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Evolution unscathed: *Darwin Devolves* argues on weak reasoning that unguided evolution is a destructive force, incapable of innovation

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Academic buildings can be quirky places. Like proteins they evolve, adapting to new functions while holding on to traces of their past, occasionally performing tasks that are in conflict with one another. Iacocca Hall is no exception. Once home to the research and development division of Bethlehem Steel, the mountaintop building now houses Lehigh University's Department of Biological Sciences. The most infamous (among scientists) and celebrated (among creationists) of our 22 faculty is Michael Behe, a well-known proponent of intelligent design and a tenured member of our department who recently released his third book, *Darwin Devolves: The New Science About DNA That Challenges Evolution* (HarperOne, 2019, 352 pp.).

Michael Behe gained notoriety in the mid-1990s after the publication of *Darwin's Black Box* (Behe 1996), in which he advanced a molecular version of the theologian William Paley's Watchmaker argument for design and introduced the concept of irreducible complexity: the notion that extant cellular systems are comprised of many interdependent parts, and thus are extremely unlikely to have evolved step-wise by random processes. Because of his visibility—stemming from the commercial success of *Darwin's Black Box*, his academic credentials, and his testimony in the 2005 Kitzmiller trial in Dover, Pennsylvania—Behe has become the de facto leader of the Intelligent Design movement.

Idolized within the intelligent design movement, Behe has cultivated a retinue of ardent supporters, but when tested publicly his views do not stand up to scientific or legal scrutiny. In his 2005 decision in *Kitzmiller v. Dover Area School District*, Judge John E. Jones III roundly rejected Behe's views, writing "[W]e have addressed the seminal question of whether ID [Intelligent Design] is science. We have concluded that it is not, and moreover that ID cannot uncouple itself from its creationist, and thus religious, antecedents." (*Kitzmiller v. Dover Area School District* 2005) Nevertheless, Behe is undeterred in his convictions and continues to refine his view of life's history.

The brand of creationism promulgated by Michael Behe is unique: closer to the scientific consensus than most. For example, Behe fully accepts that all organisms share a genealogical history. In his previous book, *The Edge of Evolution* (Behe 2007), he writes that "distantly related organisms share apparently arbitrary features of their genes that seem to have no explanation other than that they were inherited from a distant common ancestor (p3)." Regarding our closest cousins, "[i]t's hard to imagine how there could be stronger evidence for the common ancestry of chimps and humans (p72)."

Where Behe breaks with the scientific consensus is that he rejects that random mutation and natural selection alone are capable of producing new molecular functions. Instead, he invokes an intelligent designer: an agent behind the scenes who deliberately and methodically supplies new mutations (the "purposeful arrangement of parts"), thus allowing life to successfully navigate unlikely evolutionary paths. Natural selection acting on random degenerative mutations can account for diversification at the genus and species levels, according to Behe; however, "descendants that

differ from their ancestor at the level of family or higher (*Darwin Devolves*, p156)" are beyond the "edge of evolution" and require a designer.

The central premise of *Darwin Devolves*—alluded to in the title—is that the combination of random mutation and natural selection, in addition to being incapable of generating novelty, is a powerful degradative force. *Darwin Devolves* contains a few factual errors and many errors of omission that have been pointed out by others (Lents and Hunt 2019; Lents et al. 2019), but it is two critical errors of logic that undermine Behe's central premise that degradative mutations cripple evolution. First, Behe falsely equates the prevalence of loss-of-function mutations to the inevitable degradation of biological systems and the impossibility of evolution to produce novelty. By selective presentation of data, he exaggerates the role of degradative processes in evolution. Second, as he has previously, Behe attempts to argue from analogy, equating proteins with machines and convincing us that machines cannot evolve. Calling a flagellum an outboard motor may have some merit as a teaching tool, but it is not reality. Showing that a hammer cannot evolve into a fishing rod tells us nothing about real constraints on protein evolution.

The "First Rule of Adaptive Evolution" Quickly Deteriorates

Mark Twain, in an interview, offered a formula for effective storytelling: "Get your facts first . . . then you can distort 'em as much as you please" (Kipling 1899). As a credentialed academic and a card-carrying biochemist, Michael Behe has his facts—or at least he has access to them. Behe rightly points out that loss-of-function mutations are common in evolution, and that breaking or blunting a functional gene can sometimes be beneficial. This leads Behe to conclude that irreversible and deteriorating mutations are the only inevitable outcome (the "poison pills") of unguided evolution.

Inscribed on the first page of *Darwin Devolves* is Behe's central premise: "The First Rule of Adaptive Evolution: Break or blunt any functional gene whose loss would increase the number of a species' offspring." Concise, catchy and matter-of-fact, Behe's First Rule makes for a quality sound bite, but it is overly simplistic and untruthful to the data. *Darwin Devolves* overemphasizes loss-of-function mutations, and brushes off countervailing examples as nothing more than a "sideshow."

The "First Rule" appeared in a 2010 review in the *Quarterly Review of Biology* (Behe 2010), largely as a critique of the field of experimental evolution, which has grown dramatically in the last 20 years (see reviews by Fisher and Lang 2016; Lenski 2017; Van den Bergh et al. 2018). Collectively, experimental evolution has yielded new insights into the tempo of genotypic and phenotypic adaptation (Barrick et al. 2009), the role of historical contingency in the evolution of new traits (Blount et al. 2008), second-order selection on mutator alleles (Sniegowski et al. 1997), the power of sex to combine favorable (and purge deleterious) mutations (McDonald et al. 2016), the dynamics of adaptation (Lang et al. 2013; Good et al. 2017), and the seemingly unlimited potential of adaptive evolution (Wiser et al. 2013).

Behe gives a misleading account of experimental evolution by trumpeting each and every loss-of-function mutation that provides a selective advantage. In truth, loss-of-function mutations are expected to contribute disproportionately to adaptation in experimental evolution, where selective pressures are high and conditions are constant, or nearly so. Systematic studies in yeast and bacteria show that most genes can be deleted singly with little functional consequence (Giaever et al. 2002; Winzeler 1999) and that a number of gene deletions are beneficial in specific environments (Hottes et al. 2004; Pir et al. 2012; Novo et al. 2013). It is important to point out that these mutations are often pleiotropic (Qian et al. 2012) and are not necessarily beneficial outside of the defined conditions of the experiment. No deletion is beneficial in all environments and beneficial loss-of-function mutations that arise in experimental evolution are unlikely to succeed if, say, cells are required to mate (Lang et al. 2009), the static environment is disturbed (Frenkel et al. 2015), or glucose is temporarily depleted (Li et al. 2018). Yet, Behe rests his central premise on the weak claim that these data demonstrate the ineffectiveness of random mutation and natural selection in all situations.

LOSS-OF-FUNCTION MUTATIONS ON BALANCE

After reading *Darwin Devolves*, one would be forgiven for expecting that loss-of-function mutations swamp out all other forms of genetic variation no matter the context. After all, Behe states that "random mutation and natural selection are in fact fiercely devolutionary (p10)," and degrading mutations are "relentless as the tide and as futile to try to resist (p186)." However, the truth is that loss-of-function mutations account for only a small fraction of natural genetic variation. In humans only ~3.5% of exonic and splice site variants (57,137 out of 1,639,223) are putatively loss-of-function (Saleheen et al. 2017), and a survey of 42 yeast strains found that only 242 of the nearly 6000 genes contain putative loss-of-function variants (Bergström et al. 2014). Compared to the vast majority of natural genetic variants, loss-of-function variants have a much lower allele-frequency distribution (MacArthur et al. 2012). Still, Behe fixates on beneficial loss-of-function mutations, drawing heavily from situations where one expects such mutations to be favored—such as experimental evolution—and generalizes to all situations this one mechanism writ large.

To the same extent that Behe overemphasizes gene loss in *Darwin Devolves*, he neglects the processes that generate new raw material for evolution. Though one might question the utility of "devolution" as an appropriate term (Lents 2019), Behe is correct that the loss of genetic information is an important mechanism

(Albalat and Cañestro 2016). However, the opposing processes of gene duplication, horizontal gene transfer, and introgression balance out gene loss, providing a source of new genetic material—a trend that holds true across a number of phyla (Makarova et al. 2006; Putnam et al. 2007; Shen et al. 2018). For example, along the lineage leading to modern brewers' yeast (*Saccharomyces cerevisiae*), historical rates of gene loss and gene gain are nearly matched such that the inferred ancestral genomes along the way are all predicted to have around 6000 genes (Wapinski et al. 2007), despite a large flux in gene content (including a whole-genome duplication event;Wolfe and Shields 1997; Kellis et al. 2004).

STANDING VARIATION AS A SOURCE OF ADAPTIVE POTENTIAL

For decades Peter and Rosemary Grant have meticulously documented natural selection in action on the finches of the Galápagos Islands. Behe gives credit to the Grants for demonstrating that evolution by natural selection can rapidly produce genetic and phenotypic change in populations as a response to environmental changes. Yet, he holds up Darwin's finches as a shining example of the "strict limits on fundamental biological change by random mechanisms (p142)." Proudly displaying the Galápagos finches on the cover of *Darwin Devolves*, Behe waves off the impressive ecological divergence displayed by the entire finch radiation as a "twofold variation in body length, shorter, or longer beaks of greater or lesser depth . . . and not much else (p146)."

Behe goes even further, making statements that are plainly absurd to anyone with even a rudimentary understanding of evolution: Pointing to the origin of most animal phyla during the ten-million-year Cambrian Explosion, Behe muses, "[s]urely we should expect at least one crummy new phylum, class, or order to be conjured by Darwin's vaunted mechanism in the time the finches have been on the Galápagos. But no, nothing (p155)." There are several problems with comparing the ancient Cambrian oceans to the relatively recent Galápagos Islands, including niche availability and the vast time that has elapsed since these events and the present. Darwin's finches are an icon of evolution for good reason, having radiated into numerous ecological niches (Grant 1986; Lamichhaney et al. 2015) and developed diverse resource specializations (including at least one case—feeding on mature leaves—that is, to the best of our knowledge, unknown in other bird *orders*, much less families (Grant 1981)). By adopting a restrictive definition of fundamental biological change, Behe dismisses all corresponding behavioral, digestive, and physiological adaptations (e.g., Grant 1996).

Recent genomic analyses show that the alleles underlying adaptation in Darwin's finches, as well as another adaptive radiation, the African Great Lake cichlids, were present in their ancestral taxa (Brawand et al. 2014; Lamichhaney et al. 2015). Like gene duplication and horizontal gene transfer, *Darwin Devolves* writes off the significance of standing genetic variation as a reservoir of adaptive potential: "Another parallel to the finches is that many variant genes in new cichlid species did not first arise when the cichlids diversified recently in Lake Victoria. Rather, they came from mutations that arose millions of years before then and were maintained throughout the ages in the ancestor species population (p165)." True—however, this does not lessen the instrumental role of standing genetic variation in adaptation to new environments.

When marine sticklebacks independently colonized multiple freshwater glacial lakes, an allele that was segregating at low frequency in ancestral marine stickleback populations, the low-*Eda* allele, was favored by natural selection and rose to high frequency in the parallel lake populations, leading to a beneficial reduction in armored plating (Colosimo et al. 2005). Counter to Behe's thesis, none of the observed *Eda* mutations were predicted to damage the function of the protein (Colosimo et al. 2005). The causative variants are likely *cis*-regulatory changes that decreased expression of *Eda* in developing armor, but not in other tissues (O'Brown et al. 2015). *Darwin Devolves* accepts as evidence only de novo protein evolution, a restriction Behe uses to support his "First Rule" and claim that "Darwinian evolution is self-limiting." Narrow by definition and unsupported by the data, Behe's First Rule does not stand up to scrutiny.

A Metaphorical Sleight of Hand

Of all the information we retain from our introductory biology courses, nothing is recalled with such blind confidence as the assertion that the mitochondrion is the Powerhouse of the Cell. Metaphors are powerful rhetorical devices—and once engrained it is easy to overlook the inaccuracies of these vivid, but false, analogies. Behe uses metaphors effectively to draw his readers' attention away from biological reality and to make his case for design. In *Darwin Devolves*, proteins are molecular machines ("literal machines—molecular trucks, pumps, scanners, and more (p17)"), rod cells are fiber-optic cables, bacteria move using tank treads, outboard motors, and the oars and paddles of a Roman galley ship. The planthopper's hind legs are a "large, in-your-face, interacting gear system (p45)." As for the "supremely complex molecular machine called the spliceosome," simple scissors will not do. Behe opts for "an automated machine that could make fancy paper cut-out dolls (p61)." Most of the analogies in *Darwin Devolves* are not Behe's creation—he has done well to scour press coverage (Yong 2013) and the scientific literature (Burrows and Sutton 2013; Franze et al. 2007) for relatable metaphors; and he is generous with their use. But reality remains: proteins are not machines, a flagellum is not an outboard motor, and no one is claiming that mousetraps evolved gradually by natural selection.

Behe nearly catches his own error. He notes: "Metaphors, of course, do not denote the thing they are applied to. They are vague

analogies . . . [I]f metaphors are taken too seriously in science, they can be confusing at best; and they can often be actively misleading (p201)." Though he has no issue with calling a flagellum an outboard motor, or likening the cellular assembly of a magnetosome to "a fully automated human factory . . . manufacturing a compass (p53)," the metaphor he finds offensive is "natural selection" (pp. 200–203). This is not a new grievance. Creationists have long complained that "natural selection" is tautological by definition and impotent in practice: nature can never "choose" in the same way that an intelligent breeder can, they say. Over 40 years ago, Stephen Jay Gould presented a clear defense of why natural selection is a valid mechanism and not just rhetorical ploy:

> "Darwin was justified in analogizing natural selection with animal breeding. In artificial selection, a breeder's desire represents a "change of environment" for a population. In this new environment, certain traits are superior *a priori*; (they survive and spread by our breeder's choice, but this is a *result* of their fitness, not a definition of it)" (Gould 1977, emphasis in the original).

In other words, a breeder is playing the role of the environment, acting as matchmaker and executioner. Breeders do not engineer purposeful mutations into the genomes of their subjects, as Behe's Intelligent Designer does. The fodder for selection—be it artificial or natural—is the same: random variation.

IRREDUCIBLE COMPLEXITY IS A FLAWED CONCEPT

Proteins are promiscuous (Hammer et al. 2017). They moonlight, by chance interacting with other cellular components to effect phenotype outside their traditionally ascribed roles (Copley 2014). These adventitious functions can be strengthened by selection, allowing a protein to assume a new or a dual role. This topic was raised in a recent review of *Darwin Devolves* in *Science* (Lents et al. 2019), where the authors highlight a study that employed experimental evolution to strengthen the weak nascent ability of a protein in the histidine biosynthesis pathway to act on a similar substrate in tryptophan biosynthesis (Näsvall et al. 2012). For multifunctional proteins, gene duplication and divergence can parse specific functions into separate proteins, each now free to specialize to its own task (Hittinger and Carroll 2007).

By acknowledging the reality that proteins are proteins, and not machines, we immediately recognize the shortcomings of irreducible complexity—a central pillar of the intelligent design movement. An irreducibly complex system, as defined by Behe, is "a single 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 (p230)." Such systems, according to Behe, could not have arisen by unguided evolution. The concept of irreducible complexity is flawed for two reasons. First, it considers a system only in its current state and assumes that complex interdependency has always existed. Second, irreducible complexity does not consider that proteins perform multiple functions and, therefore, evolutionary paths that seem unlikely when considering only one function may be realized through a series of stepwise improvements on another function.

Simply because a system in its current form is irreducibly complex is not evidence that it did not evolve by random mutation and natural selection. Essentiality of a gene or protein is relative to its current state. For two closely related strains of yeast, between 1% and 5% of genes that are essential in one strain are dispensable in the other (Dowell et al. 2010). Conditional essentiality is not simply due to the presence of second copy (or a close paralog) of the gene in one strain but not the other; rather, conditional essentiality is a complex trait involving two or more modifying loci (Dowell et al. 2010). Because most genomes contain thousands of genes organized into complex and interconnected genetic interaction networks, subtle perturbations to these networks—even on short evolutionary time scales—will have significant effects on how we define essentiality.

TWO EXAMPLES TO ILLUSTRATE THE EVOLUTION OF COMPLEXITY

Systems that meet Behe's definition of irreducible complexity do, in fact, evolve by random unguided processes. In most eukaryotes, the vacuolar ATPase contains a six-member V_0 ring consisting of five subunits of Vma3 and one subunit of Vma16. In the ancestor of all fungi the *VMA3* gene was duplicated around the time that fungi split from all other eukaryotes, approximately one billion years ago (Finnigan et al. 2012). Initially Vma3 and its paralog, called Vma11, were interchangeable; however, over time the binding interfaces of Vma3 and Vma11 degraded such that Vma11, Vma3, and Vma16 all became essential components of the vacuolar ATPase (Finnigan et al. 2012). The increase in the complexity of the vacuolar ATPase is a clear example of how gene duplication and degenerative mutations—processes Behe admits occur by random unguided processes—can result in an increase in complexity and molecular novelty. (It is worth noting that the vacuolar ATPase is one of only a few "rotary motors" in biology; another being the exemplar of irreducible complexity: the bacterial flagellum).

As he has before, Behe is likely to object to the first purported step in this process—gene duplication—as neutral and therefore highly unlikely to occur. Ever the rigid selectionist, Behe has offered an alternative definition of irreducible complexity to contend with evolutionary scenarios like the vacuolar ATPase: "An irreducibly complex evolutionary pathway is one that contains one or more unselected steps (that is, one or more necessary-but-unselected mutations) (Behe 2000)." This formulation of irreducible complexity is weak, for two reasons. First, we have long known that many neutral or nearly neutral

genetic variants (including copy number variants) segregate in natural populations (e.g. see Dykhuizen and Hartl 1980) and are available to potentiate future adaptive events. Second, looking retrospectively, it is incorrect to assume that gene duplications, such as that of *VMA3*, are necessarily neutral. There are numerous examples of beneficial gene duplications for the sake of increasing gene dosage in extant natural populations (Karin et al. 1984; Wieland et al. 1995), in historical evolution (Connant and Wolfe 2007), and in experimental evolution (Kvitek and Sherlock 2011; Payen et al. 2014; Lauer et al. 2018). An equally valid hypothesis—though not a necessary one for the validity of this evolutionary scenario overall—is that duplication of *VMA3* was beneficial in the context in which it arose.

Irreducible complexity also fails to account for the reality that most proteins—unlike the fishing rods, hammers, and gears in *Darwin Devolves*—perform multiple functions, bind to multiple other proteins, and thus evolve on multiple fitness landscapes simultaneously. Experimental evolution of lambda bacteriophage in coculture with *E. coli* showed that phage can evolve the ability to bind a novel receptor, OmpF (Meyer et al. 2012). Each of four mutations in the phage J protein (a tail protein that mediates host binding) is required in an "all-or-none" manner in order for the J protein to bind to OmpF. This evolutionary pathway satisfies Behe's definition of irreducible complexity: remove any one of these four interacting mutations and binding to OmpF is abolished. How then did these four mutations arise? It turns out that individually, these mutations improve binding to the original receptor LamB. While adapting along a step-wise evolutionary path of improved binding to LamB, the J protein was able to acquire the ability to bind to a new receptor—to evolve a novel protein–protein interaction that was dependent upon four mutations acting in an all-or-none manner, well beyond Behe's "edge of evolution."

Conclusion and Outlook

Without a hint of irony, *Darwin Devolves* cautions us that "[t]he academic ideas of nutty professors don't always stay confined to ivory towers. They sometimes seep out into the wider world with devastating results (p257)."

Scientists—by nature or by training—are skeptics. Even the most time-honored theories are reevaluated as new data come to light. There is active debate, for example, on the relative importance of changes to regulatory versus coding sequence in evolution (Hoekstra and Coyne 2007; Stern and Orgogozo 2008), the role of neutral processes in evolution (Kern and Hahn 2018; Jensen et al. 2019), and the extent to which evolutionary paths are contingent on chance events (Blount et al. 2018). Vigorous debate is part and parcel of the scientific process, lest our field stagnate. Behe, however, belabors the lack of consensus on relatively minor matters to proclaim that evolutionary biology as a whole is on shaky ground.

By reviewing Behe's latest book, we run the risk of drawing attention—or worse, giving credibility—to his ideas. Books like *Darwin Devolves*, however, must be openly challenged and refuted, even if it risks giving publicity to misbegotten views. Science benefits from public support. Largely funded by federal grants, scientists have a moral responsibility (if not a financial obligation) to ensure that the core concepts of our respective fields are communicated effectively and accurately to the public and to our trainees. This is particularly important in evolutionary biology, where—over 150 years after *On the Origin of Species*—less than 20% of Americans accept that humans evolved by natural and unguided processes (Gallup 2014). It is hard to think of any other discipline where mainstream acceptance of its core paradigm is more at odds with the scientific consensus.

Why evolution by natural selection is difficult for so many to accept is beyond the scope of this review; however, it is not for a lack of evidence: the data (only some of which we present here) are more than sufficient to convince any open-minded skeptic that unguided evolution is capable of generating complex systems. A combination of social and historical factors creates a welcoming environment for an academic voice that questions the scientific consensus. *Darwin Devolves* was designed to fit this niche.

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