

EVOLUTION

God as Genetic Engineer

Sean B. Carroll

"The Lord hath delivered him into mine hands."

Those are the words that Thomas Huxley, Darwin's confidant and staunchest ally, purportedly murmured to a colleague as he rose to turn Bishop Samuel Wilberforce's own words to his advantage and rebut the bishop's critique of Darwin's theory at their legendary 1860 Oxford debate. They are also the first words that popped into my head as I read Michael J. Behe's *The Edge of Evolution: The Search for the Limits of Darwinism*. In it, Behe makes a new set of explicit claims about the limits of Darwinian evolution, claims that are so poorly conceived and readily dispatched that he has unwittingly done his critics a great favor in stating them.

In *Darwin's Black Box: The Biochemical Challenge to Evolution* (1), Behe had forwarded the notion that certain biochemical systems were "irreducibly complex," could not have evolved stepwise by Darwinian mechanisms, and thus were intelligently designed. Since that earlier book, Behe has played a key role in the intelligent design (ID) movement, including a star turn as a defense witness in the 2005 Dover school board case. Despite his testimony—or, I should say, partly because of what he said (2)—ID was ruled to be a religious concept and its teaching in public schools unconstitutional.

Behe, a professor of biochemistry at Lehigh University, has found an audience among various flavors of creationists who find Darwinian evolution incompatible with their religious views and see scientific validation in Behe's claims. Clearly, this book's main audience would be that constituency, although they will find some parts very discomfiting. For instance, Behe explicitly accepts the ability of random mutation and selection to account for the variation within and differences between closely related species (but not higher taxa

such as vertebrate classes). He also accepts (as he has before) the 4.5-billion-year age of Earth and that we share a common ancestor with chimpanzees. That certainly won't go over well in some camps.

Behe also explores some examples of Darwinian evolution at the molecular level, including an extensive treatment of the evolutionary "trench warfare" fought between humans and malarial parasites over the millennia—all in the context of what Darwinian evolution "can do." So what's the problem?

The problem is what Behe asserts Darwinian evolution can't do: produce more "complex" changes than those that have enabled humans to battle malaria or allowed malarial parasites to evade the drugs we throw at them. Behe's main argument rests on the

proteins evolve and how proteins interact, and he completely ignores a huge amount of experimental data that directly contradicts his faulty premises. Unfortunately, these errors are of a technical nature and will be difficult for lay readers, and even some scientists (those unfamiliar with molecular biology and evolutionary genetics), to detect. Some people will be hoodwinked. My goal here is to point out the critical flaws in Behe's key arguments

and to guide readers toward some references that illustrate why what he alleges to be beyond the limits of Darwinian evolution falls well within its demonstrated powers.

Behe's chief error is minimizing the power of natural selection to act cumulatively as traits or molecules evolve

stepwise from one state to another via intermediates. Behe states correctly that in most species two adaptive mutations occurring instantaneously at two specific sites in one gene are very unlikely and that functional changes in proteins often involve two or more

sites. But it is a non sequitur to leap to the conclusion, as Behe does, that such multiple-amino acid replacements therefore can't happen. Multiple replacements can accumulate when each single amino acid replacement affects performance, however slightly, because selection can act on each replacement individually and the changes can be made sequentially.

Behe begrudgingly allows that only "rarely, several mutations can sequentially add to each other to improve an organism's chances of survival." Rarely? This, of course, is the everyday stuff of evolution. Examples of cumulative selection changing multiple sites in evolving proteins include tetrodotoxin resistance in snakes (3), the tuning of color vision in animals (4),

cefotaxime antibiotic resistance in bacteria (5), and pyrimethamine resistance in malarial parasites (6)—a notable omission given Behe's extensive discussion of malarial drug-resistance.

Behe seems to lack any appreciation of the quantitative dimensions of molecular and trait evolution. He appears to think of the functional features of proteins in qualitative terms, as if binding or catalysis were all or nothing rather than a broad spectrum of affinities or rates. Therefore, he does not grasp the funda-

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assertion that two or more simultaneous mutations are required for increases in biochemical complexity and that such changes are, except in rare circumstances, beyond the limit of evolution. He concludes that "most mutations that built the great structures of life must have been nonrandom." In short, God is a genetic engineer, somehow designing changes in DNA to make biochemical machines and higher taxa.

But to arrive at this conclusion, Behe relies on invalid assertions about how genes and

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mental reality of a mutational path that proteins follow in evolving new properties.

This lack of quantitative thinking underlies a second, fatal blunder resulting from the mistaken assumptions Behe makes about protein interactions. The author has long been concerned about protein complexes and how they could or, rather, could not evolve. He argues that the generation of a single new protein-protein binding site is extremely improbable and that complexes of just three different proteins “are beyond the edge of evolution.” But Behe bases his arguments on unfounded requirements for protein interactions. He insists, based on consideration of just one type of protein structure (the combining sites of antibodies), that five or six positions must change at once in order to make a good fit between proteins—and, therefore, good fits are impossible to evolve. An immense body of experimental data directly refutes this claim. There are dozens of well-studied families of cellular proteins (kinases, phosphatases, proteases, adaptor proteins, sumoylation enzymes, etc.) that recognize short linear peptide motifs in which only two or three amino acid residues are critical for functional activity [reviewed in (7–9)]. Thousands of such reversible interactions establish the protein networks that govern cellular physiology.

Very simple calculations indicate how easily such motifs evolve at random. If one assumes an average length of 400 amino acids for proteins and equal abundance of all amino acids, any given two-amino acid motif is likely to occur at random in every protein in a cell. (There are 399 dipeptide motifs in a 400-amino acid protein and $20 \times 20 = 400$ possible dipeptide motifs.) Any specific three-amino acid motif will occur once at random in every 20 proteins and any four-amino acid motif will occur once in every 400 proteins. That means that, without any new mutations or natural selection, many sequences that are identical or close matches to many interaction motifs already exist. New motifs can arise readily at random, and any weak interaction can easily evolve, via random mutation and natural selection, to become a strong interaction (9). Furthermore, any pair of interacting proteins can readily recruit a third protein, and so forth, to form larger complexes. Indeed, it has been demonstrated that new protein interactions (10) and protein networks (11) can evolve fairly rapidly and are thus well within the limits of evolution.

Is it possible that Behe does not know this body of data? Or does he just choose to ignore it? Behe has quite a record of declaring what is impossible and of disregarding the scientific literature, and he has clearly not learned any

lessons from some earlier gaffes. He has again gone “public” with assertions without the benefit (or wisdom) of first testing their strength before qualified experts.

For instance, Behe once wrote, “if random evolution is true, there must have been a large number of transitional forms between the *Mesonychid* [a whale ancestor] and the ancient whale. Where are they?” (12). He assumed such forms would not or could not be found, but three transitional species were identified by paleontologists within a year of that statement. In *Darwin's Black Box*, he posited that genes for modern complex biochemical systems, such as blood clotting, might have been “designed billions of years ago and have been passed down to the present ... but not ‘turned on.’” This is known to be genetically impossible because genes that aren't used will degenerate, but there it was in print. And Behe's argument against the evolution of flagella and the immune system have been dismantled in detail (13, 14) and new evidence continues to emerge (15), yet the same old assertions for design reappear here as if they were uncontested.

The continuing futile attacks by evolution's opponents reminds me of another legendary confrontation, that between Arthur and the Black Knight in the movie *Monty Python and the Holy Grail*. The Black Knight, like evolution's challengers, continues to fight even as each of his limbs is hacked off, one by one. The “no transitional fossils” argument and the “designed genes” model have been cut clean off, the courts have debunked the “ID is science” claim, and the nonsense here about the edge of evolution is quickly sliced to pieces by well-established biochemistry. The knights of ID may profess these blows are “but a scratch” or “just a flesh wound,” but the argument for design has no scientific leg to stand on.

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EVOLUTION

A Multilevel Exploration

David Jablonski

In the natural world, as in human societies, complexity is almost always organized hierarchically. From the nested structures of armies and corporations to the classical biological progression from molecule to cell to tissue to body to species, the “particles” at each level tend to be grouped into ever more inclusive units. However, despite the ubiquity of natural hierarchies, their evolutionary implications have been anything but clear.

Evolution and the Levels of Selection is a major contribution toward putting this controversial area on a coherent conceptual and philosophical footing. Samir Okasha's argument hinges on two components, neither of them new but here powerfully and creatively integrated and extended. First is the fundamental distinction between two disparate kinds of multilevel selection (MLS), often conflated despite their formal introduction 20 years ago (1), with even earlier prece-dents. The failure to appreciate this distinction has generated an enormous amount of confusion, at times bordering on fury, and Okasha's use of this conceptual framework brings exceptional clarity and precision to a wide range of issues. In essence, for MLS1 the sole focal level is the individual (at any level), but its fitness depends partly on the group to which it belongs. The classic example is the seeming paradox of altruism: how can selection drive behavior that aids others at the

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