Molecular Machinery

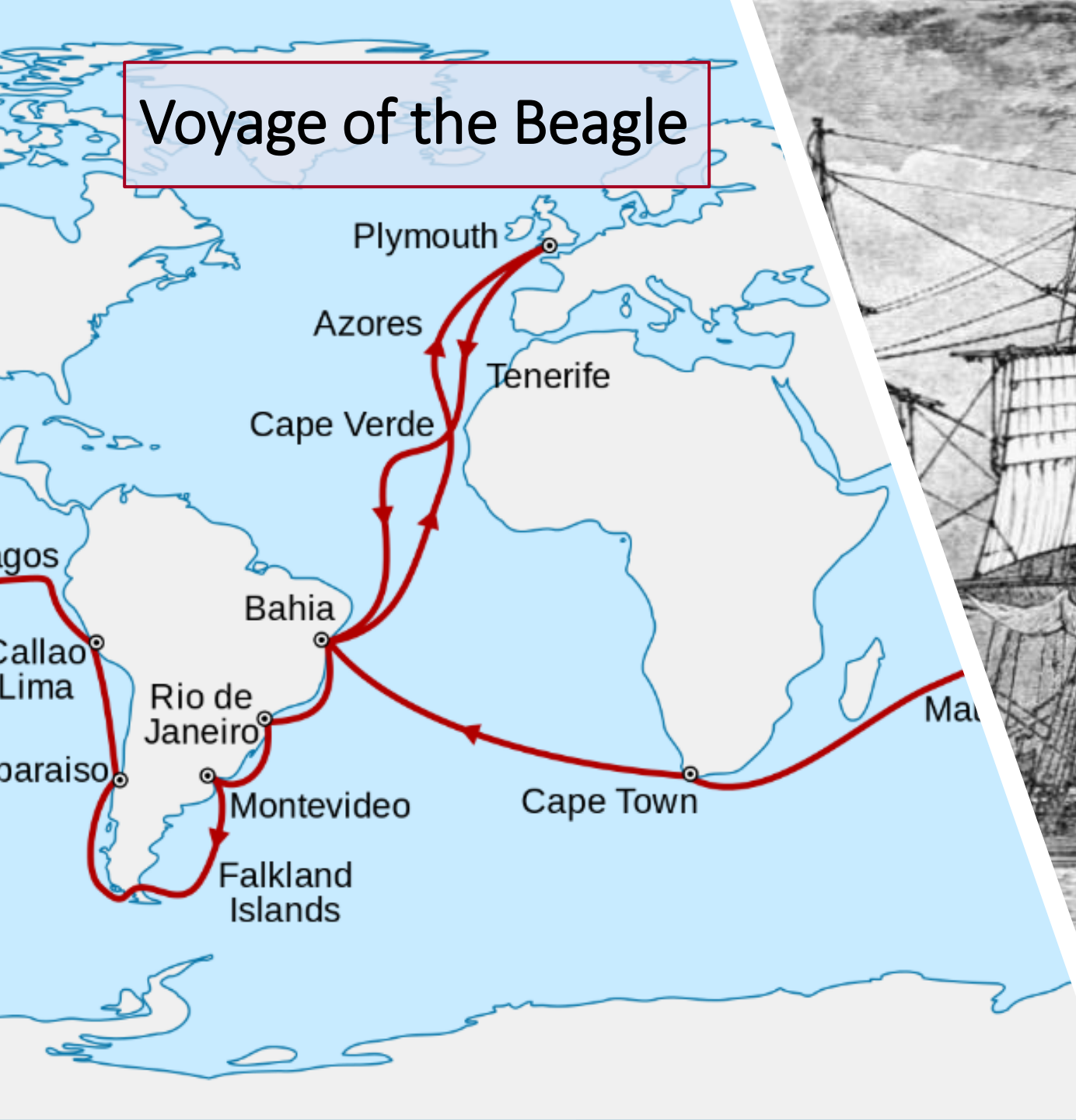
Obstacle to Darwinian Evolution &
Evidence of Purposeful Design

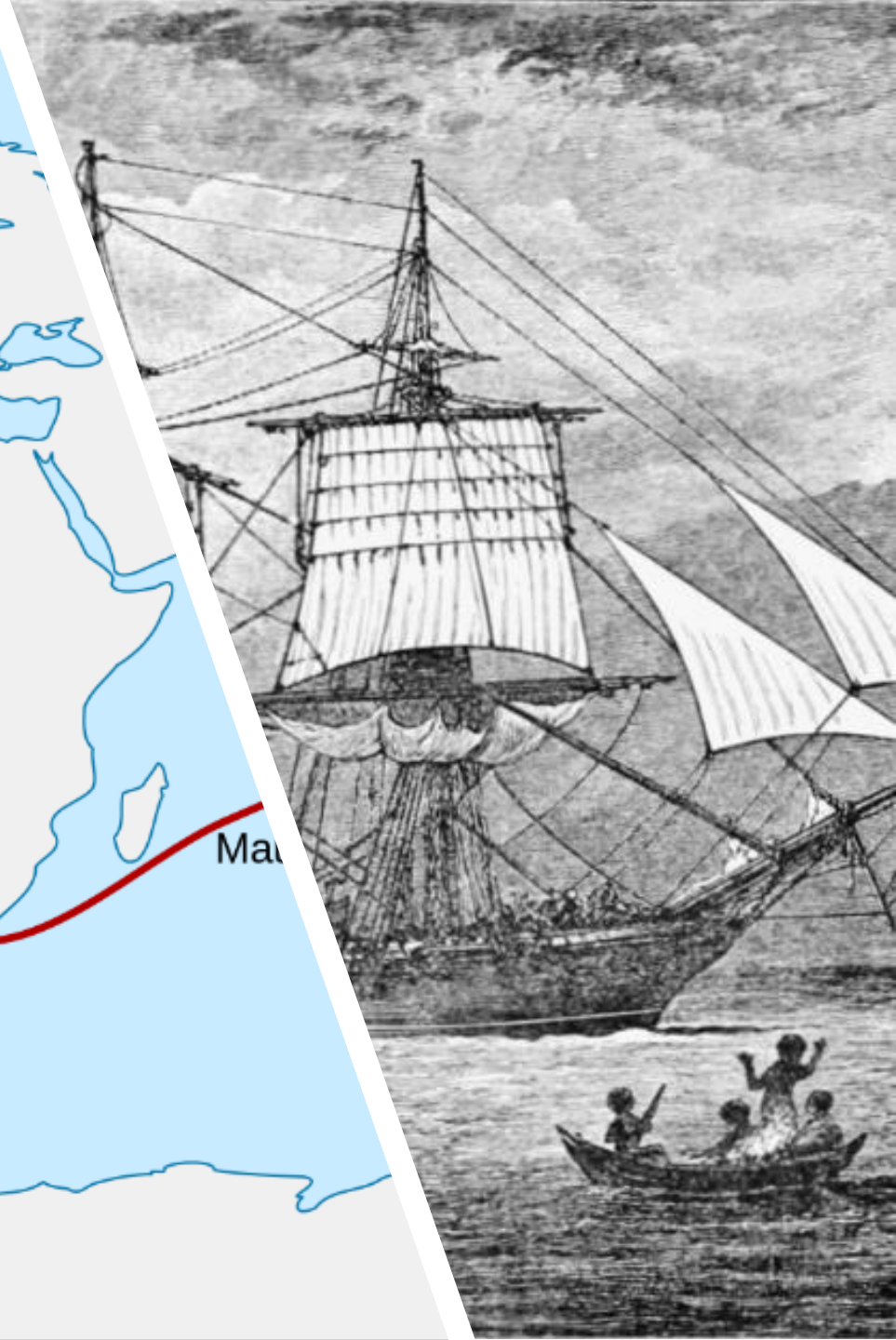
Michael J Behe
Lehigh University
Bethlehem, PA

Charles Darwin

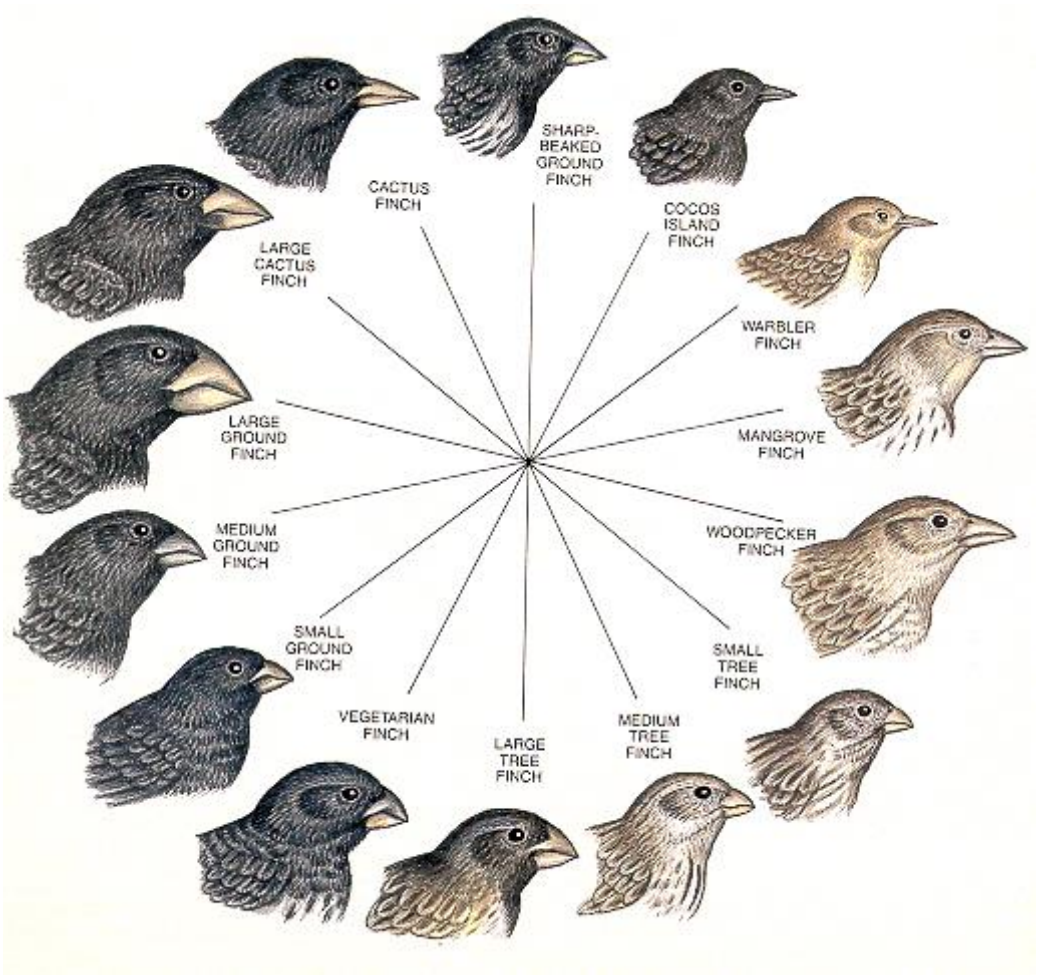
1809-1882

Voyage of the Beagle



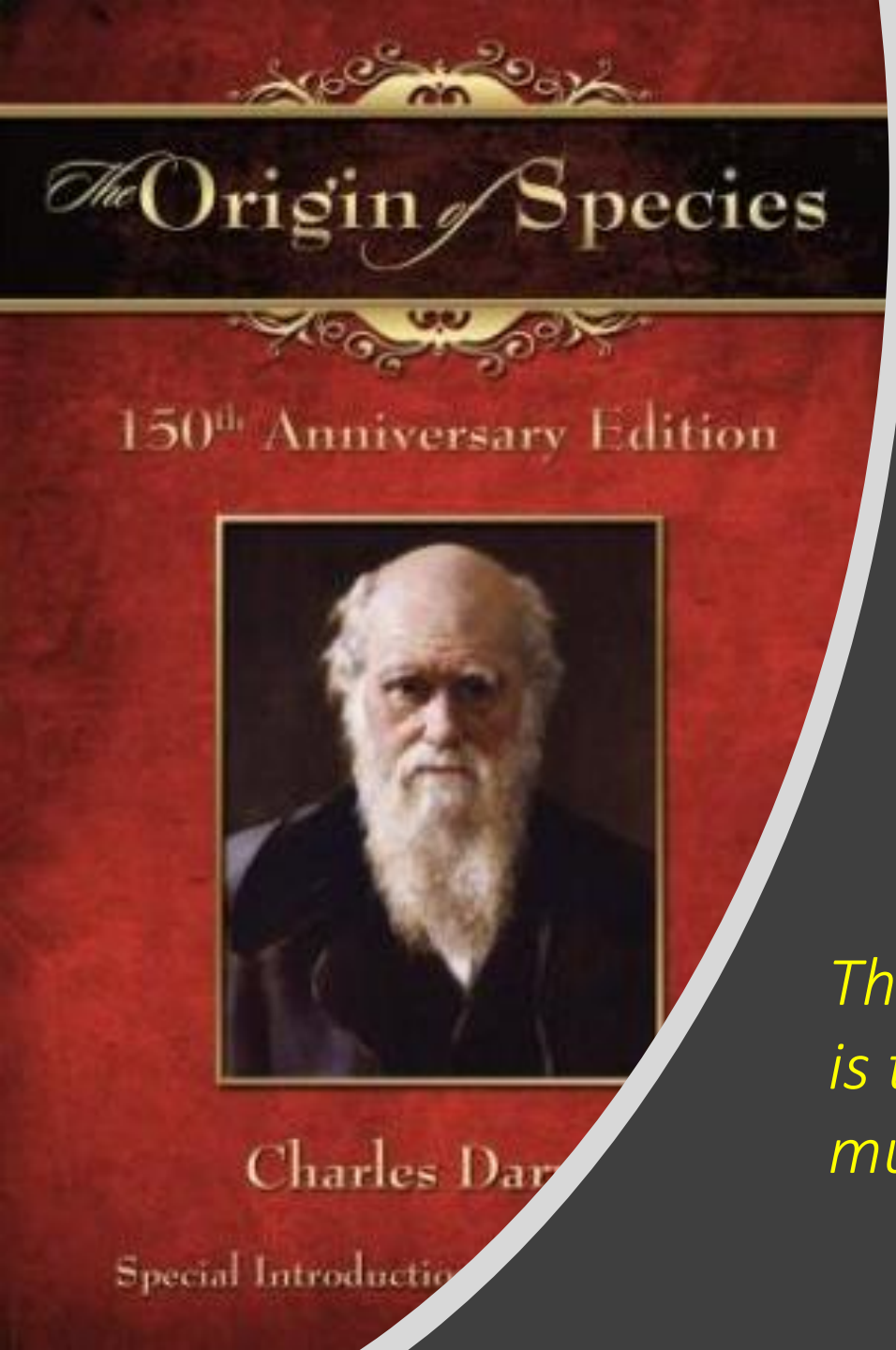


Galápagos finch species



Darwin's theory of evolution by natural selection

- Individuals of a species can vary
- Some variations favor survival
- Individuals who survive longer will leave more offspring
- If traits are inherited, over generations the species will change



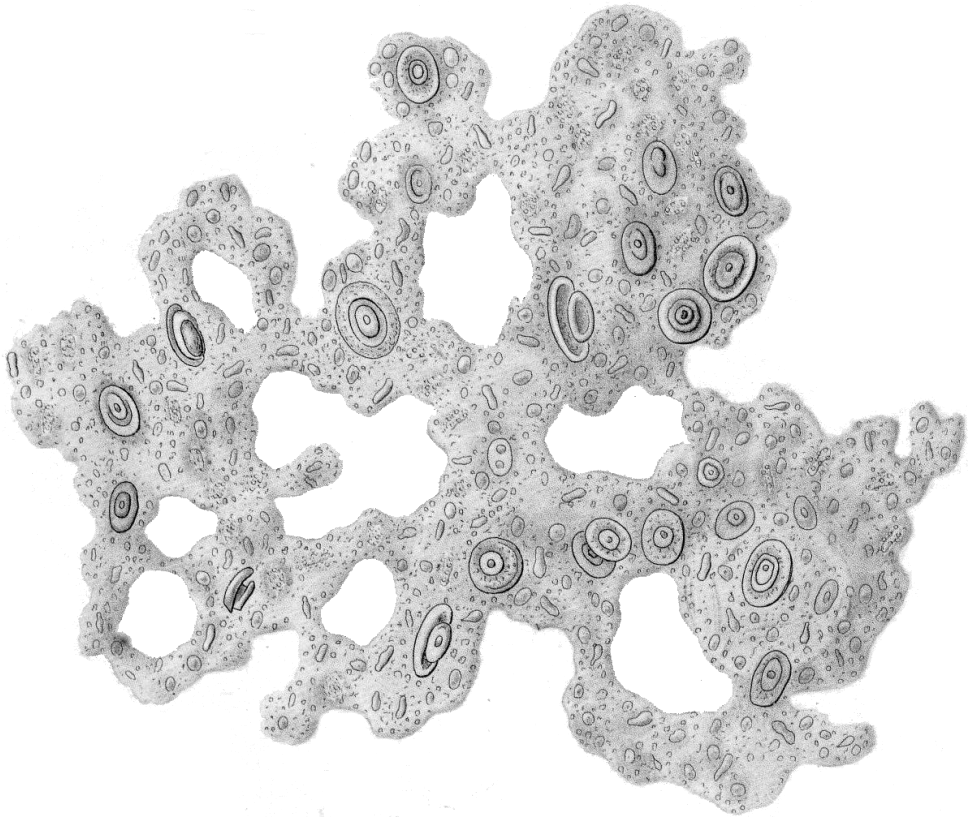
"Darwin's theory" actually has *multiple* parts. Some parts **may** be right, others wrong.

Common descent
(interesting, but trivial);
Natural selection
(interesting, but trivial);
Random mutation

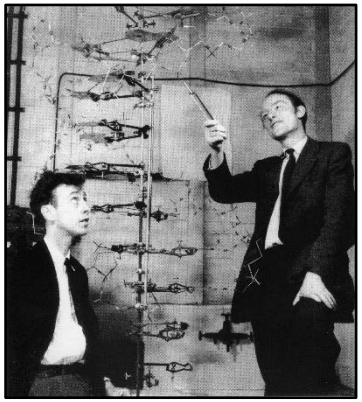
The critical claim of Darwinism is the sufficiency of random mutation

Bathybius haeckelii
1870

“Protoplasm”



Early 1950s



Late 1950s

1960s

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	TTC		TCC		TAC		TGC		C
	TTA	leu	TCA		TAA	stop	TGA	stop	A
	TTG		TCG		TAG		TGG	try	G
C	CTT	leu	CCT	pro	CAT	his	CGT	arg	T
	CTC		CCC		CAC		CGC		C
	CTA		CCA		CAA	gln	CGA		A
	CTG		CCG		CAG		CGG		G
A	ATT	ile	ACT	thr	AAT	asp	AGT	ser	T
	ATC		ACC		AAC		AGC		C
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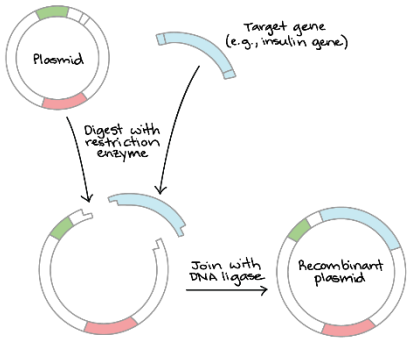
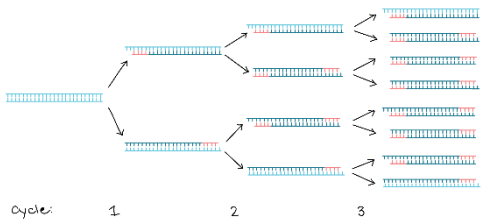
	ATG	met	ACG		AAG		AGG		G
G	GTT	val	GCT	ala	GAT	asp	GGT	gly	T
	GTC		GCC		GAC		GGC		C
	GTA		GCA		GAA	glu	GGA		A
	GTG		GCG		GAG		GGG		G

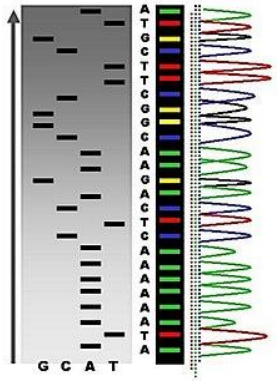
1970s

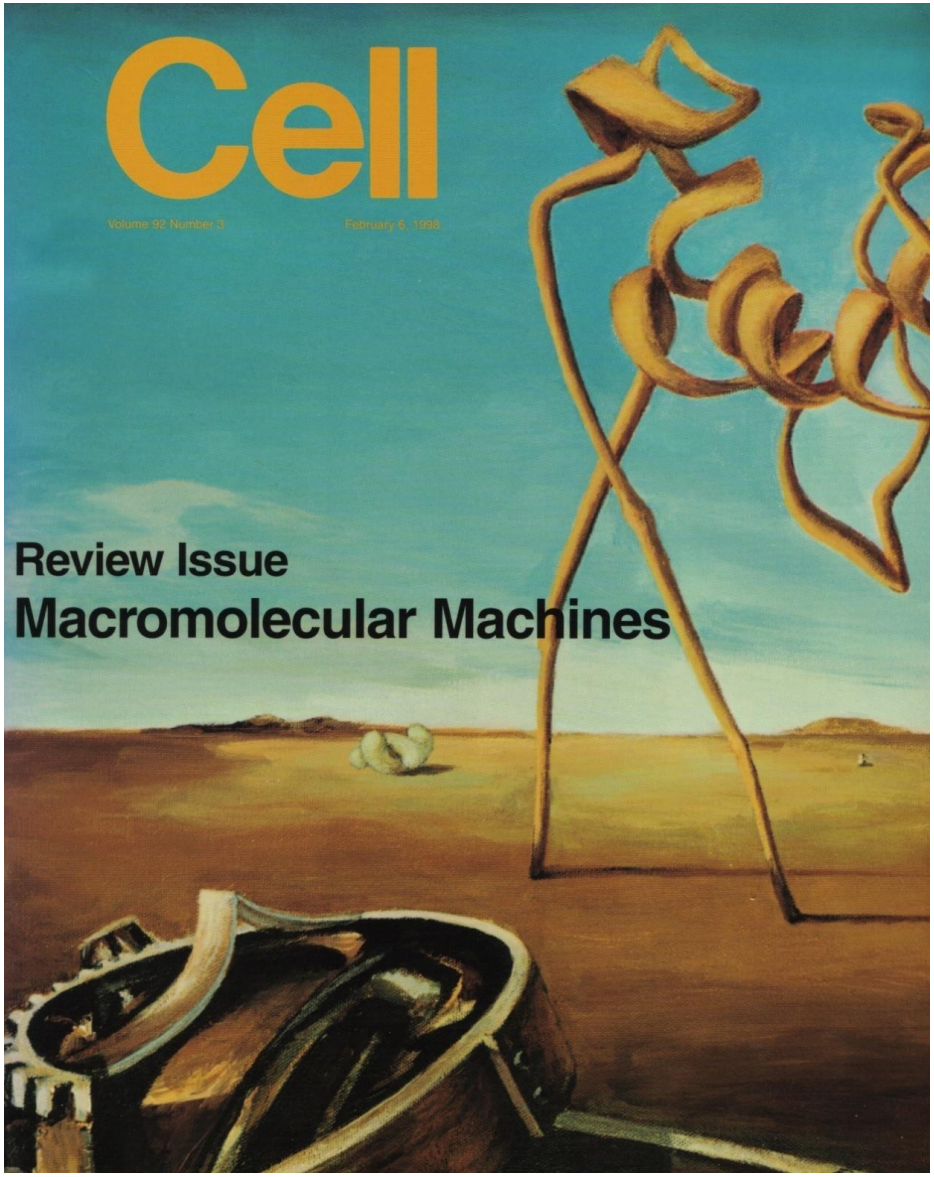


1980s



2000s

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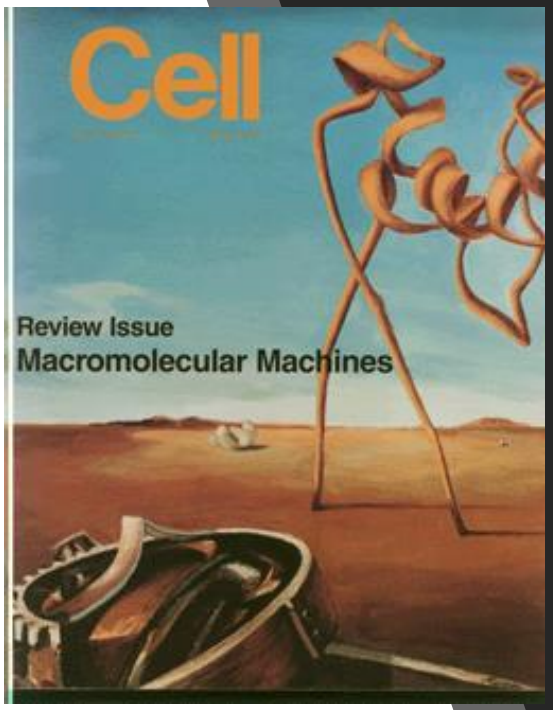
Macromolecular Machines

Cell (1998) **92**, table of contents.



- **The Cell as a Collection of Protein Machines: Preparing the Next Generation of Molecular Biologists**, Bruce Alberts
- **Polymerases and the Replisome: Machines within Machines,** Tania A Baker and Stephen P Bell
- **Eukaryotic Transcription: An Interlaced Network of Transcription Factors and Chromatin-Modifying Machines**, James T Kadonaga
- **Mechanical Devices of the Spliceosome: Motors, Clocks, Springs, and Things,** Jonathan P Staley and Christine Guthrie
- **Molecular Movement inside the Translational Engine,** Kevin S Wilson and Harry F Noller
- **The Hsp70 and Hsp60 Chaperone Machines,** Bernd Bukau and Arthur L Horwich

2020s

nature structural & molecular biology

ARTICLES

https://doi.org/10.1038/s41594-020-0503-8

Check for updates

Cryo-EM structure of the entire mammalian F-type ATP synthase

Gergely Pinke, Long Zhou and Leonid A. Sazanov

The majority of adenosine triphosphate (ATP) powering cellular processes in eukaryotes is produced by the mitochondrial F1Fo ATP synthase. Here, we present the atomic models of the membrane Fo domain and the entire mammalian (ovine) F1Fo, determined by cryo-electron microscopy. Subunits in the membrane domain are arranged in the 'proton translocation cluster' attached to the c-ring and a more distant 'hook apparatus' holding subunit e. Unexpectedly, this subunit is anchored to a lipid 'plug' capping the c-ring. We present a detailed proton translocation pathway in mammalian Fo and key inter-monomer contacts in F1Fo multimers. Cryo-EM maps of F1Fo exposed to calcium reveal a retracted subunit e and a disassembled c-ring, suggesting permeability transition pore opening. We propose a model for the permeability transition pore opening, whereby subunit e pulls the lipid plug out of the c-ring. Our structure will allow the design of drugs for many emerging applications in medicine.

The ATP synthase (F1Fo) employs a unique rotary mechanism, harvesting the proton motive force (PMF) created during respiration in mitochondria by electron transport chain (ETC) complexes[1,2]. The ATP synthase/ATPase family comprises membrane-bound protein complexes responsible either for ATP synthesis, utilizing PMF (F-type and A-type), or for establishing PMF using the energy released from ATP hydrolysis (V-type)[3,4]. F-type enzymes produce ATP in bacteria, chloroplasts and mitochondria, while V-ATPases (vacuolar) acidify the interior of eukaryotic intracellular compartments. The F1Fo complex consists of a soluble F1 domain, responsible for the synthesis of ATP, and a membrane Fo domain, involved in proton translocation. These domains are connected by a central stalk rotating inside the F1 and a stationary peripheral stalk (PS)[3,5]. During ATP synthesis, PMF-driven rotation of the c-ring in Fo is transmitted via the central stalk to power the conformational changes in the F1, resulting in the synthesis of one ATP molecule per 120° rotation (because F1 is three-fold symmetric).

F1Fo plays other important roles apart from energy generation. ETC complexes I–IV are mostly organized into supercomplexes[6–9] in flat regions of the inner mitochondrial membrane (IMM)[10]. F1Fo, on the other hand, forms rows of dimers along the highly curved cristae ridges, thus shaping them[11]. The enzyme is also implicated in the formation of the permeability transition pore (PTP), which triggers cell death[12,13].

PTP opening can be triggered by the accumulation of Ca^{2+} or by intense oxidative stress, characterizing ischemia-reperfusion injury[13–15]. The initial opening of the PTP is reversible, establishing a 2–3-nm pore, followed by mitochondria swelling and rupture, the release of pro-apoptotic factors such as cytochrome *c* and cell death[13,16]. The molecular nature of the PTP is controversial. The mitochondrial matrix protein cyclophilin D (CyPD)[17] sensitizes the PTP to Ca^{2+}. CyPD binding to its partners is blocked by cyclosporin A (CsA), which inhibits the PTP[17]. The recent discovery that CyPD binds to F1Fo subunit OSCP opened up the possibility that F1Fo forms the PTP[12]. Many recent studies have both supported[18–25] and refuted[26–28] the still hotly debated role of F1Fo in the PTP (Supplementary Note 1). Several mutagenesis studies converge on the c-ring as a possible location of the pore[18,29,30].

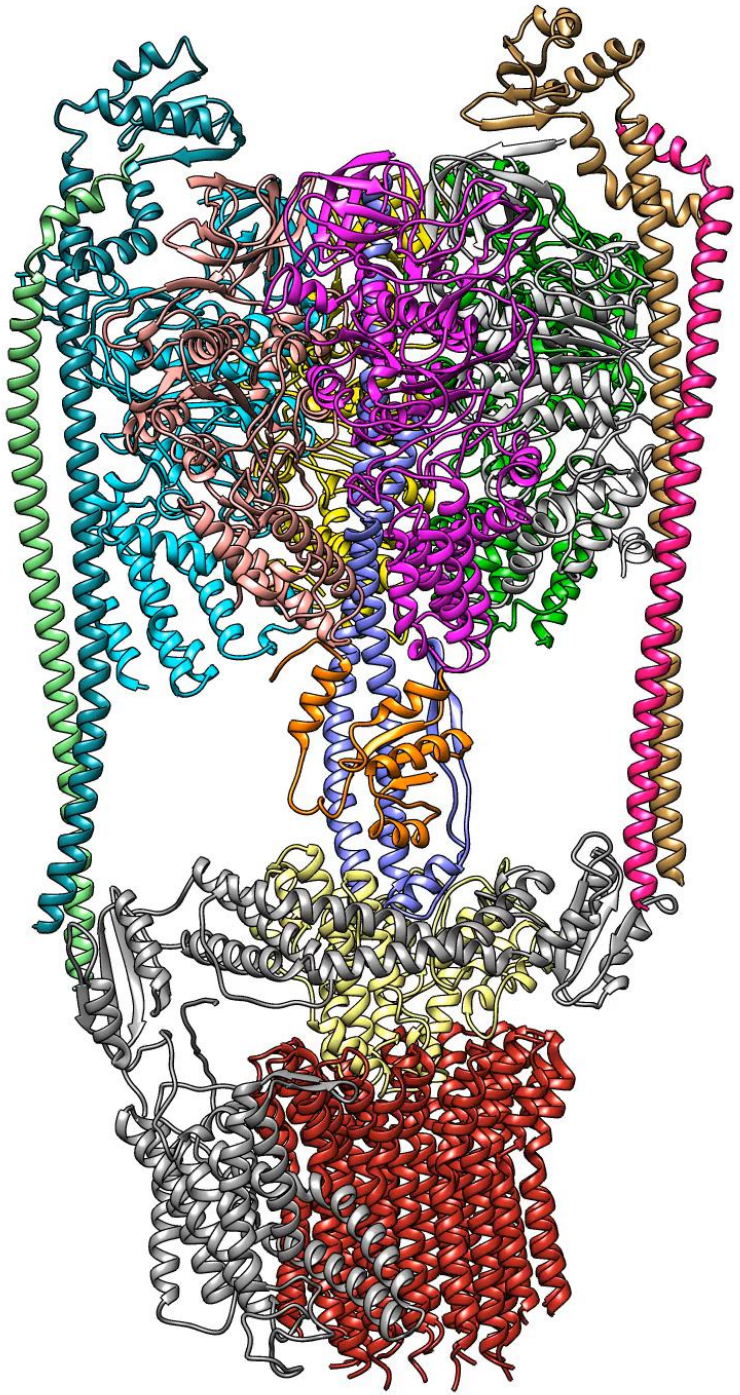
We have previously determined the first atomic structure of V/A-ATPase as a representative of the V-type family[31]. Structures of entire bacterial[32], yeast[33] and chloroplast[34] F-type ATP synthases have also been determined recently. However, knowledge about the arguably most important representative of the family—mammalian mitochondrial ATP synthase—remains incomplete. Crystallography has revealed many structures of F1 subcomplexes[3,5,35], as have cryo-EM studies on the entire complex[36]. The recent porcine enzyme model is the most complete so far[37]. However, due to the limited resolution in the membrane domain, four subunits were modeled as poly-alanine and three more were completely misplaced, so the atomic model for most of the membrane domain remains unknown.

Detailed knowledge about the Fo domain is of crucial importance because this is where the proton translocation takes place and where the monomers interact to form physiological dimers. Here, we address these questions by solving the structure of the entire mammalian F1Fo.

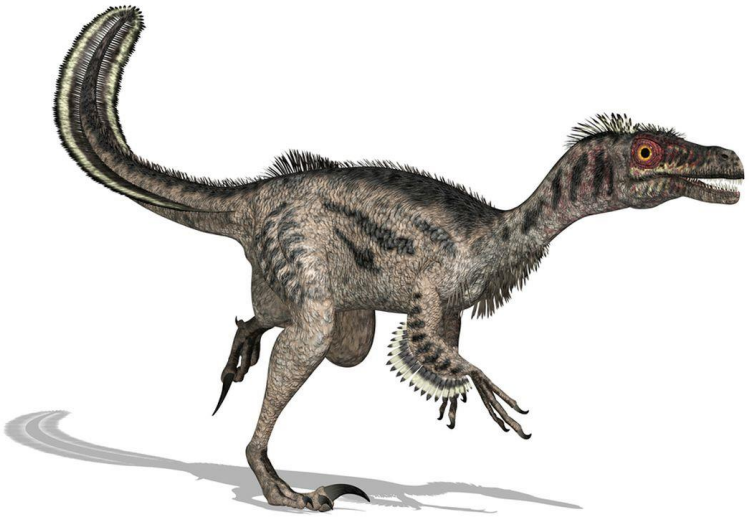
Results

Structure determination. We purified ATP synthase from ovine heart mitochondria in the mild detergent laurylmaltose neopentylglycol (LMNG) and collected two datasets, from the 'monomer' and 'multimer' fractions (Extended Data Fig. 1a–c). The most populated and best resolved ground state of the monomer (Extended Data Fig. 1d) is similar to the previously observed (at lower resolution) state 1a of bovine enzyme (PDB 5ARA)[36]. The other two main rotational states (resulting from ~120° rotation of the central stalk subunit γ) were only at ~7–8-Å resolution due to the lower number of particles (Extended Data Fig. 2). Further 'in-between' states were also present, but with some of the α/β subunits disordered, possibly due to lower enzyme stability in such states. State-1a F1Fo maps were refined to 3.8-Å resolution overall (Extended Data Figs. 1d and 3d), with focused refinements reaching 3.5 Å for the F1 domain and 4.2 Å for Fo (obtained using a novel strategy of weighted masks; Methods). Focusing on Fo classification of particles in all rotational states revealed that the majority of particles classify into one consensus class, producing, after Fo-focused refinement, a 3.8-Å-resolution map (Extended Data Fig. 3e). This map was well resolved at the side chain level in all Fo areas (Extended Data Fig. 4e,l), suggesting that,

Institute of Science and Technology Austria, Klosterneuburg, Austria. e-mail: sazanov@ist.ac.at

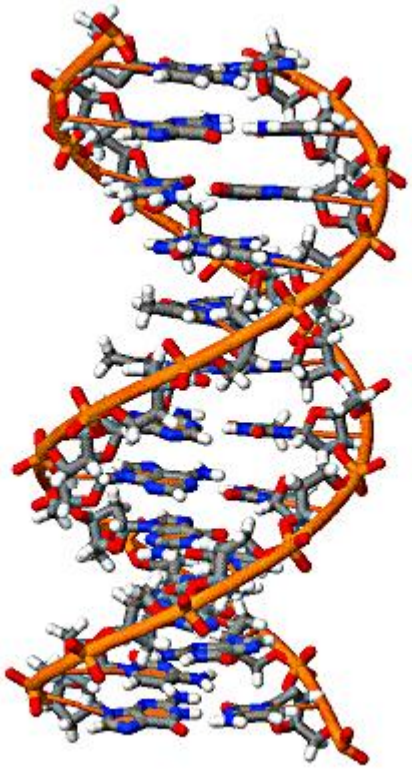


How most people think of evolution

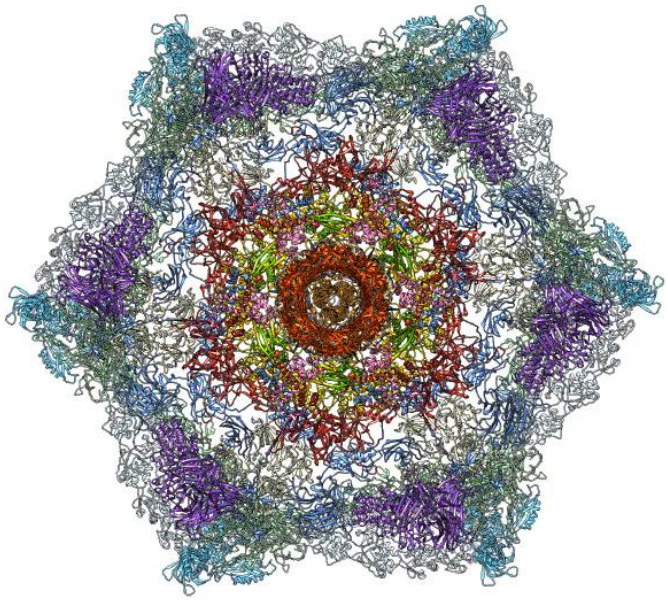


How they *should* think of evolution

information and *molecular machinery* are the basis of life



DNA



Bacteriophage T4

Why We *Should* Think That Life Was Purposely Designed

"All the News That's Fit to Print"

The New York Times

National Edition

Washington and Oregon: Primarily cloudy, a few flurries or snow showers in eastern Oregon. Partly to mostly sunny elsewhere. Highs from 30's to near 50. Weather map, Page D12.

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MONDAY, FEBRUARY 7, 2005

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ONE DOLLAR

Design for Living

By Michael J. Behe

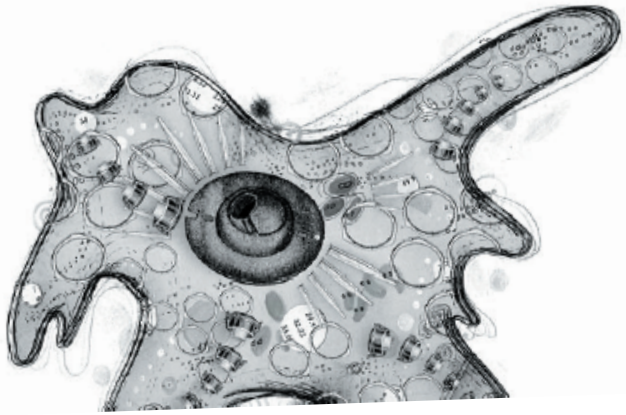
Bethlehem, Pa.

IN the wake of the recent lawsuits over the teaching of Darwinian evolution, there has been a rush to debate the merits of the rival theory of intelligent design. As one of the scientists who have proposed design as an explanation for biological systems, I have found widespread confusion about what intelligent design is and what it is not.

First, what it isn't: the theory of intelligent design is not a religiously based idea, even though devout people opposed to the teaching of evolution cite it in their arguments. For example, a critic recently caricatured intelligent design as the belief that if evolution occurred at all it could never be explained by Darwinian natural selection and could only have been directed at every stage by an omniscient creator. That's misleading. Intelligent design proponents do

mechanisms like a watch is enormously stronger than what Reverend Paley imagined. In the past 50 years modern science has shown that the cell, the very foundation of life, is run by machines made of molecules. There are little molecular trucks in the cell to ferry supplies, little outboard motors to push a cell through liquid.

In 1998 an issue of the journal Cell was devoted to molecular machines, with articles like "The Cell as a Collection of Protein Machines" and "Mechanical Devices of the Spliceosome: Motors, Clocks, Springs and Things." Referring



in the cell.

Scientists skeptical of Darwinian claims include many who have no truck with ideas of intelligent design, like those who advocate an idea called complexity theory, which envisions life self-organizing in roughly the same way that a hurricane does, and ones who think organisms in some sense can design themselves.

The fourth claim in the design argument is also controversial: in the absence of any convincing non-design explanation, we are justified in thinking that real intelligent design was involved in life. To evaluate this claim, it's important to keep in mind that it is the profound appearance of design in life that everyone is laboring to explain, not the appearance of natural selection or the appearance of self-organization.

The strong appearance of design allows a disarmingly simple argument: if it looks, walks and quacks like a duck, then, absent compelling evidence to the contrary, we have warrant to conclude it's a duck. Design should not be overlooked simply because it's so obvious.

Still, some critics claim that science

My argument:

- Design not mystical. Deduced from *physical structure* of a system
- *Everyone agrees* aspects of biology appear designed
- There are *structural obstacles* to Darwinian evolution
- Grand Darwinian claims rest on undisciplined *imagination*
- Bottom line: Strong evidence for design, little evidence for Darwinism

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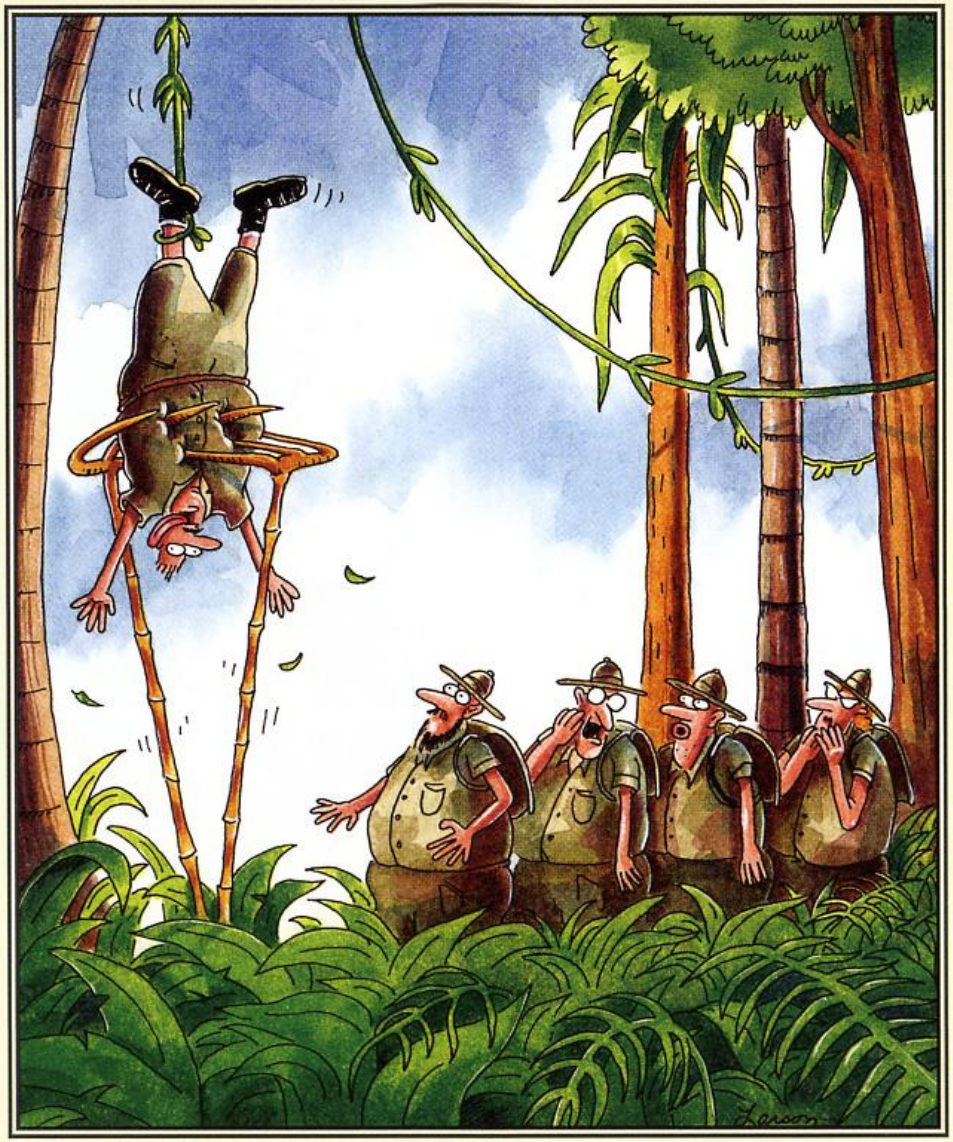
The Design Principle:

"The general principle that *intelligence … in the cause can be inferred from its marks or signs in the effect*."

Thomas Reid, d. 1796

What is "intelligent design"?

- "de-sign' (*n*) — The purposeful or inventive arrangement of parts or details", www.thefreedictionary.com
- Design is simply the *purposeful arrangement of parts*.
- We infer design whenever parts appear to have been arranged for a purpose.



"That's why I never walk in front."

A purposeful arrangement of parts is *the* way — the *only* way — that we recognize the work of a mind

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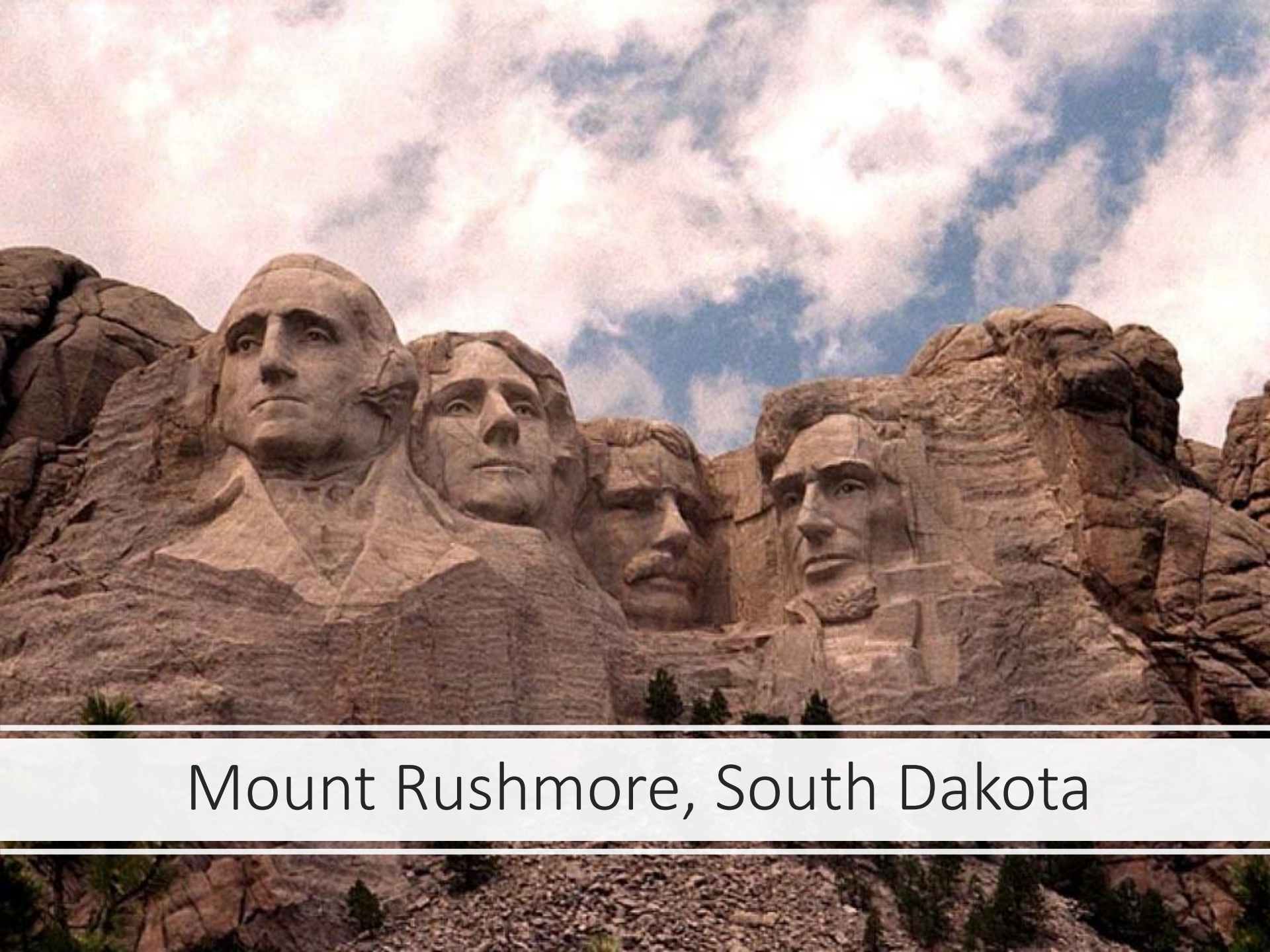
- Design is simply the *purposeful arrangement of parts*.
- We infer design whenever parts appear to have been arranged for a purpose.
- The strength of the inference is *quantitative*

Sawtooth mountains, Idaho

Old Man of the Mountain, New Hampshire



Mount Rushmore, South Dakota

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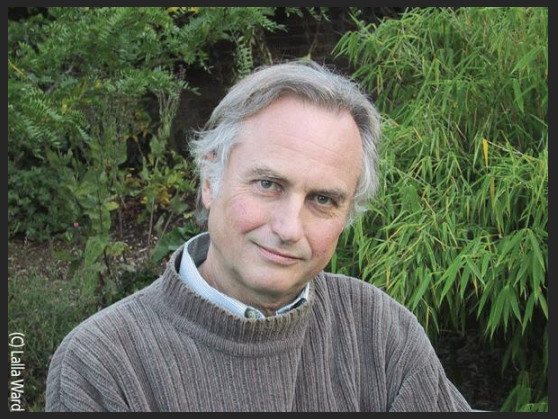
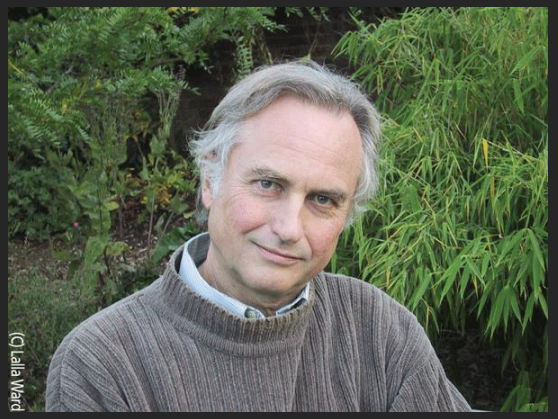
Dawkins R. 1986. *The Blind Watchmaker*. New York: Norton, p. 1



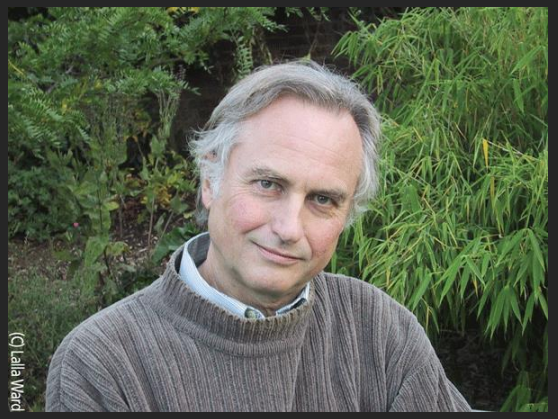
"Biology is the study of complicated things that give the appearance of having been designed for a purpose."

Dawkins R. 1986. *The Blind Watchmaker*. New York: Norton, p. 21



"We may say that a living body or organ is well designed if it has attributes that an intelligent and knowledgeable engineer might have built into it in order to achieve some sensible purpose, such as flying, swimming, seeing … [A]ny engineer can recognize an object that has been designed, even poorly designed, for a purpose, and he can usually work out what that purpose is just by looking at the structure of the object."

Dawkins R. 1986. *The Blind Watchmaker*. New York: Norton, p. 21



"Natural selection is the blind watchmaker, blind because it does not see ahead, does not plan consequences, has no purpose in view. Yet the living results of natural selection **overwhelmingly impress us with the appearance of design** as if by a master watchmaker, impress us with the illusion of design and planning."

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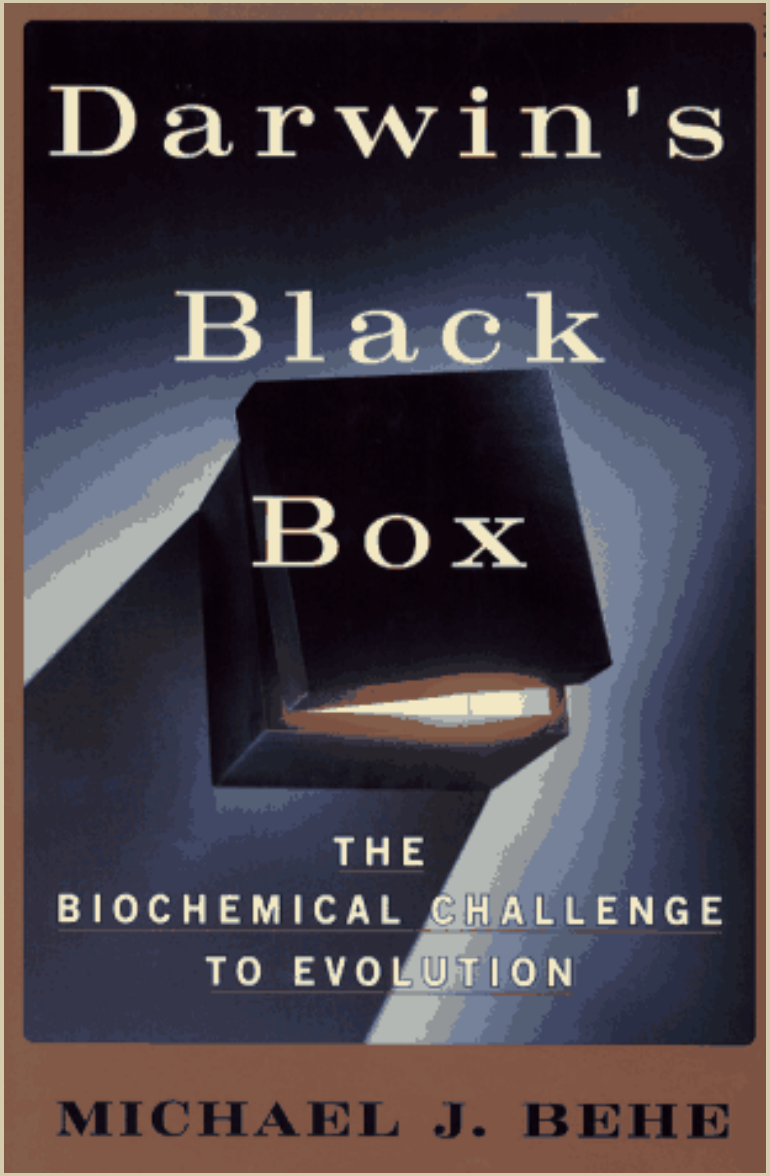
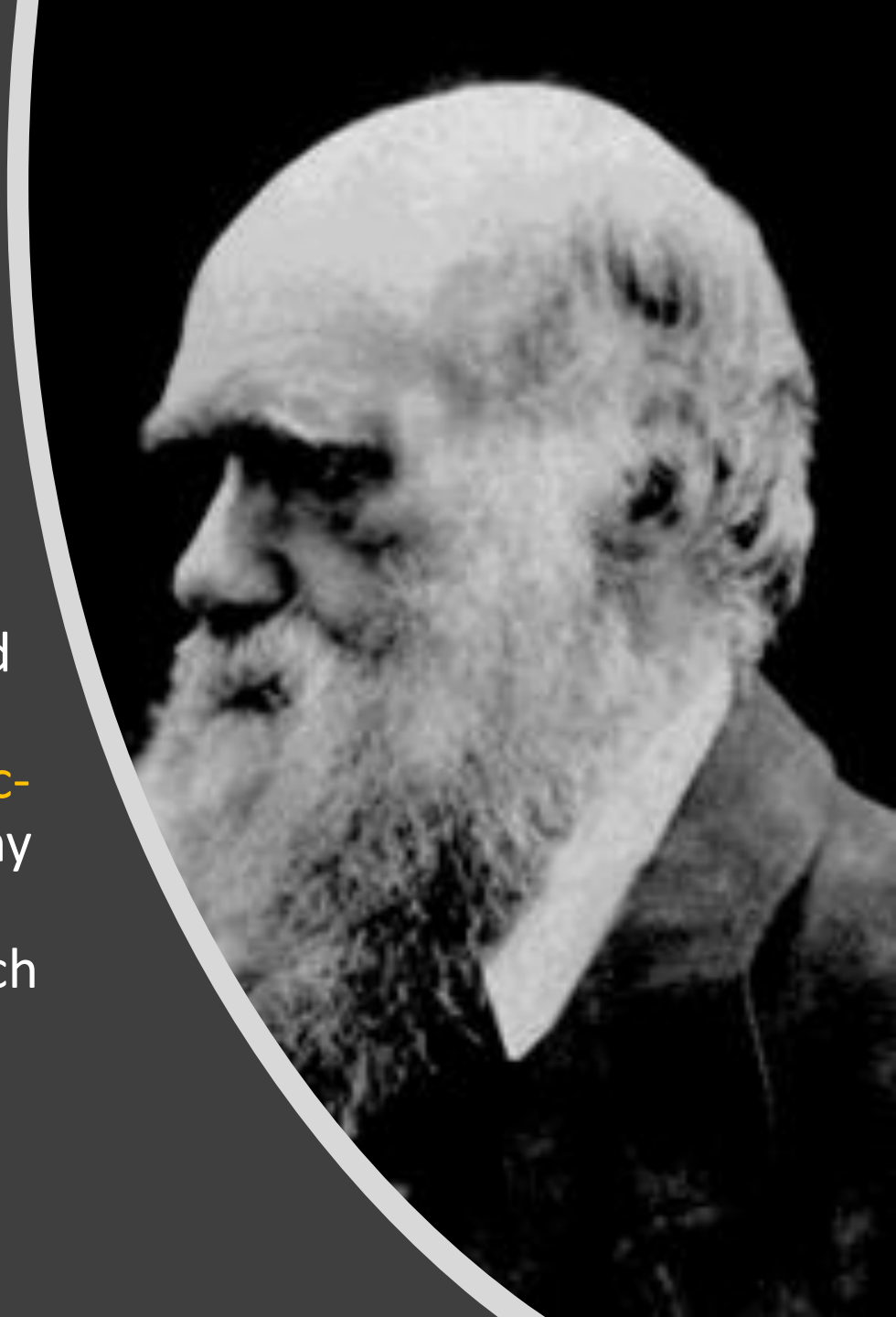
1996


Darwin's
Black
Box
THE
BIOCHEMICAL CHALLENGE
TO EVOLUTION
MICHAEL J. BEHE

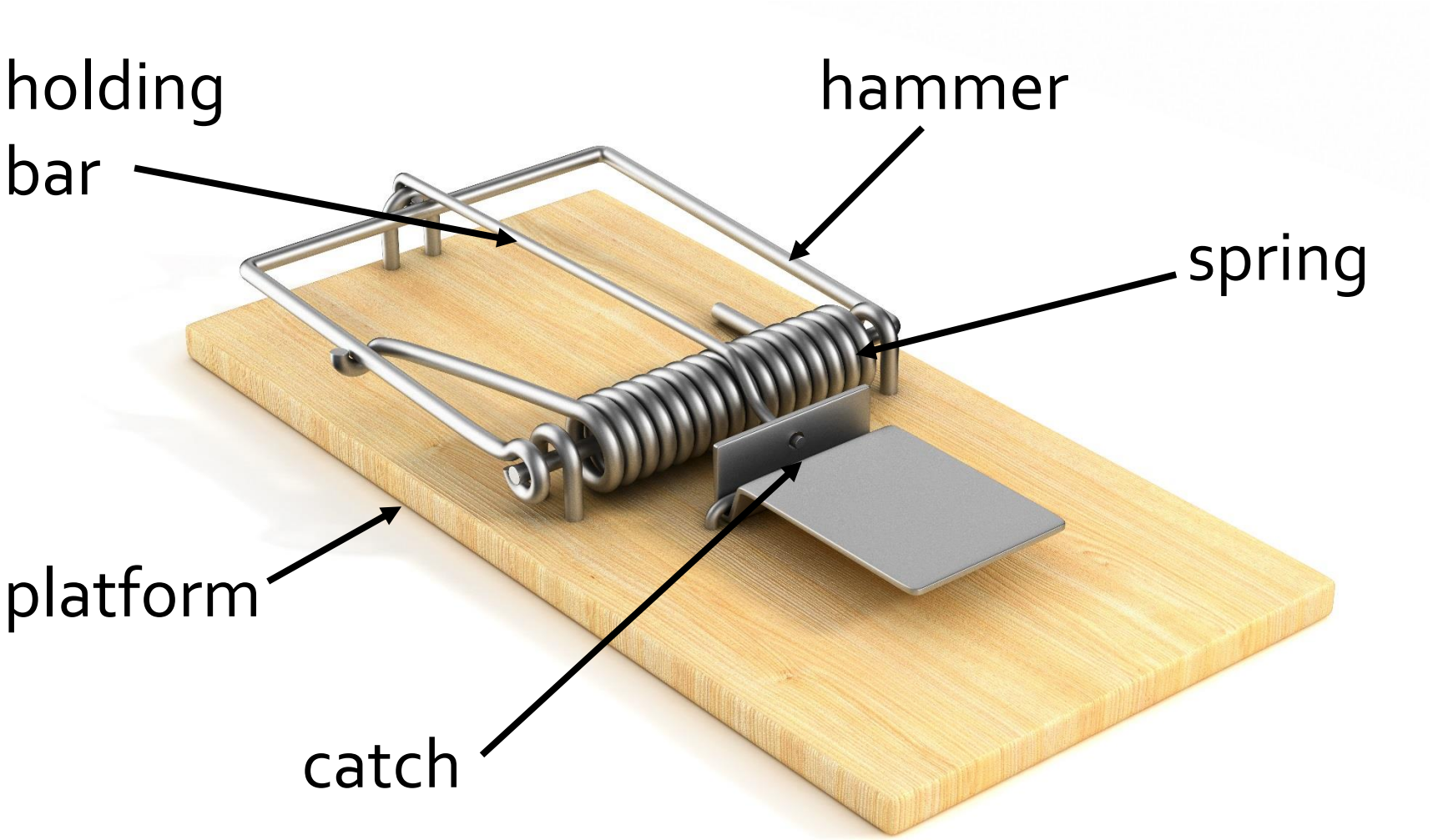
Charles Darwin, *On the Origin of Species,* p. 158

"If it could be demonstrated that any complex organ existed which could not possibly have been formed by numerous, successive, slight modifications, my theory would absolutely break down. But I can find out no such case."



Irreducible Complexity

Irreducible Complexity



The Bacterial Flagellum

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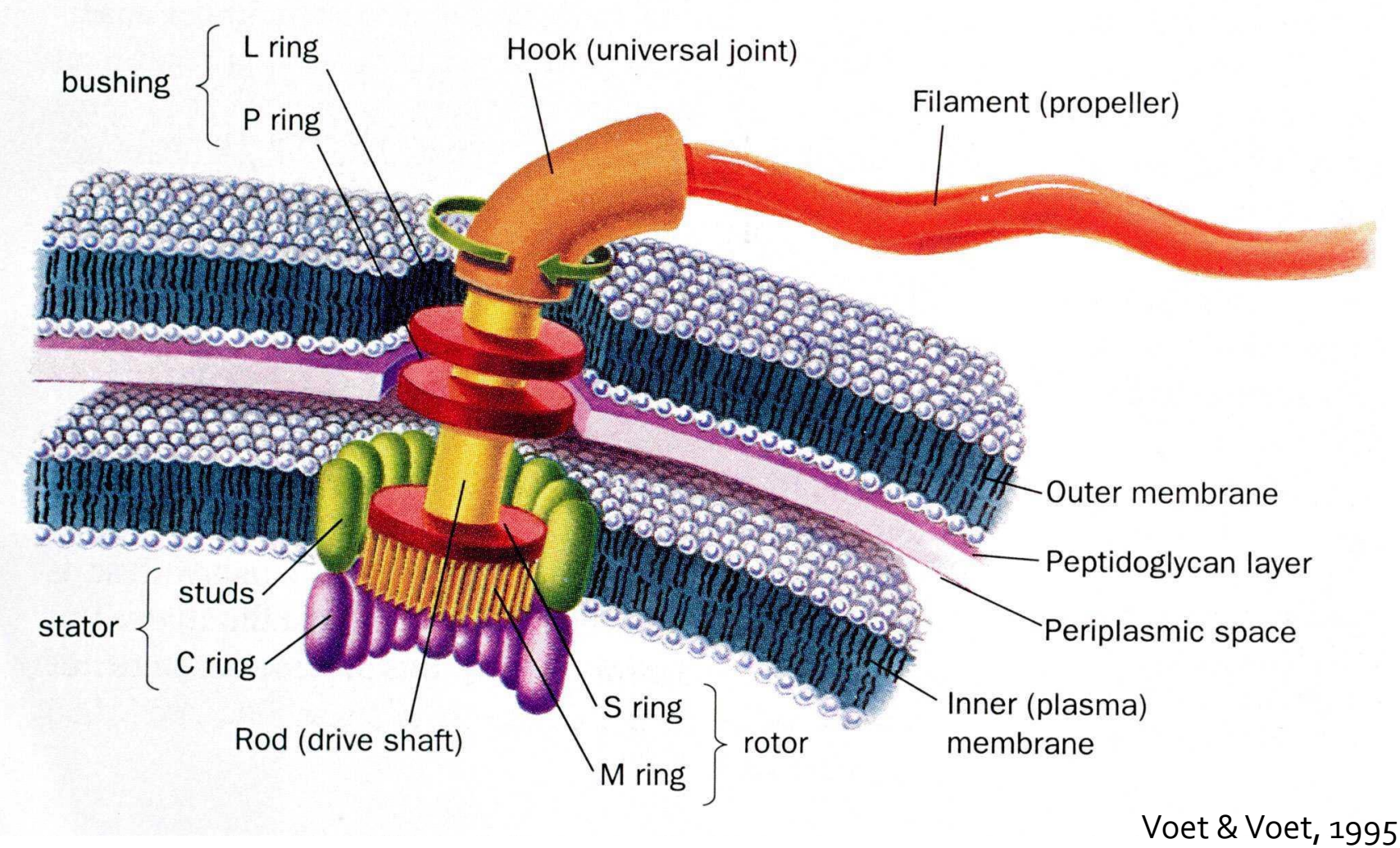
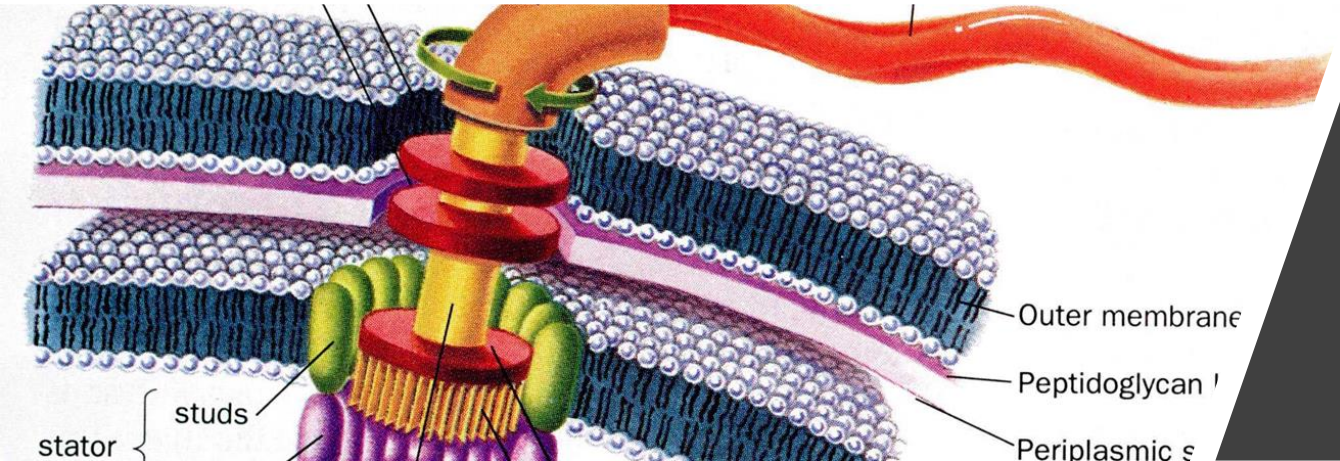


Voet & Voet, 1995

machine — IV. 6. b. A complex device, consisting of a number of interrelated parts, each having a definite function, together applying, using, or generating mechanical or (later) electrical power to perform a certain kind of work

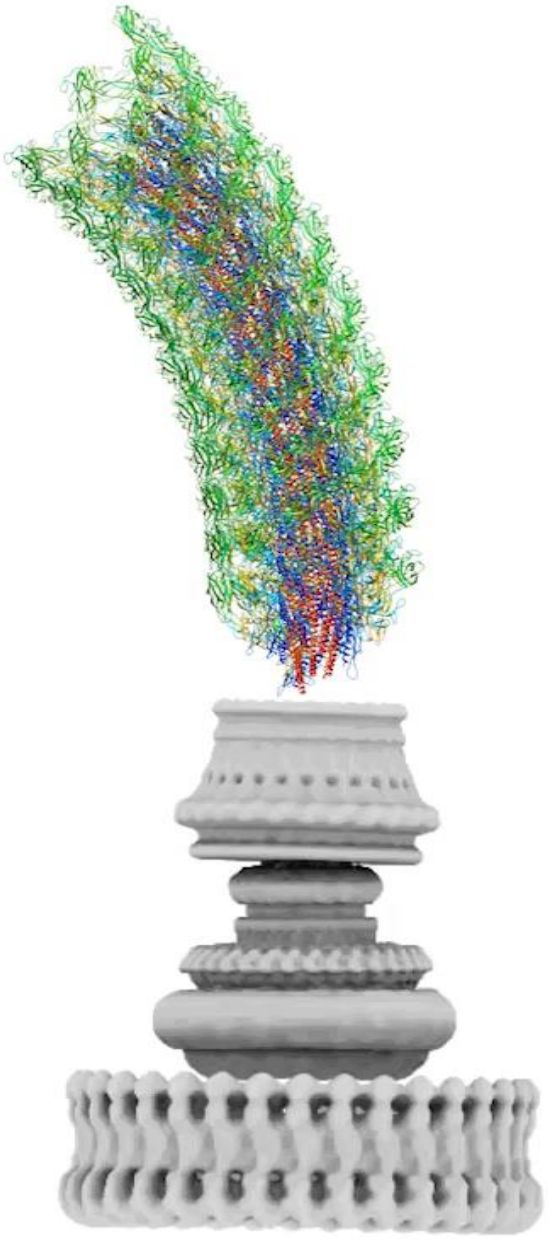
Irreducible complexity has two-fold importance:

obstacle to Darwinism & evidence of purposeful design



The elegant design of just the bacterial flagellar *hook*

Kato, T., et al. 2019. "Structure of the native supercoiled flagellar hook as a universal joint." *Nature Communications* 10:5295.



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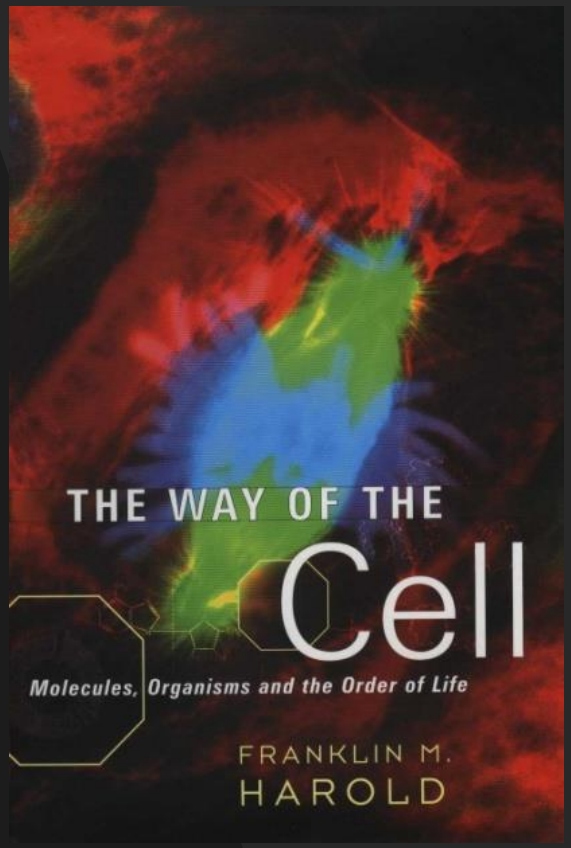
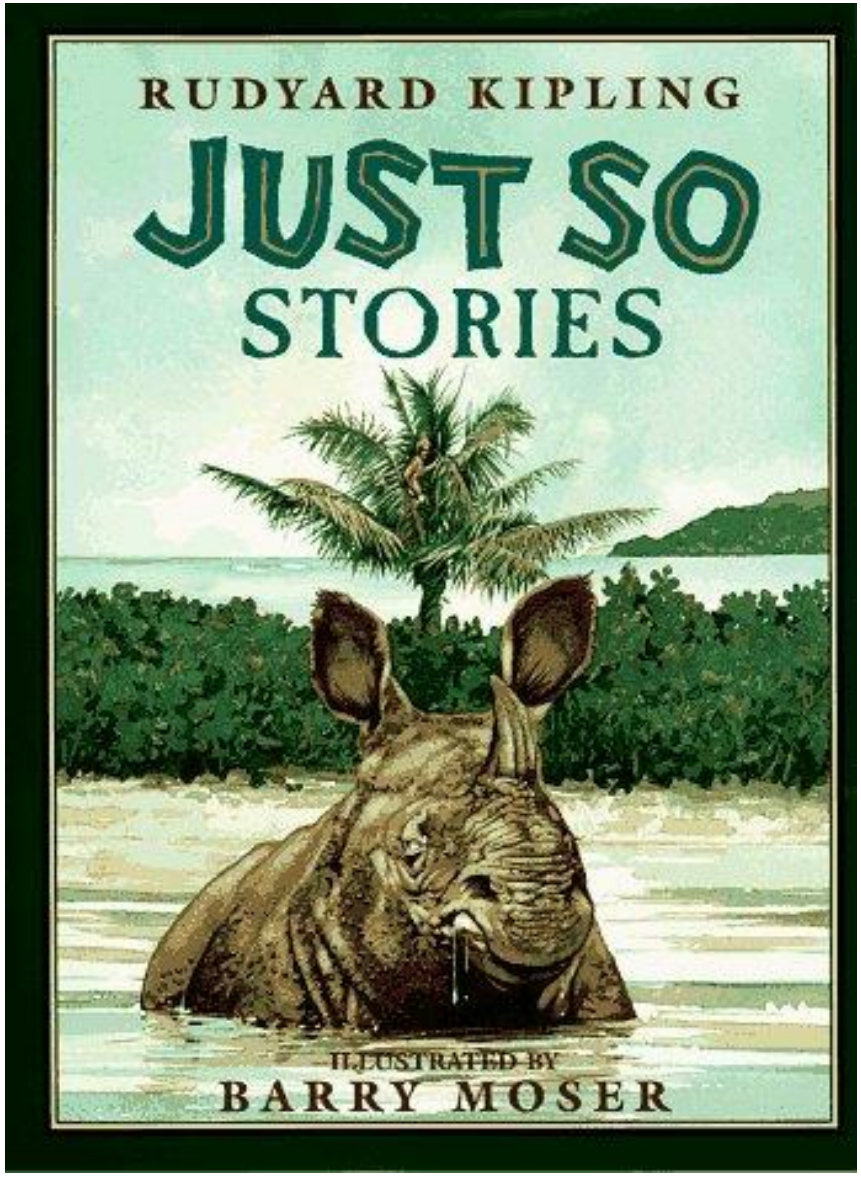
Franklin M. Harold, *The Way of the Cell*, Oxford University Press, 2001, p. 205



"We should reject, as a matter of principle, the substitution of intelligent design for the dialogue of chance and necessity (Behe 1996); but we must concede that there are presently no detailed Darwinian accounts of the evolution of any biochemical system, *only a variety of wishful speculations*."


RUDYARD KIPLING
JUST SO
STORIES
ILLUSTRATED BY
BARRY MOSER

My argument:

- Design not mystical. Deduced from *physical structure* of a system
- *Everyone agrees* aspects of biology appear designed
- There are *structural obstacles* to Darwinian evolution
- Grand Darwinian claims rest on undisciplined *imagination*
- Bottom line: Strong evidence for design, little evidence for Darwinism

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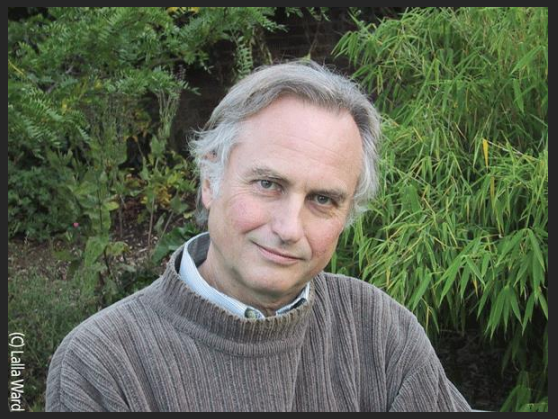
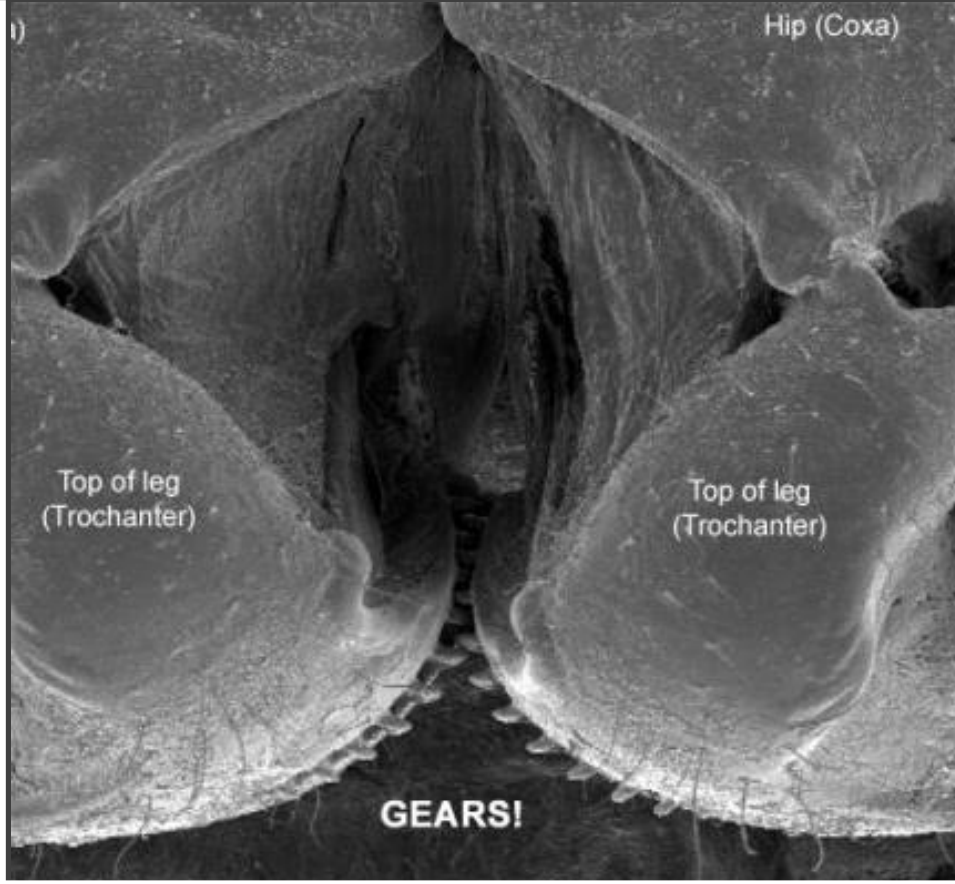
Dawkins R. 1986. *The Blind Watchmaker*. New York: Norton, p. 21



"Yet the living results of natural selection **overwhelmingly impress us with the appearance of design** as if by a master watchmaker, impress us with the illusion of design and planning."



Gears of the larval stage of the planthopper, *Issus coeleoptratus*.


GEARS!

An In-*duck*-tive Argument

Encyclopedia Brittanica

Inductive reasoning

When a person uses a number of established facts to draw a general conclusion, he uses inductive reasoning. *This is the kind of logic normally used in the sciences*. … An inductive argument, however, is never final: It is always open to the possibility of being falsified. … It is by this process of induction and falsification that progress is made in the sciences.

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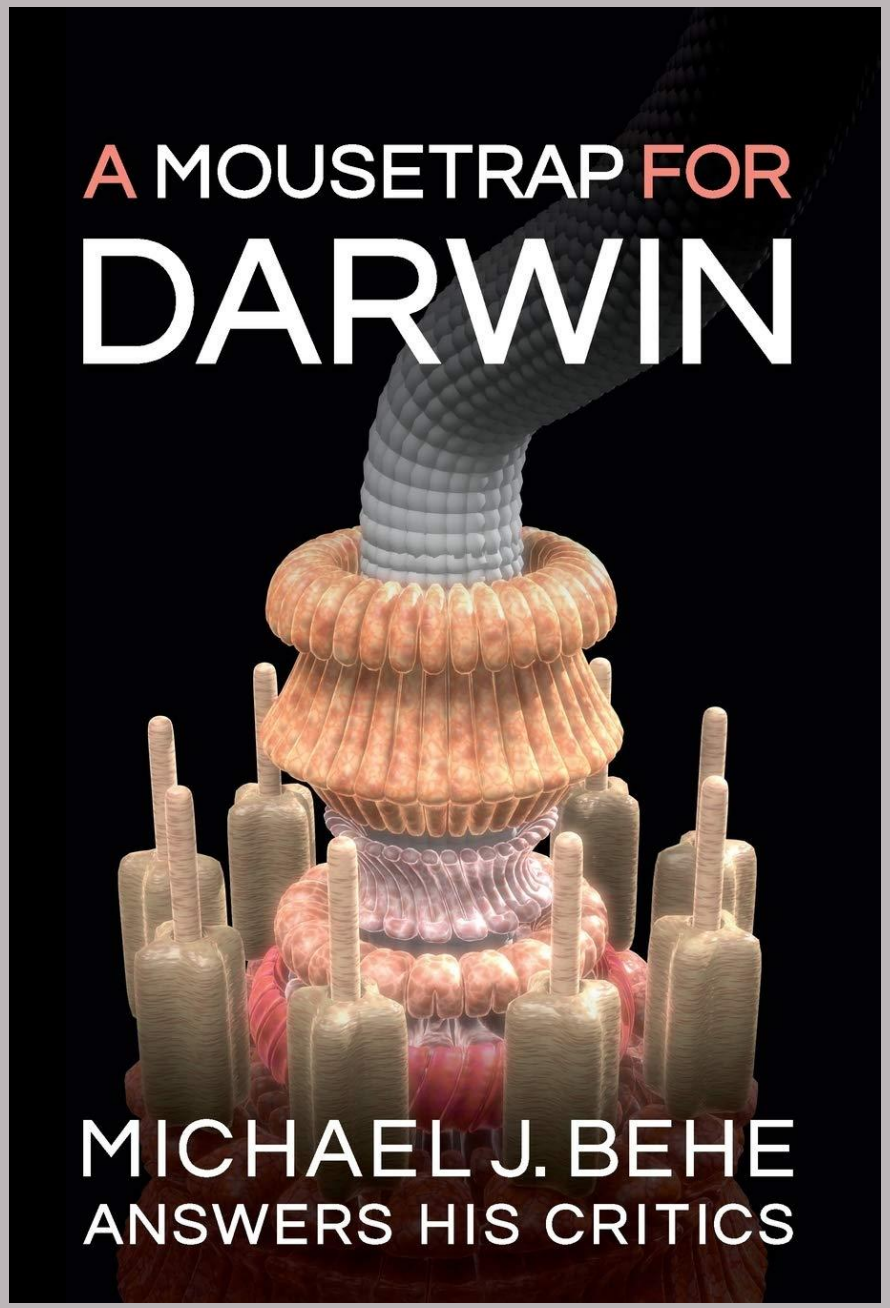
A conclusion of
intelligent design is
rationally compelling

lehigh.edu/…/behe.html

discovery.org

michaelbehe.com

My responses to critics can be found at:



2020

Vanchurin, V. et al. 2022. Toward a theory of evolution as multilevel learning. *Proceedings of the National Academy of Sciences USA* 119: e2120037119.

Modern evolutionary theory, steeped in population genetics, gives a detailed and arguably, largely satisfactory account of microevolutionary processes: that is, evolution of allele frequencies in a population of organisms under selection and random genetic drift. However, *this theory has little to say about the actual history of life, especially the emergence of new levels of biological complexity, and nothing at all about the origin of life.*

Toward a theory of evolution as multilevel learning

Vitaly Vanchurin[a,b,1], Yuri I. Wolf[a], Mikhail I. Katsnelson[c], and Eugene V. Koonin[a,1]

[a]National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD 20894; [b]Duluth Institute for Advanced Study, Duluth, MN 55804; and [c]Institute for Molecules and Materials, Radboud University, Nijmegen 6525AJ, The Netherlands

Contributed by Eugene V. Koonin; received November 2, 2021; accepted January 3, 2022; reviewed by Steven Frank and Eörs Szathmáry

We apply the theory of learning to physically renormalizable systems in an attempt to outline a theory of biological evolution, including the origin of life, as multilevel learning. We formulate seven fundamental principles of evolution that appear to be necessary and sufficient to render a universe observable and show that they entail the major features of biological evolution, including replication and natural selection. It is shown that these cornerstone phenomena of biology emerge from the fundamental features of learning dynamics such as the existence of a loss function, which is minimized during learning. We then sketch the theory of evolution using the mathematical framework of neural networks, which provides for detailed analysis of evolutionary phenomena. To demonstrate the potential of the proposed theoretical framework, we derive a generalized version of the Central Dogma of molecular biology by analyzing the flow of information during learning (back propagation) and predicting (forward propagation) the environment by evolving organisms. The more complex evolutionary phenomena, such as major transitions in evolution (in particular, the origin of life), have to be analyzed in the thermodynamic limit, which is described in detail in the paper by Vanchurin et al. [V. Vanchurin, Y. I. Wolf, E. V. Koonin, M. I. Katsnelson, *Proc. Natl. Acad. Sci. U.S.A.* 119, 10.1073/pnas.2120042119 (2022)].

theory of learning | loss function | natural selection | major evolutionary transitions | origin of life

What is life? If this question is asked in the scientific rather than in the philosophical context, a satisfactory answer should assume the form of a theoretical model of the origin and evolution of complex systems that are identified with life (1). NASA has operationally defined life as follows: "Life is a self-sustaining chemical system capable of Darwinian evolution" (2, 3). Apart from the insistence on chemistry, long-term evolution that involves (random) mutation, diversification, and adaptation is, indeed, an intrinsic, essential feature of life that is not apparent in any other natural phenomena. The problem with this definition, however, is that natural (Darwinian) selection itself appears to be a complex rather than an elementary phenomenon (4). In all evolving organisms we are aware of, for natural selection to kick off and to sustain long-term evolution, an essential condition is replication of a complex digital information carrier (a DNA or RNA molecule). The replication fidelity must be sufficiently high to provide for the differential replication of emerging mutants and survival of the fittest ones (this replication fidelity level is often referred to as Eigen threshold) (5). In modern organisms, accurate replication is ensured by elaborate molecular machineries that include not only replication and repair enzymes but also, the entire metabolic network of the cell, which supplies energy and building blocks for replication. Thus, the origin of life is a typical chicken-and-egg problem (or catch-22); accurate replication is essential for evolution, but the mechanisms ensuring replication fidelity are themselves products of complex evolutionary processes (6, 7).

Because genome replication that underlies natural selection is itself a product of evolution, origin of life has to be explained outside of the traditional framework of evolutionary biology. Modern evolutionary theory, steeped in population genetics, gives a detailed and arguably, largely satisfactory account of microevolutionary processes: that is, evolution of allele frequencies in a population of organisms under selection and random genetic drift (8, 9). However, this theory has little to say about the actual history of life, especially the emergence of new levels of biological complexity, and nothing at all about the origin of life.

The crucial feature of biological complexity is its hierarchical organization. Indeed, multilevel hierarchies permeate biology: from small molecules to macromolecules; from macromolecules to functional complexes, subcellular compartments, and cells; from unicellular organisms to communities, consortia, and multicellularity; from simple multicellular organisms to highly complex forms with differentiated tissues; and from organisms to communities and eventually, to eusociality and to complex biocenoses involved in biogeochemical processes on the planetary scale. All these distinct levels jointly constitute the hierarchical organization of the biosphere. Understanding the origin and evolution of this hierarchical complexity, arguably, is one of the principal goals of biology.

In large part, evolution of the multilevel organization of biological systems appears to be driven by solving optimization problems, which entails conflicts or trade-offs between optimization criteria at different levels or scales, leading to frustrated states, in the language of physics (10–12). Two notable cases in point are parasite–host arms races that permeate biological evolution and makes major contributions to the diversity and complexity of life-forms (13–16) and multicellular organization of complex organisms, where the tendency of individual cells to

Significance

Modern evolutionary theory gives a detailed quantitative description of microevolutionary processes that occur within evolving populations of organisms, but evolutionary transitions and emergence of multiple levels of complexity remain poorly understood. Here, we establish the correspondence among the key features of evolution, learning dynamics, and renormalizability of physical theories to outline a theory of evolution that strives to incorporate all evolutionary processes within a unified mathematical framework of the theory of learning. According to this theory, for example, replication of genetic material and natural selection readily emerge from the learning dynamics, and in sufficiently complex systems, the same learning phenomena occur on multiple levels or on different scales, similar to the case of renormalizable physical theories.

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Reviewers S.F., University of California, Irvine; and E.S., Parmenides Foundation.

The authors declare no competing interest.

[1]To whom correspondence may be addressed. Email: vitaly.vanchurin@gmail.com or koonin@ncbi.nlm.nih.gov.

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