Critical Review

The Broad Utility of the Theory of Intelligent Design to Guide Scientific Research

Casey Luskin*, **Emily Reeves, Brian Miller, and Jonathan McLatchie**
Discovery Institute, Seattle, WA 98104, USA

Abstract

Intelligent design (ID) is a scientific theory that uses the methods of historical sciences to infer that many features of nature are best explained by an intelligent cause because they exhibit forms of information and complexity that in our experience only come from intelligence. ID is fundamentally a theory of design detection, but it has also been applied as an experimental science to guide research into how the natural world operates in the present day. ID uses a positive argument, beginning its investigations by studying known-designed objects and the actions of intelligent agents to identify properties that indicate design, such as complex and specified information, irreducible complexity, purposeful coordination of parts, common design patterns, and functionality. Natural features can then be studied to determine whether they meet the criteria for detecting design. These hallmarks of design can then be further applied to model or predict how designed natural systems function. Discoveries made through such studies of natural systems can then lead to improvements in human technology through biomimetics. This paper will review how ID has been applied within a variety of fields, including protein science, genetics, and systematics. It will also detail how engineering-based methodologies grounded in ID principles, such as systems biology and systems engineering, have advanced the study of multiple biological systems, including the flagellum-chemotaxis system, glycolysis, vertebrate limbs and joints, feathers, and brain blood flow.

Cite As: Luskin C, Reeves E, Miller B, McLatchie J (2026) The Broad Utility of the Theory of Intelligent Design to Guide Scientific Research. BIO-Complexity 2026 (4):1-46. **doi:**10.5048/BIO-C.2026.4.

Editor: Robert J. Marks II

Received: November 16, 2025; **Accepted:** June 4, 2026; **Published:** July 27, 2026

Copyright: © 2026 Luskin et al. This open-access article is published under the terms of the Creative Commons Attribution License, which permits free distribution and reuse in derivative works provided the original author(s) and source are credited.

Notes: A *Critique* of this paper, when available, will be assigned **doi:**10.5048/BIO-C.2026.4.c.

*Email: cluskin@discovery.org

1. INTRODUCTION

Intelligent design (ID) is a scientific theory that employs the scientific method to determine where features of nature are best explained by an intelligent cause, because they exhibit forms of information and complexity that, in our empirically-derived experience, are always produced by intelligence. ID was initially developed as a theory of design detection, but it can also be applied to experimentally guide research into the present-day operation of nature. ID therefore has strong heuristic value, which allows it to be applied to guide multiple types of scientific research.

1.1 Types of Intelligent Design Research

Philosophy of science generally recognizes three basic types of scientific research: theoretical, historical, and experimental [1–5]. Theoretical research focuses on building and developing scientific hypotheses and models that make testable predictions or expectations. Historical and experimental scientific research investigate the validity of those hypotheses or models by testing whether their theoretical predictions or expectations are supported or are falsified by the data. Historical scientific research tests theoretical historical models by investigating their ability to explain past events in natural history. Experimental science[1] tests theoretical empirical models by investigating their ability to explain the present-day operation of nature.

Intelligent design research spans all three types of scientific research. Much theoretical research has been done to develop the theoretical basis of intelligent design (Section 1.2). The theory of intelligent design has subsequently been applied both as a historical science

[1]In this context "experiment" can mean a wide variety of modes of data collection, including (but not limited to) classical experiments performed in beakers or using instruments at a laboratory bench, observing animal behavior in the wild, mapping geological layers through fieldwork and collecting and analyzing fossils within those layers, or collecting starlight from telescopes.

and as an experimental science. In this study, research applying ID theory as a historical science will be termed "design-detection research," and the application of ID theory to experimentally study the present-day operation of nature will be termed "applied design research."

1.2 Theoretical Design Research

A significant body of ID research has developed the theoretical mathematical and philosophical foundations for detecting design. This research largely focuses on studying the causal abilities of intelligent agents, making hypotheses about what is expected to be found when an intelligent agent was at work, and developing methods for detecting when those tell-tale signs of prior intelligent agency are present to a degree that warrants making a design inference. Much of this theoretical research has focused on identifying the type of information that is produced when intelligent agents are at work.

1.2.1 Complex and Specified Information (CSI)

As a theory of design detection, ID typically uses the identification of complex and specified information (CSI) to determine whether an object, event, configuration, pattern, scenario, or system (collectively called an "outcome") was intelligently designed. ID has been called "a theory of information," where "information becomes a reliable indicator of design as well as a proper object for scientific investigation" [6]. Investigators using ID theory, therefore, detect design in natural phenomena by determining that those phenomena bear the type of information that, in our experience of the cause-and-effect structure of the world, arises from intelligent agency.

Biological systems are rich in information [7–9] and it has been estimated that the human genome contains billions of bits of information [10]. Information is often defined as a reduction in uncertainty or a means of eliminating possible outcomes [11–13]; information thus represents knowledge which excludes some possible outcomes, while allowing others. For example, looking outside and seeing a baseball game provides information about whether it is raining; and, the 5-digit zip code on an envelope provides information about where a letter is to be (or not be) delivered.

The classical definition of information developed by Shannon (1948) [11] measures information in bits (I), which reflects the mere probability (p) a pattern being observed, where $\mathrm{I} = -\log_2(p)$. However, biologists often refer to functional information, also measured in bits, which corresponds to the likelihood that a sequence of nucleotides or amino acids will perform a particular function [14, 15]. In a computer-based environment, functional information can be measured via Kolmogorov complexity, which assesses the shortest algorithm that can yield a particular output [16, 17]. Functional information and Kolmogorov complexity (coupled with p), are forms of CSI [18, 19], yet CSI is applicable in many contexts beyond computer science, including biology, cosmic fine-tuning, forensic science, and fraud detection (Table 1).

Measuring CSI requires assessing whether a feature is both complex and specified. Roughly speaking, complexity correlates with the improbability of a feature arising by chance. Improbability, however, is only a necessary, but not sufficient justification for inferring design. For instance, the probability of each player at a poker table being dealt any given hand of cards is exceedingly small. Despite this, the fact that an improbable set of hands is routinely dealt does not justify an inference that the deck was "stacked." Unlikely events happen regularly—and, in this case, it is inevitable that any combination of hands is very unlikely. Something more is needed to detect design—namely, specification, meaning that the event is predefined as special, such as corresponding to an independently-given pattern or having some significant value [19–21].

The recognition of CSI is useful in forensic science and fraud investigation for detecting the action of an intelligent agent committing a crime. Returning to poker, imagine that a card dealer deals himself a royal flush over ten consecutive rounds. With a properly shuffled deck, a particular royal flush is equally improbable in each round, as is any other possible particular hand. But in this scenario, the improbable event also corresponds to an independently given pattern or specification; that is, the card dealer has consistently dealt himself the best hand of cards. Given the unlikely event combined with the specification, we would justifiably conclude that the deck was stacked. Or, consider the real-world example recounted in Dembski (1998) [20] of an election clerk belonging to the Democratic Party who determined the order of candidates on ballots for elections, yet in 40 out of 41 elections, a Democrat was listed first on the election ballot. Typically, candidates are listed in random order to eliminate "first-position" bias, a phenomenon in which voters without a strong preference tend to choose candidates listed higher on the ballot. Thus, any particular combination of Republican or Democrat candidates being in the top ballot position would therefore be equally extremely unlikely—approximately 2^{-41}. But with the specification (independent pattern) that the top position nearly always matched the election clerk's preferred party, election fraud—where an intelligent agent sought to rig the election outcome—becomes the obvious explanation. CSI thus has utility for detecting design, as it accurately captures how we routinely identify whether an outcome was designed (Table 1).

CSI can be measured robustly. Montañez (2018) [19] developed a method for calculating CSI based upon the ratio of the probability of an outcome arising through blind natural processes (i.e., chance + law), divided by its degree of specialness. The degree of specialness is

Table 1: Examples of using CSI to detect intelligent design.

Event / Object / Scenario	Complexity (Unlikelihood)	Specification (Specialness)
Codebreaking	Complex / unlikely sequence of symbols.	Sequence matches a linguistic pattern.
Election fraud	Complex / unlikely sequence of politicians at top of ballot.	Politicians belonging to a particular political party (nearly) always given favored status.
Cheating at cards	Complex / unlikely hand of cards dealt out to players.	Dealer's hand of cards consistently matches the best possible hand.
Spoken language	Complex / unlikely series of vibrations emitted from a source.	Vibrations match spoken words belonging to a known language.
Functional machine	Irreducible complexity / unlikely arrangement of machine parts.	Multiple parts having matching interface compatibility are necessary for a system to function, allowing them to work in purposeful coordination to convert energy into mechanical work.
Physical laws and constants governing the universe	Physical laws and constants take on extremely rare values.	The laws and constants match precise values that are necessary for life to exist.

quantified via a specification function, where "specialness values" are pre-assigned to particular potential outcomes. To appreciate how this works, again consider poker. In this game, a royal flush is considered a highly "special" outcome. The likelihood of obtaining any royal flush is also very low—roughly 1 in 650,000 hands. A royal flush is both highly improbable and highly special, and therefore represents high CSI.

While specialness is easily determined in a game of poker with well-defined winning outcomes, it can also be measured in contexts where definitions of "special" may be less obvious. Dembski and Ewert (2023) [21] developed a linguistic method of measuring specification based upon description length, drawing from the insight that objects, events, or scenarios with short linguistic descriptions tend to be significant, special, and/or convey large amounts of meaningful information. Thus, under their method, the shorter the specification needed to describe an outcome, the greater the specialness. Miller (2026) [22] demonstrated that when natural languages are used for specifications, the methods of Montañez (2018) and Dembski and Ewert (2023) are mathematically equivalent, as the value of the specification function can be directly determined by the number of words in the description.

Dembski (2002) [23], as well as subsequent publications by other ID theorists [24–30], have also investigated, developed, and reinforced "no free lunch" (NFL) theorems and the Law of Conservation of Information, which hold that blind natural mechanisms can shuffle around pre-existing information, but truly novel CSI always requires the action of intelligence. A related concept is "active information," defined as the information necessary to be inputted into some search function to enable it to find a target [24, 25, 31–34]. These methodologies have been applied to a variety of evolutionary algorithms to identify where programmers smuggled in active information to allow the simulation to reach some predefined goal [25, 35–44], further showing the need for intelligence to generate new information. These methods can also be used to measure active information in biological systems [45, 46] or the finely-tuned laws of nature, aiding in design detection. Additional theoretical research has developed algorithmic specified complexity (ASC) as an improved method for quantifying specification as a function of linguistic description length [21, 47–49]. Various types of CSI (e.g., functional information, Kolmogorov complexity, ASC, and IC), have been unified into a general model of canonical CSI by Montañez (2018) [19].

The result of this body of research [50] is to demonstrate that intelligence is required to generate new CSI—establishing a key ID-based prediction that leads to testable hypotheses about what should be found if design occurred in the origin of some system.

1.2.2 Irreducible Complexity

A particular form of CSI often used in detecting design is irreducible complexity (IC), wherein multiple parts are necessary for a system to function. Conceptually developed by Behe (1996), IC exists in a "system composed of several well-matched, interacting parts that contribute to the basic function, wherein the removal of any one of the parts causes the system to effectively cease functioning" [51]. IC is often cited in molecular machines, which are said to meet Darwin's criterion of a biological feature which "could not possibly have been formed by

numerous, successive, slight modifications" [52] because multiple parts—called the "irreducible core" [23]—are necessary for the machine to function. If any components of the irreducible core are missing, the system will not function and provide a selective advantage to the organism, thereby causing Darwinian evolution to "break down" [52].

IC systems are said to indicate design because they contain parts "arranged to serve a purpose" [53] and "In all irreducibly complex systems in which the cause of the system is known by experience or observation, intelligent design or engineering played a role [in] the origin of the system" [54]. Moreover, intelligent agency is "the one thing in our experience that co-opts irreducibly complex machines and uses their parts to build a new and more intricate machine" [55]. IC is also a form of CSI because it represents an unlikely arrangement of parts that matches a precise pattern necessary for a machine to function [23].

1.2.3 Methods of Design Detection

A crucial aspect of theoretical ID research is the development of methods for detecting design. ID theorists have developed multiple methods of design detection, which although distinct, are complementary in that they seek to identify empirical evidence that a mind was at work. These methods operate on the principle that minds know how to reliably recognize the action of other minds, and each offers insights into how the prior action of a mind can be recognized.

Dembski (1998) [20] was the first to propose CSI as a general informational pattern that reliably indicates the prior action of intelligence. That work [20] also articulated the "explanatory filter" as a logical methodology for discriminating between (1) chance, (2) law, (3) chance + law, and (4) design. Explanations (1) through (3) all reduce to strictly blind material causes, and stand in contrast to explanation (4), which is intelligent causation. According to the explanatory filter, when (1), (2), and (3) can be ruled out as plausible explanations, then design is the only remaining viable explanatory option. ID theory maintains that high CSI is a property that always derives from category (4)—intelligent design (see Section 1.2.1).

According to Behe (1996), another method of detecting design is by identifying a purposeful arrangement of parts: "we conclude design from the physical evidence, when we see a number of elements coming together to accomplish an identifiable function—the purposeful arrangement of parts" [51]. He cites irreducibly complex molecular machines as examples of purposeful arrangements that warrant a design inference:

> [D]esign is positively apprehended in the purposeful arrangement of parts. Looked at this way, irreducibly complex systems such as mousetraps and flagella serve both as negative arguments against gradualistic explanations like Darwin's and as positive arguments for design. The negative argument is that such interactive systems resist explanation by the tiny steps that a Darwinian path would be expected to take. The positive argument is that their parts appear arranged to serve a purpose, which is exactly how we detect design. [53]

Because IC is a form of CSI, Behe's method is highly complementary to Dembski's methods of detecting design through discovering CSI.

Montañez (2018) [19] demonstrated that design detection is possible using standard methods used for testing hypotheses in statistics (see also [8, 56, 57]). Under this method, design is treated as a hypothesis which can be statistically accepted or rejected based on whether its probability divided by degree of specialness (a variable called K, which also serves as a proxy for CSI), is below a statistically significant cutoff value (a variable called α). If $K < \alpha$, then design is detected (because it is statistically likely to be correct). Under this method, K is treated like a p-value, and the smaller the p-value, the more confidence we have that the design hypothesis is true. This method also operates under the principle that high CSI is a reliable indicator of design.

Another method for detecting design, developed largely by philosopher of science Stephen Meyer, is making an inference to design as the best explanation by comparing multiple hypotheses and demonstrating that the design hypothesis explains more data than other known competing hypotheses. As Meyer (2013) explains:

> Contemporary philosophers of science such as Peter Lipton have called this method of reasoning 'inference to the best explanation.' Scientists often use this method when trying to explain the origin of an event or structure from the past. They compare various hypotheses to see which would, if true, best explain it. They then provisionally affirm the hypothesis that best explains the data as the one that is most likely to be true. [58]

How can one determine when an explanation "best explains" the data? A classical example, paraphrased from [59], considers coming across a wet driveway and attempting to explain how it became wet. Possible explanations include: (a) rain, (b) automatic sprinklers, or (c) washing a car. All three explanations can explain the wet driveway, however additional observations provide data that can only be explained by particular models. For example, it is further observed that a nearby lawn and the street are perfectly dry, and there are no clouds

in the sky—observations that cannot be explained by (a) rain. Moreover, if the sprinklers had watered the driveway, the lawn should also be wet, but the dry lawn cannot be explained by (b) automatic sprinklers. Finally, a bucket of soapy water and a sponge are observed sitting next to a car on the driveway—evidence that can only be explained by explanation (c) washing a car. The "(a) rain" or "(b) automatic sprinkler" hypotheses cannot explain all the observed data points. Only the "(c) washing a car" hypothesis can explain all the evidence, making it the "best explanation."

Meyer's method is highly compatible with the explanatory filter in that it requires that design is a superior explanation to chance/law-based explanations. It also incorporates insights from other methods that only intelligent agency can explain the origin of high CSI. This method is further elaborated in the following section, 1.3.

Lastly, this review argues that design can be detected using the scientific method. Under this approach, observations of the causal powers of intelligent agents lead to positive predictions or expectations of design theory, which can then be tested through the study of nature (experimentation). Since high CSI is a positive prediction of intelligent design, and CSI is experimentally detectable, this method is also highly aligned with the other methods of design detection. This method is elaborated further in Section 2.

Though each method has its distinctives, these methods share important commonalities. In particular, each method seeks to detect design by finding reliable indicators that an intelligent agent was at work—in particular, the presence of high CSI.

It must be emphasized that using CSI to detect design is not a "gaps"-based argument that depends upon finding negative evidence against evolution. To the contrary, because intelligent design is grounded in empirical observations that intelligent agents are known to produce high CSI, ID is a decisively positive theory that is based upon finding in nature the kind of information and complexity that, in our experience, only comes from intelligence. Many other observations about the causal abilities of intelligent agents lead to positive expectations of the theory of intelligent design, making ID a theory that is strongly grounded in positive evidence.

1.3 Design-Detection Research: Intelligent Design as a Historical Science

The theory of intelligent design primarily operates as a historical science which seeks to determine whether intelligent causation is the best explanation for the origin of a natural feature [60].[2] Historical sciences rely heavily on abductive reasoning and the principle of uniformitarianism, which holds that "causes which can be observed acting at the present day" [62] can be used to explain events of the past [63]. Historical scientists thus observe present-day causes to understand their causal powers—i.e., what they are capable of doing. This allows predictions to be made about what should be found in the natural world if a particular cause was at work in the past. Meyer (2013) [58] (p. 348) elaborated that these causes must "be known to have the power to produce the kind of effect, feature, or event in question." By studying a present-day cause, scientists can make testable predictions or expectations about what should be discovered on the hypothesis that the same cause was in operation in the past. Fulfillment of these expectations provides positive evidence that this cause was in fact at work.

For example, a geologist observes in the present day that a stream is removing sediment from a streambed, causing it to deepen at a rate of approximately 1 cm per year. This cause, water in a stream stripping sediment, is observed in the present day to produce a particular effect—the deepening of a streambed. Then, the geologist encounters a gorge that is 100 meters deep and has a river flowing at the bottom. By applying uniformitarian reasoning, the geologist may conclude that the river flowing through the gorge is a cause that can explain the presence of the gorge.

In a similar manner, the theory of ID employs the standard methods routinely employed by other historical sciences to determine whether certain features of the universe and living organisms are explained by intelligent causation. Intelligent agency is a cause "now in operation" [6] that can be studied in the world around us in the "present day" [62] and which has the "power to produce" information-rich systems [58]. Thus, as a historical science, ID employs the principle of uniformitarianism by beginning with present-day observations of how intelligent agents operate and of the properties of known-designed objects, and then it converts those observations into positive expectations of what scientists should find if some object is the product of intelligent design.

Human and animal intelligence, and human-engineered systems, provide a large empirical dataset for studying what features result from intelligent action. Based upon our empirical experience of the world, we observe that intelligent agents alone are known to generate high CSI. Dembski (2001) [6] observes that "[t]he principal characteristic of intelligent agency is directed contingency, or what we call choice," and when an intelligent agent acts, "it chooses from a range of competing possibilities" to create some complex and specified event. It is this ability of intelligent agents—the capability of foresight to choose from among a large range of possi-

[2] Evolutionary theory also operates as a historical science, seeking to explain the origin of biological features. Though they come to divergent conclusions, the theory of intelligent design and evolutionary biology have key methodological similarities and in important respects can be called "methodologically equivalent" [61].

ble options and select one that fulfills some necessary requirement—that allows intelligent minds to generate high CSI. This means that when we find high CSI in an object or other natural phenomenon, we are justified in concluding that it had been designed. This is called "detecting design" or making a "design inference."

ID, therefore, attempts to identify in nature the kind of information—high CSI—that we know from observation-based experience is always and only produced by intelligent agents. Language, codes, and machines are all CSI-rich structures; in our experience, these things always derive from an intelligent mind (Table 1). By studying the actions of humans and human-engineered systems, we can understand what to expect to find when an intelligent agent has been at work, allowing us to construct positive, testable expectations about what should be found (high CSI) if the hypothesis of design is correct.

This positive argument for design thus follows not only the methods of historical sciences, but also the standard scientific method of observation, hypothesis, experiment, and conclusion. The positive case for design begins with observations of intelligent agents and what they produce when they design things. This leads to hypotheses (expectations) about what we should find if intelligent agency was involved in the origin of a structure, event, or scenario. These expectations are experimentally testable. Depending upon the outcome of the experiments and the nature of the data, the hypothesis/expectation is either supported to some degree or falsified.

In many cases, historical sciences face scenarios where there are multiple possible explanations, each of which can explain the observed data to different degrees. In such a case, the explanatory power of multiple causes can be compared, and the cause with the greatest explanatory power and scope is inferred to be the most likely to be correct [4, 5]. As Meyer (2004) puts it, historical scientists "assess or test competing hypotheses by evaluating which hypothesis would, if true, provide the best explanation for some set of relevant data" [60]. This is called making an "inference to the best explanation" [60, 64] (see also [4]). This precise method is used by the theory of intelligent design: When the predictions of design are fulfilled, but material causes (such as random mutation or natural selection) cannot explain the data, this leads to a (tentative) conclusion that design is the best causal explanation.

To elaborate, in various cases, such as the origin of certain proteins, molecular machines, or the cell itself, it can be demonstrated that the probability of an unguided evolutionary origin exceeds the available probabilistic resources—e.g., the universal probability bound, the galactic probability bound, the solar-system probability bound, or the Earth-based probability bound [20, 23, 58, 65, 66]. To give one example, Axe (2004) [67] demonstrated the likelihood of a random sequence of amino acids generating a functional β-lactamase fold to be less than 1 in 10^{77}. Yet, as discussed by [58], no more than 10^{40} cells have lived over the entire history of life on Earth (see also [68]), effectively providing a type of biological probability bound. If every organism that has ever lived was somehow given a random sequence of about 150 amino acids—an extremely generous (and unrealistic) assumption that is biased heavily in favor of evolutionary theory—the likelihood of evolutionary mechanisms generating such a functional enzyme fold would still be 1 in 10^{37}. In such cases, standard evolutionary mechanisms clearly cannot explain the data. High CSI in proteins, irreducible complexity in molecular machines, and top-down irreducibly complex design in cells represent informational patterns known to come from intelligence; therefore, intelligent design can be confirmed as the *best explanation* for the origin of these features.

In such cases where design theory leads us to expect the observed data, and evolutionary explanations are falsified because the probabilistic resources they require exceed the relevant probability bound, we can say with great confidence that intelligent design is the best explanation. However, there may be other cases where intelligent design is the correct explanation, but design-detection methods fail to infer design. This is because in practice, the theory of intelligent design is applied very conservatively under a philosophy which holds that false positives are much more important to avoid than false negatives. This allows design theorists to detect design with a high degree of confidence in particular cases, and in other cases await further data before determining that intelligent design is the best explanation.

1.4 Applied Design Research: Intelligent Design as an Experimental Science

Once evidence for design in the origins of natural features has been established (see Section 2, and Table 4), design theorists are justified in starting with teleological assumptions for their research, and can then use design-based methodologies and hypotheses to model and predict how natural systems operate.

Some critics have maintained that when design detection research concludes that design occurred in the origin of some natural feature, this ends the inquiry—effectively becoming a "science stopper" [69, 70]. This review argues that the conclusion of design is a useful finding in and of itself, as scientists seek to understand questions about origins and the processes that generated patterns in the historical record. Nonetheless, this review also shows that the theory of intelligent design extends well beyond design detection, and can also be applied to investigate the present-day operation of natural systems. As Dembski (1998) [71] explains: "intelligent design is hardly finished once it answers whether an object was

designed. ... Intelligent design's positive contribution to science is to reverse engineer objects shown to be designed. The design theorist is a reverse engineer."

Experimental sciences typically begin by making observations of some natural feature which requires explanation. Observations will also have been made about the natural world to help develop a hypothesis or model to explain how the feature operates or why it occurs. Experimental work can then test the merits of the hypothesis or model [3–5]. But how are those explanatory hypotheses and models generated? If intelligent design was involved in the origin of a natural feature, this can lead to expectations about how it works in the present day.

For example, ID provides justification for using design-based methodologies, such as reverse systems engineering, to interrogate the workings of complex natural systems. As will be elaborated in Section 3.4, these methodologies generally assume that systems are intelligently designed with a top-down system-wide goal, wherein many hierarchically arranged functional parts are coordinated to contribute to the overall function of the system. This approach starts by modeling systems as if they were built with foresight and a goal-oriented architecture, designed using a top-down approach rather than built blindly from the bottom up. ID-based methodologies thus allow theorists to model or predict what natural systems should look like if they were designed—effectively applying design-detection criteria to set expectations regarding what exists in nature.

As another example, ID theorists observe that when intelligent agents design systems, they typically incorporate components that have a function or purpose within that system. This leads to a natural prediction or expectation that components within biological systems will have a function or a purpose. An obvious application of such a model is that so-called junk DNA will not be functionless but will, in fact, turn out to perform important roles within cells. This is an experimentally testable prediction, and in this manner, ID can lead to experimentally testable models about how natural features operate in the present day (see Section 3.2.3).

Or, consider the observation that intelligent agents generate systems with high CSI. As noted, proteins with high CSI require extremely specific amino acid sequences in order to function, and will likely be less tolerant to perturbation, mutations, or amino acid substitutions. ID theory's expectation of high CSI in proteins leads to a natural prediction that biological systems will be fine-tuned to perform their functions and require highly specific informational sequences to do their jobs. This leads to direct expectations about the plasticity and mutability of proteins, with implications for protein functionality and their bioengineering design (see Section 3.1).

1.5 The Nature of "Predictions," "Retrodictions," and "Expectations" in Science

As noted, intelligent design is a scientific theory that uses positive arguments based upon finding in nature the type of information and complexity which in our experience only are generated only by intelligence. Our empirically-based knowledge of the causal powers of intelligent agents can lead to positive "predictions" about what should be found in nature if a system was designed. However, the typical understanding of the term "prediction" implies that a data point was anticipated *prior* to it having been discovered. Similarly, a "retrodiction" usually describes a situation where a data point is explained by a scientific model, but the model was developed *after* the data point was already known to exist. Yet with historical and experimental sciences, the exact chronology of data collection or discovery versus when the "prediction" was made (i.e., was it a "prediction" or a "retrodiction") is irrelevant to determining whether the cause indicated by the theory can explain the data point in question and thereby "predicts" its existence. In that regard, with scientific theories, what matters is the explanatory capability of the cause being invoked—i.e., whether the theory has the ability to account for or explain the data set in question, not whether the model happened to be developed before the data set was known (and thereby "predicted" it) or was developed later (and thereby "retrodicted" the data set). This paper will use the term "expectations" to cover both predictions and retrodictions which represent data points that are expected on a theory based upon its explanatory power.

Our preference for the term "expectation" reflects the fact that a data point can be expected or well-explained by a theory regardless of when that data point was first discovered in comparison to the timing of the development of the theory. To return to the example of the gorge being produced by erosion from a river, surely the gorge existed for millennia and was even known by humans to exist long before modern geological theories were developed to explain its origin. Long after the "data point" (i.e., the gorge) was first known to exist by humans, scientists studying geology made observations about the ability of a river to erode through rock and create a gorge. The hypothesis that the gorge was produced by the erosive action of a river is strongly supported by present-day observations about our knowledge of the erosive powers of water flow, but in this hypothetical situation, there was no "prediction" made where the "river erosion" model was developed prior to our knowledge of the existence of the gorge. In this case, the river's ability to explain the gorge entails a retrodiction—but this in no way minimizes or detracts from the successful explanatory power of this model.

This applies to the theory of intelligent design as follows: We have vast knowledge of the causal powers of

intelligent agents through our present-day observations of the actions of intelligent agents and objects that are known to have been designed. Our knowledge of the causal powers of intelligent agents allows us to propose various "expectations" about the natural phenomena which should exist if an intelligent agent were at work in the past. However, many data points that are well-explained by intelligent causation were already known at the time the theory of intelligent design was being developed.[3] For example, in all of our experience, information-rich, language-based codes always come from intelligence [60]. Yet it has been known since the 1950s and 1960s that life is fundamentally based upon an information-rich language-based code. The modern theory of intelligent design was not developed until the 1980s, 1990s, and 2000s—long after the information-rich DNA code at the heart of life was discovered. The existence of a language-based code at the foundation of living systems provides powerful evidence for intelligent design, and the fact that this was "retrodicted" or explained "after the fact" does not negate intelligent design's ability to account for, explain, or expect this core aspect of biology.

Thus, because both historical and experimental scientific models succeed or fail based upon their explanatory capabilities, the fact that some hypotheses predict and others retrodict is a mere accident of the chronology of human history and when particular data points or scientific knowledge happened to be collected or gained. "Prediction" versus "retrodiction" is not relevant to understanding whether a scientific model works. In this article, therefore, the word "expectation" refers to the explanatory capability of a model—not whether the model actually temporally asserted the existence of a data point prior to it having been discovered.

Intelligent design's "expectations" and the explanatory capabilities of the theory can also be understood in a Bayesian context.[4] Citing philosopher Timothy McGrew, Meyer (2021) [72] proposes the hypothetical example of a hiker who encounters a cabin in the woods, and inside the cabin finds a hot kettle of tea steeping on a stove.[5] The best explanation for the tea kettle is obviously that an intelligent cause—a human being who inhabits the cabin—filled the kettle with water and heated it on the stove with the intention of preparing a cup of tea. Now, the "intelligent causation" hypothesis does not necessarily render it highly probable, and therefore strongly expected, that a hiker in the woods *must* come across a cabin containing a kettle of tea steeping on a stove. For example, the cabin could have been empty, or there might have been no hot drink brewing inside, or the hot drink could have been coffee. Nonetheless, under a Bayesian analysis, the probability of the observation of a hot tea kettle on a stove inside a cabin in the woods is much higher on the hypothesis that an intelligent cause is responsible (i.e., a human being who inhabits the cabin), than on some other hypothesis (such as the cabin being uninhabited with no intelligent agent present, or the entire cabin and tea kettle event arising due to blind natural mechanisms). Thus, the intelligent causation hypothesis has strong explanatory capability to account for the observed data. In the same way, we can develop many soft "expectations" or "predictions" of what might be found if an intelligent agent were at work, because we have observation-based experience of what intelligent agents can do, even if these are not necessarily absolute entailments of what *must* be found in all cases if intelligent design is correct.

2. OVERVIEW OF ID RESEARCH METHODS

Intelligent design research has followed three main phases, which partially overlap in time, though their approximate starting points are sequential (Figure 1). During the first phase, termed "ID 1.0," the theoretical foundations of design detection (Section 1.2.3) were laid through the development of concepts such as CSI (Section 1.2.1), irreducible complexity (Section 1.2.2), and inferences to the best explanation (sections 1.2.3 and 1.3). The second phase, "ID 2.0," saw the first rigorous experimental application of design theory to address the origin of specific biological features, applying ID as a historical science in design-detection research (see e.g., sections 1.3, 3.1, 3.2, 3.3). During the third and most recently-commenced phase of research, "ID 3.0," the theory of intelligent design is being applied as an experimental science to investigate the present-day operation of natural systems—applied design research (see e.g., sections 1.4, 3.2.3, 3.4, 3.5).

Both design-detection research and applied design research use the scientific method, and there is often overlap between these two types of ID research. The scientific method is generally described as a multi-step process that includes (1) observation, (2) hypothesis, (3) experimentation, and (4) conclusion [76, 77]. Intelligent design works by using this scientific method to identify, detect, and determine where intelligent causation is the

[3]This makes intelligent design similarly situated to Darwin's theory of evolution. When Darwin published *Origin of Species* in 1859, he was largely trying to apply his theory to explain previously known data.

[4]Bayesian logic can be articulated formally (i.e., via mathematical formulae), or as a heuristic analogy, where a qualitative assessment is made to determine which model best anticipates the data. While the purpose of this paper is not to delve into a detailed formal Bayesian analysis, such formal Bayesian analyses can certainly be performed to validate design inferences [8, 21]. For present purposes it is sufficient to show how Bayesian logic can qualitatively validate design inferences by demonstrating that a particular dataset is more expected within a design framework than within a blind evolutionary scenario.

[5]This hypothetical example has been slightly modified from that of Meyer (2021) [72].

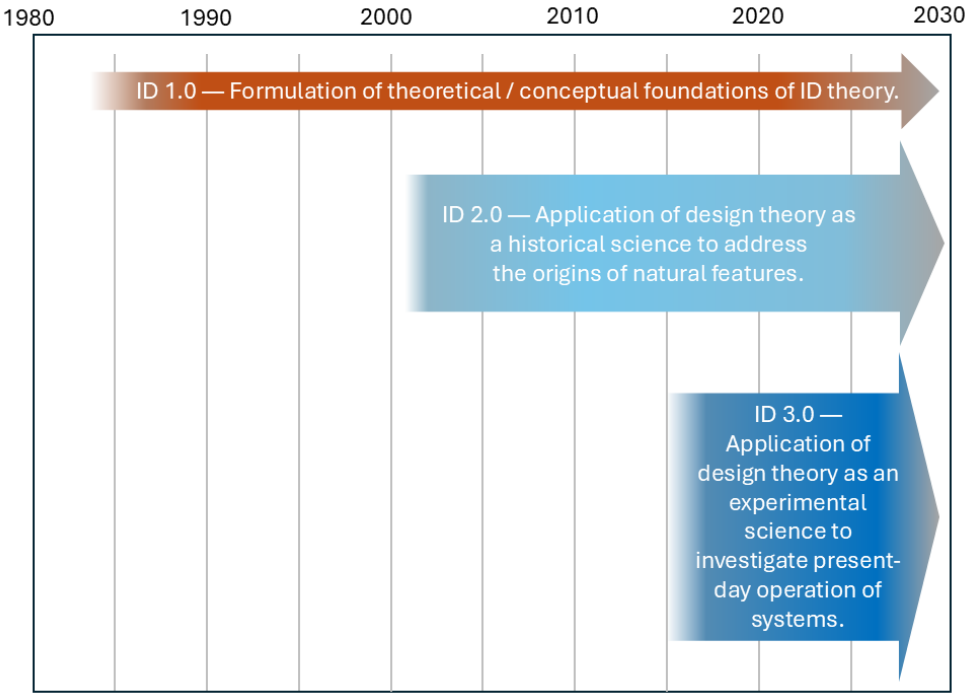

Figure 1: Gantt chart showing an approximate past and future timeline of the three main phases of ID research. ID 1.0 commenced approximately in 1984 with the publication of *The Mystery of Life's Origin* which proposed an "intelligent cause" behind information in DNA [73]. This phase went on to elucidate the conceptual, theoretical, and philosophical foundations for detecting design (Section 1.2). ID 2.0 commenced approximately with the publication of Axe (2000) [74] which investigated protein rarity, a proxy for CSI in proteins, and a direct indicator of design. This phase used the methods of design detection in ID 1.0 to apply ID as a historical science and address questions about the origins of various natural features (sections 1.3, 3.1, 3.2, 3.3). The third phase commenced around 2016 with the formal establishment of the "ID 3.0 research program" [75], and has expanded with the application of engineering to biology (sections 1.4, 3.2.3, 3.4, 3.5). This phase includes multiple projects applying the expectations of design theory (many of which were first elucidated in part in ID 1.0 research) to investigate the operation of present-day biological systems, effectively applying ID as an experimental science. Grey-to-white shading indicates fuzzy time boundaries. Research representing all three phases of ID is ongoing as of the writing of this review.

best explanation for natural features, and to study how natural features operate in the present day. What follows is a step-by-step explanation of how ID theory uses the scientific method to conduct scientific investigations.

Step 1: Use Observations to Recognize the Effects of Intelligent Design ID research begins with observations of what intelligent agents produce when they act, and what properties are found in objects that are known to have been intelligently designed. These observations reveal the causal powers of intelligent agents (Table 2; Appendix A).

Step 2: Propose Hypotheses and Expectations About What Should Be Found if Intelligent Design Is Correct Observations about the causal abilities of intelligent agents can then be directly used to develop criteria which reflect what to expect when an intelligent agent has been at work, effectively allowing us to construct positive, testable expectations about what we should find if intelligent design has occurred. These design-detection criteria effectively represent hypotheses, predictions, or expectations, of what can be anticipated in designed systems (Table 3).

Step 3: Study Nature (e.g., through Experimentation) to Assess If Design-Based Expectations Are Fulfilled Having developed ID-based expectations, predictions, and retrodictions in steps 1 and 2, investigators can then study features of the natural world whose origin is as-of-yet unknown to determine whether they meet the previously established expectations, hypotheses, and criteria for detecting design. Investigators can also use the criteria for design-detection to yield predictions, expectations, or models that guide research into how natural features operate in the present day.

This step of the scientific method is often called "experimentation," however in this context "experiment" can potentially mean a wide variety of modes of studying nature, including (but not limited to) classical experiments performed in beakers or using instruments at a laboratory bench, observing animal behavior in the wild, mapping geological layers through fieldwork and collecting and analyzing fossils within those layers, or collecting starlight from telescopes. The theory of intelligent design

Table 2: Observations about the causal powers of intelligent agents. (Extended documentation provided in Appendix A.) There may be some overlap among some of these observations about the causal abilities of intelligent agents, however these observations are listed separately because they provide slightly different descriptions of what intelligent agents can do.

1.	Operate in a goal-directed manner [78, 79]
2.	Generate high CSI [80]
3.	Find rare solutions to complex problems [58, 81]
4.	Implement a top-down design where multiple parts are coordinated to accomplish a purpose or goal, including a hierarchical design, wherein subcomponents are coordinated to contribute to higher functions at each level [82–86]
5.	Produce irreducibly complex systems (such as machines) [54, 87]
6.	Reuse similar functional components in different systems [55, 88]
7.	Optimize competing constraints [66, 89]
8.	Include components for the purpose of performing a function [90–92]
9.	Rapidly generate large amounts of new information, including generating new systems which are fully formed and different from previous systems [58, 80]

Table 3: Expectations of what should be found if a natural feature or system is the result of intelligent design.

1.	Goal-directed operation
2.	Presence of high CSI
3.	Existence of rare solutions to complex problems
4.	Structured with a top-down design where multiple parts are coordinated to accomplish a purpose or goal, including a hierarchical design, wherein subcomponents are coordinated to contribute to higher functions at each level
5.	Presence of irreducibly complex systems (e.g., machines)
6.	Reuse of functional components in different systems
7.	Performance optimized to meet competing constraints
8.	Components have a purpose and function
9.	Rapid appearance of new information, where systems are fully formed and designed to be functional from the outset, showing some degree of discontinuity from other pre-existing systems

can thus be applied to experimentally study nature for two general purposes[6]:

> (a) As a historical science to study the *origins* of natural features (see Table 4).
>
> (b) As an experimental science to study *the present-day operation* of a designed feature (see Table 5).

As elaborated below, these applications of ID theory can be achieved by experimentally testing for features such as CSI, irreducible complexity, function in a system, abrupt appearance, rare solutions to complex problems, coordination of parts, top-down hierarchical design, optimization, and reusage of functional components. When such criteria are fulfilled, and other competing hypotheses cannot account for the data, design is implicated (Table 4). Alternatively, such tell-tale signs of design can be experimentally tested for, and identified, to elucidate how a system works (Table 5). This scientific methodology allows the theory of intelligent design to be applied in a variety of different fields.

Step 4: Make Scientific Conclusions When experimentation and other studies of nature confirm the observation-based expectations and hypotheses generated from ID, then a conclusion can be made that evidence for design has been found (Table 4), or about how a designed system operates (Table 5).[7] When other known models are unable or less able to account for the evidence, design can be detected and inferred as the "best explanation" [58, 60, 66, 72]. As is the case with any scientific theory, the conclusions of design are held tentatively, subject to future scientific discoveries [76].

Thus, as seen in Tables 4 and 5, intelligent design can be applied in a variety of scientific fields both to detect design and to investigate the operation of natural systems in the present day. The remainder of this article will review specific examples of how ID has been, is being, and can be applied in design-detection research as a historical science (ID 2.0), and in applied design research as an experimental science (ID 3.0).

3. OVERVIEW OF ID RESEARCH RESULTS

As noted, there are multiple ways that the assumption of design can enhance biological investigations through applied design research. Design-based expectations are yielding fruit in understanding proteins, genetics, and systematics. Methodologies based upon engineering-design, such as systems biology and reverse systems engineering, can help elucidate the operation of biological systems.

[6]There is often overlap between these two types of research, where investigations into origins can also yield insights into the present-day operation of a system, and vice versa.

[7]Many sources cited in Tables 4 and 5 are from pro-ID authors and studies, however, in quite a few cases the sources are not supportive of design, and in still other cases the authors may represent mixed viewpoints. However, the personal views of the authors (i.e., a given author's degree of support for intelligent design) are immaterial to the whether the data they present in fact fulfills a prediction or expectation of intelligent design.

Table 4: How the theory of intelligent design uses the scientific method of historical sciences to detect design in the origin of some natural feature. The number(s) listed in parentheses after each field listed correspond(s) to the numbered observations and expectations of ID listed in tables 2 and 3 that are being tested and applied in each particular case.

Field	Step in Scientific Method	Explanation
Biochemistry (2, 5)	Observation	Intelligent agents think with an end goal in mind, allowing them to solve complex problems by taking many parts or symbols and arranging them in intricate patterns that perform a specific function—i.e., they generate high CSI. Intelligent agents also produce irreducibly complex machines.
	Hypothesis / expectation	Finely tuned high-CSI structures will be found in biology, including irreducibly complex systems (like machines) that require multiple components to function.
	Experiment (data collection)	Research shows that irreducibly complex molecular machines exist in biology which contain irreducible cores that require multiple protein-parts and/or subsystems to be present in order to function [53, 93–97]. Research similarly shows that the amino acid sequences of many functional proteins must be highly complex and specified in order to function [67, 74, 98–104].
	Conclusion	High CSI systems and machine-like structures are common in biology, originating through intelligent design.
Paleontology (9)	Observation	Intelligent agents often rapidly infuse large amounts of information into systems, yielding new systems that are different and discontinuous from other systems.
	Hypothesis / expectation	Novel biological forms requiring large amounts of new genetic information will often appear abruptly in the fossil record, "fully formed" and discontinuous from previous designs.
	Experiment (data collection)	Discontinuity is prevalent in biology. Biological novelty commonly appears in the fossil record abruptly in a pattern of "explosions" [60, 81, 105–107]. The Cambrian explosion is a prime example wherein most of the major animal phyla appear "fully formed" in a geologically abrupt manner [58, 60, 81, 108, 109], but there are other examples in the fossil record, including a bird explosion [110–113], the abrupt appearance of angiosperms [114, 115], a mammal explosion [110, 116–119], and the abrupt appearance of the genus *Homo* [120, 121].
	Conclusion	Many higher taxa appear suddenly, without similar direct precursors, indicating design.
Systematics (6)	Observation	Intelligent agents reuse functional components in different systems (e.g., wheels for cars and airplanes, or keyboards on cell phones and computers), but do so according to functional needs, where functional dependencies may create some treelike structure in comparative relationships, but ultimately traits need not be distributed in a treelike pattern [122–124].
	Hypothesis / expectation	Genes and other functional parts will be reused in different and unrelated organisms in patterns that match functional needs, and need not necessarily match a "tree" or nested hierarchy.

(Table 4 continued)

Field	Step in Scientific Method	Explanation
Systematics (cont'd)	Experiment (data collection)	Similar morphological traits and genes have been found reused in widely different organisms even where it is believed that the common ancestor did not have the trait in question. Echolocation exists in bats and whales, and similar genes even help produce this trait, though the presumed common ancestor of bats and whales is not thought to have had this ability [123–128]. Similar genes control eye or limb growth in different organisms, though their presumed common ancestors are not thought to have had such forms of eyes or limbs [129, 130]. Genes and functional parts are frequently not distributed in a "treelike" pattern or nested hierarchy, but rather, show phylogenetic incongruity reflecting reusage of components in a non-nested pattern [123, 124, 131–141]. As Dávalos et al. (2012) [142] acknowledge: "Incongruence between phylogenies derived from morphological versus molecular analyses, and between trees based on different subsets of molecular sequences has become pervasive as datasets have expanded rapidly in both characters and species... phylogenetic conflict is common, and frequently the norm rather than the exception."
	Conclusion	Phylogenetic incongruity is prevalent throughout life, and this reusage of highly similar and complex parts in non-treelike patterns is best explained by the action of an intelligent agent.
Physics (3)		
	Observation	Intelligent agents find extremely rare or highly unlikely solutions to complex problems.
	Hypothesis / expectation	The laws and constants of nature will have rare values that match what is necessary for life to exist (i.e., fine-tuning).
	Experiment (data collection)	Multiple physical laws and constants must be finely tuned for the universe to be inhabited by advanced forms of life. These include the strength of gravity (the gravitational constant) compared to the strong nuclear force, which must be fine-tuned to 1 part in 10^{35} [143]; the gravitational force compared to the electromagnetic force, which must be fine-tuned to 1 part in 10^{40} [144]; the expansion rate of the universe, which must be fine-tuned to 1 part in 10^{55} [144, 145]; the cosmic mass density at Planck time, which must be fine-tuned to 1 part in 10^{60} [144, 146]; the cosmological constant, which must be fine-tuned to 1 part in 10^{120} [144]; and the initial entropy of the universe, which must be fine-tuned to 1 part in $10^{10^{123}}$ [144, 147]. The Nobel Prize-winning physicist Charles Townes observed: "Intelligent design, as one sees it from a scientific point of view, seems to be quite real. This is a very special universe: it's remarkable that it came out just this way. If the laws of physics weren't just the way they are, we couldn't be here at all" [148].
	Conclusion	The laws of nature are fine-tuned with extremely rare values that allow life to exist in our universe, indicating that the cosmic architecture of the universe was designed.

Table 5: How the theory of intelligent design uses the scientific method of experimental sciences to investigate the operation of natural features in the present day. The number(s) listed in parentheses after each field listed correspond(s) to the numbered observations and expectations of ID listed in tables 2 and 3 that are being tested and applied in each particular case.

Field	Step in Scientific Method	Explanation
Genetics (8)		
	Observations	*About intelligent agents:* Intelligent agents generate structures that have a purpose and function. / *About an unexplained natural feature:* Much DNA does not encode proteins and the reason for its existence is unexplained.
	Hypothesis / expectation	"Junk" DNA will perform valuable biological functions.
	Experiment (data collection)	Numerous studies provide evidence of widespread function for "junk DNA" (reviewed in [149]), including evidence of widespread biochemical function in the human genome [150, 151]. Specific examples include functionality in pseudogenes, microRNAs, introns, endogenous retroviruses, and repetitive DNA including LINE, SINE, and *Alu* elements [152–161]. A 2021 article in *Nature* reported that over 130,000 specific genomic elements were "previously called junk DNA" [162], followed by a paper in *Genome Biology and Evolution* that concluded, "The days of 'junk DNA' are over" [163].
	Conclusion	Functionality for junk DNA is prevalent, and aligns directly with a strong ID-based prediction that components will have function.
Systems Biology (1, 4, 6, 7)		
	Observations	*About intelligent agents:* Intelligent agents design systems that operate with overarching goals, where every part and subcomponent is oriented towards supporting the overall goal or purpose of the system. Intelligent agents also reuse optimal architectures in multiple systems. / *About an unexplained natural feature:* Glycolysis is a metabolic pathway which is found near-universally throughout life, and its widespread use remains to be explained.
	Hypothesis / expectation	Glycolysis is nearly ubiquitous among living organisms due to its efficient, goal-oriented design which serves multiple higher-level functions within biological systems.
	Experiment (data collection)	Glycolysis is the subsystem found widespread across life whereby glucose is broken down into energy and biomass precursors. This system is subject to higher-level requirements and within glycolysis there are also lower-level processes subject to the requirements of glycolysis itself, showing a goal-directed and top-down design. The glycolytic topology or architecture has also been shown to be pareto-optimized around key cellular requirements, rationalizing why the architecture is used over and over again across life. For different tissues of an organism, glycolytic enzymes are unique in that they are optimized for tissue-specific roles while the main architecture of the pathway is the same. The very sequence of glycolysis exhibits foresight in that energy must be invested up front before payoff results at the end of the pathway. This is expected from a top-down design process. [164]
	Conclusion	Glycolysis has an efficient, top-down design which serves multiple higher-level needs of organisms, fulfilling predictions of intelligent design.

(Table 5 continued)

Field	Step in Scientific Method	Explanation
Comparative Anatomy and Biomechanics (6, 7)		
	Observation	*About intelligent agents:* Intelligent agents frequently reuse functional and versatile designs in different systems that are optimized to perform functions. / *About an unexplained natural feature:* The limb pattern consisting of a single-bone stylopod (e.g., humerus), two-bone zeugopod (e.g., radius and ulna), and multi-boned autopod with digits (e.g., wrist bones plus fingers) is found throughout nearly all vertebrate tetrapods.
	Hypothesis / expectation	The vertebrate limb pattern is a highly functional, optimal, and versatile design, explaining its widespread reusage.
	Experiment (data collection)	The limb pattern found reused in virtually all tetrapods is "highly versatile and optimal not just for arms and legs but also for flippers and wings" since it uses "networks of segmented bones that enable smooth morphing of shapes as well as multifunctioning structures" and "linkage mechanisms that fine-tune motions and mechanical advantage" [165]. The similarities between the homologous bones in the vertebrate limb are therefore due to the high functionality of the skeletal pattern.
	Conclusion	The optimality, versatility, functionality, and widespread reusage of the vertebrate limb pattern are highly consistent with the expectations of intelligent design.
Neurophysiology (1, 4)		
	Observation	*About intelligent agents:* Intelligent agents design systems (e.g., circuits) with top-down design, where multiple parts coordinate to achieve a goal, including mechanisms for dampening signals, movement, or vibration. / *About an unexplained natural feature:* Blood flow in the brain does not destroy or damage highly fragile capillaries in the brain.
	Hypothesis / expectation	Signal dampening strategies known from the fields of electrical and mechanical engineering are coordinated in the brain to prevent the pulse of blood flow from damaging fragile capillaries.
	Experiment (data collection)	Brain blood flow is controlled by a band-stop filter, and cerebrospinal fluid flow is controlled by a band-pass filter which buffer and absorb blood flow pulses and prevent "unwanted vibration," preventing damage to capillaries [166, 167].
	Conclusion	The usage of signal dampening mechanisms known from the fields of electrical and mechanical engineering to control pulsatility of blood flow through the brain shows a top-down, goal-directed design that is highly consistent with the expectations of intelligent design.

3.1 Protein Science

ID theory's expectation of high levels of CSI in living systems has led to a natural interest in whether the amino acid sequences in proteins represent unlikely sequences that match the precise ordering needed to yield functional proteins. A variety of ID-inspired research projects have improved our understanding of protein rarity and protein evolvability, with direct implications for drug development.

3.1.1 Protein Rarity

ID research conducted by Axe (2000, 2004) [67, 74] experimentally investigated the β-lactamase enzyme, finding that only 1 in 10^{77} possible amino acid sequences would yield a functional protein fold in this fairly typical enzyme. This represents high CSI—up to 256 bits of functional specified complexity [168], which exceeds Earth-based probability bounds for the maximum amount of specified information which can be produced by natural mechanisms alone [65]. A variety of other studies by non-ID scientists have confirmed high CSI in protein sequences, with findings that typical protein rarities range from 1 in 10^{24} to 1 in 10^{126} sequences [102]. Miller (2024) [103] found that these rarities are far below the percolation threshold, below which random mutation and natural selection would be unlikely to find functional protein sequences in a sequence space that is not unrealistically biased. This has direct implications for protein design and drug design, which should use targeted rather than random searches to find functional protein sequences.

3.1.2 Protein-Protein Conversions

A bacterial population genetics study by Axe (2010) [169] found that biological features which require seven or more mutations to be present before providing a functional advantage would be unlikely to evolve even in a large population of bacteria over the entire history of the Earth. Gauger and Axe (2011) [101] found that converting one enzyme (2-amino-3-ketobutyrate CoA ligase, or Kbl_2), to perform the metabolic function of a similar and closely related protein (8-amino-7-oxononanoate synthase, or BioF_2), would require a minimum of seven mutations—above the maximum threshold determined by Axe (2010) [169]. Previous studies showed that only a few mutations can alter an enzyme's function, but only if the protein's structure does not change [170]. In contrast, the conversion study focused on proteins with very similar, but non-identical structures. A follow-up study by Reeves et al. (2014) [104] found that after inducing all possible single mutations in the GABA-aminotransferase family enzymes and many other combinations of mutations, converting one protein to perform the function of a closely related protein would take over 10^{15} years, a duration much longer than the age of the Earth.

The aforementioned studies examined protein evolvability via direct wet-lab experimentation. But Behe and Snoke (2004) [171] performed *in silico* theoretical calculations to evaluate the evolvability of a functional bond between two cysteine residues within multicellular organisms. They found that the evolution of such a feature, which would require more than two point mutations, would require population sizes and generation times in excess of what is typical for multicellular organisms. A critical study evaluating Behe (2007) [82] found that to obtain only two coordinated mutations via Darwinian evolution in a population such as "humans with a much smaller effective population size, this type of change would take $>$ 100 million years," which was said to be "very unlikely to occur on a reasonable timescale" [172]. Other ID research studies have investigated whether the "waiting times" to obtain multiple specific coordinated mutations outstrip the time available to the evolutionary process [94, 173, 174].

3.1.3 Applications of Protein-Science Research

Research into protein science and protein rarity can be considered design-detection research because it has direct implications for CSI in biology that are useful for detecting design and investigating origins. However, there are also crucial design-based applications for understanding protein functionality. Detecting high CSI in proteins [67, 74] is relevant to understanding which amino acids are vital for a protein's function, e.g., the location and configuration of active sites, and how those amino acids contribute towards protein stability. This understanding can aid in the design of artificial proteins. Additionally, these studies show that features that require multiple coordinated mutations before providing any advantage would be very difficult to evolve in both unicellular and multicellular organisms. This has implications for treatments of antibiotic-resistant bacterial infections, supporting the effectiveness of drug cocktails that rely upon the principle that there are limits to how much living systems can evolve. Quantifying the rarity of proteins in pathogens can help identify those most vulnerable to targeted attack, as rarer proteins will be more susceptible to mutational damage and less able to acquire mutations that could confer resistance. Furthermore, estimating rarity within a class of proteins can guide strategies for engineering novel variants. For instance, the percolation-based method developed by Miller (2024) [103] can help guide the search for functional sequences based on proteins' thermodynamic stability, and can also help predict the extent to which an initial protein can change without significant information about a new target. The comparative bioinformatics methods developed by Thorvaldsen and Hössjer (2023) [168] and Deweese and colleagues [175, 176] can also inform about the information content of a protein and which specific residues are vital for its function. The rarer a new target protein, the more detailed structural information will be needed before directed evolution can be effectively applied to

discover and optimize for a novel function.

3.2 Genetics

A key expectation of intelligent design is the presence of function, in particular functional information. This expectation has implications within genetics, where the evolutionary view has led to the contrasting expectation that genomes are full of non-functional "junk" DNA or that genes must always show material connections—i.e., sequence homology—to other genes. According to intelligent design, information can arise from a mind rather than from material antecedents; therefore, function will not only be prevalent, but it can also appear in discontinuous sequences and locations that are unexpected under standard evolutionary models.

3.2.1 Orphan Genes

Standard evolutionary models predict that genes evolve from other genes, and potential evolutionary gene sources are identified by finding other genes with similar DNA sequences. However, as more genomes have been sequenced, it has been discovered that large numbers of genes in many species are unique and unlike any other known genes. These are referred to as "orphan genes." Some non-ID studies have estimated that up to 10% to 30% of coding sequences in a genome might represent orphan genes [177]. Orphan genes show genetic discontinuity between species, challenging standard evolutionary models because they have no known gene source from which to evolve. Orphan genes are surprising under standard evolutionary models but are expected under intelligent design theory, because information in biology need not be connected to material antecedents. Information is discontinuous from other material entities because it comes from a mind. Because of these expectations, ID theorists are surveying orphan genes and creating improved tools for identifying them and studying their functions [178, 179].

3.2.2 Topoisomerase Function

The topoisomerase II enzyme untangles DNA during replication and transcription. However, the importance of its C-terminus, which differs between species and between isoforms (e.g., topoisomerase IIα and IIβ in many eukaryotes), has been largely ignored because of the assumption of standard evolutionary models that a lack of sequence conservation reflects a lack of function. Intelligent design expects that function and informational importance of biochemical sequences need not correlate with sequence conservation (i.e., purifying selection after descent from a common ancestor). Based on design reasoning, biochemist Joseph Deweese and colleagues predicted that the C-terminus of topoisomerase plays a role in regulating the enzyme's function, and that the isoform-specific differences reflect differentiated roles that may provide opportunities for selective therapeutic targeting [180–182]. His research has explored critical functions of the C-terminus [176, 181–185], showing the utility of design theory to predict and elucidate important biochemical functions. This work also led to the development of software tools that predict features of protein structure (and potentially, function) based upon amino acid sequence [175, 176].

3.2.3 Junk DNA

One of the great surprises of the Human Genome Project was that only approximately 1.5-2% of the human genome codes for proteins [186]. The importance of the rest of the genome has been a subject of intense scientific interest since that time, with many from the evolutionary biology community predicting that large proportions of non-protein-coding regions constitute "junk DNA" [187–190]. As noted in Section 2, Step 2, because intelligent agents produce systems which have function or purpose, a key prediction of intelligent design is functionality. As a consequence, ID theorists long predicted that so-called junk DNA would turn out to be largely functional. In 1994, pro-ID scientist Forrest Mims submitted a letter to *Science* warning against assuming that "junk" DNA was "useless" [191]. Dembski (1998) further predicted function of junk DNA on the basis of intelligent design:

> [Intelligent] design is not a science stopper. Indeed, design can foster inquiry where traditional evolutionary approaches obstruct it. Consider the term "junk DNA." Implicit in this term is the view that because the genome of an organism has been cobbled together through a long, undirected evolutionary process, the genome is a patchwork of which only limited portions are essential to the organism. Thus on an evolutionary view we expect a lot of useless DNA. If, on the other hand, organisms are designed, we expect DNA, as much as possible, to exhibit function. And indeed, the most recent findings suggest that designating DNA as "junk" merely cloaks our current lack of knowledge about function. ... Design encourages scientists to look for function where evolution discourages it. [92]

Richard Sternberg, a biologist who later joined the ID community, further critiqued the idea of junk DNA: "[N]eo-Darwinian 'narratives' have been the primary obstacle to elucidating the effects of these enigmatic components of chromosomes. ... the selfish DNA narrative and allied frameworks must join the other 'icons' of neo-Darwinian evolutionary theory that, despite their variance with empirical evidence, nevertheless persist in the literature" [152]. In 2004 pro-ID biologist Jonathan Wells made a similar argument: "The fact that 'junk DNA' is not junk has emerged not because of evolutionary theory but in spite of it. On the other hand,

people asking research questions in an ID framework would presumably have been looking for the functions of non-coding regions of DNA all along, and we might now know considerably more about them" [91]. Again, these predictions flow naturally from an ID paradigm which observes that intelligent agents produce things for a purpose and with a function.

In contrast, scientists operating within an evolutionary paradigm have frequently predicted a lack of function in many aspects of biological systems, where much of the non-coding DNA is "junk" with no benefit to the organism that has accumulated over evolutionary history. King and Jukes (1969) proposed that "99 percent of mammalian DNA is not true genetic material" [192] and Ohno (1972) predicted that "at least 90%" of mammalian DNA could be "nonsense" [193]. Indeed, this has been used as an argument against intelligent design, since it seems implausible that a conscious engineer would purposefully place useless, nonfunctional sequences into genomes. Or, as Miller (1994) wrote, "The human genome is littered with pseudogenes, gene fragments, 'orphaned' genes, ' junk' DNA, and so many repeated copies of pointless DNA sequences that it cannot be attributed to anything that resembles intelligent design" [194]. This is not at all surprising on the hypothesis that our genome is the end result of a mindless, unguided process of random mutations acted on by natural selection. For example, Dawkins (2009) asserted that "the greater part (95 percent in the case of humans) of the genome might as well not be there, for all the difference it makes" [188]. Doolittle and Sapienza (1980) proposed that "Natural selection operating within genomes will inevitably result in the appearance of DNA with no phenotypic expression whose only 'function' is survival within genomes" [195]. They proposed that the search for function for junk DNA may be "folly" and "prove, if not intellectually sterile, ultimately futile." Orgel and Crick (1980) similarly assumed that "much DNA in higher organisms is little better than junk" and noted that "The idea of selfish DNA is firmly based on this general theory of natural selection" [196].

Many other authors have made similar claims. Francis Collins, who headed the Human Genome Project, maintained prior to ENCODE [151] that "roughly 45 percent of the human genome" consists of "genetic flotsam and jetsam" [187]. Kitcher (2007) summarized the logical basis for why evolution predicts junk: "The most striking feature of the genomic analyses we now have is how much apparently nonfunctional DNA there is ... From the Darwinian perspective all this is explicable—the molecular equivalent of the tinkering that is pervasive in the history of life at the anatomical level" [197]. More recently, Moran (2023) has claimed that "90 percent of [the human] genome is junk" [190]. Mortola and Long (2021) noted how widespread this adherence to the idea of junk DNA is.

> For most of the history of genetics, the most prominent experts of the field have held that you, your mom, your great-great-uncle, Abraham Lincoln, all the emperors of Rome, and every one of Genghis Khan's Mongol Army all inherited a vast amount of "junk DNA." As we discovered in 2003 with the conclusion of the Human Genome Project, a monumental 13-year-long research effort to sequence the entire human genome, approximately 98.8 percent of our DNA was categorized as junk. [189]

Again, the expectation of genomes filled with junk flows quite naturally from an evolutionary perspective, according to which genomes arose through trial-and-error tinkering over many eons while neutral evolutionary mutations filled genomes with useless genetic debris. Conversely, intelligent design leads us to hypothesize that the preponderance of our genome is functional. In other words, genetic "noise" should be the exception rather than the norm. Research into functions of so-called "junk DNA" is, therefore, an area where intelligent design motivates scientific inquiry.

Though there is still much work needed to gain a full understanding of the non-coding regions of the genome, the research trend over the past two decades has been toward the discovery of functions for an increasing number of non-coding elements [162], with reports in the literature of a paradigm shift away from the concept of junk DNA [198, 199]. Below we present a brief review of a few functions that have been identified for various classes of DNA that were once considered to be "junk."

A key development in our understanding of the preponderance of functional elements in our genome came with the ENCODE ("ENCyclopedia Of DNA Elements") consortium, a large project involving hundreds of biologists around the world who studied the activity and function of non-coding DNA [150, 151]. What emerged from this work is that at least 80% of the human genome shows evidence of biochemical functionality—it is transcribed into mRNA, bound by regulatory proteins, or associated with epigenetic modifications [151]. Though this is not a decisive confirmation that the preponderance of the genome is functional [200], this finding does provide *prima facie* evidence of functionality. Indeed, Gates et al. (2021) [162] surveyed the literature and found that over 130,000 genetic elements "previously called junk DNA" have been discovered, noting that the rate of discovery of such genetic elements "shows no signs of slowing" down:

> [I]t is now appreciated that the majority of functional sequences in the human genome

> do not encode proteins. Rather, elements such as long non-coding RNAs, promoters, enhancers and countless gene-regulatory motifs work together to bring the genome to life. Variation in these regions does not alter proteins, but it can perturb the networks governing protein expression... With the HGP [Human Genome Project] draft in hand, the discovery of non-protein-coding elements exploded. So far, that growth has outstripped the discovery of protein-coding genes by a factor of five, and shows no signs of slowing. Likewise, the number of publications about such elements also grew in the period covered by our data set. For example, there are thousands of papers on non-coding RNAs, which regulate gene expression. [162]

A common criticism of the functionalist interpretation of ENCODE is that many of these transcripts are of low abundance and therefore may represent transcriptional noise ("junk RNA") rather than functional RNA [201]. However, studies have shown that transcription in mammalian cells is nonrandom, and the "majority of observed transcription in the native human genome is not readily attributable to background noise" [202] (see also [203]). Moreover, even for DNA transcribed at low levels, "it has been known for decades that transcription factors function at concentrations measured in nanomolar" [204], and non-coding RNAs, even when their copy number is low, "can punch above their weight," and "act in a nonstoichiometric way to amplify effects" [205]. Likewise, Mercer et al. (2011) noted that functional long non-coding RNAs (lncRNAs) "were present at an average of ∼0.0006 transcripts per cell, indicating expression in only a small subpopulation of the cells sampled," and noted that some *Hox* regulatory gene transcripts may be present at a rate of "an average ∼0.13 transcripts per cell" [206]—yet these are obviously functional transcripts despite their low transcript copy number. The term "average" is also key here, because many non-coding genetic elements are only functional in particular cell types at particular stages of the human life cycle. Thus, while numbers of transcript copies may be low when averaged across many cell types, in the particular cell types where a given transcript is produced and functional, it may be present in much higher copy numbers necessary to perform its particular function.

In addition to this *prima facie* evidence of widespread functionality in the human genome, many classes of genetic elements once presumed to be "junk," have later turned out to be functional. For example, pseudogenes, first identified in 1975, resemble a functional gene but were long believed to have lost their protein-coding ability due to disabling mutations [207]. They have, therefore, been considered "genomic fossils" that no longer perform their original function. Processed pseudogenes are thought to form by retrotransposition, where a transcript is reverse-transcribed and re-inserted into the genome. Since it lacks regulatory sequences, it is rendered (so it was believed) inactive. Non-processed pseudogenes result from gene duplications, but have been (seemingly) rendered non-functional by mutations. Unitary pseudogenes are once-functional genes that have been (apparently) rendered nonfunctional, without a duplication event.

Though pseudogenes were once considered to be "relics of evolution" [207], research over the last few decades has revealed that many pseudogenes are, in fact, functional. Indeed, a recent review paper reported that "a broad misunderstanding of pseudogenes, perpetuated in part by the pejorative inference of the 'pseudogene' label, has led to their frequent dismissal from functional assessment and exclusion from genomic analysis" [158]. For example, a 5S ribosomal RNA pseudogene was recently shown to induce an innate immune response in humans against viral infection [208]. A non-processed pseudogene, *HBBP1*, was called "broken" and "nonfunctional" [209], and an "inert gene" that is "not going to do anything" [210]. According to Miller (2008) [69], *HBBP1* has "molecular errors" meaning that "in a court of genetic copyright law, any motion that a designer could claim originality for the human genome would be tossed out in a flash." Yet Moleirinho et al. (2013) inferred "strong functional constraints" for this pseudogene based upon its conservation between humans and various nonhuman primates [157], and Ma et al. (2021) found that it is "essential for erythropoiesis" (i.e., red blood cell formation), demonstrating its "indispensability" [159]. Even in the case of processed pseudogenes, functions have been identified. In humans, a retrocopy of the phosphoglycerate kinase gene, called *PGK2*, is expressed in the testis and has a conserved coding sequence [211, 212]. Processed pseudogenes have been demonstrated to regulate neural function [213], antiviral immune response [214], and cancer [215]. It has often been assumed that a pseudogene that is missing part of the parental sequence must be devoid of function. This too has turned out to be incorrect as truncated pseudogenes have been shown to be capable of regulating the expression of their parental genes [216–218]. While there remain many pseudogenes whose specific functions have not yet been discovered, function can be anticipated because "[w]here pseudogenes have been studied directly they are often found to have quantifiable biological roles" [158] and "pseudogenes that have been suitably investigated often exhibit functional roles" [219]. However, because pseudogene function has been "prematurely dismissed" due to "dogma" [158], little effort has been devoted to developing technologies needed to study pseudogenes. As a consequence, "the study of functional pseudogenes is just at the beginning" and it is predicted that "more and more functional pseu-

dogenes will be discovered as novel biological technologies are developed in the future" [220].

A significant portion of the human genome is comprised of repetitive DNA including transposons, long and short interspersed retrotransposable elements (LINEs and SINEs), and retroviral-like sequences (i.e., endogenous retroviruses, or ERVs). Of those transposable elements, approximately a quarter is contributed by roughly 1.2 million *Alu* SINE elements. Though transposon-derived sequences have often been assumed to be generally non-functional, many of these sequences have likewise turned out to have important functions. Indeed, the original International Human Genome Sequencing Consortium paper reported in 2001 that "the organization of Alu elements...suggests that there may be strong selection in favour of preferential retention of Alu elements in GC-rich regions and that these 'selfish' elements may benefit their human hosts" [186]. Later work demonstrated "that Alu and B1 elements have been selectively retained in the upstream and intronic regions of genes belonging to specific functional classes" [221].

Many specific functions have been associated with transposable elements. For example, transposable elements can serve as promoters or transcription start sites [156, 160, 161, 222–229], as well as enhancers in embryonic stem cells [230, 231]; they can contribute to DNA methylation and histone modification, affecting chromatin structure and thereby gene expression [161, 232–241]; they serve as targets for parental imprinting [242]; they play a role in embryogenesis and tissue differentiation [243]; they influence microRNA and long non-coding RNA expression [244–246]; and they contribute to telomere and centromere function [247] in addition to many other functional roles [248, 249].

Even retroviral-like sequences have turned out to have important functions. For example, syncytin (a protein involved in cellular fusion that is crucial for the formation of the syncytiotrophoblast, essential for the development of the placenta) is encoded by the *env* gene of retroviral-like elements [250]. ERV-derived gene products also enable cells to resist infection by exogenous retroviruses [251, 252]. As a consequence, "the evolutionary program has contributed little to the discovery of the functions" for ERVs, suggesting, at least, "an ambivalent verdict on the success of the evolutionary research program" [253].

The literature surveyed here cover a small fraction of the functions that have been identified for what had hitherto been presumed to be "junk DNA." These findings have had a profound impact upon the way junk DNA is viewed in the literature. Mattick (2023) [198] and Ho et al. (2026) [199] reported a Kuhnian "paradigm shift" away from the idea of junk DNA. Stitz et al. (2021) also noted this shift in thinking:

> The days of "junk DNA" are over. When the senior authors of this article studied genetics at their respective universities, the common doctrine was that the nonprotein coding part of eukaryotic genomes consists of interspersed, "useless" sequences, often organized in repetitive elements such as satDNA. The latter might have accumulated during evolution, for example, as a consequence of gene duplication events to separate and individualize gene function. This view has fundamentally changed... [163]

Intelligent design has led scientists to anticipate these discoveries and to expect that the preponderance of the genome is functional (with non-function being the exception rather than the norm), and there are researchers in the ID community investigating function for "junk" DNA. Intelligent design, therefore, has strong heuristic value in motivating research into functions of "junk" DNA, and this field represents another useful application of the theory of intelligent design.

3.3 Systematics

As noted, designers regularly reuse parts in different systems according to the functional requirements of those systems, often called "common design" [90, 123, 254]. The mapping of such functional dependencies in biological systems leads to new insights into why traits are distributed in correlated patterns across different organisms. Ewert (2018) [123] proposed a dependency graph model of trait distribution and organismal relationships "based on the technique used by software developers to reuse code among different software projects," and found that a dependency graph model based upon the concept of common design fit the distribution of various gene families in animals 10^{3000} times better than a classical nested hierarchy, i.e., a phylogenetic tree. Ewert (2023) [124] applied the dependency graph model to the distribution of echolocation, a complex trait found in bats and whales which are distant on the mammalian tree. The standard explanation for this shared trait is convergent evolution, since it is not thought that the most recent common ancestor of bats and whales could echolocate. Ewert (2023) [124] showed that this convergence is not only morphological but also genetic, and a common-design-based dependency graph model is superior to an evolutionary model. This confirms the engineering expectation that a designer's reuse of parts in different organisms for functional reasons is a possible explanation for organismal similarities. While this model is still relatively new, it has the potential to lead to predictions about genetic or physiological traits that may be present and shared in otherwise different organisms.

3.4 Applying ID-Based Engineering Principles to Study Biology

The connection between engineering principles and biology has been long recognized by intelligent design researchers [53, 71]. Although intelligent design did not explicitly begin as a study of human engineering, the overlap between the two is substantial. ID research has greatly expanded our understanding of the causal powers of intelligent agents (Table 2; Appendix A), with human engineering serving as the primary real-world domain in which these powers are expressed and observed.

Early ID research revealed an exquisite match between what human agents are capable of producing (Table 2; Appendix A) and the sophisticated features we observe in living systems. This strong correspondence justifies further study of the engineering process itself both to uncover additional design principles and to apply them to biology through the practice of reverse engineering.

Overlap in design principles between human engineering and biology is expected from two main factors: they operate within the same physical world (a shared "design possibility space"), and they often pursue similar goals that require solutions operating under multiple tight constraints. For example, the functional requirements for flight lead to notable similarities between a bird's wing and a jet airplane's wing, even though they are implemented distinctly. Parallel requirements for function and shared physical constraints between biology and engineering explain why many solutions in the two domains converge, a pattern that is particularly striking in systems design.

In system design, the solution space narrows sharply, due to the tight constraints (i.e., requirements) governing complex systems. This narrowing is analogous to the reduction of solutions to sets of equations as the number of equations increases: in three-dimensional space, one equation defines a plane, two equations intersect in a line, and three equations can converge on only a single point. Requirements for engineering solutions, like simultaneously solving equations, greatly restrict the range of solutions [255], resulting in similar design patterns appearing in biology and engineering, such as the camera-type eye or the four-bar linkage joint.

A related correspondence between biology and engineering is that each exhibits purpose-driven, top-down design [256–258]. As in engineering, the architecture of most biological systems represents a nested hierarchy in which the top level is dedicated to major life goals, subsystems focus on subgoals, and components focus on subdivisions of subgoals [259–261]. The need for a hierarchical architecture that reflects the continuous subdivision of goals arises because system components function effectively only when they need to address a limited number of variables. A car engine would not function as effectively if it were not only controlling gas flow and emitting sparks but also controlling braking and steering, and cooling the passenger compartment. Attempting to control an increasing number of variables results in an explosion of contingencies that must be accommodated, which quickly becomes unmanageable [262].

Engineering is the only framework suited to analyzing hierarchical architectures derived from goals and functional requirements. Engineering also provides the necessary knowledge base and tools to study the design patterns that recur in both. And engineers have an extensive understanding of the design concerns that undergird both domains, such as risk management, signal processing, manufacturing, and maintenance. The close correspondence between engineering and biological systems has been demonstrated by several studies that apply systems engineering tools to biological systems, yielding a more comprehensive understanding of these systems [164, 263–266].

It is important to note that the use of ID principles to investigate biological systems can bear fruit regardless of whether the investigators themselves support intelligent design as an explanation for living systems. Mainstream biologists are increasingly rejecting traditional reductionist methodologies in favor of design-based methodologies for studying complex natural systems. Mantri and Thomas (2019) disagree with intelligent design but nonetheless endorsed the utility of design-based methods for investigating biology, including "reverse-engineering," analyzing the "hierarchical" operation of systems, and understanding how "functional requirements" lead to "design parameters" [267]. Alon (2023), also not an ID-theorist, recognizes the overlap between human engineering and the design of biological systems:

> These features of biological systems – reuse of a small set of network motifs, robustness to component tolerances and constrained optimal design – are also found in a completely different context: systems designed by human engineers. Biological systems have additional features in common with engineered systems, such as modularity and hierarchical design. These similarities hint at a deeper theory that can unify our understanding of evolved and designed systems. [268]

Similarly, Bialek (2024) does not support ID, but finds that adopting design-based predictions such as optimality in information transmission through a system can yield accurate understandings about the workings of biological phenomena: "evidence for near-optimal performance could be turned around and formulated as a theoretical principle from which aspects of mechanism and function can be derived" [204]. This has led him to

conclude that "optimality" is a fruitful assumption, and "optimization principles make quantitative predictions that can be tested in modern experiments." Bialek also acknowledges it is unclear whether evolution makes any predictions about the degree of optimality that should be found since "we certainly don't know enough to calculate how long it would take evolution to find the optimal tradeoff" [204]. Furthermore the notion that biology may be optimized is even opposed by some evolutionary biologists who believe "optimization is nonsense because evolution is not about being best, but about being better than the competition" [204]. In contrast, a design framework gives justification for assuming optimality in biological systems and then conducting rigorous analyses to test whether that assumption holds [269]. One caveat is that design proponents also acknowledge that biology is subject to decay over time. Consequently, what we observe today may no longer reflect the optimal design originally intended. To effectively study complex biological systems, new design-based methodological frameworks are needed. The effectiveness of these new methodological frameworks and their use by both pro-ID and non-ID scientists reflect the utility of applying ID-based assumptions when investigating life.

3.4.1 Systems Biology

Systems biology is an approach to studying biology that assumes there is a hierarchical, top-down design in living systems. The approach differs from reductionism, which assumes that the physical and chemical interactions of biomolecules should eventually lead to a bottom-up understanding of life's higher-level operations and organization. Compared to the reductionistic approach, "system-level understanding, the approach advocated in systems biology, requires a shift in our notion of 'what to look for' in biology" [270]. Biologists who study complex systems are increasingly making this shift—rejecting the reductionist approach, and instead looking at life as a collection of integrated systems composed of multiple components that are coordinated towards some higher function [271, 272].

Systems biology has thus become popular among mainstream biologists because it accurately describes how living systems operate [273]. Central to this shift is the adoption of assumptions that flow directly out of design theory:

- Instead of assuming that life should often display suboptimality due to evolutionary history, biologists increasingly effectively assume that life exhibits design and optimizes trade-offs between competing constraints [204, 274–276].
- Rather than viewing life as a collection of Rube Goldberg machines—complicated contraptions that achieve simple tasks through convoluted, disconnected mechanisms—researchers increasingly recognize that life exhibits top-down design [277]. In this framework, an overarching goal and specific design constraints guide the engineering of complex traits [259, 260, 278].
- Instead of assuming that human engineering principles have no analogs in biological systems, researchers increasingly recognize that life demonstrates design logic that strongly resembles the logic found in human engineering [267, 279, 280].
- The ID concept of irreducible complexity [281] has become an implicit tenet of the field, although the literature often uses the term *holism* [271, 282].
- Also motivating this approach is the recognition that biological systems exhibit the design features of robustness [283] and motif reuse [284].

This top-down approach has advanced our understanding by illuminating why biological systems function as they do, enabling predictions for unexplored areas, making sense of big data, and deepening insights into complex diseases. Its predictive success is evident in the proliferation of dedicated journals and specialized departments.[8] One key contribution is Alon's *An Introduction to Systems Biology* [268] which provides a foundation for understanding what we see in biology by introducing three core principles that characterize well-engineered systems: network motifs, robustness, and optimality.

The work of James A. Shapiro, also not an ID supporter, has also brought improvements to the fields of micro- and evolutionary biology, largely through his application of systems thinking [285, 286]. His research highlights the systems-level capacity of cells to actively reorganize their genomes in response to environmental stressors, a process he terms natural genetic engineering (NGE) [285]. Systems biology has also yielded insights for drug design. As a paper titled "Systems biology: A disruptive biopharmaceutical research paradigm" observed: "[t]he pharmaceutical industry has gradually evolved from a purely chemistry-based paradigm to an information-based paradigm" [287].

Systems biology has also helped biologists make sense of advances in "big data." Innovations in DNA sequencing and mass spectrometry led to the collection of massive genomic, proteomic, and transcriptomic datasets. A reductionist view of biology would not anticipate high levels

[8]This includes *Molecular Systems Biology*, *Nature Systems Biology and Applications*, *BMC Systems Biology*, *Systems Biology in Reproductive Medicine*, and *PLOS Computational Biology*. Additionally, numerous prestigious institutions have established specialized departments, such as Harvard Medical School's Department of Systems Biology, Columbia University's Department of Systems Biology, MD Anderson Cancer Center's Department of Systems Biology, MIT's Computational and Systems Biology program, and Yale's Systems Biology Institute.

of coherence or coordination within this data that represent system-level operations [288]. However, systems biology-based analyses of large datasets have revealed integrated, hierarchical dynamic operations. One example is The Cancer Genome Atlas (TCGA) project, which collects profiles of human tumors, allowing the study of molecular differences in DNA, RNA, protein expression, and epigenetics. This initiative has laid a critical foundation for advancing cancer research and treatment [289]. Another example of advancement for disease research is the "network based approach to human disease" [290]. Disease phenotypes are rarely caused by a single problem, but reflect multiple "things gone wrong" in a complex network. This suggests the study of the underlying causes of disease is "similar to an automotive technician's inability to fix a car's electrical problem without an accurate assembly and wiring diagram" since "a comprehensive understanding of most diseases requires a map of the cell's intricate wiring diagram, whose breakdown is ultimately responsible for the emergence of a particular disease phenotype" [290]. Thus, a systems biology approach to studying disease provides a needed holistic perspective that offers great promise for improving patient outcomes [290].

The holistic approach of systems biology has also produced advancement in modeling. Karr et al. (2012) [291] developed a whole-cell model of *Mycoplasma genitalium*, a pathogen with the smallest known genome (525 genes). This model computationally depicts the life cycle of a single cell through division, capturing individual molecules and their interactions, while accurately predicting system-level behavior [291]. Another significant achievement in modeling from systems biology is the genome-scale reconstruction of the *Escherichia coli* metabolic network, which comprehensively details the metabolism of this well-studied organism. This model clarifies which and how many parameters are necessary to use the reconstruction predictively, enhancing our understanding of *E. coli* metabolism [292].

While systems biology has grown in popularity due to its utility within biology [273], in some cases its acceptance has been hindered due to its implications, particularly regarding teleology and agency. For example:

- **Agency and Purpose**: Ball (2024) [293] notes that agency—living organisms' ability to manipulate their environments to achieve goals—is increasingly discussed in biology. Yet biologists have been hesitant to embrace this approach due to implications regarding intelligent design:

  > This makes agency inextricably linked to ideas about purpose. That is probably why the problem of agency has been (absurdly) neglected for so long in the life sciences, where questions of purpose have long been shunned as quasi-mystical teleology, perhaps only one step away from the dreaded concept of intelligent design. The result of this neglect and avoidance is that we can end up skirting around the most characteristic feature of all life. I propose that the time has come to embrace it—and that there is nothing to fear in doing so. [293]

- **Design Without a Designer**: Mantri and Thomas (2019) [267] recognized the "seemingly insurmountable gap between design-theory and biological 'designs'," and seeks to "bridge" that gap without actually invoking intelligent design.

- **Optimization**: Bialek (2024) highlights the polarizing nature of optimization in biology, stating "optimization comes along with an aesthetic that you might or might not find appealing" [204]. He explains, "For some, optimization is obvious because evolution has had billions of years to get things right. For others, optimization is nonsense because evolution is not about being best, but about being better than the competition" [204]. What Bialek (2024) [204] is alluding to is that highly optimized systems have not historically been predicted by Darwinian evolution. Optimality is, however, an expectation of intelligent design [66], which is precisely why some do not find it "appealing."

In contrast, ID theorists have embraced systems biology because it reflects the information-based, top-down, hierarchical design of systems that is predicted by their model. Snoke (2014) explains:

> [T]he most productive new paradigm in systems biology is actually much more compatible with a belief in the intelligent design of life than with a belief in neo-Darwinian evolution. This new paradigm in system[s] biology, which has arisen in the past ten years or so, analyzes living systems in terms of systems engineering concepts such as design, information processing, optimization, and other explicitly teleological concepts. This new paradigm offers a successful, quantitative, predictive theory for biology. Although the main practitioners of the field attribute the presence of such things to the outworking of natural selection, they cannot avoid using design language and design concepts in their research, and a straightforward look at the field indicates it is really a design approach altogether. [294]

Systems biology thus adopts a design-based framework, albeit one typically employed by scientists who

would not consider themselves pro-ID. These non-ID scientists use systems biology simply because it works well to investigate and describe biological systems. But could even more explicit application of design principles from the field of engineering further enhance biological investigation? Research conducted by design scientists over the past five years has extended the design-based assumptions of systems biology through the development of reverse systems engineering methodology.

3.4.2 Reverse Systems Engineering

Systems engineering is a "methodical, multidisciplinary, top-down approach to efficiently design and develop an engineered system meeting a set of requirements covering the desired functionality" [164]. As noted, the systems engineering approach is justified in biological systems as they exhibit features of top-down design such as optimality [204, 275, 276], robustness [283], and reuse of design motifs [284]. System engineering methodology has been successfully employed by NASA, SpaceX, Intel, Image Guided Technologies, and Stryker [263]. The field of systems engineering parallels systems biology in that both approaches assume that systems are built in a top-down manner, with an overarching goal or function, and then subcomponents are arranged hierarchically to contribute to that goal. There are a variety of systems engineering methodologies, namely the waterfall methodology [295], the Vee diagram [296, 297], and the Kossiakoff Lifecycle [298], all of which outline the forward engineering of a multiscale system. Importantly, most biologists are naïve of these systems engineering approaches, the steps they employ, and how these steps contribute to complex system development. Common among the methodologies is a top-down specification whereby the purpose of the system, its environment, its resources, its constitution, and its physical limits are specified by stakeholders. This produces a formal Functional Requirements Specification document, and designs meeting those requirements are written into a system design specification. There may be multiple satisfactory designs, but the requirements severely restrict the number of viable solutions in possibility space. All of these also must be within the constraints imposed by chemistry and physics. After the design phase, systems engineering transitions to build and test systems, starting with the components, and integrates components and subsystems up to the top-level system. By testing at each level before further integration, problems are identified and corrected earlier in the process.

Adopting systems engineering in biology means embracing an explicit design-based methodology, and the advancements in understanding biology that result from this approach demonstrate the utility of intelligent design. Multiple systems-engineering analyses of biology have been conducted by scientists and engineers supportive of intelligent design, showing the utility of this approach.

Initial Systems Engineering Analysis of the Bacterial Flagellum and Chemotaxis In a trilogy of publications, Schulz [263–265] uses a "top-down view from a systems engineering viewpoint" [264] to investigate the bacterial flagellum, a molecular machine which has long been cited as an example of intelligent design in biology [53]. Schulz (2021a) provides a formal demonstration of the necessary functional requirements for a bacterial flagellum via constraint considerations, a requirements specification, and modeling. This documentation outlines what would be required to bioengineer a motility system for a bacterium, providing engineering-based reasons for the selection of a rotary motor-driven propulsion system, a randomized redirection system, and a short-term memory of environmental inputs. Various propulsion mechanisms were considered, including legs, a squirting design that would convert power to motion via an output nozzle, and a jellyfish-like rhythmically flexing body. However, Schulz (2021a) [263] demonstrates that a rotary motor is a superior design solution. For example, legs would be an inefficient means of bacterial motility due to the absence of semi-solid surfaces in typical bacterial environments. Examining the rotary motor design, Schulz (2021a) [263] further specifies the need for continuous power, static subassemblies to provide counter-torque, a drive shaft, and a propeller, while acknowledging unique molecular-level challenges that remain poorly understood, such as molecular wear in bearings and seals. These requirements are then formalized into a dependency graph—a graphical representation of the system requirements that captures the purpose, environment, and constraints of the propulsion system. Schulz (2021a) [263] emphasizes that these requirements represent a minimal level of complexity, and notes that it is hard to imagine how a partial flagellum could provide a selective advantage to a bacterium, given the interconnected nature of the system and its failure to function if parts are missing. This work improves understanding of the flagellum in that it predicts what a functional top-down designed flagellum should look like. The documentation also anticipates trade-offs which can explain subtle differences in flagellar systems.

Schulz (2021b) [264] conducts a comprehensive literature review of *E. coli* and *Salmonella enterica* flagella, adopting a systems perspective to survey their known purpose, function, components, and structure. The study then uses Systems Biology Graphical Notation (SBGN) to formalize details of the flagellar assembly process, resulting in an improved description of what is necessary for the flagellum to assemble. This work has implications for evolutionary biology since any evolutionary scenario must provide a detailed explanation for how the origin of this tightly constrained, interlocking, coherent assembly of parts could emerge incrementally without guidance.

Schulz (2021c) [265] discusses how his approach

yielded new insights into the design and operation of the bacterial flagellum, such as how flagellar proteins have constrained pairwise relationships. Many flagellar proteins face additional constraints, including binding affinity, physical shape (including diameter), scaffolding needs for assembly, non-interaction with other neighboring components. Schulz (2021c) [265] shows that the greater the number of constraints, the more restricted in design space a certain component becomes: "each of the structural proteins of each of the flagellum's subassemblies requires an extremely precise molecular configuration in order to simultaneously comply with several very specific required properties."

In summary, Schulz's engineering approach to studying the flagellum [263–265] provides novel insights into flagellar construction, operation, and overall design.

Later Systems Engineering Analysis of the Bacterial Flagellum and Chemotaxis Johansen (2024) [266] built on the work of Schulz [263–265] to further develop the systems engineering approach for studying biological systems. He applied Systems Modeling Language (SysML)—a standard systems engineering modeling tool—to the *E. coli* flagellum to gain new system-level insights about its organization and operation. Johansen (2024) called this process RE-OOSEM: Reverse-Engineering Object-Oriented Systems Engineering Method, which assumes a "top-down system understanding." In contrast to forward engineering, reverse engineering "is the process of analyzing an existing system to understand what the system does (i.e., functionality) and how it works" [164]. RE-OOSEM methodology uses six steps: (1) survey academic articles and textbook sources; (2) capture descriptive information from sources; (3) convert into engineering prescriptive information; (4) generate high-level functional architecture; (5) capture system architecture in SysML; (6) and evaluate the system architecture. Computer modelling via model-based systems engineering (MBSE) is a key part of this process because construction of a model reflecting the system's operation, informed by scientific literature and requirements analysis, allows the system to be understood more holistically. Several established modeling tools facilitate MBSE, including SysML, Systems Biology Graphical Notation (SBGN), and Object Process Methodology (OPM). Johansen (2024) affirms the utility of these tools, noting "it is helpful to have a model-based digital twin that captures the details of the architecture that grows in detail and complexity as the system matures" [266].

The novel contribution of Johansen (2024) [266] was application of SysML to the bacterial flagellum. SysML typically consists of nine types of diagrams that map a system's structure, behavior, requirements, and parameters, with each diagram highlighting a different facet of a complex system. SysML's diagrams "translate [...] biological research descriptive information into prescriptive information that captures the biological system function in the context of its environment and frames it in engineering terms" [266]. In this application, Johansen (2024) took existing knowledge of the *E.coli* flagella and formalized it into the following nine types of diagrams: (1) block definition diagrams (BDDs); (2) internal block diagrams (IBDs) showing functions and interfaces; (3) requirements lists (REQs); (4) organizational package layout diagrams (PKGs); (5) system activity process flow diagrams (ACTs); (6) use case scenarios with stake holders (UCs); (7) temporal sequences of activities diagrams (SDs); (8) inter-relationship and transitions of operational state diagrams (STMs), and (9) physical attributes and constraints (PARs). These diagrams "shed light on the biological system's organization" [266].

In forward engineering, such diagrams are completed in conjunction with a systems requirements review. From this point executable models can then be generated. The diagrams inform and mature the systems models as more downstream details are fleshed out and problems sorted through. In reverse engineering the models are not static but are updated as new information is learned. However, this does not prevent meaningful insights from being gained. Johansen (2024) provides examples of how his "best for now" [266] SysML models facilitate system observations made from the engineering layout described in this paper. His analysis reveals several engineering principles at play:

1. **Autonomous Decentralized Control**: Johansen (2024) identifies chemotaxis as having a distributed control system where components function as interdependent agents, rather than relying on a centralized control paradigm. Autonomous decentralized control is a design that enhances robustness, allowing the system to function despite component failures. Local decision making allows rapid responses to changes in the environment without waiting for instructions from a central authority. Additionally, a reduced need for constant communication with a central hub saves energy and bandwidth.

2. **Minimalist Design for Short-Term Memory**: The analysis highlights the efficiency of phosphorylation-based short-term memory in chemotaxis, since the chemotaxis control process leverages the resources that already exist in a multifunctional way to achieve short-term memory without bringing in additional components.

3. **On-Demand Component Production**: Unlike many engineered control systems with premanufactured, hardwired components, chemotaxis control components like CheY and CheB are activated on demand via phosphorylation. This allows for easy refurbishing of components.

4. **Unified Sensory Array**: The analysis shows that chemoreceptors function as a coordinated sensory array, with activation rates of CheA, CheY, and CheB synchronized to support the higher-level goal of navigating toward attractants or away from repellents.

5. **Coordinated Time Scales**: Activation time scales for control components and processes are finely tuned to align with the system's navigation objectives, ensuring efficient and precise responses.

6. **Closed-Loop Control:** The flagellar system requires a closed-loop control, and this function is accomplished through multiple interacting subsystems, as dictated by the systems architecture. Each reaction type was implemented to match the required timescales for each subsystem. Again, this shows coordination of subsystems for the higher-level goal of navigating toward attractants and away from repellants.

Johansen (2024)'s [266] application of SysML and development of RE-OOSEM provides a proof-of-principle study that not only advances the understanding of chemotaxis but also provides a detailed system model. By confirming the intelligent-design-based prediction that chemotaxis reflects top-down design akin to human-engineered complex systems, this reverse systems engineering-based study illuminates operational principles of chemotaxis, demonstrating the utility of this engineering-based approach to studying biological systems [266].

A Formalized Reverse Systems Engineering Approach for Biology Building from Schulz (2021a, 2021b, 2021c) [263–265] and Johansen (2024) [266], Fudge and Reeves (2024) [164] formally united key elements of systems engineering into a model-based reverse system engineering (MBRSE) methodology that provides biologists with a step-by-step approach to formalize observations, build predictive models, and characterize complex systems. Their methodology is grounded in the assumption of top-down design, a characteristic of intelligently designed systems:

> Our reverse systems engineering approach is motivated by the fact that biological systems exhibit features that are traditionally associated with good top-down requirements-driven system engineering practices, such as modularity, optimality, robustness, common protocols, and design reuse. Furthermore, reductionism, which asserts that biological systems can best be understood from the low-level components, has been the dominant approach in biology for decades despite having been found inadequate with notably inaccurate predictions. Finally, top-down approaches to understand biological systems, even if not requirements driven, have been successfully employed, illustrating the promise of top-down systems thinking in biology. [164]

Fudge and Reeves (2024) simplify and formalize the reverse systems engineering methodology, tailoring it to be user-friendly for biologists who lack formal engineering training, as "many biologists are still not sure how to effectively use systems principles, and tractable methodologies for them remain an important gap in the systems biology revolution" [164].

Similar to Johansen (2024) [266], Fudge and Reeves (2024) [164] present a methodology that begins with observations, which often originate from the scientific literature since it serves as the repository of historical biological discoveries. Once sufficient observations are collected, they state that corresponding requirements should be inferred and then modeling can begin. They highlighted the importance of requirements analysis, noting that "very little attention has been paid" previously to requirements in the biological context, and "[i]n many reverse engineering situations, including biological systems, the requirements are not given. Therefore, we must infer the requirements from observations" [164]. In forward engineering, stakeholders establish the overarching requirements that guide the top-down design process for a system. Analogously, in biology, a designing intelligence could define the overarching requirements for each organism, which then cascade hierarchically, informing downstream subsystem specifications. For example, the overarching requirements for a cheetah (e.g., run 60-70 mph and accelerate from 0 to 60 in 3 seconds) could lead to downstream subsystem specifications for the cheetah's body plan, the tissues composing that body, the constituent cells supporting those tissues, the proteins supporting those cells, and the genetic information generating those proteins. Although the requirements for a biological system are not known to researchers in advance, through engineering analyses of biological systems [164, 263–266] requirements can be successfully inferred from higher-level functions and a top-down analysis of overarching goals. The hierarchical structure of a system implies that higher-level requirements govern those at lower levels, establishing a clear top-down, requirement-driven prediction for similarities and differences between organisms. The significance of requirements lies in their role as the parameters for design solutions, which emerge through the optimization of these specifications against physical constraints and design trade-offs.

Using MBRSE to Understand the Ubiquity of the Glycolysis Topology Fudge and Reeves (2024) [164] then apply their MBRSE methodology to glycolysis, deriving twenty-

two requirements, uncovering five gaps in knowledge, and generating six predictions for this core metabolic pathway. One significant contribution of their work concerns systems-engineering-based reasons for the similarities and differences in glycolysis across organisms.

The topologies of glycolysis are highly conserved, where topology means the sequence of the pathway steps that lead from glucose to pyruvate, the intermediates produced, and the enzymes' functional roles [299, 300]. There are two predominant topologies in the glycolysis pathway: the Entner-Doudoroff (ED) topology and the Embden-Meyerhof-Parnas (EMP) topology. The EMP topology, commonly featured in high school biology textbooks, yields two ATP molecules per glucose molecule, whereas the ED topology produces only one ATP per glucose. Historically, the consistency of topologies across life's diversity has been attributed to inheritance from a common ancestor. However, Fudge and Reeves (2024) [164] argue there are key system engineering-based reasons for the topologies to be similar across organisms, which may better explain the reuse of common architectures.

The first systems-engineering-based reason they provide for glycolytic pathway uniformity is that these two topologies are better design solutions than are other possible configurations for energy extraction and biomass production. The architecture of having a preparatory phase, where the molecule of glucose is prepared, followed by a payoff phase, is highly efficient based on kinetic and thermodynamic analysis [301]. The payoff phase, which is highly similar between the ED and EMP topologies, enables maximal biochemical flux under constraints of metabolite and enzyme concentrations [302]. Every single intermediate in *E. coli's* central carbon metabolism is either essential for building biomass or for ATP production, meaning that the 10-step pathway is minimally complex [276]. The EMP and ED glycolytic topology are pareto-optimized, specifically to balance ATP production against biomass production while simultaneously minimizing protein synthesis cost to the cell. The ED topology yields only one ATP/glucose molecule, but has a much lower protein synthesis cost compared to the EMP topology, which yields two ATP/glucose but has a high protein synthesis cost. Organisms with different ATP vs. protein synthesis requirements use the topology that best fits their requirements [303]. Thus, multiple independent research groups have identified optimality for different aspects of the glycolytic topologies. This supports the argument of Fudge and Reeves (2024) [164] that optimality, a systems-engineering-based rationale, may account for much of the observed uniformity across the ecosystem.

A second systems-engineering-based reason for glycolytic uniformity concerns the necessity of standardized metabolites for efficient ecosystem energy exchange. From a systems perspective, the standardization of energy storage molecules such as glucose facilitates both efficient energy uptake and waste recycling. Fudge and Reeves (2024) [164] note that the extent to which standardization constrains organism metabolism is little explored. They propose the extent to which ecosystem requirements for compatibility and sustainability contribute to uniformity in the glycolytic topology is an important area for research.

Notably, while the topologies are conserved across organisms, the glucose transporters and glycolytic enzyme sequences are divergent. Fudge and Reeves (2024) [164] suggest these differences derive from subsystem-specific (e.g., organism, tissue or cellular) design requirements and constraints. They note how mammalian glucose transporters comprising 14 subtypes illustrate this principle at the tissue level. Each characterized transporter fulfills a distinct role in systemic glucose regulation, suggesting that transporter isoform diversity is explainable by tissue- or cell-specific requirements. Given these findings, they anticipate that glycolytic enzyme differences between organisms may be similarly justified by organism-specific requirements. They suggest that their hypothesis is strengthened by the finding that sequence divergence of enzymes in the glycolytic pathway poorly correlates with predictions of common ancestry, which has led to skepticism towards the long-held assumption that the pathway had a single evolutionary origin [299].

The Warburg Effect A second insight from the system-engineering approach of Fudge and Reeves (2024) [164] concerns the Warburg effect, which is a drastic shift from oxidative phosphorylation to reliance upon glycolysis that occurs in many types of cancer. Their consideration of organismal energy requirements and the glycolysis system context yielded the prediction that the Warburg effect in cancer may be an aberrant manifestation of a natural tissue injury response, destabilized by a breakdown in the feedback mechanisms of the tissue injury control system.

This hypothesis is supported by the observation that glycolysis, despite a lower ATP yield per glucose molecule compared to oxidative phosphorylation, offers a higher rate of ATP generation. This provides a critical advantage in the context of embryonic development or tissue repair [304, 305]. Fudge and Reeves (2024) [164] state that research should be directed as to the role of the Warburg effect beyond cancer, hypothesizing that its dysregulation in cancer may stem from a failure to reverse course after an initial adaptive metabolic shift for something like tissue injury.

Collectively, these represent novel insights stemming from the application of MBRSE to glycolysis.

3.5 Reverse and Forward Engineering of Anatomical and Physiological Systems

Engineering principles, especially from mechanical and electrical engineering, have significantly advanced the study of anatomy and physiology. Reverse engineering in this context uses the tools and frameworks of mechanical and electrical engineering to understand biological designs and their underlying mechanisms. Like molecular biology, macroscopic features in anatomy and physiology exhibit patterns consistent with top-down organization, optimization, functional integration, and modularity [257].

ID-based engineering analyses have helped reveal key functional aspects of a variety of biological systems. These insights have then been directly applied to inspire imitation of biological design in engineering and the design of human technology. These efforts fall within the field of biomimetics (also called biomimicry), a form of forward engineering that builds on insights gained through the reverse engineering of biological structures. Within biomimetics, there is the expectation that biology demonstrates superior design to human technology. Journals on bioinspired design[9] feature hundreds of case studies of technology improved by copying nature. These studies demonstrate that optimality in biology is normative, contrary to the expectations of design critics. ID proponents have frequently cited, predicted, and studied biological optimality in relation to the potential for biomimicry to advance human engineering [21, 22, 78, 165, 269, 306–320], further showing the utility of ID-based engineering analyses within biology.

3.5.1 Reverse and Forward Mechanical Engineering of Vertebrate Joints and Limbs

Stuart Burgess, a prominent British engineering professor and ID theorist, has reverse-engineered biological systems to both demonstrate their optimality and to improve diverse technologies. In the process, he has discovered key features of these systems that are necessary for them to function.

Burgess (2021; 2022; 2023; 2024a; 2024b) evaluated the optimality of vertebrate joints and limbs using performance maps, kinetic and structural evaluations, and multivariable trade-off maps. Burgess (2021) observes that "[m]any of the design features used by engineers in linkage mechanisms are seen in nature, such as short coupler links, extended bars, elastic energy storage and latch mechanisms" [313]. For example:

> There are several existing similarities between the linkage mechanisms in biology and engineering. For example, the parallelogram pantograph mechanism of the bird wing is analogous to the pantograph mechanism of an angle poise lamp, and the over-centre locking feature in the snipefish is analogous to the locking mechanism in locking pliers. The force amplification achieved in the parrotfish has conceptual parallels with the force amplification in geared four-bar robotic claws used in robots and also the gearing system used in geared shears. [313]

Burgess (2021) further notes that "[l]inkage mechanisms are very important in mechanical systems because they enable the optimisation of forces and motions" [313]. He found that many diverse animals have linkage mechanisms, including fish jaws, lizard jaws, snake jaws, bird wings, insect wings, shrimp appendages, and the human knee joint. Many of these linkage mechanisms are multi-functioning, which "helps to produce packaging efficiency by placing a high degree of functionality into a small space" [313]. The study concludes that "highly optimised linkage mechanisms found in animals have potential for bioinspired engineering applications, especially where there are tight space constraints or where multifunctionality is desired. Such objectives are common in mobile robots and so this is an area with significant potential for bioinspired designs" [313].

The Human Foot Burgess (2026) [269] used design-based analyses based upon decades of study to find that "the human foot is indeed a masterpiece of engineering." Burgess et al. (2023) [312] highlights that "the human foot is far superior to any prosthetic foot engineers have produced," as it gives agility for diverse activities including running, climbing, kicking, and dancing. Burgess et al. (2023) [321] found that the ankle-foot complex exhibits "four highly specialised mechanical features" which show "a very high degree of complexity and fine-tuning: i) a multi-arched structure; ii) a multifunctioning midfoot; iii) elastic hinge joints; and iv) a fibula linkage mechanism". These allow multiple functions, including flexibility, which fosters shock absorption; strength and rigidity, which supports the body while standing or moving; plantar-dorsiflexion, which fosters joint movement for locomotion; pronation-supination, which allows rolling of the ankle; and balance, which is crucial for both standing and locomotion. These features also make the foot stiff enough to push off from the ground before a jump, but flexible enough to absorb the impact of the landing. Burgess (2022) [321] likewise found that the foot itself must be a "multifunctioning precision device" which can "act as a strong and stiff lever" to foster forward motion; "act as a flexible platform to absorb shocks"; and "provide 3-point contact with the ground" which allows fine-tuned propulsion and adjustment of motion. These functions are furthered by three "interconnecting flexible arches" in the foot which each have their

[9] See e.g., *Journal of Biomimetics, Journal of Bioinspiration and Biomimetics, Journal of Design and Nature,* and *Journal of Bionics.*

own specific functions. Some 17 multi-functioning elastic hinge-joints in the foot also promote flexibility and shock absorption, load-bearing, energy storage, and ultra-low friction, and provide a fail-safe design. Although Lents (2018) [322] argued against intelligent design on the basis that the ankle-foot complex contains bones that serve no function, Burgess (2022) showed that "all the bones of the ankle-foot complex have very important roles in the specialised design features" [321].

Since the design-engineering approach yields insights into the function of this system, these insights can be applied when designing or improving human technology. Burgess et al. (2023) thus applied biomimetics by copying the anatomy of a human foot to improve prosthetic foot design. They used 3D scans of foot bones, which they then reproduced via 3D printing to develop a prosthetic foot which reproduced the three point contact of the human foot which enables stability during upright standing [269, 312].

The Human Leg Complex Burgess (2024a) studied the human leg-foot complex and found that "the advanced capabilities of human legs show that they are highly optimised for bipedal locomotion" since "the vertebrate limb pattern is ideal for the folding and extending action of bipedal walking and running" [165]. Burgess has also examined the knee joint, finding that it employs a structural compression joint and a kinematic four-bar linkage mechanism which provide "a separation of functions" making it "easier to achieve optimisation of design because the two mechanisms can be optimised fully for their particular function" [319] (see also [318]). Within this four-bar linkage mechanism, cross links are formed by the anterior and posterior cruciate ligaments, enabling a moving center of rotation, thus "giving potential for optimal mechanical advantage" [319]. The kneecap protects this joint and responds to loads produced by the quadriceps [269].

Burgess has noted that one aspect of the knee that engineers have not been able to copy is its range of motion. Unlike other joints the knee is a floating joint which means it has no fixed center of rotation, delivering additional range of motion. Two requirements in the knee joint are 1) large load capacity and 2) large range of motion. These are met by the movement of the femur over the tibia (the design of the floating joint) which Burgess (2026) calls "seriously advanced engineering" [269].

Having identified these key aspects of knee operation, Burgess and colleagues used biomimetics to create plastic and metal artificial knee joints, modeled upon the human knee joint, for use in robotics [318, 319]. Their design "mimics the curved profiles of the human knee joint in order to achieve the benefits of high conformity and high stiffness and strength" [319]. Burgess (2026) recounts that during the design process his team became aware of how perfectly the curved profiles of the bones must be in order for the whole apparatus to function: "One feature of the knee joint that astonished us is that the curved profile of the femur and tibia has to exactly match the motion of the four-bar mechanism; otherwise the knee will lock up" [269]. He notes "most of my researchers who worked on the knee joint were at the end of the process, convinced the joint was intentionally designed" [269].

The Human Hand-Wrist-Arm Complex Burgess (2024a, 2024b) showed the optimality of the design of the human hand-wrist-arm complex [165, 323]. He described how each finger is actuated by different tendons, allowing for different degrees of flexion and extension, where "the bones of the hand take compressive loads whilst the muscles and tendons form a network of tension loads" [165]. He also described how the thumb, palm, and finger allow for different types of grips and pinches, allowing the grasp of a wide variety of different types of objects. And he found that the human hand-wrist-arm complex exhibits engineering trade-offs that result in optimality for a full range of motion:

> Even though the human arm can be vulnerable to instability in the shoulder and wrist, this is a consequence of having a large range of motion at these joints, i.e. the arm design has an appropriate compromise between stability and range of motion. [165].

In addition, Burgess identified that a common design strategy in human joint anatomy is multifunctionality, where a single bone, joint, or subsystem performs multiple distinct functions. Burgess studied the human wrist and found that the eight individual bones are multifunctional and collectively perform four different "major functions" to yield a universal joint [323]. He concludes that, "When considering the whole set of functional requirements, the human arm and hand can be judged as having a highly optimal design" [165]. This system requires top-down design and integration of multiple components to function properly.

Again, Burgess and colleagues applied insights from their engineering-based analysis of human anatomy to further biomimetics. In this case, they produced an advanced exoskeleton which "includes a novel four-bar mechanism designed to reproduce natural thumb opposition and a novel synchro-motion pulley mechanism for coordinated finger motion" [320].

3.5.2 Vertebrate Limb Design

Homology (similarity purportedly due to inheritance from a common ancestor) among vertebrate limbs has been a longstanding argument for evolution. The widespread skeletal pattern consists of a single-bone stylopod (e.g., humerus), two-bone zeugopod (e.g., radius

and ulna), and multi-boned autopod with digits (e.g., carpal bones plus digits). It is claimed that the reason for skeletal similarities in limbs of vertebrate tetrapods with highly divergent lifestyles and modes of locomotion can only be inheritance from a common ancestor. However, if there are functional engineering-design-based reasons for the vertebrate limb structure, then other possible explanations for the shared similarities emerge, such as common design (see Section 3.3).

Burgess (2024a) used a design-based engineering analysis to investigate optimality in the skeletal pattern of the vertebrate limb, and found that there are good functional reasons for its widespread reuse:

> [T]he vertebrate limb pattern is highly versatile and optimal not just for arms and legs but also for flippers and wings. One key design feature of the vertebrate limb pattern is that of networks of segmented bones that enable smooth morphing of shapes as well as multi-functioning structures. Another key design feature is that of linkage mechanisms that fine-tune motions and mechanical advantage. [165]

Features such as wrist and digit joints in whale flippers have long been considered vestiges from a common ancestor. However, Burgess (2026) [269] reports that the whale wrist plays a key role in absorbing load during swimming deceleration. In addition, the wrist and associated bones maintain and fine-tune the shape and mechanical performance of the flipper. Burgess (2024a) also found the whale flipper shows an "optimal hydrofoil shape" that gives a high lift-to-drag ratio; a "highly mobile ball and socket shoulder joint that enables three rotational degrees of freedom;" and "[f]unctional wrist and digit joints" which "fine-tune the stiffness and shape of the flipper" [165]. Therefore, the whale flipper is not merely a "stiff paddle with no functioning joints" but rather is a "'variable stiffness and deformable paddle' with fully functioning wrist and digit joints" where "the elbow, wrist and digit joints are ideal for meeting the morphing and structural functions of the flipper" [165]. Burgess's findings stand in direct contrast to the evolutionary paradigm which views the whale's flipper as a "rigid, rudder-like paddle" [324]. He concludes that "the vertebrate limb pattern is ideal for the whale flipper because it allows for finetuning of stiffness and shape which is essential for precise and efficient swimming" which "challenges the commonly held view that features in the flipper skeleton (e.g. elbow, wrist and digits) only make sense when seen to be a consequence of being forced on the flipper design by evolutionary inheritance" [165].

Similarly, Burgess (2024a) finds that bird wings outperform "small human-designed air vehicles" in "every measure of performance," as "flight range is three orders of magnitude better for birds partly due to the wing design and partly due to the energy density of fat being over an order of magnitude better than current batteries" and birds have "a relatively high level of flying stability and control compared to human-designed air vehicles" [165]. Like the whale flipper, "the segmented bone and feather layout allows the wings to morph into different shapes whilst maintaining smooth curvatures and hence low drag coefficients" [165]. He concludes that "the vertebrate limb pattern is ideal for a bird wing and can be an inspiration for human-made aircraft wings" [165].

After evaluating the general limb layout in a variety of vertebrates, Burgess (2024a) finds that "The vertebrate limb pattern is a remarkably versatile design solution that can be fine-tuned to produce a vast range of shapes and motions as well as perform structural functions" [165]. He notes that this finding "challenges the limb homology argument that the skeletal layouts of the whale flipper and bird wing are not what would be expected for those applications and make sense only when seen to be a consequence of evolutionary inheritance" [165]. This shows that a design-based analysis of the vertebrate limb yields insights into limb function that were missed under evolutionary models which assumed that the similarities were mere relics or incidental vestiges left over from a common ancestor.

After making these discoveries about the design of vertebrate limbs, Burgess proposes that this skeletal pattern could be mimicked in human technology:

> It is hard to think of a better skeletal design for meeting the various kinematic and structural functions. The conclusion of optimal design is important for bioinspired design because instead of treating the flipper skeletal layout as a suboptimal design it can be treated as a highly optimal design with potential areas for copying such as the multi-jointed digits that produce smooth curved deflections. [165]

He concludes that "The vertebrate limb has significant potential for the bioinspired design of robotic and prosthetic limbs..." [165]. Once again, a design-based engineering analysis has uncovered functionality of components, coordination of parts, recurring application of useful functional designs via common design, and optimization to fulfill multiple design constraints—effectively applying reverse engineering principles and design criteria to understand how these systems operate. And these discoveries have practical benefits for human technology through biomimetics.

3.5.3 Feathers

Burgess (2007, 2026) [269, 325] and McIntosh (2009) [326] analyzed bird feathers through an engineering lens,

concluding that their structure reflects a hierarchical top-down design, as well as optimization across multiple competing constraints, including strength, weight, and flexibility. Feathers are composed of keratin, a material ideally suited to satisfy these requirements. Moreover, feather filaments exhibit shape changes that enhance performance under bending loads. At a finer scale, the hierarchical interlocking system of hooks and barbs is exquisitely tuned: it prevents air penetration during the powerful downstroke while permitting controlled airflow during the upstroke. Burgess (2007) notes that "engineers [have] adopted a design philosophy of integrating different functions together in single components and mechanisms" and "from a design point of view" feathers exhibit "the existence of multiple functions and multi-optimisation in a single component or mechanism" [325].

According to Burgess (2007), feathers show "hierarchy of structures" where "the main feather stem comes first, then the barbs and finally the barbules" such that "[t]he flight feathers of birds can be considered to have three major functions: an aerodynamic function, a fail-safe function and a lightweight structural function" [325]. Thus, "the hierarchical structure is optimal for all three functions" [325]. Macintosh (2009) summarizes his results as follows:

> [T]here is multifunctioning and multioptimisation in feather construction. There are the features which are immediately apparent such as aerodynamic loading and the material construction of rachis and barbs to sustain this. however, there are also more subtle features such as the arrangement of hooks and barbules primarily for keeping the feather together, such that they prevent air from going through them during the downstroke but allowing some air to pass through in the upstroke, thus maximising the efficiency of energy use in wing flap. The keratin itself has an extremely high specific strength, and the shape of the filament cross sections used in rachis construction moves from near circular near the root to a curved and ribbed rectangular shape away from the root for structural efficiency under bending and potentially buckling loads. [326]

He concludes, "The evidence is consistent with the design thesis both from the fossils found of flight in the past, and in the multifunctional nature of wings today" [326]. These design-based investigations of mechanical engineering in living systems reveal how the subcomponents are meticulously engineered to function efficiently and interconnect seamlessly, illustrating how the system is optimized to fulfill multiple functional objectives simultaneously.

After finding that "The design of bird feathers demonstrates that multi-functioning and multi-optimisation can produce large benefits in performance" Burgess (2007) proposes that "engineering design" should "move towards multi-functioning in single components and structures" [325]. He likewise proposes that the hierarchical structure of feathers should be mimicked because "hierarchical structure enables fine-tuning of shapes and layout and enables a very large number of localised sub-mechanisms to exist." He concludes that "Nature can be a rich source of ideas and inspiration that can help to achieve multi-functioning in engineering." [325] Indeed, later research by non-ID scientists has used feathers as inspiration for new technologies [327, 328].

3.5.4 Biomimicry of Insect Designs

The use of engineering design analyses to yield biomimetic applications is not restricted to vertebrates; ID researchers have also applied these methods to study invertebrates, such as insects. For example, McIntosh (2009) found that the Bombardier beetle has a sophisticated mechanism for defense against predators:

> The Bombardier beetle heats up a toxic aqueous mixture of quinones to above boiling point in a tiny combustion chamber less than 1mm in size by an exothermic chemical reaction and then sprays it from a moveable turret in its back end in any direction it wishes—even over its head. [306]

The reaction requires two components—hydrogen peroxide and hydroquinone—which do not react until carefully mixed in the combustion chamber with catalysts. It also involves a spray nozzle with directional control mechanisms.

McIntosh and colleagues propose biomimetic applications of this system, including pharmaceutical sprays such as nebulisers, fuel injection mechanisms in cars, and fire extinguishers. McIntosh and Beheshti (2008) [309] built a pulse spray mechanism based upon the design of the Bombardier beetle, and McIntosh (2007) found that "The development of a fast mass ejection device has a particular application to gas turbine igniters where it is important to eject vapourized fuel into the part of the combustion chamber where the combustion may have temporarily ceased" [308].

Micro air vehicles (MAVs) have also been built by mimicking flying insects. Burgess and colleagues [314, 329–332] studied flying insects due to their "agile flight in complex environments" which makes use of a "highly elastic natural oscillator" which "enables resonant excitation to take advantage of the amplified the flapping stroke and greatly reduced inertial power demands" [314]. These MAVs aim to "replicate insect wing kinematics" [317] where "insects flap their wings at the

resonant frequencies of their flapping mechanisms" [329]. While truly insect-like MAVs have yet to be produced, this research has led to deeper understanding of insect wing kinematics [332] and inspired the development of artificial muscles and parallel crank rocker (PCR) mechanisms [331]. If developed they promise "a variety of novel military and civil applications" [317].

3.5.5 Applications of Engineering to Understand Brain Blood Flow

Each time the heart beats, it pulses blood into and through the brain; however, if these pulses of blood flow were not carefully controlled, they would burst the fragile capillaries throughout the brain. Applying the assumption that the brain is a "designed system" operating under engineering principles, Egnor and colleagues [166, 167] applied concepts from electrical engineering and reported that brain capillary blood flow is controlled by a band-stop filter, and cerebrospinal fluid flow is controlled by a band-pass filter. This article exemplifies how the design paradigm can be useful to scientists who seek to understand how biological systems function. By viewing biological systems as designed, researchers expect them to exhibit certain engineering principles that we observe in human-designed technology. This can help solve questions that are vexing biologists and clinicians. As Egnor (2019) explains:

> I propose that a useful approach to understanding these counterintuitive aspects of intracranial pulsatility is to consider the dynamics of the cerebral windkessel as that of a designed system. Such a system manifests design principles that accomplish specified goals, which for the cerebral windkessel is the buffering of arterial pulsatility—an unwanted 'vibration'—in cerebral blood flow, while at the same time maintaining optimal cerebral blood flow and minimizing energy dissipation. This approach to exploring intracranial pulsatility entails reverse engineering of the cerebral windkessel, in accordance with established engineering principles of vibration control. [166]

Egnor (2019)'s conclusion that "[t]he cerebral windkessel is a dynamic pulsation absorber" is based upon careful analysis of the signal of blood flow in the body and the brain [166]. This model is inspired by the view that aspects of biology were designed based on rational engineering principles and have analogues in human-designed systems, as "The cerebral windkessel has analogues in mechanical engineering (a dynamic vibration absorber), electrical engineering (a wavetrap circuit), acoustic engineering (a cavity resonator) and systems analysis (a band stop filter)" [166]. This model of brain blood flow has wide potential for improving treatments of hydrocephalus and "may provide new and counterintuitive insight into disorders of intracranial dynamics" [166], and points to "a new understanding of the pathophysiology and treatment of hydrocephalus and other disorders of intracranial dynamics" which resolves "serious problems with the pressure-volume models of intracranial dynamics" [167].

4. DISCUSSION

Intelligent design is a scientific theory which can be applied to yield insights in a variety of scientific fields through theoretical research, historical scientific research into the origins of natural features, and experimental research into the present-day operation of natural systems. The theory begins with observations of the types of information and complexity produced by intelligent agents. This leads to testable expectations about what might be found if natural structures were intelligently designed. Observations of intelligent agents reveal that they produce high levels of CSI and that they engineer systems in a top-down hierarchical manner that optimizes competing constraints, which are expectations of intelligent design. These insights have yielded many applications of design theory, leading to a variety of scientific advancements.

In protein science, ID's expectation that systems will contain high CSI has led to research discovering the extreme rarity of amino acid sequences that yield functional proteins [67, 74, 99, 101, 103, 104]. This expectation has also led to innovative comparative methods of measuring protein specificity [168], as well as a general solution for a percolation threshold below which random mutation and natural selection are unlikely to traverse sequence space to find new functional sequences [103]. Other design-based research has found that producing new protein-protein conversions would exceed population-genetics-based limits of the maximum number of mutations that can arise before providing a functional advantage [101, 104, 169]. This research can inform drug design by helping identify optimal protein targets in pathogens and by guiding the engineering of novel pharmaceutical proteins.

Within genetics, design theory relies heavily upon the observation that intelligent agents produce features that are functional, and that a mind can develop new information-rich sequences that need not have material antecedents in other systems. This has led ID researchers to study orphan genes and to develop tools to identify and catalogue these enigmatic sequences [178, 179]. Because design theory anticipates function will be prevalent, ID researchers have successfully sought to understand the role played by the C-terminus domain of the topoisomerase II enzyme [176, 182, 183], leading to advancements in our understanding of the operation of this vital molecular

machine.

Using similar predictions, design theory has been applied within genetics and genomics to directly predict and explore function for junk DNA. For decades, evolutionary biologists predicted that the bulk of the non-coding DNA in our genome was genetic junk. Yet based upon the observation that intelligent agents tend to design artifacts with a function and for a purpose, ID theorists had long predicted that the human genome would turn out to be largely functional [6, 149, 191]. This prediction was correct, as the results of [151] showed that over 80% of the genome shows evidence of biochemical function. The literature has reported that a Kuhnian paradigm shift has occurred away from the idea of "junk DNA" [198, 199] and concluded that "the days of junk DNA are over" [163]. Researchers in the ID community are investigating function for junk DNA [75], showing that the ID prediction has borne good fruit in guiding research into function for junk DNA. Within systematics, common design-based dependency graphs can also shed light on why diverse organisms share similar genetic or physiological traits [123, 124].

Observations of intelligent agents and design-based expectations are highly compatible with systems biology and systems engineering, which study biological systems under the assumption of a hierarchical, top-down design where subcomponents are coordinated to contribute to overarching goals. Various design-based studies [164, 263–266] have therefore implemented such approaches to yield insights into how biological systems operate.

Schulz [263–265] demonstrated the utility of an engineering approach in studying the bacterial flagellar-chemotaxis system by identifying a list of necessary parts for a nanoscale rotary propulsion system, and using Systems Biology Graphical Notation to formalize details of the flagellar assembly process. The engineering analysis yielded expectations about flagellar construction and operation that were confirmed by empirical studies reported in the literature, and yielded insights into the design and operation of the bacterial flagellum including the fact that flagellar proteins have constrained pairwise relationships, where proteins must be designed to interface with multiple binding partners, and meet binding, structural, and assembly constraints.

Johansen (2024) [266] built upon Schulz [263–265] to implement a reverse-engineering approach to studying the flagellum-chemotaxis system. This Reverse-Engineering Object-Oriented Systems Engineering Method ("RE OOSEM") assumes a top-down design of biological systems, and uses multiple steps to build engineering models of a system. In this investigation, Johansen (2024) [266] demonstrated the utility of using SysML to studying biological systems, which shed light on the workings of the flagellum. For example, chemotaxis was identified as having autonomous decentralized control where multiple components operate as interdependent agents. The "short-term memory" of phosphorylation was identified as an efficient element in chemotaxis control, and it was shown that chemotaxis uses closed-loop control accomplished through multiple interacting subsystems.

Fudge and Reeves (2024) [164] then performed a reverse systems engineering analysis that used object process methodology (OPM) to investigate glycolytic pathways. They propose that there may be functional reasons for the reuse of common glycolytic pathways across the tree of life that reflect the reuse of systems to meet common design constraints rather than mere inheritance from a common ancestor. This analysis showed that the conservation of the glycolysis topologies across many organisms may be due to their efficiency of energy extraction and biomass production. The EMP topology is pareto-optimized, meaning it is maximally optimized given a number of constraints. They also proposed possible ecosystem-level constraints for the glycolytic topologies:

> The near-uniformity of central metabolism across life has traditionally been attributed solely to universal common descent. However, from a systems engineering perspective, there are two requirement-based reasons why uniformity might be expected. First, we would expect some level of biomass commonality to maximize thermodynamic efficiency in reusing complex molecules by minimizing the amount of required biomolecule breakdown and rebuild. Second, waste buildup can be reduced via commonly used recyclable waste products, and thus simplify maintenance of ecosystem homeostasis. [266]

Fudge and Reeves (2024)'s [266] conclusions can be accounted for within the theory of ID given the observation that intelligent agents often reuse efficient functional components or designs in different systems. This observation has been applied in other ID-based engineering analyses. Burgess [165, 312, 313, 321, 323] used a mechanical engineering analysis to examine vertebrate joints and limbs, creating performance maps, performing kinetic and structural evaluations, and making multivariable trade-off maps from a design perspective. While common ancestry is typically employed to explain why the vertebrate limb pattern is reused in diverse organisms (e.g., bats, whales, horses, dogs, humans, etc.), Burgess (2024a) found that there are good functional reasons for this reusage, as the limb-structure is optimal and can be fine-tuned for a variety of vertebrate modes of locomotion and lifestyles [165].

These insights could have applications for human-designed technologies, since "The vertebrate limb has

significant potential for the bioinspired design of robotic and prosthetic limbs" [165]. Burgess (2021) applied similar analyses to show that the reuse of linkage mechanisms in many diverse animals enables the "optimisation of forces and motions" as well as multifunctional components that efficiently compact "a high degree of functionality into a small space" [313]. An engineering analysis of the human foot and ankle complex [312, 321], knee [323], and wrist [165], conducted in rebuttal to "bad design" arguments, revealed numerous insights about the design and construction of bones and joints in the human body that are crucial for locomotion. For example, although design critics argued that "most or all the bones of the ankle-foot complex have no purpose or function," from a design perspective, Burgess (2022)'s investigation shows that "all the bones of the ankle-foot complex have very important roles in the specialised design features" [321]. These design-based engineering analyses of vertebrate joints and limbs have thus uncovered functionality of components, coordination of parts, reuse of efficient functional designs via common design, and optimization to fulfill multiple design constraints—effectively applying design criteria to understand how these systems operate.

Burgess (2007) [325] and McIntosh (2009) [326] have shown that bird feathers have a similarly efficient design. The materials used to build feather structures (keratin), and the design of feather filaments and the hierarchical barb-hook-barbule design show "the existence of multiple functions and multi-optimisation in a single component or mechanism" [325]. Again, design-based expectations of hierarchical function and reuse of functional components have yielded insights into why biological systems work the way they do.

These engineering-design-based studies yield insights not only into the workings of nature but also have applications for improving human technology through biomimetics. This field seeks to model human technology based upon biology, but it is most fruitful when operating under the paradigm that biological systems themselves were designed and therefore can serve as templates for human technology.

Lastly, design theory also shows utility for making medical advancements. Egnor and colleagues [166, 167] predicted and demonstrated that brain blood flow uses design principles known from "mechanical engineering (a dynamic vibration absorber), electrical engineering (a wavetrap circuit), acoustic engineering (a cavity resonator) and systems analysis (a band stop filter)" [166]. These insights have the potential to lead not only to improved understanding of brain function, but also to new treatments for hydrocephalus and other disorders.

5. CONCLUSIONS

The theory of intelligent design uses scientific methods to detect design in the origins of natural features, and applied design research uses design-based principles to predict, expect, investigate, and describe how natural systems operate. Design is positively detected by finding in nature the type of information and complexity which in our experience is produced by intelligent agents.

We have reviewed examples of how intelligent design theory is being applied within five fields (protein science, genetics, systematics, systems biology, and engineering) to make novel contributions in biology. Our understanding of protein rarity and function has been enhanced by design-based empirical and theoretical studies [67, 74, 103], with implications for improving protein and drug design. Within genetics, ID theorists directly predicted function for junk DNA [6, 149, 191]—a prediction which has proven correct and has guided research for some investigators within that field. The study of orphan genes has also been guided by intelligent design [178, 179], and design has led to advances in systematics through the development of dependency graph models of organismal relationships [123, 124]. The field of systems biology, which uses design-oriented assumptions such as "top-down design" in biological systems, is being advanced by ID-based papers within its subfield of reverse systems engineering, yielding insights into the internal operation and construction of the bacterial flagellum-chemotaxis system and glycolysis [164, 263–266]. The application of design-based engineering principles and reverse-engineering methods to vertebrate anatomy has yielded insights into the function and distribution of vertebrate joints and limbs [165, 312, 313, 321, 323], as well as feathers [325, 326], showing in turn how biomimetics can use these biological systems as models for human engineers [83, 313, 318, 332]. The application of design theory can also advance our understanding of human physiology, even leading to improved medical treatments [166, 167].

Collectively, this research demonstrates that the possibility of a "design science" [8] is becoming and has already become a reality in these and other scientific fields [75]. Intelligent design can thus broadly be applied in a variety of scientific subdisciplines to guide research and make new discoveries.

ACKNOWLEDGMENTS

Emily Nordhagen Sandico and Bruce Gordon are thanked for their helpful edits and feedback during the preparation of this article. The anonymous reviewers of this article are also thanked for their extremely helpful feedback which led to many improvements in the manuscript.

APPENDIX A. EXTENDED DOCUMENTATION FOR TABLE 2: OBSERVATIONS ABOUT THE CAUSAL POWER OF INTELLIGENT AGENTS

(There may be some overlap among some of these observations about the causal abilities of intelligent agents, however these observations are listed separately because they provide slightly different descriptions which together encapsulate what intelligent agents can do.)

This appendix lists the nine observations of the causal powers of intelligent agents enumerated in Table 2. However, following each causal ability, documentation is listed from the writings of ID theorists and others who study intelligent agents explaining the observations that led to our understanding of that causal ability.

1. Operate in a goal-directed manner.
    - "Intelligence is a goal-directed process that is capable of thinking with will, forethought, and intentionality to achieve some end-goal." [78]
    - "Intelligent design thus represents the best and, indeed, the only causally adequate explanation for the many examples of apparent foresight in the natural world, of situations where problems are ingeniously solved with on-time delivery of multiple, essential, and well-orchestrated parts." [79]
2. Generate high CSI.
    - "Intelligent design provides a sufficient causal explanation for the origin of large amounts of information, since we have considerable experience of intelligent agents generating informational configurations of matter." [80]
3. Find rare solutions to complex problems.
    - "Agents can arrange matter with distant goals in mind. In their use of language, they routinely 'find' highly isolated and improbable functional sequences amid vast spaces of combinatorial possibilities." [81]
    - "Intelligent agents have foresight. Such agents can determine or select functional goals before they are physically instantiated. They can devise or select material means to accomplish those ends from among an array of possibilities. They can then actualize those goals in accord with a preconceived design plan or set of functional requirements. Rational agents can constrain combinatorial space with distant information-rich outcomes in mind." [58]
4. Implement a top-down design where multiple parts are coordinated to accomplish a purpose or goal, including a hierarchical design, wherein subcomponents are coordinated to contribute to higher functions at each level.
    - "Design is the purposeful arrangement of parts. Rational agents can coordinate pieces into a larger system ... to accomplish a purpose. Although sometimes the purpose of the system is obscure to an observer who stumbles upon it, so the design goes unrecognized, usually the purpose can be discerned by examining the system. What's more, the arrangement of the pieces is frequently one that is quite unlikely to occur by chance." [82]
    - "Two ... design practices [are] commonly used in nearly all design and engineering. Together, these work like 'divide and conquer' for complex systems design. One is known as separation of concerns, wherein a large problem is solved by breaking it into separate subproblems that are easier to solve. Different concerns are solved by different subsystems. ... Human engineers apply this practice iteratively, top-down. Each subproblem is broken into still more subproblems, and so on. This is how a design hierarchy is made. This is a normal consequence of the problem of cascading problems ... Purpose is always defined top-down..." [83]
    - "All inventions, whether common or technical, share the characteristic hierarchical structure ... Consider my writing of this [argument]... Each of these main points will have at least one section devoted to it. The crafting of each of these sections requires writing several paragraphs that work together, each making a more specific point. Likewise, the point of each paragraph is conveyed by constructing several sentences that convey even more specific points in a coordinated way. All of these points are designed to achieve the top-level goal. Each occupies its own position in an organized hierarchy, working together with points at the same level to make a point at the next higher level, all of which contribute to the big point. And of course, the hierarchy goes all the way down from the sentence level to the elementary constituents of

written communication—the letters of the alphabet. We conceive of writing projects in a top-down way, but we accomplish them in a bottom-up way—arranging letters to spell words, in order to form sentences, in order to build paragraphs, in order to achieve our main writing objective. This hierarchical organization is a hallmark of invention, present in everything from three-course dinners to communications satellites. I refer to it as functional coherence—the coordinated combination of functions over a succession of levels to achieve a single top-level function. Intuitively, we all know that nothing but intelligent action can construct things in this way." [84]

- "The reason we perceive purpose in inventions—busy wholes and whole projects—is precisely the reason they can't occur by accident: they exhibit an organized functional coherence that can only come from deliberate, intelligent action. They are conceived from the top down..." [85]
- "Top-down design (TDD) is an efficient product design method for bridging the gap between the product design specification and components detail design. The task of TDD is to transfer criteria down from the top-level of the product's structure to all of the affected subsystems until base components are defined." [86]

5. Produce irreducibly complex systems (such as machines).

    - "In all irreducibly complex systems in which the cause of the system is known by experience or observation, intelligent design or engineering played a role [in] the origin of the system." [54]
    - "[W]hat accounts for the machinery itself? In our uniform, unbroken experience, what is the only explanation for the purposeful arrangement of parts? ... [B]ecause minds can choose to order whatever is within their power to manipulate, intelligence is detected by perceiving a purposeful arrangement of parts ... the effects of a mind can be recognized by the purposeful arrangement of parts." [87]

6. Reuse similar functional components in different systems.

    - "An intelligent cause may reuse or redeploy the same module in different systems, without there necessarily being any material or physical connection between those systems. Even more simply, intelligent causes can generate identical patterns independently. ... If we suppose that an intelligent designer constructed organisms using a common set of polyfunctional genetic modules — just as human designers, for instance, may employ the same transistor or capacitor in a car radio or a computer, devices that are not 'homologous' as artifacts — then we can explain why we find the 'same' genes expressed in the development of what are very different organisms." [88]
    - "According to this [evolutionary] argument, the Darwinian principle of common ancestry predicts such common features, vindicating the theory of evolution. One problem with this line of argument is that people recognized common features long before Darwin, and they attributed them to common design. Just as we find certain features cropping up again and again in the realm of human technology (e.g., wheels and axles on wagons, buggies and cars), so too we can expect an intelligent designer to reuse good design ideas in a variety of situations where they work." [55]

7. Optimize competing constraints.

    - "We also know that designers often seek to optimize one or more objectives, and where they seek to optimize several, they often do so by balancing competing objectives and by making judicious compromises or 'elegant' tradeoffs between them." [66]
    - "When a new design removes one of these annoyances, it more likely than not fails to address some others or adds a new one of its own. This is what makes engineering and inventing so challenging. All design involves conflicting objectives and hence compromise, and the best designs will always be those that come up with the best compromise." [89]

8. Include components for the purpose of performing a function.

    - "[I]ntelligent agents tend to produce functional objects ...intelligent agents produce structures that have a purpose. It seems unlikely that an intelligent agent would design something that does absolutely nothing. ... design encourages researchers to investigate functions..." [90]

- "Since non-coding regions do not produce proteins, Darwinian biologists have been dismissing them for decades as random evolutionary noise or 'junk DNA.' From an ID perspective, however, it is extremely unlikely that an organism would expend its resources on preserving and transmitting so much 'junk'." [91]
- "[Intelligent] design is not a science stopper. Indeed, design can foster inquiry where traditional evolutionary approaches obstruct it. Consider the term 'junk DNA.' Implicit in this term is the view that because the genome of an organism has been cobbled together through a long, undirected evolutionary process, the genome is a patchwork of which only limited portions are essential to the organism. Thus on an evolutionary view we expect a lot of useless DNA. If, on the other hand, organisms are designed, we expect DNA, as much as possible, to exhibit function." [92]

9. Rapidly generate large amounts of new information, including generating new systems which are fully formed and different from previous systems.

    - "We know from experience that intelligent agents often conceive of plans prior to the material instantiation of the systems that conform to the plans—that is, the intelligent design of a blueprint often precedes the assembly of parts in accord with a blueprint or preconceived design plan." [80]
    - "'Top-down' causation begins with a basic architecture, blueprint, or plan and then proceeds to assemble parts in accord with it. The blueprint stands causally prior to the assembly and arrangement of the parts. But where could such a blueprint come from? One possibility involves a mental mode of causation. Intelligent agents often conceive of plans prior to their material instantiation — that is, the preconceived design of a blueprint often precedes the assembly of parts in accord with it. An observer touring the parts section of a General Motors plant will see no direct evidence of a prior blueprint for GM's new models, but will perceive the basic design plan immediately upon observing the finished product at the end of the assembly line. Designed systems, whether automobiles, airplanes, or computers, invariably manifest a design plan that preceded their first material instantiation. But the parts do not generate the whole. Rather, an idea of the whole directed the assembly of the parts." [58]
    - "Intelligent agents sometimes produce material entities through a series of gradual modifications (as when a sculptor shapes a sculpture over time). Nevertheless, intelligent agents also have the capacity to introduce complex technological systems into the world fully formed. Often such systems bear no resemblance to earlier technological systems—their invention occurs without a material connection to earlier, more rudimentary technologies. When the radio was first invented, it was unlike anything that had come before, even other forms of communication technology. For this reason, although intelligent agents need not generate novel structures abruptly, they can do so." [58]

1. Nakagawa S, Armitage D, Froese T, Yang Y, Lagisz M (2025) Poor hypotheses and research waste in biology: learning from a theory crisis in psychology. BMC Biology 23(1):33. doi:10.1186/s12915-025-02134-w
2. Lewis R (1988) Biology: A hypothetico-deductive science. The American Biology Teacher 50(6):362–366. doi:10.2307/4448762
3. Gray R (2014) The distinction between experimental and historical sciences as a framework for improving classroom inquiry. Science Education 98(2):327–341. doi:10.1002/sce.21098
4. Cleland C (2002) Methodological and epistemic differences between historical science and experimental science. Philosophy of Science 69(3):474–496. doi:10.1086/342455
5. Cleland C (2001) Historical science, experimental science, and the scientific method. Geology 29(11):987. doi:10.1130/0091-7613(2001)029%3C0987:hsesat%3E2.0.co;2
6. Dembski W (2002) Intelligent design as a theory of information. In: Pennock R, ed. Intelligent Design Creationism and Its Critics: Philosophical, Theological, and Scientific Perspectives. MIT Press (Cambridge, MA), pp 553–573
7. Landenmark H, Forgan D, Cockell C (2015) An estimate of the total DNA in the biosphere. PLoS Biology 13(6):e1002168. doi:10.1371/journal.pbio.1002168
8. Thorvaldsen S, Hössjer O (2020) Using statistical methods to model the fine-tuning of molecular machines and systems. Journal of Theoretical Biology 501(110352):110352. doi:10.1016/j.jtbi.2020.110352
9. Gleick J (2011) The Information: A History, A Theory, A Flood. Pantheon Books (New York, NY)
10. Lloyd S (2007). Seth lloyd—life: What a concept! https://www.edge.org/conversation/seth_lloyd-seth-lloyd%E2%80%94life-what-a-concept. Accessed online
11. Shannon C (1948) A mathematical theory of communication. The Bell System Technical Journal 27(3):379–423. doi:10.1002/j.1538-7305.1948.tb01338.x
12. Griffiths P, Pocheville A, Calcott B, Stotz K, Kim H, Knight

R (2015) Measuring causal specificity. Philosophy of Science 82(4):529–555. doi:10.1086/682914
13. Dretske F (1981) Knowledge And The Flow Of Information. MIT Press (London, England)
14. Hazen R, Griffin P, Carothers J, Szostak J (2007) Functional information and the emergence of biocomplexity. Proceedings of the National Academy of Sciences (USA) 104(Suppl 1):8574–8581. doi:10.1073/pnas.0701744104
15. Szostak J (2003) Functional information: Molecular messages. Nature 423(6941):689. doi:10.1038/423689a
16. Kolmogorov A (1968) Three approaches to the quantitative definition of information. International Journal of Computer Mathematics 2(1–4):157–168. doi:10.1080/00207166808803030
17. Chaitin G (1975) A theory of program size formally identical to information theory. Journal of the ACM 22(3):329–340. doi:10.1145/321892.321894
18. Thorvaldsen S, Øhrstrøm P, Hössjer O (2024) The representation, quantification, and nature of genetic information. Synthese 204(1). doi:10.1007/s11229-024-04613-z
19. Montañez G (2018) A unified model of complex specified information. BIO-Complexity 2018(4):1–26. doi:10.5048/bio-c.2018.4
20. Dembski W (1998) The Design Inference: Eliminating Chance Through Small Probabilities. Cambridge University Press (Cambridge, England)
21. Dembski W, Ewert W (2023) The Design Inference: Eliminating Chance Through Small Probabilities (2nd Edition). Discovery Institute Press (Seattle, WA)
22. Miller B (2026) Framing dembski and ewert's specification model for design detection within montañez's canonical specified complexity formalism. BIO-Complexity 2026(1):1–8. doi:10.5048/BIO-C.2026.1
23. Dembski W (2002) No Free Lunch: Why Specified Complexity Cannot Be Purchased Without Intelligence. Roman & Littlefield (Lanham, MD)
24. Dembski W, Marks R (2009) Bernoulli's principle of insufficient reason and conservation of information in computer search. In: 2009 IEEE International Conference on Systems, Man and Cybernetics, 2647–2652. doi:10.1109/icsmc.2009.5346119
25. Dembski W, Marks RJ I (2009) Conservation of information in search: Measuring the cost of success. IEEE Transactions on Systems, Man, and Cybernetics. Part A, Systems and Humans 39(5):1051–1061. doi:10.1109/tsmca.2009.2025027
26. Ewert W, Marks R, Dembski W (2013) Conservation of information in relative search performance. In: IEEE 45th Southeastern Symposium on System Theory, Waco, TX, USA, 2013, 71–74. doi:10.1109/ssst.2013.6524963
27. Ewert W, Marks RJ I (2017) Conservation of information in coevolutionary searches. BIO-Complexity 2017(1):1–15. doi:10.5048/bio-c.2017.1
28. Dembski W (2010) The search for a search: Measuring the information cost of higher level search. Journal of Advanced Computational Intelligence and Intelligent Informatics 14(5):475–486. doi:10.20965/jaciii.2010.p0475
29. Dembski W (2025) The law of conservation of information: Search processes only redistribute existing information. BIO-Complexity 2(2025):1–58. doi:10.5048/BIO-C.2025.2
30. Williams J, Tadesse A, Sam T, Sun H, Montañez G (2020) Limits of transfer learning. In: Nicosia G, V O, Giesselbach S, Pardalos M, Umeton R, eds. Machine Learning, Optimization, And Data Science. Springer International Publishing (Cham), pp 382–393. doi:10.1007/978-3-030-64580-9_32
31. Maina-Kilaas A, Montanez G, Hom C, Ginta K, Lay C (2021) The hero's dilemma: Survival advantages of intention perception in virtual agent games. In: 2021 IEEE Conference on Games (CoG), Copenhagen, Denmark, 2021, 1–8. doi:10.1109/cog52621.2021.9619071
32. Maina-Kilaas A, Hom C, Ginta K, Montanez G (2021) The predator's purpose: Intention perception in simulated agent environments. In: 2021 IEEE Congress on Evolutionary Computation (CEC), Kraków, Poland, 2021, 1619–1626. doi:10.1109/cec45853.2021.9504885
33. Kamath A, Zhao J, Grisanti N, Montañez G (2022) The gopher grounds: Testing the link between structure and function in simple machines. In: Proceedings of the 14th International Conference on Agents and Artificial Intelligence, 528–540. doi:10.5220/0010900900003116
34. Hom C, Maina-Kilaas A, Ginta K, Lay C, Montañez G (2021) The gopher's gambit: Survival advantages of artifact-based intention perception. In: Proceedings of the 13th International Conference on Agents and Artificial Intelligence, 205–215. doi:10.5220/0010207502050215
35. Ewert W, Dembski W, Marks R (2009) Evolutionary synthesis of nand logic: Dissecting a digital organism. In: 2009 IEEE International Conference on Systems, Man and Cybernetics, San Antonio, TX, USA, 2009, 3047–3053. doi:10.1109/icsmc.2009.5345941
36. Ewert W, Montanez G, Dembski W, Marks R (2010) Efficient per query information extraction from a hamming oracle. In: 2010 42nd Southeastern Symposium on System Theory (SSST), Tyler, TX, USA, 2010, 290–297. doi:10.1109/ssst.2010.5442816
37. Ewert W, Dembski W, Marks R (2012) Climbing the steiner tree—sources of active information in a genetic algorithm for solving the euclidean steiner tree problem. BIO-Complexity 2012(1):1–14. doi:10.5048/BIO-C.2012.1
38. Ewert W, Dembski W, Gauger A, Marks RJ I (2012) Time and information in evolution. BIO-Complexity 2012(4):1–7. doi:10.5048/bio-c.2012.4
39. Ewert W, Dembski W, Marks RJ I (2013) Active information in metabiology. BIO-Complexity 2013(4):1–10. doi:10.5048/bio-c.2013.4
40. Ewert W (2014) Digital irreducible complexity: A survey of irreducible complexity in computer simulations. BIO-Complexity 2014(1):1–10. doi:10.5048/bio-c.2014.1
41. Montañez G, Ewert W, Dembski W, Marks RJ I (2010) A vivisection of the ev computer organism: Identifying sources of active information. BIO-Complexity 2010(3):1–6. doi:10.5048/bio-c.2010.3
42. Ewert W (2015) Overabundant mutations help potentiate evolution: The effect of biologically realistic mutation rates on computer models of evolution. BIO-Complexity 2015(4):1–11. doi:10.5048/bio-c.2015.1
43. Lauw J, Macias D, Trikha A, Vendemiatti J, Montañez G (2020) The bias-expressivity trade-off. In: Proceedings of the 12th International Conference on Agents and Artificial Intelligence (ICAART 2020) - Volume 2, 141–150. doi:10.5220/0008959201410150
44. Montañez G, Hayase J, Lauw J, Macias D, Trikha A, Vendemiatti J (2019) The futility of bias-free learning and search. In: J L, Bailey J, eds. AI 2019: Advances in Artificial Intelligence. Springer (Cham), pp 277–288. doi:10.1007/978-3-030-35288-2_23
45. Bartlett J (2020) Measuring active information in biological systems. BIO-Complexity 2020(2):1–11. doi:10.5048/bio-c.2020.2
46. Díaz Pachón D, Marks RJ I (2020) Active information requirements for fixation on the wright-fisher model of population genetics. BIO-Complexity 2020(4):1–6. doi:10.5048/bio-c.2020.4
47. Ewert W, Dembski W, Marks RJ I (2015) Measuring meaningful information in images: algorithmic spec-

ified complexity. IET Computer Vision 9(6):884–894. doi:10.1049/iet-cvi.2014.0141
48. Ewert W, Dembski W, Marks R (2015) Algorithmic specified complexity in the game of life. IEEE Transactions on Systems, Man, and Cybernetics. Systems 45(4):584–594. doi:10.1109/tsmc.2014.2331917
49. Ewert W, Marks R, Dembski W (2013) On the improbability of algorithmic specified complexity. In: 45th Southeastern Symposium on System Theory, Waco, TX, USA, 2013, 68–70. doi:10.1109/ssst.2013.6524962
50. Marks RJ I, Dembski W, Ewert W (2017) Introduction to Evolutionary Informatics. World Scientific (Singapore)
51. Behe M (1996) Darwin's Black Box: The Biochemical Challenge To Evolution. The Free Press (New York, NY)
52. Darwin C (1859) On The Origin Of Species. John Murray (London (UK))
53. Behe M (2006) Darwin's Black Box: The Biochemical Challenge To Evolution (Reprint). The Free Press (New York, NY)
54. Minnich S, Meyer S (2004) Genetic analysis of coordinate flagellar and type III regulatory circuits in pathogenic bacteria. In: Collins M, Brebbia C, eds. Proceedings of the Second International Conference on Design & Nature, Rhodes Greece. WIT Press (Southampton, UK), pp 295–304
55. Dembski W, Witt J (2010) Intelligent Design Uncensored: An Easy-To-Understand Guide To The Controversy. InterVarsity Press (Downers Grove, IL)
56. Yik W, Serafini L, Lindsey T, Montañez G (2022) Identifying bias in data using two-distribution hypothesis tests. In: Proceedings of the 2022 AAAI/ACM Conference on AI, Ethics, and Society, 831–844. doi:10.1145/3514094.3534169
57. Hom C, Yik W, Montañez G (2023) Finite-sample bounds for two-distribution hypothesis tests. In: 2023 IEEE 10th International Conference on Data Science and Advanced Analytics (DSAA), Thessaloniki, Greece, 2023, 1–11. doi:10.1109/dsaa60987.2023.10302643
58. Meyer S (2013) Darwin's Doubt: The Explosive Origin Of Animal Life And The Case For Intelligent Design. Harper Collins (San Francisco, CA)
59. Meyer S, Nelson P, Moneymaker J, Minnich S, Seelke R (2013) Explore Evolution: The Arguments For And Against Neo-Darwinism. Hill House (Melbourne, Australia)
60. Meyer S (2004) The origin of biological information and the higher taxonomic categories. Proceedings of the Biological Society of Washington 117:213–239. doi:10.5281/zenodo.13648071
61. Meyer S (1999) The scientific status of intelligent design: The methodological equivalence of naturalistic and non-naturalistic origins theories. In: Science And Evidence For Design In The Universe, The Proceedings Of The Wethersfield Institute, 151–212. Ignatius Press, San Francisco, CA
62. Secord J, editor (1997) Notes to chapters 10-26. In: Secord J, ed. Principles of Geology. Penguin (London), pp 430
63. Lyell C, Deshayes G, Murray J (2022) Principles Of Geology; Being An Attempt To Explain The Former Changes Of The Earth's Surface By Reference To Causes Now In Operation. Legare Street Press (New York, NY)
64. Lipton P (1991) Inference To The Best Explanation. Routledge (London, England)
65. Abel D (2009) The universal plausibility metric (UPM) & principle (UPP). Theoretical Biology & Medical Modelling 6(1):27. doi:10.1186/1742-4682-6-27
66. Meyer S (2009) Signature In The Cell: DNA And The Evidence For Intelligent Design. HarperOne (San Francisco, CA)
67. Axe D (2004) Estimating the prevalence of protein sequences adopting functional enzyme folds. Journal of Molecular Biology 341(5):1295–1315. doi:10.1016/j.jmb.2004.06.058
68. Whitman W, Coleman D, Wiebe W (1998) Prokaryotes: the unseen majority. Proceedings of the National Academy of Sciences (USA) 95(12):6578–6583. doi:10.1073/pnas.95.12.6578
69. Miller K (2008) Only A Theory: Evolution And The Battle For America's Soul. Viking Books (New York, NY)
70. Pennock R (2000) Tower Of Babel: The Evidence Against The New Creationism. Bradford Books (Cambridge, MA)
71. Dembski W (1998) Introduction. In: Dembski W, ed. Mere Creation: Science, Faith, And Intelligent Design. InterVarsity Press (Downers Grove, IL), pp 13–30
72. Meyer S (2021) Return Of The God Hypothesis: Three Scientific Discoveries That Reveal The Mind Behind The Universe. HarperOne (San Francisco, CA)
73. Thaxton C, Bradley W, Olsen R (1984) The Mystery Of Life's Origins. Lewis and Stanley (Dallas, TX)
74. Axe D (2000) Extreme functional sensitivity to conservative amino acid changes on enzyme exteriors. Journal of Molecular Biology 301(3):585–595. doi:10.1006/jmbi.2000.3997
75. Institute D (2024). ID 3.0 research program. https://www.discovery.org/id/research/. Accessed online
76. of Sciences NA, of Behavioral D, Sciences S, Education, on Science Education B, on Teaching Evolution WG (1998) Teaching About Evolution And The Nature Of Science. National Academies Press (Washington, DC). doi:10.17226/5787
77. Kosso P (2011) A Summary Of Scientific Method. Springer (Dordrecht, Netherlands). doi:10.1007/978-94-007-1614-8
78. Kemper G, Kemper H, Luskin C (2013) Discovering Intelligent Design: A Journey Into The Scientific Evidence. Discovery Institute (Seattle, WA)
79. Eberlin M (2019) Foresight: How The Chemistry Of Life Reveals Planning And Purpose. Discovery Institute (Seattle, WA)
80. Meyer S, Ross M, Nelson P, Chien P (2003) The cambrian explosion: Biology's big bang. In: Campbell J, Meyer S, eds. Darwinism, Design, And Public Education. Michigan State University Press (East Lansing, MI), pp 323–402
81. Meyer S (2004) The cambrian information explosion: Evidence for intelligent design. In: Dembski W, M R, eds. Debating Design: From Darwin To DNA. Cambridge University Press (Cambridge, MA), pp 371–391
82. Behe M (2007) The Edge of Evolution: The Search for the Limits of Darwinism. Free Press (New York, NY)
83. Laufmann S, Glicksman H (2022) Your Designed Body. Discovery Institute (Seattle, WA)
84. Axe D (2017) Three good reasons for people of faith to reject darwin's explanation of life. In: Moreland J, Meyer S, C S, Gauger A, Grudem W, eds. Theistic Evolution: A Scientific, Philosophical, And Theological Critique. Crossway (Wheaton, IL), pp 83–104
85. Axe D (2016) Undeniable: How Biology Confirms Our Intuition That Life Is Designed. Harper Collins (San Francisco, CA)
86. Chu D, Chu X, Lv G, Su Y, Chen D (2014) Multi-skeleton model for top-down design of complex modular products. In: 2014 IEEE International Conference on Industrial Engineering and Engineering Management, 968–972. doi:10.1109/ieem.2014.7058782
87. Behe M (2019) Darwin Devolves: The New Science About DNA That Challenges Evolution. HarperOne (New York, NY)
88. Nelson P, Wells J (2003) Homology in biology: Problem for naturalistic science and prospect for intelligent design. In: Campbell J, Meyer S, eds. Darwinism, Design, And Public

Education. Michigan State University Press (East Lansing, MI), pp 303–322
89. Petroski H (1998) Invention By Design; How Engineers Get From Thought To Thing. Harvard University Press (London, England). doi:10.2307/j.ctv1pncnzm
90. Luskin C (2008) Finding intelligent design in nature. In: House HW, ed. Intelligent Design 101: Leading Experts Explain The Key Issues. Kregel (Grand Rapids, MI), pp 67–111
91. Wells J (2004) Using intelligent design theory to guide scientific research. Progress in Complexity, Information, and Design 3.1(2):1–14
92. Dembski W (1998) Intelligent science and design. First Things 86:21–27
93. Macnab R (1987) Flagella. In: Neidhardt F, Ingraham J, KB L, Magasanik B, Schaechter M, Umbarger H, eds. Escherichia coli And Salmonella typhimurium: Cellular And Molecular Biology, Volume 1. American Society for Microbiology (Washington DC), pp 70–83
94. McLatchie J (2024) Phylogenetic challenges to the evolutionary origin of the eukaryotic cell cycle. BIO-Complexity 2024(4):1–19. doi:10.5048/bio-c.2024.4
95. Pallen M, Matzke N (2006) From the origin of species to the origin of bacterial flagella. Nature Reviews Microbiology 4(10):784–790. doi:10.1038/nrmicro1493
96. Rajagopala S, Titz B, Goll J, Parrish J, Wohlbold K, McKevitt M, Palzkill T, Mori H, Finley RL J, Uetz P (2007) The protein network of bacterial motility. Molecular Systems Biology 3(1):128. doi:10.1038/msb4100166
97. Wolf Y, Koonin E (2007) On the origin of the translation system and the genetic code in the RNA world by means of natural selection, exaptation, and subfunctionalization. Biology Direct 2(1):14. doi:10.1186/1745-6150-2-14
98. Sauer R, Milla M, Waldburger C, Brown B, Schildbach J (1996) Sequence determinants of folding and stability for the P22 arc repressor dimer. FASEB Journal 10(1):42–48. doi:10.1096/fasebj.10.1.8566546
99. Durston K, Chiu D, Abel D, Trevors J (2007) Measuring the functional sequence complexity of proteins. Theoretical Biology & Medical Modelling 4(1):47. doi:10.1186/1742-4682-4-47
100. Gauger A, Ebnet S, Fahey P, Seelke R (2010) Reductive evolution can prevent populations from taking simple adaptive paths to high fitness. BIO-Complexity 2010(2):1–9. doi:10.5048/bio-c.2010.2
101. Axe D, Gauger A (2011) The evolutionary accessibility of new enzymes functions: A case study from the biotin pathway. BIO-Complexity 2011(1). doi:10.5048/bio-c.2011.1
102. Tian P, Best R (2017) How many protein sequences fold to a given structure. A coevolutionary analysis. Biophysical Journal 113(8):1719–1730. doi:10.1016/j.bpj.2017.08.039
103. Miller B (2024) A percolation theory analysis of continuous functional paths in protein sequence space affirms previous insights on the optimization of proteins for adaptability. PLoS One 19(12):e0314929. doi:10.1371/journal.pone.0314929
104. Reeves M, Gauger A, Axe D (2014) Enzyme families—shared evolutionary history or shared design. A study of the GABA-aminotransferase family. BIO-Complexity 2014(4):1–16. doi:10.5048/BIO-C.2014.4
105. Lonnig WE (2004) Dynamic genomes, morphological stasis, and the origin of irreducible complexity. In: Parisi V, Fonzo VD, Aluffi-Pentini F, eds. Dynamical Genetics. Research Signpost (Kerala, India), pp 101–119
106. Ochoa C (2025) Patterns and rates: Challenging gradualism and punctuated equilibrium. In: Hierarchical Evolutionary-Developmental Theory, Evolutionary Biology – New Perspectives on Its Development 9, 245–281. Springer, Cham, Switzerland
107. Bechly G, Meyer S (2017) The fossil record and universal common ancestry. In: Moreland J, Meyer S, C S, Gauger A, Grudem W, eds. Theistic Evolution: A Scientific, Philosophical, And Theological Critique. Crossway Books (Wheaton, IL), pp 331–362
108. Barnes R, etc, Calow P, Olive P, Dove M (2000) The Invertebrates. Blackwell Science (Philadelphia, PA)
109. Erwin D, Valentine J (2013) The Cambrian Explosion: The Construction Of Animal Biodiversity. Roberts & Company (Greenwood Village, CO)
110. Feduccia A (1995) Explosive evolution in tertiary birds and mammals. Science 267(5198):637–638. doi:10.1126/science.267.5198.637
111. Feduccia A (2020) Romancing The Birds And Dinosaurs. Brown Walker Press (Irvine, CA)
112. Cooper A, Fortey R (1998) Evolutionary explosions and the phylogenetic fuse. Trends in Ecology & Evolution 13(4):151–156. doi:10.1016/s0169-5347(97)01277-9
113. Gill F (2006) Ornithology (3rd Ed.). W.H. Freeman (New York, NY)
114. Crane P, Friis E, Pedersen K (1995) The origin and early diversification of angiosperms. Nature 374(6517):27–33. doi:10.1038/374027a0
115. De Bodt S, Maere S, Van de Peer Y (2005) Genome duplication and the origin of angiosperms. Trends in Ecology & Evolution 20(11):591–597. doi:10.1016/j.tree.2005.07.008
116. Ward P (2006) Out Of Thin Air: Dinosaurs, Birds, And Earth's Ancient Atmosphere. Joseph Henry Press (Washington DC)
117. Martin R (2015) Missing Links: Evolutionary Concepts And Transitions Through Time. McDonald & Woodward Publishing Company (Granville, OH)
118. O'Leary M, Bloch J, Flynn J, Gaudin T, Giallombardo A, Giannini N, Goldberg S, Kraatz B, Luo ZX, Meng J, Ni X, Novacek M, Perini F, Randall Z, Rougier G, Sargis E, Silcox M, Simmons N, Spaulding M, Velazco P, Weksler M, Wible J, Cirranello A (2013) Response to comment on "the placental mammal ancestor and the post-k-pg radiation of placentals.". Science 341(6146):613. doi:10.1126/science.1238162
119. Godinot M (2015) Fossil record of the primates from the paleocene to the oligocene. In: Handbook Of Paleoanthropology, 1137–1259. Springer Berlin Heidelberg, Berlin, Heidelberg. doi:10.1007/978-3-642-39979-4_68
120. Mayr E (2004) What Makes Biology Unique? Considerations On The Autonomy Of A Scientific Discipline. Cambridge University Press (Cambridge, England)
121. Luskin C (2022) Evolutionary models of palaeoanthropology, genetics and psychology fail to account for human origins: A review. In: Niekerk FV, Vorster N, eds. Science And Faith In Dialogue. Aosis (Cape Town, South Africa), pp 243–281
122. Miller B (2022) Engineering principles better explain biological systems than evolutionary theory. In: Niekerk FV, Vorster N, eds. Science And Faith In Dialogue. Aosis (Cape Town, South Africa), pp 175–211
123. Ewert W (2018) The dependency graph of life. BIO-Complexity 2018(3):1–27. doi:10.5048/bio-c.2018.3
124. Ewert W (2023) Aminograph analysis of the auditory protein prestin from bats and whales reveals a dependency-graph signal that is missed by the standard convergence model. BIO-Complexity 2023(2):1–15. doi:10.5048/BIO-C.2023.1
125. Morris S (2009) Life's Solution: Inevitable Humans In A Lonely Universe. Cambridge University Press (Cambridge, England). doi:10.1017/cbo9780511535499

126. Christin PA, Weinreich D, Besnard G (2010) Causes and evolutionary significance of genetic convergence. Trends in Genetics 26(9):400–405. doi:10.1016/j.tig.2010.06.005
127. Li Y, Liu Z, Shi P, Zhang J (2010) The hearing gene prestin unites echolocating bats and whales. Current Biology 20(2):R55–6. doi:10.1016/j.cub.2009.11.042
128. Jones G (2010) Molecular evolution: gene convergence in echolocating mammals. Current Biology 20(2):R62–4. doi:10.1016/j.cub.2009.11.059
129. Quiring R, Walldorf U, Kloter U, Gehring W (1994) Homology of the eyeless gene of drosophila to the small eye gene in mice and aniridia in humans. Science 265(5173):785–789. doi:10.1126/science.7914031
130. Wake D, Wake M, Specht C (2011) Homoplasy: from detecting pattern to determining process and mechanism of evolution. Science 331(6020):1032–1035. doi:10.1126/science.1188545
131. Aguinaldo A, Turbeville J, Linford L, Rivera M, Garey J, Raff R, Lake J (1997) Evidence for a clade of nematodes, arthropods and other moulting animals. Nature 387(6632):489–493. doi:10.1038/387489a0
132. Mushegian A, Garey J, Martin J, Liu L (1998) Large-scale taxonomic profiling of eukaryotic model organisms: a comparison of orthologous proteins encoded by the human, fly, nematode, and yeast genomes. Genome Research 8(6):590–598. doi:10.1101/gr.8.6.590
133. Doolittle W (1999) Phylogenetic classification and the universal tree. Science 284(5423):2124–2129. doi:10.1126/science.284.5423.2124
134. Degnan J, Rosenberg N (2009) Gene tree discordance, phylogenetic inference and the multispecies coalescent. Trends in Ecology & Evolution 24(6):332–340. doi:10.1016/j.tree.2009.01.009
135. Lawton G (2009) Axing darwin's tree. New Scientist 201(2692):34–39. doi:10.1016/s0262-4079(09)60231-1
136. Bapteste E, van Iersel L, Janke A, Kelchner S, Kelk S, McInerney J, Morrison D, Nakhleh L, Steel M, Stougie L, Whitfield J (2013) Networks: expanding evolutionary thinking. Trends in Genetics 29(8):439–441. doi:10.1016/j.tig.2013.05.007
137. Teeling E, Hedges S (2013) Making the impossible possible: rooting the tree of placental mammals. Molecular biology and evolution 30(9):1999–2000. doi:10.1093/molbev/mst118
138. Rokas A (2013) My oldest sister is a sea walnut. Science 342(6164):1327–1329. doi:10.1126/science.1248424
139. Jarvis E, Mirarab S, Aberer A, Li B, Houde P, Li C, Ho S, Faircloth B, Nabholz B, Howard J, Suh A, Weber C, da Fonseca R, Li J, Zhang F, Li H, Zhou L, Narula N, Liu L, Ganapathy G, Boussau B, Bayzid M, Zavidovych V, Subramanian S, Gabaldón T, Capella-Gutiérrez S, Huerta-Cepas J, Rekepalli B, Munch K, Schierup M, Lindow B, Warren W, Ray D, Green R, Bruford M, Zhan X, Dixon A, Li S, Li N, Huang Y, Derryberry E, Bertelsen M, Sheldon F, Brumfield R, Mello C, Lovell P, Wirthlin M, Schneider M, Prosdocimi F, Samaniego J, Vargas Velazquez A, Alfaro-Núñez A, Campos P, Petersen B, Sicheritz-Ponten T, Pas A, Bailey T, Scofield P, Bunce M, Lambert D, Zhou Q, Perelman P, Driskell A, Shapiro B, Xiong Z, Zeng Y, Liu S, Li Z, Liu B, Wu K, Xiao J, Yinqi X, Zheng Q, Zhang Y, Yang H, Wang J, Smeds L, Rheindt F, Braun M, Fjeldsa J, Orlando L, Barker F, Jønsson K, Johnson W, Koepfli KP, O'Brien S, Haussler D, Ryder O, Rahbek C, Willerslev E, Graves G, Glenn T, McCormack J, Burt D, Ellegren H, Alström P, Edwards S, Stamatakis A, Mindell D, Cracraft J, Braun E, Warnow T, Jun W, Gilbert M, Zhang G (2014) Whole-genome analyses resolve early branches in the tree of life of modern birds. Science 346(6215):1320–1331. doi:10.1126/science.1253451
140. Liebeskind B, Hillis D, Zakon H, Hofmann H (2016) Complex homology and the evolution of nervous systems. Trends in Ecology & Evolution 31(2):127–135. doi:10.1016/j.tree.2015.12.005
141. Parins-Fukuchi C, Stull G, Smith S (2021) Phylogenomic conflict coincides with rapid morphological innovation. Proceedings of the National Academy of Sciences (USA) 118(19):e2023058118. doi:10.1073/pnas.2023058118
142. Dávalos L, Cirranello A, Geisler J, Simmons N (2012) Understanding phylogenetic incongruence: lessons from phyllostomid bats. Biological Reviews of the Cambridge Philosophical Society 87(4):991–1024. doi:10.1111/j.1469-185X.2012.00240.x
143. Lewis G, Barnes L (2020) A Fortunate Universe: Life In A Finely Tuned Cosmos. Cambridge University Press (Cambridge, England)
144. Leslie J (1996) Universes. Routledge (London, England)
145. Guth A (1981) Inflationary universe: A possible solution to the horizon and flatness problems. Physical Review D: Particles and Fields 23(2):347–356. doi:10.1103/physrevd.23.347
146. Davies P (1982) The Accidental Universe. Cambridge University Press (Cambridge, England)
147. Penrose R (2009) The Emperor's New Mind: Concerning Computers, Minds And The Laws Of Physics. Vintage (London, England)
148. Powell B (2005). Explore as much as we can: Nobel prize winner charles townes on evolution, intelligent design, and the meaning of life. UC berkeley news center,. https://newsarchive.berkeley.edu/news/media/releases/2005/06/17_townes.shtml. Accessed online
149. Wells J (2011) The Myth Of Junk DNA. Discovery Institute (Seattle, WA)
150. Consortium EP (2007) Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project. Nature 447(7146):799–816. doi:10.1038/nature05874
151. Consortium EP (2012) An integrated encyclopedia of DNA elements in the human genome. Nature 489(7414):57–74. doi:10.1038/nature11247
152. von Sternberg R (2002) On the roles of repetitive DNA elements in the context of a unified genomic-epigenetic system. Annals of the New York Academy of Sciences 981(1):154–188. doi:10.1111/j.1749-6632.2002.tb04917.x
153. Hakimi MA, Bochar D, Schmiesing J, Dong Y, Barak O, Speicher D, Yokomori K, Shiekhattar R (2002) A chromatin remodelling complex that loads cohesin onto human chromosomes. Nature 418(6901):994–998. doi:10.1038/nature01024
154. Shapiro J, von Sternberg R (2005) Why repetitive DNA is essential to genome function. Biological Reviews of the Cambridge Philosophical Society 80(2):227–250. doi:10.1017/s1464793104006657
155. Conley A, Piriyapongsa J, Jordan I (2008) Retroviral promoters in the human genome. Bioinformatics 24(14):1563–1567. doi:10.1093/bioinformatics/btn243
156. Faulkner G, Kimura Y, Daub C, Wani S, Plessy C, Irvine K, Schroder K, Cloonan N, Steptoe A, Lassmann T, Waki K, Hornig N, Arakawa T, Takahashi H, Kawai J, Forrest A, Suzuki H, Hayashizaki Y, Hume D, Orlando V, Grimmond S, Carninci P (2009) The regulated retrotransposon transcriptome of mammalian cells. Nature Genetics 41(5):563–571. doi:10.1038/ng.368
157. Moleirinho A, Seixas S, Lopes A, Bento C, Prata M, Amorim A (2013) Evolutionary constraints in the β-globin cluster: the signature of purifying selection at the δ-globin (HBD) locus and its role in developmental gene regulation. Genome Biology and Evolution 5(3):559–571. doi:10.1093/gbe/evt029

158. Cheetham S, Faulkner G, Dinger M (2020) Overcoming challenges and dogmas to understand the functions of pseudogenes. Nature Reviews Genetics 21(3):191–201. doi:10.1038/s41576-019-0196-1
159. Ma Y, Liu S, Gao J, Chen C, Zhang X, Yuan H, Chen Z, Yin X, Sun C, Mao Y, Zhou F, Shao Y, Liu Q, Xu J, Cheng L, Yu D, Li P, Yi P, He J, Geng G, Guo Q, Si Y, Zhao H, Li H, Banes G, Liu H, Nakamura Y, Kurita R, Huang Y, Wang X, Wang F, Fang G, Engel J, Shi L, Zhang Y, Yu J (2021) Genome-wide analysis of pseudogenes reveals HBBP1's human-specific essentiality in erythropoiesis and implication in β-thalassemia. Developmental Cell 60(12):1807. doi:10.1016/j.devcel.2025.05.021
160. Ludwig A, Rozhdestvensky T, Kuryshev V, Schmitz J, Brosius J (2005) An unusual primate locus that attracted two independent alu insertions and facilitates their transcription. Journal of molecular biology 350(2):200–214. doi:10.1016/j.jmb.2005.03.058
161. Hermant C, Torres-Padilla ME (2021) Tfs for tes: the transcription factor repertoire of mammalian transposable elements. Genes & Development 35(1–2):22–39. doi:10.1101/gad.344473.120
162. Gates A, Gysi D, Kellis M, Barabási AL (2021) A wealth of discovery built on the human genome project - by the numbers. Nature 590(7845):212–215. doi:10.1038/d41586-021-00314-6
163. Stitz M, Chaparro C, Lu Z, Olzog V, Weinberg C, Blom J, Goesmann A, Grunau C, Grevelding C (2021) Satellite-like w-elements: Repetitive, transcribed, and putative mobile genetic factors with potential roles for biology and evolution of schistosoma mansoni. Genome Biology and Evolution 13(10). doi:10.1093/gbe/evab204
164. Fudge G, Reeves E (2024) A model-based reverse system engineering methodology for analyzing complex biological systems with a case study in glycolysis. IEEE Open Journal of Systems Engineering 2:119–134. doi:10.1109/ojse.2024.3431868
165. Burgess S (2024) Universal optimal design in the vertebrate limb pattern and lessons for bioinspired design. Bioinspiration & Biomimetics 19(5):051004. doi:10.1088/1748-3190/ad66a3
166. Egnor M (2019) The cerebral windkessel as a dynamic pulsation absorber. BIO-Complexity 2019(3):1–35. doi:10.5048/bio-c.2019.3
167. Egnor M, Yang L, Mani R, Fiore S, Djurić A (2023) A quantitative model of the cerebral windkessel and its relevance to disorders of intracranial dynamics. Journal of Neurosurgery: Pediatrics 32:302–311
168. Thorvaldsen S, Hössjer O (2023) Estimating the information content of genetic sequence data. Journal of the Royal Statistical Society Series C: Applied Statistics 72:1310–1338
169. Axe D (2010) The limits of complex adaptation: An analysis based on a simple model of structured bacterial populations. BIO-Complexity 2010(4):1–10. doi:10.5048/bio-c.2010.4
170. Dellus-Gur E, Toth-Petroczy A, Elias M, Tawfik D (2013) What makes a protein fold amenable to functional innovation. Fold polarity and stability trade-offs. Journal of Molecular Biology 425(14):2609–2621. doi:10.1016/j.jmb.2013.03.033
171. Behe M, Snoke D (2004) Simulating evolution by gene duplication of protein features that require multiple amino acid residues. Protein Science 13(10):2651–2664. doi:10.1110/ps.04802904
172. Durrett R, Schmidt D (2008) Waiting for two mutations: with applications to regulatory sequence evolution and the limits of darwinian evolution. Genetics 180(3):1501–1509. doi:10.1534/genetics.107.082610
173. Hössjer O, Bechly G, Gauger A (2021) On the waiting time until coordinated mutations get fixed in regulatory sequences. Journal of Theoretical Biology 524(110657):110657. doi:10.1016/j.jtbi.2021.110657
174. Thorvaldsen S, Hössjer O (2024) Use of directed quasi-metric distances for quantifying the information of gene families. BioSystems 243(105256):105256. doi:10.1016/j.biosystems.2024.105256
175. Townsley T, Wilson J, Akers H, Bryant T, Cordova S, Wallace T, Durston K, Deweese J (2022) Psicalc: a novel approach to identifying and ranking critical non-proximal interdependencies within the overall protein structure. Bioinformatics Advances 2(1):vbac058. doi:10.1093/bioadv/vbac058
176. Endsley C, Moore K, Townsley T, Durston K, Deweese J (2024) Bioinformatic analysis of topoisomerase iiα reveals interdomain interdependencies and critical c-terminal domain residues. International Journal of Molecular Sciences 25(11):5674. doi:10.3390/ijms25115674
177. Wissler L, Gadau J, Simola D, Helmkampf M, Bornberg-Bauer E (2013) Mechanisms and dynamics of orphan gene emergence in insect genomes. Genome Biology and Evolution 5(2):439–455. doi:10.1093/gbe/evt009
178. Nelson P, Buggs R (2016) Next generation apomorphy: the ubiquity of taxonomically restricted genes. In: Olson P, Hughes J, Cotton J, eds. Next Generation Systematics. Cambridge University Press (Cambridge), pp 237–263. doi:10.1017/cbo9781139236355.013
179. Gunasekera R, Raja K, Hewapathirana S, Tundrea E, Gunasekera V, Galbadage T, Nelson P (2023) Orfanid: A web-based search engine for the discovery and identification of orphan and taxonomically restricted genes. PLoS One 18(10):e0291260. doi:10.1371/journal.pone.0291260
180. Murphy M, Mercer S, Deweese J (2017) Inhibitors and poisons of mammalian type II topoisomerases. Advances in Molecular Toxicology 11:203–240
181. Deweese J, Hoang K, Menzie R, Fief C, Ayes C, Keck J, Wilson J, Cordova S, Nelson C (2019) The variable c-terminal domain of human type II topoisomerases as a functionally relevant therapeutic target. FASEB Journal 33(S1). doi:10.1096/fasebj.2019.33.1_supplement.793.4
182. Hoang K, Menzie R, Rhoades J, Fief C, Deweese J (2020) Reviewing the modification, interactions, and regulation of the c-terminal domain of topoisomerase iiα as a prospect for future therapeutic targeting. EC Pharmacology and Toxicology 8.6:27–43
183. Dougherty A, Hawaz M, Hoang K, Trac J, Keck J, Ayes C, Deweese J (2021) Exploration of the role of the c-terminal domain of human DNA topoisomerase iiα in catalytic activity. ACS Omega 6(40):25892–25903. doi:10.1021/acsomega.1c02083
184. Chang J, O'Brian A, Thomas A, Hardin M, Latham B, Ngabonziza D, Simpson L, Wade B, Kühnhenrich L, Thompson N, Endsley C, Deweese J (2025) Mutagenesis of intrinsically disordered domain impacts topoisomerase iiα catalytic activity. International Journal of Molecular Sciences 26(8):3604. doi:10.3390/ijms26083604
185. Nartey C, Deweese J (2025) Evaluating alphafold 3 folding of the intrinsically disordered human DNA topoisomerase iiα c-terminal domain. DNA 5(4):46. doi:10.3390/dna5040046
186. Consortium IHGS (2001) Initial sequencing and analysis of the human genome. Nature 409(6822):860–921. doi:10.1038/35057062
187. Collins F (2006) The Language Of God: A Scientist Presents Evidence For Belief. Simon & Schuster (London, England)
188. Dawkins R (2009) The Greatest Show On Earth: The Evidence For Evolution. Free Press (New York, N.Y)
189. Mortola E, Long M (2021) Turning junk into us: How genes are born. American Scientist 109(3). doi:10.1511/2021.109.3.174

190. Moran L (2023) What's In Your Genome?: 90% Of Your Genome Is Junk. University of Toronto Press (Toronto, ON, Canada)
191. Mims F (1994) Letter to the Editor. Submitted to Science (Unpublished)
192. King J, Jukes T (1969) Non-darwinian evolution. Science 164(3881):788–798. doi:10.1126/science.164.3881.788
193. Ohno S (1972) An argument for the genetic simplicity of man and other mammals. Journal of Human Evolution 1(6):651–662. doi:10.1016/0047-2484(72)90011-5
194. Miller K (1994) Life's grand design. MIT Technology Review 97:24–32
195. Doolittle W, Sapienza C (1980) Selfish genes, the phenotype paradigm and genome evolution. Nature 284(5757):601–603. doi:10.1038/284601a0
196. Orgel L, Crick F (1980) Selfish d. N.A.: the ultimate parasite. Nature 284(5757):604–607. doi:10.1038/284604a0
197. Kitcher P (2009) Living With Darwin: Evolution, Design, And The Future Of Faith. Oxford University Press (New York, NY)
198. Mattick J (2023) A kuhnian revolution in molecular biology: Most genes in complex organisms express regulatory rnas. BioEssays 45(9):e2300080. doi:10.1002/bies.202300080
199. Ho J, Douse C, Marazzi I (2026) Transposable element DNA and RNA: Drivers of gene expression, evolution, and disease. Cell 189(12):3513–3540. doi:10.1016/j.cell.2026.05.003
200. Graur D, Zheng Y, Price N, Azevedo R, Zufall R, Elhaik E (2013) On the immortality of television sets: "function" in the human genome according to the evolution-free gospel of ENCODE. Genome Biology and Evolution 5(3):578–590. doi:10.1093/gbe/evt028
201. Kellis M, Wold B, Snyder M, Bernstein B, Kundaje A, Marinov G, Ward L, Birney E, Crawford G, Dekker J, Dunham I, Elnitski L, Farnham P, Feingold E, Gerstein M, Giddings M, Gilbert D, Gingeras T, Green E, Guigo R, Hubbard T, Kent J, Lieb J, Myers R, Pazin M, Ren B, Stamatoyannopoulos J, Weng Z, White K, Hardison R (2014) Defining functional DNA elements in the human genome. Proceedings of the National Academy of Sciences (USA) 111(17):6131–6138. doi:10.1073/pnas.1318948111
202. Adey B, Maddock D, Hermann-Le Denmat S, Dinger M, Gardner P, Poole A, Ganley A (2026) Pervasive transcription in the human genome exceeds background noise. Genome Biology and Evolution 18(5). doi:10.1093/gbe/evag042
203. Camellato B, Brosh R, Ashe H, Maurano M, Boeke J (2024) Synthetic reversed sequences reveal default genomic states. Nature 628(8007):373–380. doi:10.1038/s41586-024-07128-2
204. Bialek W (2024) Ambitions for theory in the physics of life. SciPost Physics Lecture Notes (84). doi:10.21468/scipostphyslectnotes.84
205. Marx V (2022) Some roads ahead for noncoding rnas. Nature Methods 19(10):1171–1174. doi:10.1038/s41592-022-01628-7
206. Mercer T, Gerhardt D, Dinger M, Crawford J, Trapnell C, Jeddeloh J, Mattick J, Rinn J (2011) Targeted RNA sequencing reveals the deep complexity of the human transcriptome. Nature Biotechnology 30(1):99–104. doi:10.1038/nbt.2024
207. Jacq C, Miller J, Brownlee G (1977) A pseudogene structure in 5s DNA of xenopus laevis. Cell 12(1):109–120. doi:10.1016/0092-8674(77)90189-1
208. Chiang J, Sparrer K, van Gent M, Lässig C, Huang T, Osterrieder N, Hopfner KP, Gack M (2018) Viral unmasking of cellular 5s rrna pseudogene transcripts induces RIG-i-mediated immunity. Nature Immunology 19(1):53–62. doi:10.1038/s41590-017-0005-y
209. Miller K (2005) Transcript of Proceedings of the Morning Session, Kitzmiller v. Dover Area School District (400 F. Supp. 2d 707 (M.D. Pa. 2005))
210. Scott E (2007). What do creationists believe about human evolution? https://www.youtube.com/watch?v=iZhO7_GhDH0. Accessed online
211. McCarrey J (1987) Nucleotide sequence of the promoter region of a tissue-specific human retroposon: comparison with its housekeeping progenitor. Gene 61(3):291–298. doi:10.1016/0378-1119(87)90192-2
212. McCarrey J, Thomas K (1987) Human testis-specific PGK gene lacks introns and possesses characteristics of a processed gene. Nature 326(6112):501–505. doi:10.1038/326501a0
213. Burki F, Kaessmann H (2004) Birth and adaptive evolution of a hominoid gene that supports high neurotransmitter flux. Nature genetics 36(10):1061–1063. doi:10.1038/ng1431
214. Sayah D, Sokolskaja E, Berthoux L, Luban J (2004) Cyclophilin a retrotransposition into TRIM5 explains owl monkey resistance to HIV-1. Nature 430(6999):569–573. doi:10.1038/nature02777
215. Hayashi H, Arao T, Togashi Y, Kato H, Fujita Y, De Velasco M, Kimura H, Matsumoto K, Tanaka K, Okamoto I, Ito A, Yamada Y, Nakagawa K, Nishio K (2015) The OCT4 pseudogene POU5F1B is amplified and promotes an aggressive phenotype in gastric cancer. Oncogene 34(2):199–208. doi:10.1038/onc.2013.547
216. Dennis M, Nuttle X, Sudmant P, Antonacci F, Graves T, Nefedov M, Rosenfeld J, Sajjadian S, Malig M, Kotkiewicz H, Curry C, Shafer S, Shaffer L, de Jong P, Wilson R, Eichler E (2012) Evolution of human-specific neural SRGAP2 genes by incomplete segmental duplication. Cell 149(4):912–922. doi:10.1016/j.cell.2012.03.033
217. Charrier C, Joshi K, Coutinho-Budd J, Kim JE, Lambert N, de Marchena J, Jin WL, Vanderhaeghen P, Ghosh A, Sassa T, Polleux F (2012) Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. Cell 149(4):923–935. doi:10.1016/j.cell.2012.03.034
218. Fiddes I, Lodewijk G, Mooring M, Bosworth C, Ewing A, Mantalas G, Novak A, van den Bout A, Bishara A, Rosenkrantz J, Lorig-Roach R, Field A, Haeussler M, Russo L, Bhaduri A, Nowakowski T, Pollen A, Dougherty M, Nuttle X, Addor MC, Zwolinski S, Katzman S, Kriegstein A, Eichler E, Salama S, Jacobs F, Haussler D (2018) Human-specific NOTCH2NL genes affect notch signaling and cortical neurogenesis. Cell 173(6):1356–1369.e22. doi:10.1016/j.cell.2018.03.051
219. Balakirev E, Ayala F (2003) Pseudogenes: are they "junk" or functional DNA. Annual Review of Genetics 37(1):123–151. doi:10.1146/annurev.genet.37.040103.103949
220. Wen YZ, Zheng LL, Qu LH, Ayala F, Lun ZR (2012) Pseudogenes are not pseudo any more. RNA Biology 9(1):27–32. doi:10.4161/rna.9.1.18277
221. Tsirigos A, Rigoutsos I (2009) Alu and b1 repeats have been selectively retained in the upstream and intronic regions of genes of specific functional classes. PLoS Computational Biology 5(12):e1000610. doi:10.1371/journal.pcbi.1000610
222. Speek M (2001) Antisense promoter of human L1 retrotransposon drives transcription of adjacent cellular genes. Molecular and Cellular Biology 21(6):1973–1985. doi:10.1128/MCB.21.6.1973-1985.2001
223. Nigumann P, Redik K, Mätlik K, Speek M (2002) Many human genes are transcribed from the antisense promoter of L1 retrotransposon. Genomics 79(5):628–634. doi:10.1006/geno.2002.6758
224. Feschotte C, Pritham E (2007) DNA transposons and the evolution of eukaryotic genomes. Annual Review of Genetics 41(1):331–368. doi:10.1146/annurev.genet.40.110405.090448

225. Romanish M, Lock W, van de Lagemaat L, Dunn C, Mager D (2007) Repeated recruitment of LTR retrotransposons as promoters by the anti-apoptotic locus NAIP during mammalian evolution. PLoS Genetics 3(1):e10. doi:10.1371/journal.pgen.0030010
226. Feschotte C (2008) Transposable elements and the evolution of regulatory networks. Nature Reviews Genetics 9(5):397–405. doi:10.1038/nrg2337
227. Gerdes P, Richardson S, Mager D, Faulkner G (2016) Transposable elements in the mammalian embryo: pioneers surviving through stealth and service. Genome Biology 17(1):100. doi:10.1186/s13059-016-0965-5
228. Trizzino M, Park Y, Holsbach-Beltrame M, Aracena K, Mika K, Caliskan M, Perry G, Lynch V, Brown C (2017) Transposable elements are the primary source of novelty in primate gene regulation. Genome Research 27(10):1623–1633. doi:10.1101/gr.218149.116
229. Roller M, Stamper E, Villar D, Izuogu O, Martin F, Redmond A, Ramachanderan R, Harewood L, Odom D, Flicek P (2021) LINE retrotransposons characterize mammalian tissue-specific and evolutionarily dynamic regulatory regions. Genome Biology 22(1):62. doi:10.1186/s13059-021-02260-y
230. Meng S, Liu X, Zhu S, Xie P, Fang H, Pan Q, Fang K, Li F, Zhang J, Che Z, Zhang Q, Mao G, Wang Y, Hu P, Chen K, Sun F, Xie W, Luo Z, Lin C (2023) Young LINE-1 transposon 5' utrs marked by elongation factor ELL3 function as enhancers to regulate naïve pluripotency in embryonic stem cells. Nature Cell Biology 25(9):1319–1331. doi:10.1038/s41556-023-01211-y
231. Sakamoto M, Ishiuchi T (2024) YY1-dependent transcriptional regulation manifests at the morula stage. microPublication biology 2024. doi:10.17912/micropub.biology.001108
232. Whitelaw E, Martin D (2001) Retrotransposons as epigenetic mediators of phenotypic variation in mammals. Nature Genetics 27(4):361–365. doi:10.1038/86850
233. Slotkin R, Martienssen R (2007) Transposable elements and the epigenetic regulation of the genome. Nature Reviews Genetics 8(4):272–285. doi:10.1038/nrg2072
234. Gehring M, Bubb K, Henikoff S (2009) Extensive demethylation of repetitive elements during seed development underlies gene imprinting. Science 324(5933):1447–1451. doi:10.1126/science.1171609
235. Chueh A, Northrop E, Brettingham-Moore K, Choo K, Wong L (2009) LINE retrotransposon RNA is an essential structural and functional epigenetic component of a core neocentromeric chromatin. PLoS genetics 5(1):e1000354. doi:10.1371/journal.pgen.1000354
236. Brind'Amour J, Kobayashi H, Richard Albert J, Shirane K, Sakashita A, Kamio A, Bogutz A, Koike T, Karimi M, Lefebvre L, Kono T, Lorincz M (2018) LTR retrotransposons transcribed in oocytes drive species-specific and heritable changes in DNA methylation. Nature Communications 9(1):3331. doi:10.1038/s41467-018-05841-x
237. Jönsson M, Ludvik Brattås P, Gustafsson C, Petri R, Yudovich D, Pircs K, Verschuere S, Madsen S, Hansson J, Larsson J, Månsson R, Meissner A, Jakobsson J (2019) Activation of neuronal genes via LINE-1 elements upon global DNA demethylation in human neural progenitors. Nature Communications 10(1):3182. doi:10.1038/s41467-019-11150-8
238. Lanciano S, Philippe C, Sarkar A, Pratella D, Domrane C, Doucet A, van Essen D, Saccani S, Ferry L, Defossez PA, Cristofari G (2024) Locus-level L1 DNA methylation profiling reveals the epigenetic and transcriptional interplay between l1s and their integration sites. Cell Genomics 4(2):100498. doi:10.1016/j.xgen.2024.100498
239. Lippman Z, Gendrel AV, Black M, Vaughn M, Dedhia N, McCombie W, Lavine K, Mittal V, May B, Kasschau K, Carrington J, Doerge R, Colot V, Martienssen R (2004) Role of transposable elements in heterochromatin and epigenetic control. Nature 430(6998):471–476. doi:10.1038/nature02651
240. McCue A, Nuthikattu S, Reeder S, Slotkin R (2012) Gene expression and stress response mediated by the epigenetic regulation of a transposable element small RNA. PLoS Genetics 8(2):e1002474. doi:10.1371/journal.pgen.1002474
241. Min B, Park J, Jeong Y, Jeon K, Kang YK (2020) Dnmt1 binds and represses genomic retroelements via DNA methylation in mouse early embryos. Nucleic Acids Research 48(15):8431–8444. doi:10.1093/nar/gkaa584
242. Bogutz A, Brind'Amour J, Kobayashi H, Jensen K, Nakabayashi K, Imai H, Lorincz M, Lefebvre L (2019) Evolution of imprinting via lineage-specific insertion of retroviral promoters. Nature Communications 10(1):5674. doi:10.1038/s41467-019-13662-9
243. Miao B, Fu S, Lyu C, Gontarz P, Wang T, Zhang B (2020) Tissue-specific usage of transposable element-derived promoters in mouse development. Genome Biology 21(1):255. doi:10.1186/s13059-020-02164-3
244. Qin S, Jin P, Zhou X, Chen L, Ma F (2015) The role of transposable elements in the origin and evolution of micrornas in human. PLoS One 10(6):e0131365. doi:10.1371/journal.pone.0131365
245. Lubelsky Y, Ulitsky I (2018) Sequences enriched in alu repeats drive nuclear localization of long rnas in human cells. Nature 555(7694):107–111. doi:10.1038/nature25757
246. Carlevaro-Fita J, Polidori T, Das M, Navarro C, Zoller T, Johnson R (2019) Ancient exapted transposable elements promote nuclear enrichment of human long noncoding rnas. Genome Research 29(2):208–222. doi:10.1101/gr.229922.117
247. Hartley G, O'Neill R (2019) Centromere repeats: Hidden gems of the genome. Genes 10(3):223. doi:10.3390/genes10030223
248. Fueyo R, Judd J, Feschotte C, Wysocka J (2022) Roles of transposable elements in the regulation of mammalian transcription. Nature Reviews Molecular Cell Biology 23(7):481–497. doi:10.1038/s41580-022-00457-y
249. Gebrie A (2023) Transposable elements as essential elements in the control of gene expression. Mobile DNA 14(1):9. doi:10.1186/s13100-023-00297-3
250. Durnaoglu S, Lee SK, Ahnn J (2021) Syncytin, envelope protein of human endogenous retrovirus (HERV): no longer "fossil" in human genome. Animal Cells and Systems 25(6):358–368. doi:10.1080/19768354.2021.2019109
251. Malfavon-Borja R, Feschotte C (2015) Fighting fire with fire: endogenous retrovirus envelopes as restriction factors. Journal of Virology 89(8):4047–4050. doi:10.1128/JVI.03653-14
252. Srinivasachar Badarinarayan S, Sauter D (2021) Switching sides: How endogenous retroviruses protect us from viral infections. Journal of virology 95(12). doi:10.1128/JVI.02299-20
253. Jorritsma R (2026) The evolution of functional endogenous retroviruses. Biological Theory. doi:10.1007/s13752-026-00543-w
254. Dembski W, Wells J (2009) The Design Of Life. Foundation for Thought & Ethics (Richardson, TX)
255. Diachenko A, Rivers R, Sobkowiak-Tabaka I (2023) Convergent evolution of prehistoric technologies: The entropy and diversity of limited solutions. Journal of Archaeological Method and Theory 30(4):1168–1199. doi:10.1007/s10816-023-09623-8
256. Mossio M, Bich L (2017) What makes biological organisation teleological. Synthese 194(4):1089–1114. doi:10.1007/s11229-014-0594-z

257. Szallasi Z, Stelling J, Periwal V, editors (2006) System Modeling in Cellular Biology: From Concepts to Nuts and Bolts. MIT Press (Cambridge, Massachusetts)
258. Corning P, Kauffman S, Noble D, Shapiro J, Vane-Wright R, Pross A, editors (2023) Evolution "On Purpose": Teleonomy In Living Systems. MIT Press (Cambridge, MA)
259. Noble D (2001) The principle of biological relativity: Origins and current status. In: Voosholz J, Gabriel M, eds. Top-Down Causation And Emergence, Synthese Library 439. Springer (Cham, Switzerland), pp 117–133
260. Pezzulo G, Levin M (2016) Top-down models in biology: explanation and control of complex living systems above the molecular level. Journal of the Royal Society, Interface 13(124). doi:10.1098/rsif.2016.0555
261. Merel J, Botvinick M, Wayne G (2019) Hierarchical motor control in mammals and machines. Nature Communications 10(1):5489. doi:10.1038/s41467-019-13239-6
262. Haug S, Marks R, Dembski W (2022) Exponential contingency explosion: Implications for artificial general intelligence. IEEE Transactions on Systems, Man, and Cybernetics. Systems 52(5):2800–2808. doi:10.1109/tsmc.2021.3056669
263. Schulz W (2021) An engineering perspective on the bacterial flagellum: Part 1—constructive view. BIO-Complexity 2021(1):1–14. doi:10.5048/bio-c.2021.1
264. Schulz W (2021) An engineering perspective on the bacterial flagellum: Part 2—analytic view. BIO-Complexity 2021(2):1–16. doi:10.5048/bio-c.2021.2
265. Schulz W (2021) An engineering perspective on the bacterial flagellum: Part 3—observations. BIO-Complexity 2021(3):1–7. doi:10.5048/bio-c.2021.3
266. Johansen J (2024) Bacterial chemotaxis control process analysis with sysml. Systems engineering 27(5):827–849. doi:10.1002/sys.21752
267. Mantri P, Thomas J (2019) Nature's designs: The biology of survival. MATEC Web of Conferences 301:00023. doi:10.1051/matecconf/201930100023
268. Alon U (2023) An Introduction To Systems Biology. CRC Press (London, England)
269. Burgess S (2026) Ultimate Engineering: An Engineer Investigates The Biomechanics Of The Human Body. Discovery Institute (Seattle, WA)
270. Kitano H (2002) Systems biology: a brief overview. Science 295(5560):1662–1664. doi:10.1126/science.1069492
271. Gatherer D (2010) So what do we really mean when we say that systems biology is holistic. BMC Systems Biology 4(1):22. doi:10.1186/1752-0509-4-22
272. Morange M (2008) The death of molecular biology. History and Philosophy of the Life Sciences 30(1):31–42
273. Braillard P (2010) Systems biology and the mechanistic framework. History and Philosophy of the Life Sciences 32(1):43–62
274. Tsiantis N, Balsa-Canto E, Banga J (2018) Optimality and identification of dynamic models in systems biology: an inverse optimal control framework. Bioinformatics 34(14):2433–2440. doi:10.1093/bioinformatics/bty139
275. Freeland S, Hurst L (1998) The genetic code is one in a million. Journal of Molecular Evolution 47(3):238–248. doi:10.1007/pl00006381
276. Noor E, Eden E, Milo R, Alon U (2010) Central carbon metabolism as a minimal biochemical walk between precursors for biomass and energy. Molecular Cell 39(5):809–820. doi:10.1016/j.molcel.2010.08.031
277. Walker S, Davies P (2013) The algorithmic origins of life. Journal of the Royal Society, Interface 10(79):20120869. doi:10.1098/rsif.2012.0869
278. Walker S, Cisneros L, Davies P (2012) Evolutionary transitions and top-down causation. Artificial Life 13:283–290. doi:10.7551/978-0-262-31050-5-ch038
279. Reeves G, Hrischuk C (2016) Survey of engineering models for systems biology. Computational Biology Journal 2016:1–12. doi:10.1155/2016/4106329
280. Stelling J, Sauer U, Doyle F, Doyle J (2010) Complexity and robustness of cellular systems. In: Szallasi Z, Stelling J, Periwal V, eds. System Modeling In Cellular Biology: From Concepts To Nuts And Bolts. MIT Press (Cambridge, MA), pp 19–40
281. Behe M (2004) Irreducible complexity: obstacle to darwinian evolution. In: Dembski W, M R, eds. Debating Design: From Darwin To DNA. Cambridge University Press (Cambridge, UK), pp 352–370
282. Muskhelishvili G, Travers A (2013) Integration of syntactic and semantic properties of the DNA code reveals chromosomes as thermodynamic machines converting energy into information. Cellular and Molecular Life Sciences 70(23):4555–4567. doi:10.1007/s00018-013-1394-1
283. Hopfield J (1974) Kinetic proofreading: a new mechanism for reducing errors in biosynthetic processes requiring high specificity. Proceedings of the National Academy of Sciences (USA) 71(10):4135–4139. doi:10.1073/pnas.71.10.4135
284. Andrews S, Wiley H, Sauro H (2024) Design patterns of biological cells. BioEssays 46(3):e2300188. doi:10.1002/bies.202300188
285. Shapiro J (2002) A 21(st) century view of evolution. Journal of Biological Physics 28(4):745–764. doi:10.1023/A:1021207310080
286. Shapiro J (2007) Twenty-first century view of evolution: Genome system architecture, repetitive DNA, and natural genetic engineering. In: Bastolla U, Porto M, eds. Structural Approaches To Sequence Evolution: Molecules, Networks, Populations. Springer (Berlin, Germany), pp 129–147
287. Allarakhia M, Wensley A (2007) Systems biology: A disruptive biopharmaceutical research paradigm. Technological Forecasting and Social Change 74(9):1643–1660. doi:10.1016/j.techfore.2006.07.012
288. Aderem A (2005) Systems biology: its practice and challenges. Cell 121(4):511–513. doi:10.1016/j.cell.2005.04.020
289. Network CGAR, Weinstein J, Collisson E, Mills G, Shaw K, Ozenberger B, Ellrott K, Shmulevich I, Sander C, Stuart J (2013) The cancer genome atlas pan-cancer analysis project. Nature Genetics 45(10):1113–1120. doi:10.1038/ng.2764
290. Barabási AL, Gulbahce N, Loscalzo J (2011) Network medicine: a network-based approach to human disease. Nature Reviews Genetics 12(1):56–68. doi:10.1038/nrg2918
291. Karr J, Sanghvi J, Macklin D, Gutschow M, Jacobs J, Bolival B J, Assad-Garcia N, Glass J, Covert M (2012) A whole-cell computational model predicts phenotype from genotype. Cell 150(2):389–401. doi:10.1016/j.cell.2012.05.044
292. Feist A, Henry C, Reed J, Krummenacker M, Joyce A, Karp P, Broadbelt L, Hatzimanikatis V, BØ P (2007) A genome-scale metabolic reconstruction for escherichia coli k-12 MG1655 that accounts for 1260 orfs and thermodynamic information. Molecular Systems Biology 3(1):121. doi:10.1038/msb4100155
293. Ball P (2023) How Life Works: A User's Guide To The New Biology. University of Chicago Press (Chicago, IL). doi:10.7208/chicago/9780226826691.001.0001
294. Snoke D (2014) Systems biology as a research program for intelligent design. BIO-Complexity 2014(3):1–11. doi:10.5048/BIO-C.2014.3
295. Royce W (2021) Managing the development of large software systems (1970). In: Ideas That Created The Future, 321–332. MIT Press, Cambridge, MA
296. Estefan J (2007) Survey of model-based systems engineering (MBSE) methodologies. INCOSE MBSE Focus Group 25:1–2

297. Forsberg K, Mooz H (1992) The relationship of systems engineering to the project cycle. Engineering Management Journal 4:36–43. doi:10.1002/j.2334-5837.1991.tb01484.x
298. Kossiakoff A, Biemer S, Seymour S, Flanigan D (2025) Systems Engineering Principles And Practice. John Wiley & Sons (Nashville, TN). doi:10.1002/9781119516699
299. Rivas M, Becerra A, Lazcano A (2018) On the early evolution of catabolic pathways: A comparative genomics approach. I. the cases of glucose, ribose, and the nucleobases catabolic routes. Journal of Molecular Evolution 86(1):27–46. doi:10.1007/s00239-017-9822-8
300. Chandel N (2021) Glycolysis. Cold Spring Harbor Perspectives in Biology 13(5):a040535. doi:10.1101/cshperspect.a040535
301. Ebenhöh O, Heinrich R (2001) Evolutionary optimization of metabolic pathways. Theoretical reconstruction of the stoichiometry of ATP and NADH producing systems. Bulletin of Mathematical Biology 63(1):21–55. doi:10.1006/bulm.2000.0197
302. Court S, Waclaw B, Allen R (2015) Lower glycolysis carries a higher flux than any biochemically possible alternative. Nature Communications 6(1):8427. doi:10.1038/ncomms9427
303. Ng C, Wang L, Chowdhury A, Maranas C (2019) Pareto optimality explanation of the glycolytic alternatives in nature. Scientific Reports 9(1):2633. doi:10.1038/s41598-019-38836-9
304. Vander Heiden M, Cantley L, Thompson C (2009) Understanding the warburg effect: the metabolic requirements of cell proliferation. Science 324(5930):1029–1033. doi:10.1126/science.1160809
305. Liberti M, Locasale J (2016) The warburg effect: How does it benefit cancer cells. Trends in Biochemical Sciences 41(3):211–218. doi:10.1016/j.tibs.2015.12.001
306. McIntosh A (2009) Biomimetic inspiration from fire and combustion in nature including the bombardier beetle. In: Martin-Palma R, Lakhtakia A, eds. Biomimetics and Bioinspiration, Proc. of SPIE Vol. 7401. Of SPIE Vol. 7401 (1–9), pp 1–9. doi:10.1117/12.825477
307. Sewell G (2023) Human engineered self-replicating machines. Biocosmos 2023(1). doi:10.2478/biocosmos-2023-0002
308. McIntosh A (2007) Combustion, fire, and explosion in nature - some biomimetic possibilities. Proceedings of the Institution of Mechanical Engineers, Part C: Journal of Mechanical Engineering Science 221(10):1157–1163. doi:10.1243/09544062jmes541
309. McIntosh A, Beheshti N (2008) Insect inspiration. Physics World 21(04):29–31. doi:10.1088/2058-7058/21/04/35
310. Axe D, Gauger A (2013) Explaining metabolic innovation: Neo-darwinism versus design. In: RJ Marks I, MJ B, Dembski W, Gordon B, Sanford A, eds. Biological Information: New Perspectives. World Scientific (Singapore), pp 489–507
311. Lock R, Burgess S, Vaidyanathan R (2014) Multi-modal locomotion: from animal to application. Bioinspiration & Biomimetics 9(1):011001. doi:10.1088/1748-3182/9/1/011001
312. Burgess S, Beeston A, Carr J, Siempou K, Simmonds M, Zanker Y (2023) A bio-inspired arched foot with individual toe joints and plantar fascia. Biomimetics 8(6):455. doi:10.3390/biomimetics8060455
313. Burgess S (2021) A review of linkage mechanisms in animal joints and related bioinspired designs. Bioinspiration & Biomimetics 16(4):041001. doi:10.1088/1748-3190/abf744
314. Cao C, Burgess S, Conn A (2018) Flapping at resonance: Realization of an electroactive elastic thorax. In: 2018 IEEE International Conference on Soft Robotics (RoboSoft), 327–332. doi:10.1109/robosoft.2018.8404940
315. Leisola M, Witt J (2018) Heretic: One Scientist's Journey From Darwin To Design. Discovery Institute (Seattle, WA)
316. Cassell E (2021) Animal Algorithms: Evolution And The Mysterious Origin Of Ingenious Instincts. Discovery Institute (Seattle, WA)
317. Conn A, Burgess S, Chung S (2007) The parallel crank-rocker flapping mechanism: An insect-inspired design for micro air vehicles. International Journal of HR: Humanoid Robotics 04(04):625–643. doi:10.1142/s0219843607001199
318. Burgess S, Etoundi A (2014) Performance maps for a bio-inspired robotic condylar hinge joint. Journal of Mechanical Design 136(11):115002. doi:10.1115/1.4028168
319. Etoundi A, Burgess S, Vaidyanathan R (2013) A bio-inspired condylar hinge for robotic limbs. Journal of Mechanisms and Robotics 5(3):031011. doi:10.1115/1.4024471
320. Burton T, Vaidyanathan R, Burgess S, Turton A, Melhuish C (2011) Development of a parametric kinematic model of the human hand and a novel robotic exoskeleton. IEEE International Conference on Rehabilitation Robotics 2011:5975344. doi:10.1109/ICORR.2011.5975344
321. Burgess S (2022) Why the ankle-foot complex is a masterpiece of engineering and a rebuttal of "bad design" arguments. BIO-Complexity 2022(3):1–10. doi:10.5048/bio-c.2022.3
322. Lents N (2018) Human Errors: A Panorama Of Our Glitches, From Pointless Bones To Broken Genes. Houghton Mifflin (Boston, MA)
323. Burgess S (2024) How multifunctioning joints produce highly agile limbs in animals with lessons for robotics. Biomimetics 9(9):529. doi:10.3390/biomimetics9090529
324. of Natural History AM (2013). Whales giants of the deep
325. Burgess S (2007) Multi-functioning and multi-optimisation in feathers. International Journal of Design & Nature 1:1–10
326. McIntosh A (2009) Evidence of design in bird feathers and avian respiration. International Journal of Design & Nature and Ecodynamics 4:154–169
327. Chang E, Matloff L, Stowers A, Lentink D (2020) Soft biohybrid morphing wings with feathers underactuated by wrist and finger motion. Science Robotics 5(38):eaay1246. doi:10.1126/scirobotics.aay1246
328. Sedky G, Simon N, Othman A, Wiswell H, Wissa A (2024) Distributed feather-inspired flow control mitigates stall and expands flight envelope. Proceedings of the National Academy of Sciences (USA) 121(45):e2409268121. doi:10.1073/pnas.2409268121
329. Cao C, Burgess S, Conn A (2018) Toward a dielectric elastomer resonator driven flapping wing micro air vehicle. Frontiers in Robotics and AI 5:137. doi:10.3389/frobt.2018.00137
330. Conn A, Burgess S, Ling C (2007) Design of a parallel crank-rocker flapping mechanism for insect-inspired micro air vehicles. Proceedings of the Institution of Mechanical Engineers, Part C: Journal of Mechanical Engineering Science 221(10):1211–1222. doi:10.1243/09544062jmes517
331. Conn A, Burgess S, Ling C, Vaidyanathan R (2008) The design optimisation of an insect-inspired micro air vehicle. International Journal of Design & Nature and Ecodynamics 3(1):12–27. doi:10.2495/d&ne-v3-n1-12-27
332. Conn A, Ling C, Burgess S (2011) Biomimetic analysis of insect wing kinematics for flapping mavs. International Journal of Micro Air Vehicles 3(1):1–11. doi:10.1260/1756-8293.3.1.1