the science of cybernetics. *Syst. Res. Behav. Sci.* 24, 297–311. <https://doi.org/10.1002/sres.808>.
- Corning, P.A., 2014. Evolution ‘on purpose’: how behaviour has shaped the evolutionary process. *Biol. J. Linn. Soc.* 112, 242–260. <https://doi.org/10.1111/bij.12061>.
- Corning, P., 2018. *Synergistic Selection: How Cooperation Has Shaped Evolution and the Rise of Humankind*. World Scientific, Singapore, London, New Jersey.
- Corning, P.A., 2019. Teleonomy and the proximate-ultimate distinction revisited. *Biol. J. Linn. Soc.* 127 (4), 912–916. <https://doi.org/10.1093/biolinnean/blz087>.
- Corning, P.A., Szathmáry, E., 2015. ‘Synergistic selection’: a Darwinian frame for the evolution of complexity. *J. Theor. Biol.* 371, 45–58. <https://doi.org/10.1002/0470018860.s00716>.
- Craig, N.L., 2002. *Mobile DNA II*. American Society for Microbiology Press, Washington, D.C.
- Craig, N.L., Chandler, M., Gellert, M., Lambowitz, A., Rice, P.A. (Eds.), 2015. *Mobile DNA III*. American Society for Microbiology, Washington, D.C.
- Crick, F.H.C., 1970. Central dogma of molecular biology. *Nature* 227, 561–563. <https://doi.org/10.1038/227561a0>.
- Crisp, A., Boschetti, C., Perry, M., Tunnacliffe, A., Micklem, G., 2015. Expression of multiple horizontally acquired genes is a hallmark of both vertebrate and invertebrate genomes. *Genome Biol.* 16, 50. <https://doi.org/10.1186/s13059-015-0607-3>.
- Danchin, É., Charmantier, A., Champagne, F.A., Mesoudi, A., Pujol, B., Blanchet, S., 2011. Beyond DNA: integrating inclusive inheritance into an extended theory of evolution. *Nat. Rev. Genet.* 12, 475–486. <https://doi.org/10.1038/nrg3028>.
- Darwin, C.R., 1968/1859. *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*. Penguin, Baltimore, MD.
- Dawkins, R., 1989/1976. *The Selfish Gene*. Oxford University Press, New York.
- Dobzhansky, T., 1937. *Genetics and the Origin of Species*. Columbia University Press, New York.
- Eldredge, N., Gould, S.J., 1972. Punctuated equilibria: an alternative to phyletic gradualism. In: Schopf, T.J.M. (Ed.), *Models in Paleobiology*. Freeman Cooper, New York, pp. 82–115.
- Fisher, R.A., 1999/1930. *The Genetical Theory of Natural Selection*. Oxford University Press, Oxford, UK.
- Gilbert, S.F., Sapp, J., Tauber, A.I., 2012. A symbiotic view of life: we have never been individuals. *Q. Rev. Biol.* 87 (4), 325–341. <https://doi.org/10.1086/668166>.
- Gilroy, S., Trewavas, A., 2001. Signal processing and transduction in plant cells: the end and the beginning. *Nat. Rev. Mol. Cell Biol.* 2, 307–314. <https://doi.org/10.1038/35067109>.
- Gladyshev, E.A., Arkhipova, I.R., 2011. A widespread class of reverse transcriptase-related cellular genes. *Proc. Natl. Acad. Sci. Unit. States Am.* 108 (51), 20311–20316. <https://doi.org/10.1073/pnas.1100266108>.
- Goldbogen, J.A., Cade, D.E., Wisniewska, D.M., Potvin, J., Segre, P.S., Savoca, E.L., Hazen, M.F., Czapanskiy, S.R., Kahane-Rapport, S.L., DeRuiter, S., et al., 2019. Why whales are big but not bigger: physiological drivers and ecological limits in the age of ocean giants. *Science* 366 (6471), 1367–1372. <https://doi.org/10.1126/science.aax9044>.
- Gontier, N., 2007. Universal symbiosis: an alternative to universal selectionist accounts of evolution. *Symbiosis* 44, 167–181.
- Goodman, M.F., 1998. Purposeful mutations. *Nature* 395 (6699), 221–223. <https://doi.org/10.1038/26111>.
- Gould, S.J., Lewontin, R.C., 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. *Proc. R. Soc. Lond. [Biol.]* 205 (1161), 581–598. <https://doi.org/10.1098/rspb.1979.0086>.
- Haldane, J.B.S., 1932. *The Causes of Evolution*. Harper & Row, New York.
- Hamilton, W.D., 1964. The genetical evolution of social behaviour, I. *J. Theor. Biol.* 7 (1–16), 17–52. [https://doi.org/10.1016/0022-5193\(64\)90039-6](https://doi.org/10.1016/0022-5193(64)90039-6).
- Huneman, P., Walsh, D.M., 2017. *Challenging the Modern Synthesis: Adaptation, Development, and Inheritance*. Oxford University Press, New York.
- Huxley, J.S., 1942. *Evolution: the Modern Synthesis*. Harper & Row, New York.
- Jablonka, E., 2013. Epigenetic inheritance and plasticity: the responsive germline. *Prog. Biophys. Mol. Biol.* 111, 99–107. <https://doi.org/10.1016/j.jbiomolbio.2012.08.014>.
- Jablonka, E., Lamb, M.J., 2014. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioural, and Symbolic Variation in the History of Life (Rev. edn.)*. MIT Press, Cambridge, MA.
- Jablonka, E., Raz, G., 2009. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. *Q. Rev. Biol.* 84 (2), 131–176. <https://doi.org/10.1086/598822>.
- Kimura, M., 1968. Evolutionary rate at the molecular level. *Nature* 217, 624–626. <https://doi.org/10.1038/217624a0>.
- King, J.L., Jukes, T.H., 1969. Non-Darwinian evolution. *Science* 164, 788–797. <https://doi.org/10.1126/science.164.3881.788>.
- Kolbert, E., 2014. *The Sixth Extinction: an Unnatural History*. Henry Holt and Company, New York.
- Koonin, E.V., 2009. The Origin at 150: is a new evolutionary synthesis in sight? *Trends Genet.* 25 (11), 473–475. <https://doi.org/10.1016/j.tig.2009.09.007>.
- Koonin, E.V., 2011. *The Logic of Chance: the Nature and Origin of Biological Evolution*. FT Press Science, Upper Saddle River, NJ.
- Koonin, E.V., 2016. Viruses and mobile elements as drivers of evolutionary transitions. *Philos. Trans. R. Soc. London, Ser. B* 371, 20150442. <https://doi.org/10.1098/rstb.2015.0442>.
- Kuhn, T., 1962. *The Structure of Scientific Revolutions*. University of Chicago Press,

- Chicago.
- Laland, K.N., Odling-Smee, F.J., Feldman, M.W., 1999. Evolutionary consequences of niche construction and their implications for ecology. *Proc. Natl. Acad. Sci. Unit. States Am.* 96, 10242–10247. <https://doi.org/10.1073/pnas.96.18.10242>.
- Laland, K.N., Odling-Smee, F.J., Hoppitt, W., Uller, T., 2013. More on how and why: cause and effect in biology revisited. *Biol. Philos.* 28 (5), 719–745. <https://doi.org/10.1007/s10539-012-9335-1>.
- Laland, K., Uller, T., Feldman, M., Sterelny, K., Müller, G.B., Moczek, A., Jablonka, E., Odling-Smee, J., 2014. Does evolutionary theory need a rethink? (Yes, urgently.). *Nature* 514 (7521), 161–164. <https://doi.org/10.1038/514161a>.
- Laland, K.N., Uller, T., Feldman, M.W., Sterelny, K., Müller, G.B., Moczek, A., Jablonka, E., Odling-Smee, J., 2015. The extended evolutionary synthesis: its structure, assumptions and predictions. *Philos. Trans. R. Soc. London, Ser. B* 370, 20150119. <https://doi.org/10.1098/rspb.2015.0119>.
- Lamarck, J.-B., 1844/1809. *Zoological Philosophy: an Exposition with Regard to the Natural History of Animals*. University of Chicago Press, Chicago (Elliot, H., trans.).
- Lamichaney, S., Han, F., Webster, M.T., Andersson, L., Grant, B.R., Grant, P., 2018. Rapid hybrid speciation in Darwin's finches. *Science*. <https://doi.org/10.1126/science.aao4593>. <http://www.ncbi.nlm.nih.gov/pubmed/29170277>.
- Laubichler, M.D., Renn, J., 2015. Extended evolution: a conceptual framework for integrating regulatory networks and niche construction. *J. Exp. Zool.* 324B, 565–577. <https://doi.org/10.1002/jez.b.22631>.
- Margulis, L., 1993. *Symbiosis in Cell Evolution*, second ed. W.H. Freeman, New York.
- Margulis, L., 1998. *Symbiotic Planet: A New Look at Evolution*. Basic Books, New York.
- Margulis, L., Fester, R. (Eds.), 1991. *Symbiosis as a Source of Evolutionary Innovation: Speciation and Morphogenesis*. MIT Press, Cambridge, MA.
- Margulis, L., Sagan, D., 2002. *Acquiring Genomes: A Theory of the Origins of Species*. Basic Books, New York.
- Mattick, J.S., 2018. The state of long non-coding RNA biology. *Noncoding RNA* 4 (3), 17. <https://doi.org/10.3390/ncrna4030017>. <http://www.ncbi.nlm.nih.gov/pubmed/30103474>.
- Maynard Smith, J., Szathmáry, E., 1995. *The Major Transitions in Evolution*. Freeman Press, Oxford, UK.
- Mayr, E., 1942. *Systematics and the Origin of Species from the Viewpoint of a Zoologist*. Harvard University Press, Cambridge, MA.
- Mayr, E., 1960. The emergence of evolutionary novelties. In: Tax, S. (Ed.), *Evolution after Darwin* (Vol. I). University of Chicago Press, Chicago, pp. 349–380.
- Mayr, E., 1961. Cause and effect in biology. *Science* 134 (3489), 1501–1506. <https://doi.org/10.1126/science.134.3489.1501>.
- Mayr, E., 2001. *What Evolution Is*. Basic Books, New York.
- McClintock, B., Moore, J.A. (Eds.), 1987. *The Discovery and Characterization of Transposable Elements: the Collected Papers of Barbara McClintock*. Garland Publishers, New York.
- Michod, R.E., 1999. *Darwinian Dynamics: Evolutionary Transitions in Fitness and Individuality*. Princeton University Press, Princeton, NJ.
- Monod, J., 1971. *Chance and Necessity*. Alfred A. Knopf, New York (Wainhouse A., trans.).
- Müller, G.B., Newman, S.A. (Eds.), 2003. *Origination of Organismal Form: beyond the Gene in Developmental and Evolutionary Biology*. MIT Press, Cambridge, MA.
- Noble, D., 2006. *The Music of Life: Biology beyond the Genes*. Oxford University Press, Oxford, UK.
- Noble, D., 2011. Neo-Darwinism, the modern synthesis and selfish genes: are they of use in physiology? *J. Physiol.* 589 (5), 1007–1015. <https://doi.org/10.1111/jphysiol.2010.201384>.
- Noble, D., 2013. Physiology is rocking the foundations of evolutionary biology. *Exp. Physiol.* 98 (8), 1235–1243. <https://doi.org/10.1111/expphysiol.2012.071134>. <https://search.crossref.org/?q=Physiology+is+rocking+the+foundations+of+evolutionary+biology>.
- Noble, D., 2015. Evolution beyond neo-Darwinism: a new conceptual framework. *J. Exp. Biol.* 218 (Pt 1), 7–13. <https://doi.org/10.1242/jeb.106310>.
- Noble, D., 2017. *Dance to the Tune of Life: Biological Relativity*. Cambridge University Press, Cambridge, UK.
- Noble, D., 2018. Central dogma or central debate? *Physiol.* 33, 246–249. <https://doi.org/10.1152/physiol.00017.2018>.
- Noble, D., 2019a. Evolution in Revolution (Review of Paul Davies, the Demon in the Machine.) Inference (in press).
- Noble, D., 2019b. Exosomes, gemmules, pangenesis, and Darwin. In: Edelstein, L., Smythies, J., Quesenberry, P., Noble, D. (Eds.), *Exosomes: A Clinical Compendium*. Academic Press, New York, pp. 487–501.
- Nowak, M.A., 2006. Five rules for the evolution of cooperation. *Science* 314, 1560–1563. <https://doi.org/10.1126/science.1133755>.
- Odling-Smee, F.J., Laland, K.N., Feldman, M.W., 2003. *Niche Construction: the Neglected Process in Evolution*. Princeton University Press, Princeton, NJ.
- Pan, D., Zhang, L., 2009. Burst of young retrogenes and independent retrogene formation in mammals. *PLoS One* 4 (3), e5040. <https://doi.org/10.1371/journal.pone.0005040>. <http://www.ncbi.nlm.nih.gov/pubmed/19325906>.
- Pigliucci, M., Müller, G.B. (Eds.), 2010. *Evolution: the Extended Synthesis*. MIT Press, Cambridge, MA.
- Pross, A., 2016. *What is Life? How Chemistry Becomes Biology*, second ed. Oxford University Press, Oxford, UK.
- Pross, A., 2018. Early life on Earth: tracing the chemical path from non-living to living. In: Elmegreen, B.G., Tóth, L.V., Güdel, M. (Eds.), *Origins: from the Protosun to the First Steps of Life*, Proceedings IAU Symposium No. 345. Cambridge University Press, Cambridge, UK, pp. 206–214.
- Ridley, M., 2003. *Evolution*, third ed. Wiley-Blackwell, Oxford, UK.
- Roe, A., Simpson, G.G. (Eds.), 1958. *Behavior and Evolution*. Yale University Press, New Haven, CT.
- Rose, M.R., Oakley, T.H., 2007. The new biology: beyond the modern synthesis. *Biol. Direct* 2 (30), 30. <https://doi.org/10.1186/1745-6150-2-30>.
- Rosen, R., 1970. *Dynamical Systems Theory in Biology*. Wiley Interscience, New York.
- Rosen, D.E., 1978. Darwin's demon. *Syst. Zool.* 27, 370–373. <https://doi.org/10.2307/2412892>.
- Rosen, R., 1991. *Life Itself: A Comprehensive Inquiry into the Nature, Origin, and Fabrication of Life*. Columbia University Press, New York.
- Salvucci, E., 2016. Microbiome, holobiont and the net of life. *Crit. Rev. Microbiol.* 42 (3), 485–494. <https://doi.org/10.3109/1040841X.2014.962478>.
- Sapp, J., 1994. *Evolution by Association: A History of Symbiosis*. Oxford University Press, New York.
- Sapp, J., 2004. The dynamics of symbiosis: an historical overview. *Can. J. Bot.* 82, 1046–1056. <https://doi.org/10.1139/cjb-2017-0064>.
- Sapp, J., 2009. *The New Foundations of Evolution, on the Tree of Life*. Oxford University Press, Oxford, UK.
- Schilthuisen, M., 2018. *Darwin Comes to Town: How the Urban Jungle Drives Evolution*. Picador, New York.
- Shapiro, J.A., 2011. *Evolution: A View from the 21st Century*. FT Press Science, Upper Saddle River, NJ.
- Shapiro, J.A., 2013. How life changes itself: the Read–Write (RW) genome. *Phys. Life Rev.* 10, 287–323. <https://doi.org/10.1016/j.plrev.2013.07.001>.
- Simpson, G.G., 1953. The Baldwin effect. *Evolution* 2, 110–117. <https://doi.org/10.1111/j.1558-5646.1953.tb00069>.
- Smocovitis, V.B., 1996. *Unifying Biology: the Evolutionary Synthesis and Evolutionary Biology*. Princeton University Press, Princeton, NJ.
- Stebbins, G.L., 1951. Cataclysmic evolution. *Sci. Am.* 184 (4), 54–59. <https://doi.org/10.1038/scientificamerican0451-54>.
- Tinbergen, N., 1963. On aims and methods of ethology. *Z. Tierpsychol.* 20, 410–433. <https://doi.org/10.1111/j.1439-0310.1963.tb01161.x>.
- Trewavas, A., 2014. *Plant Behaviour and Intelligence*. Oxford University Press, Oxford, UK.
- Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C., Knight, R., Gordon, J.I., 2007. The human microbiome project. *Nature* 449 (7164), 804–810. <https://doi.org/10.1038/nature06244>.
- Valentine, J.W., Campbell, C.A., 1975. Genetic regulation and the fossil record. *Am. Sci.* 63 (6), 673–680.
- Waddington, C.H., 1942. Canalization of development and the inheritance of acquired characters. *Nature* 15, 563–565. <https://doi.org/10.1038/150563a0>.
- Waddington, C.H., 1952. Selection of the genetic basis for an acquired character. *Nature* 169, 278. <https://doi.org/10.1038/169625b0>.
- Waddington, C.H., 1957. *The Strategy of the Genes: A Discussion of Some Aspects of Theoretical Biology*. Macmillan, New York.
- Waddington, C.H., 1961. *The Nature of Life*. Harper & Row, New York.
- Wade, M.J., 2011. The neo-modern synthesis: the confluence of new data and explanatory concepts. *Bioscience* 61 (5), 407–408. <https://doi.org/10.1525/bio.2011.61.5.10>.
- Walsh, D.M., 2015. *Organisms, Agency, and Evolution*. Cambridge University Press, Cambridge, UK.
- Weismann, A., 1892. *Das Keimplasma: Eine Theorie der Vererbung* [The Germ Plasm: A Theory of Inheritance]. Fischer, Jena, Austria.
- West-Eberhard, M.J., 2003. *Developmental Plasticity and Evolution*. Oxford University Press, Oxford, UK.
- West-Eberhard, M.J., 2005a. Developmental plasticity and the origin of species differences. *Proc. Natl. Acad. Sci. Unit. States Am.* 102 (Suppl. 1), 6543–6549. <https://doi.org/10.1073/pnas.0501844102>. <http://www.ncbi.nlm.nih.gov/pubmed/15851679>.
- West-Eberhard, M.J., 2005b. Phenotypic accommodation: adaptive innovation due to developmental plasticity. *J. Exp. Zool. B Mol. Dev. Evol.* 304 (6), 610–618. <https://doi.org/10.1002/jez.b.21071>. <http://www.ncbi.nlm.nih.gov/pubmed/16161068>.
- Wilson, E.O., 1975. *Sociobiology: the New Synthesis*. Harvard University Press, Cambridge, MA.
- Wilson, D.S., 1997a. Introduction: multilevel selection theory comes of age. *Am. Nat.* 150 (Suppl. 1), S1–S4. <https://doi.org/10.1086/286046>.
- Wilson, D.S., 1997b. Altruism and organism: disentangling the themes of multilevel selection theory. *Am. Nat.* 150 (Suppl. 1), S122–S124. <https://doi.org/10.1086/286053>.
- Woese, C.R., 2004. A new biology for a new century. *Microbiol. Mol. Biol. Rev.* 68 (2), 173–186. <https://doi.org/10.1128/MMBR.68.2.173-186>, 2004.
- Wray, G.A., Hoekstra, H.E., Futuyma, D.J., Lenski, R.E., Mackay, T.F.C., Schluter, D., Strassman, J.E., Hoekstra, H.E., 2014. Does evolutionary theory need a rethink? (No, all is well). *Nature* 514 (7521), 161–164. <https://doi.org/10.1038/514161a>.
- Wright, S., 1931. Evolution in mendelian populations. *Genetics* 16 (2), 97–159.
- Wright, S., 1932. The roles of mutation, inbreeding, crossbreeding and selection in evolution. In: *Proc. 6th Int. Cong. Genet.*, vol. 1, pp. 356–366.