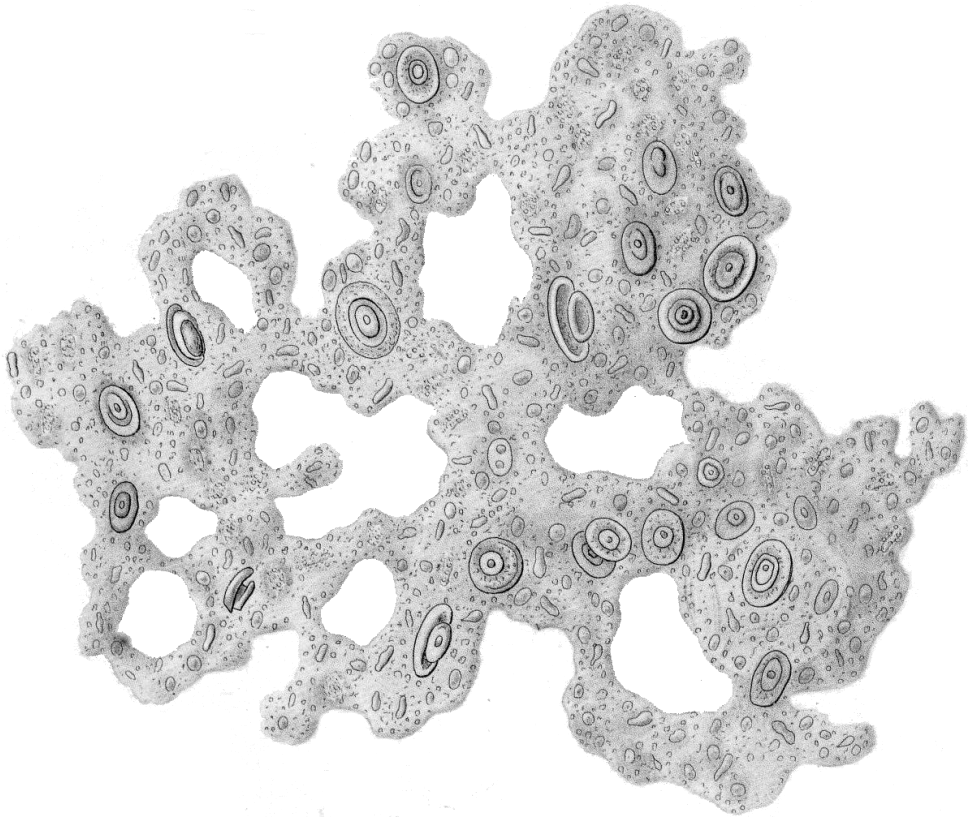
Devolution

Darwin's Mechanism Works Chiefly by Squandering Genetic Information for Short-term Gain

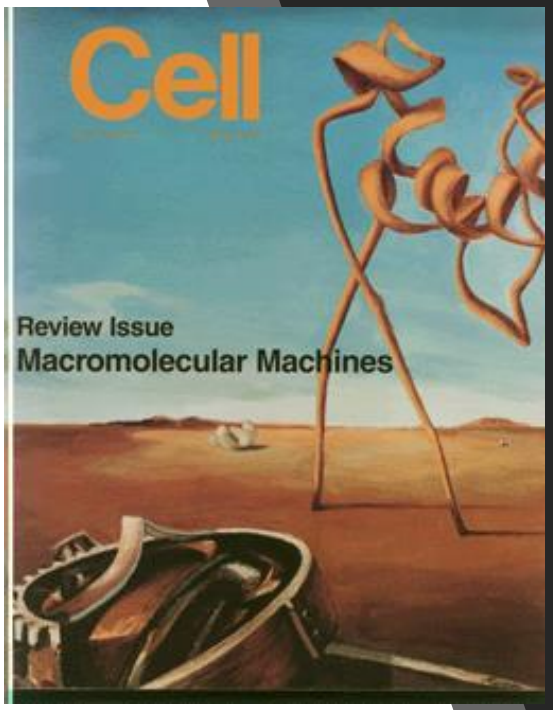
Michael J Behe
Lehigh University
Bethlehem, PA

Bathybius haeckelii
1870

“Protoplasm”



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



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- **Polymerases and the Replisome: Machines within Machines,** Tania A Baker and Stephen P Bell
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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,

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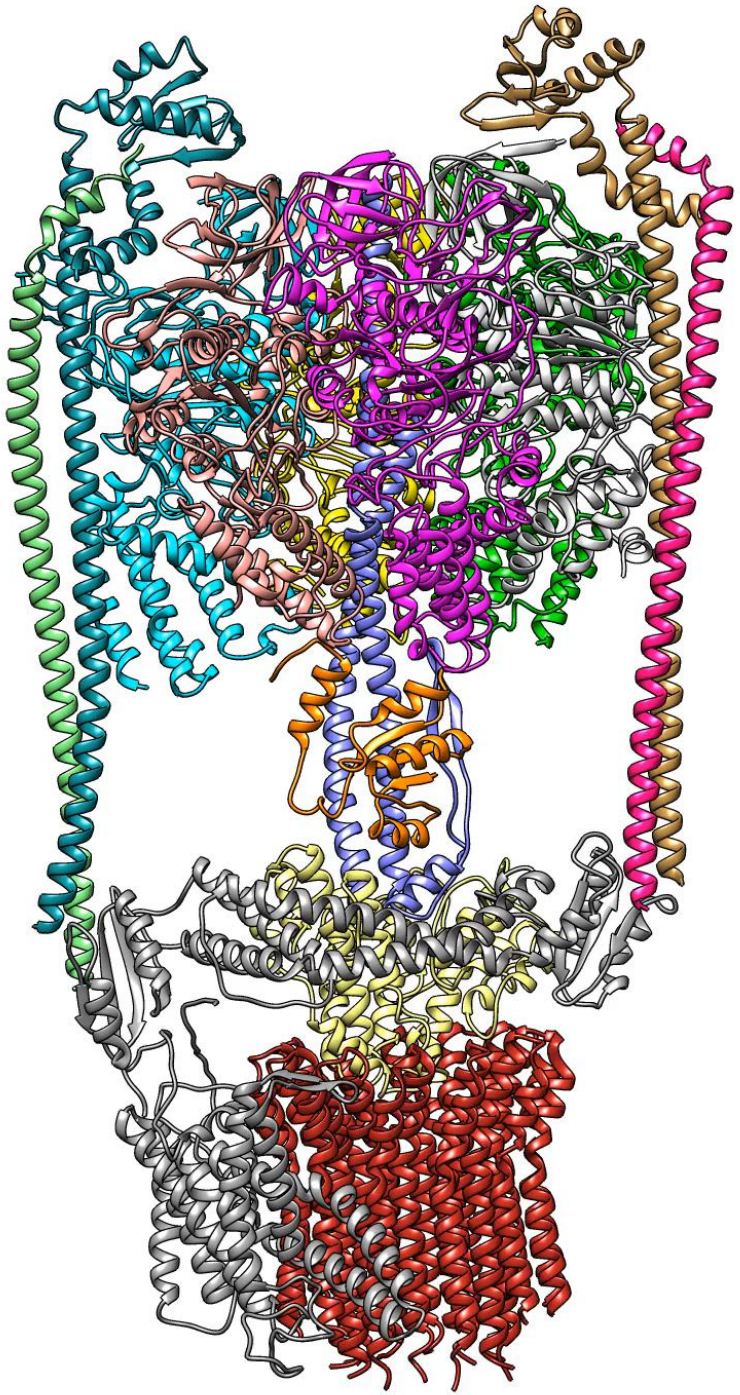
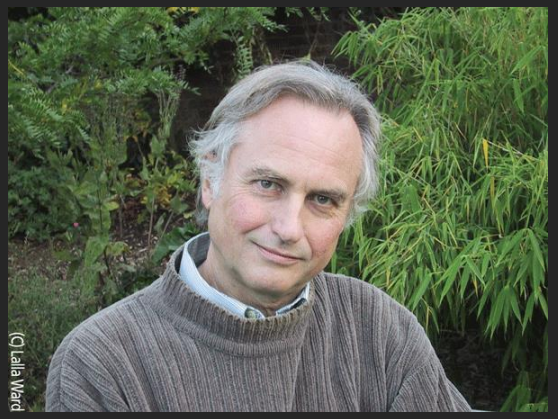
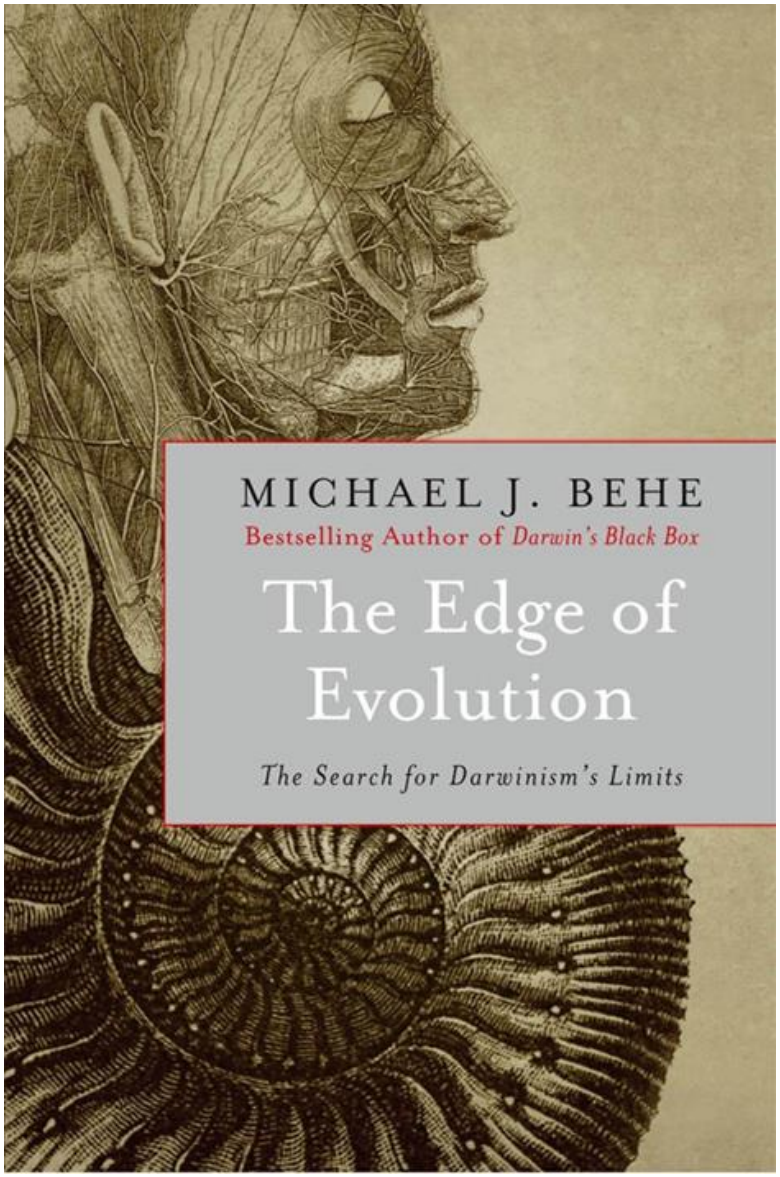


Dawkins R. 1986. *The Blind Watchmaker*. New York: Norton, p. 43



"We have seen that living things are too improbable and too beautifully 'designed' to have come into existence by chance. How, then, did they come into existence? … by gradual, step-by-step transformations from simple beginnings…"

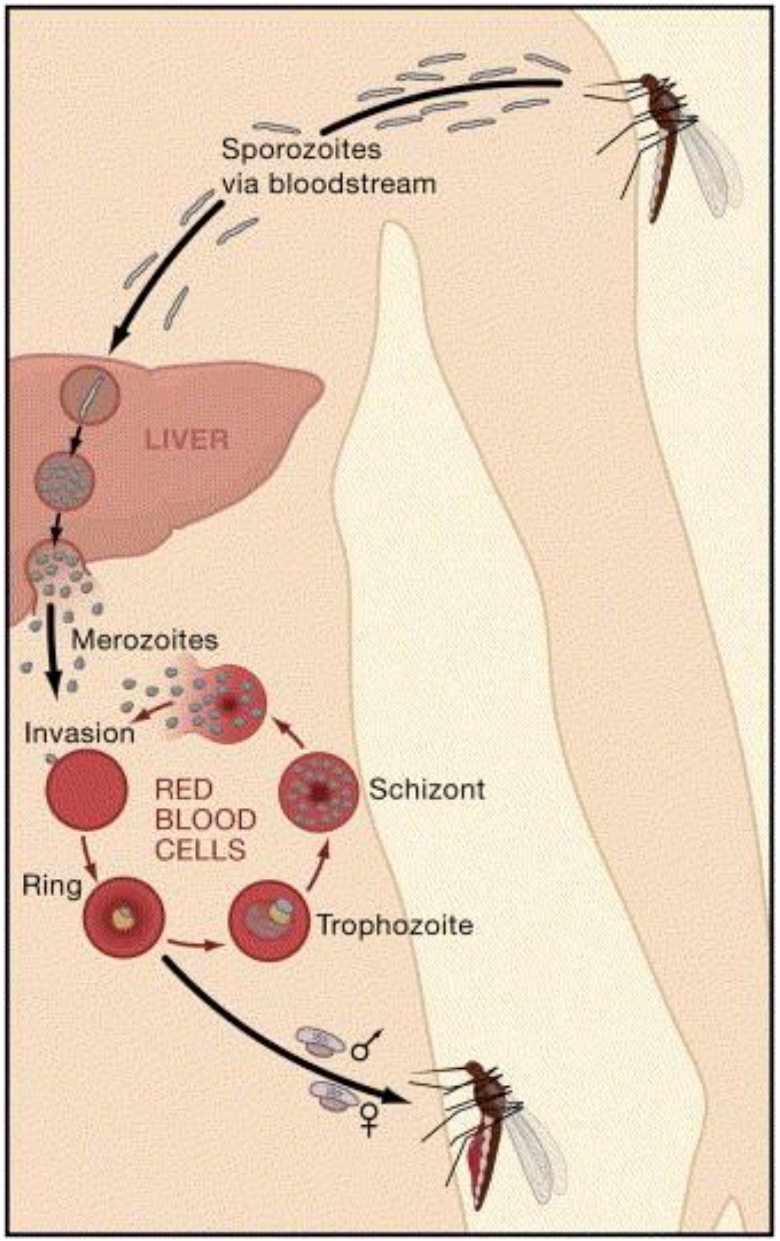

MICHAEL J. BEHE
Bestselling Author of Darwin's Black Box
The Edge of Evolution
The Search for Darwinism's Limits

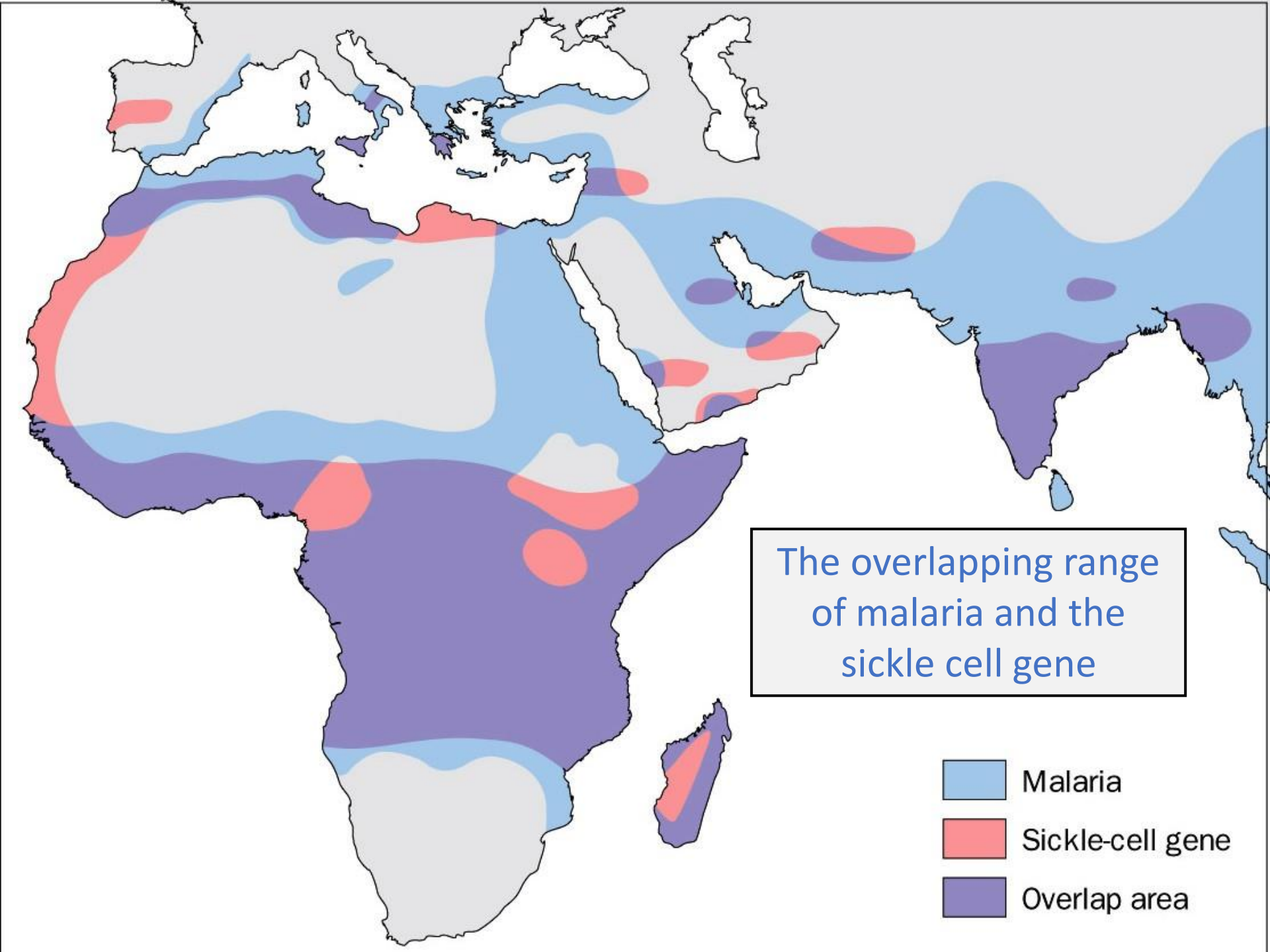
2007

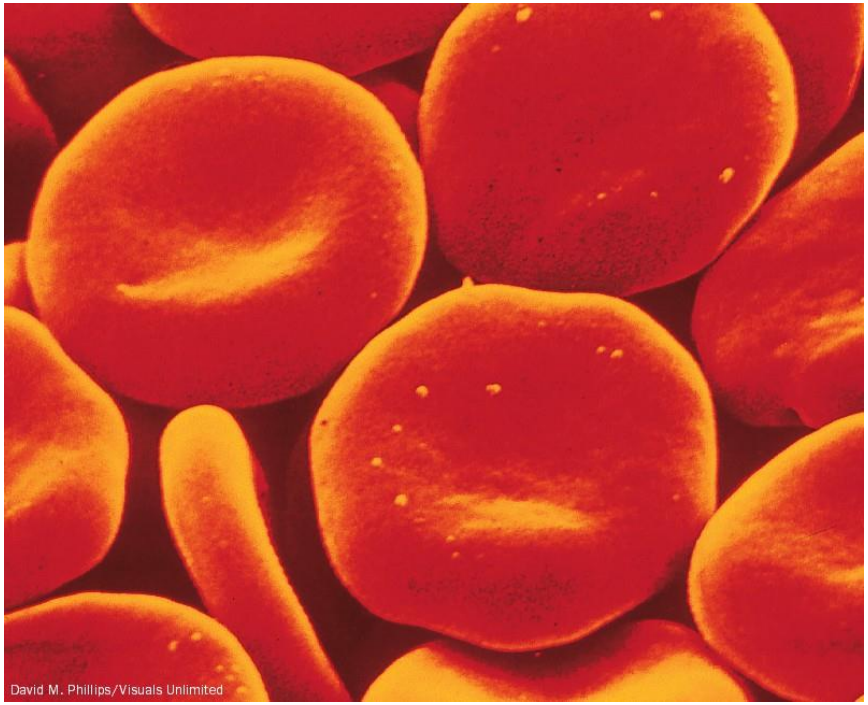
What is our best **evidence** of what Darwinian processes can actually do?

- The best evidence we have to assess the abilities of Darwinian processes comes from studies of *malaria*, both in genetic changes of humans and in the parasite (*Plasmodium falciparum*) itself.
- Reasons:
  - Detailed genetic studies
  - Sheer population sizes

Infection of a human by the malarial parasite, *Plasmodium falciparum*



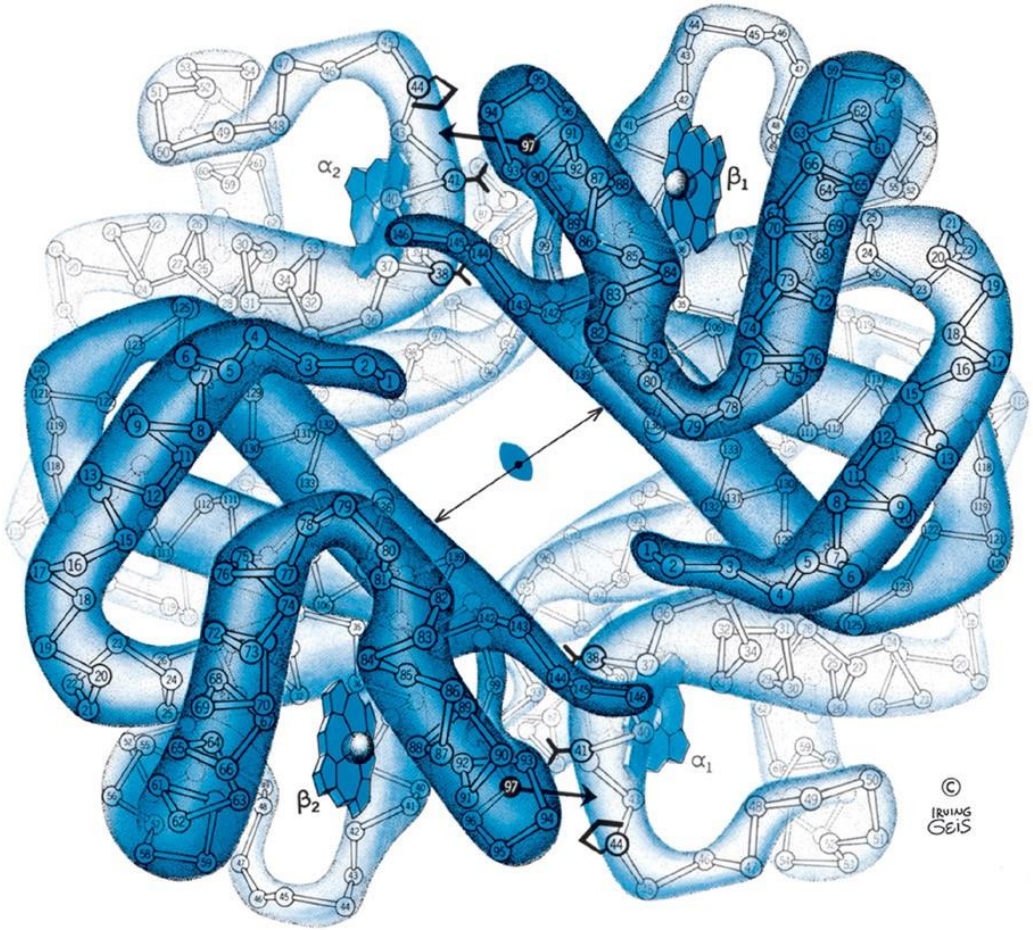

The overlapping range of malaria and the sickle cell gene
Malaria
Sickle-cell gene
Overlap area



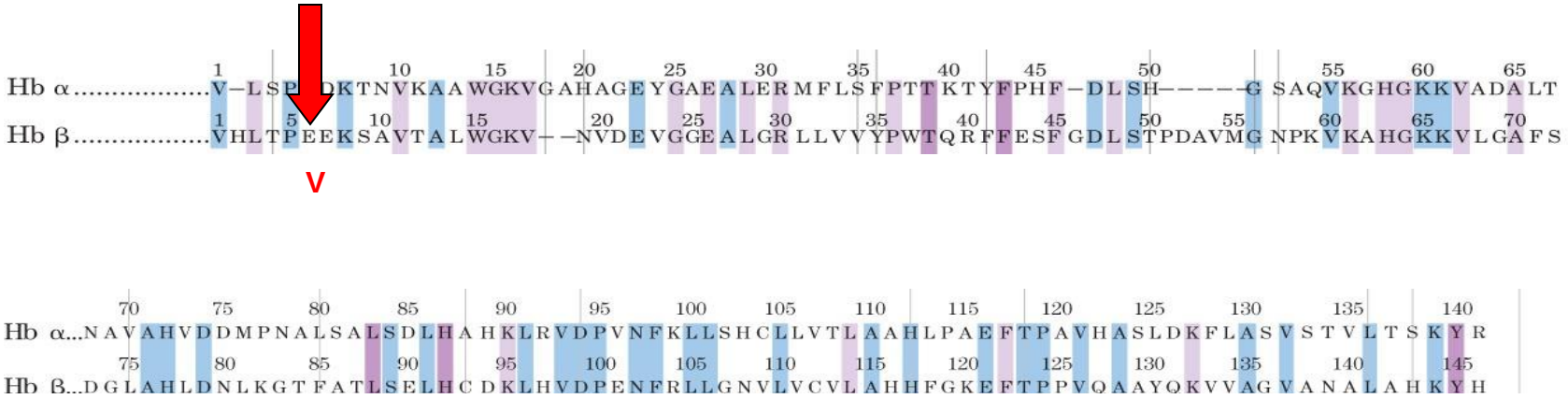
Normal red blood cells

Sickle red blood cells

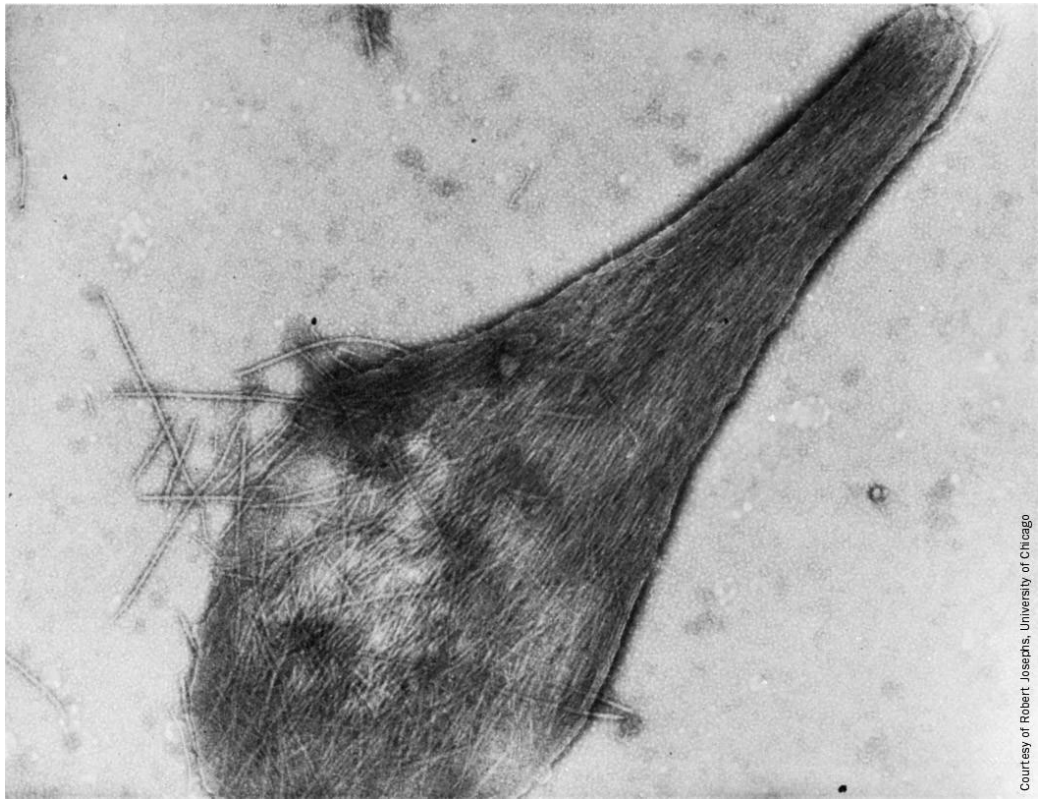
The molecular structure of hemoglobin



The Amino Acid Sequences of the α and β Chains of Human Hemoglobin



Electron micrograph of deoxygenated sickle hemo-globin fibers

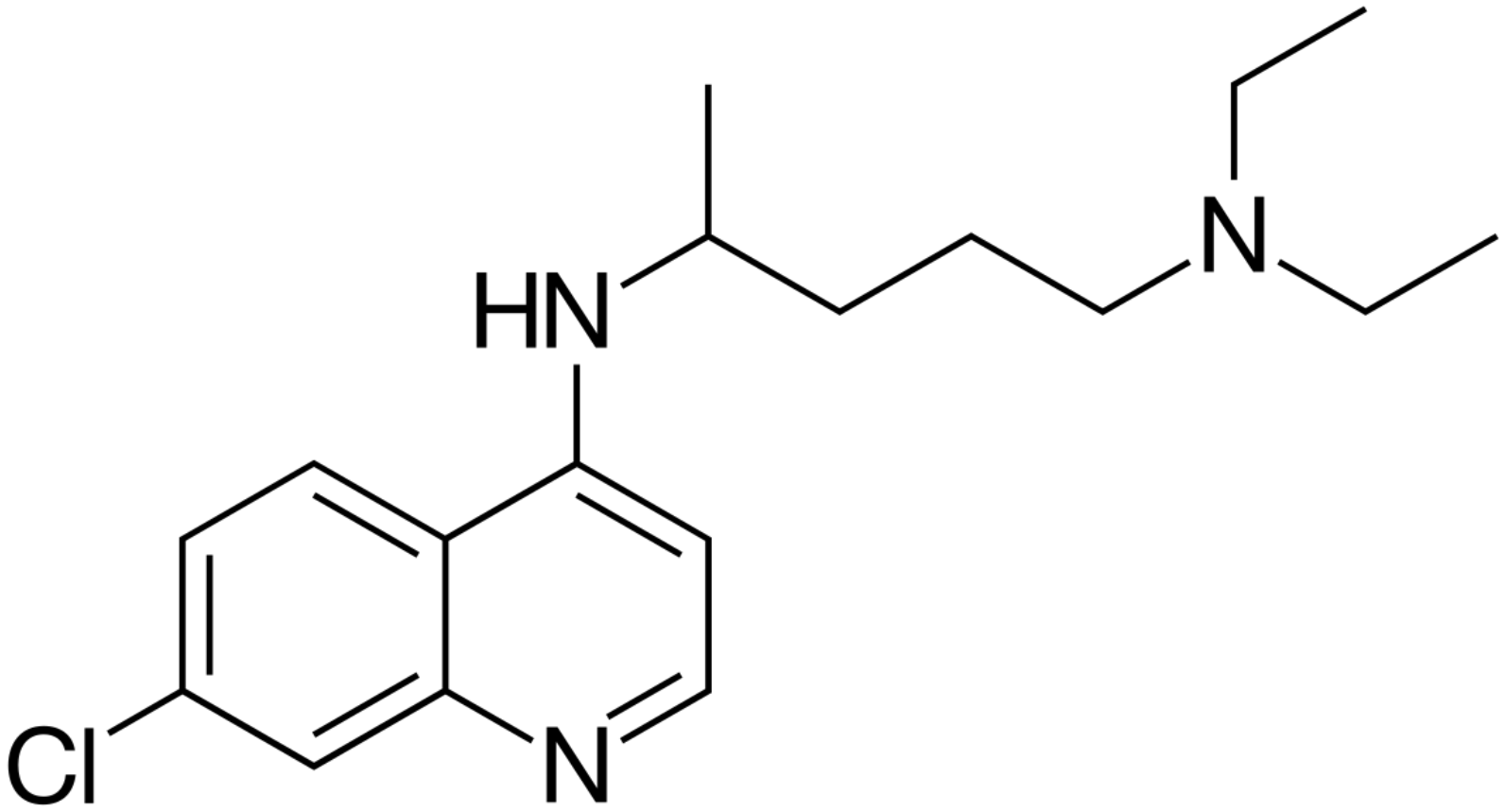


Human genetic effects selected for resistance to malaria

Gene	Mutation	Adverse effects
Hemoglobin	HbS	Sickle cell disease
	alpha-thalassemia	Anemia/ broken gene
	beta-thalassemia	Anemia/ broken gene
	Hereditary persistence of fetal hemoglobin	Broken genetic controls
G6PD	Point mutations, deletions	Anemia / decrease or loss of G6PD function
Band 3 protein	deletion	Lethal in two copies / broken gene
Duffy antigen	Point mutation	Protein expression lost in red blood cells

Plasmodium falciparum

Chloroquine



A Requiem for Chloroquine

I. M. Hastings, P. G. Bray, S. A. Ward

Chloroquine (CQ) has historically been the mainstay of malaria treatment, particularly in the worst affected regions of sub-Saharan Africa. The recent development of widespread CQ resistance in *Plasmodium falciparum*, the most dangerous of the four malaria parasite species, has contributed significantly to escalating mortality rates in Africa (*1*) and to the resurgence of malaria as an immediate public health priority (*2*). Several pressing scientific questions have emerged within the context of this humanitarian disaster: What is the molecular basis for CQ resistance, and how has this influenced the dynamics of resistance? Why did CQ remain effective for 20 years, yet its immediate replacement sulfadoxine-pyrimethamine (SP) last less than 5 years? Has the widespread deployment of CQ jeopardized the use of other drugs targeting the same parasite biochemical pathways? As reported on page 210 of this issue, Sidhu *et al.* (*3*) have obtained data relevant to all three questions by creatively exploiting the *pfcrt* gene, which encodes a putative transporter protein in the digestive vacuole membrane of the malaria parasite. They replaced the endogenous *pfcrt* gene in a CQ-sensitive strain of *P. falciparum* with a *pfcrt* gene from each of three CQ-resistant strains. All such replacement strains ("constructs") showed CQ resistance in vitro, demonstrating that *pfcrt* mutations are sufficient, within their selected genetic background, to encode resistance. Reduced levels of *pfcrt* gene expression in the constructs also showed that up-regulation of *pfcrt* is not required for resistance. Next, the authors investigated cross-resistance tween CQ and other antimalarial drugs.

Previous work from this and other gr has implicated eight or nine different mutations in the development of CQ r tance (*4*). The sequential accumulatic these mutations plausibly explains the served genetics and epidemiology of CC sistance (see the figure). So why did CQ so much longer than SP as a frontline malarial? First, four sequential mutatio the *dhfr* gene—which encodes dihydrof reductase, an enzyme essential for par folate metabolism and targeted by the pyrimethamine—appear sufficient for S sistance (*5*). These four mutations accu late much faster than the nine require CQ resistance. Second, CQ persists at tl peutically useful concentrations for a n shorter period than SP, leading to lower s tion pressures for resistance (*6*). Third, resistance may involve genes other than *p* such that sexual recombination during malaria life cycle breaks down genetic binations, slowing resistance (*7*, *8*). The tive involvement of other genes remains troversial. Sidhu *et al.* show that *pfcrt* a

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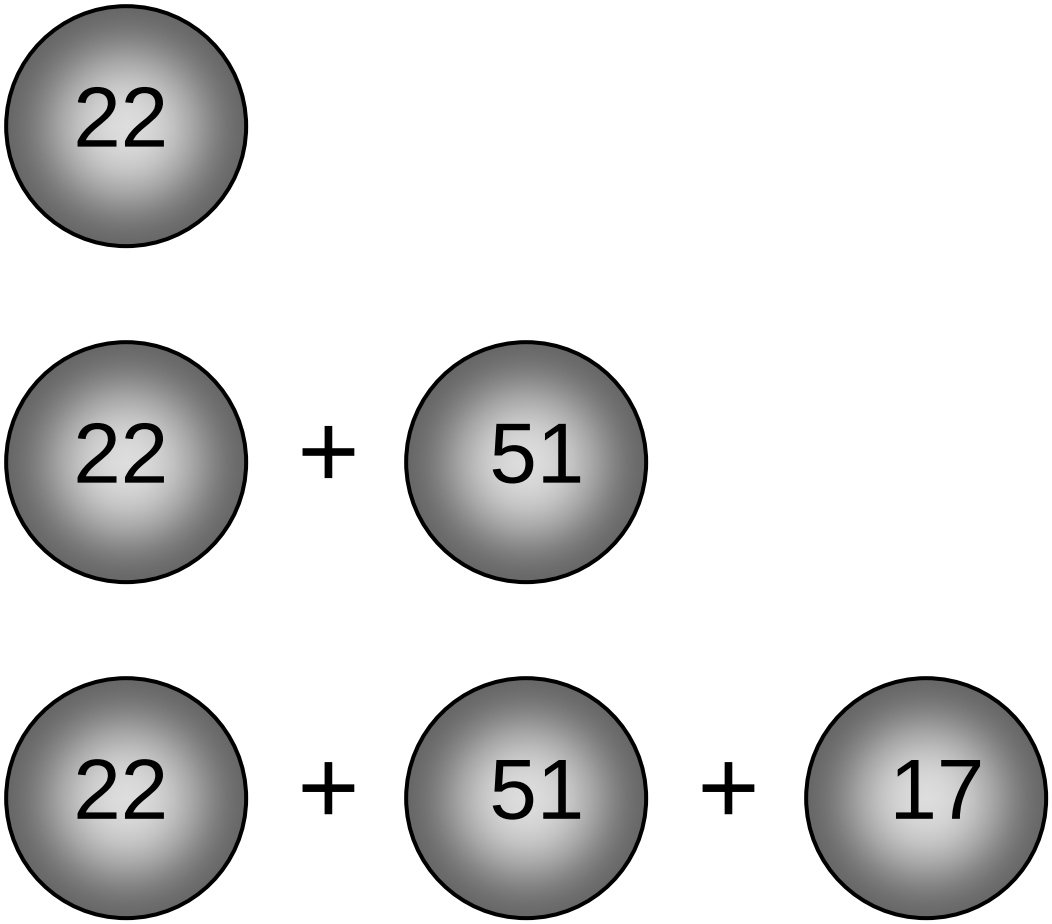
Frequency of the development of antibiotic resistance of *P. falciparum*

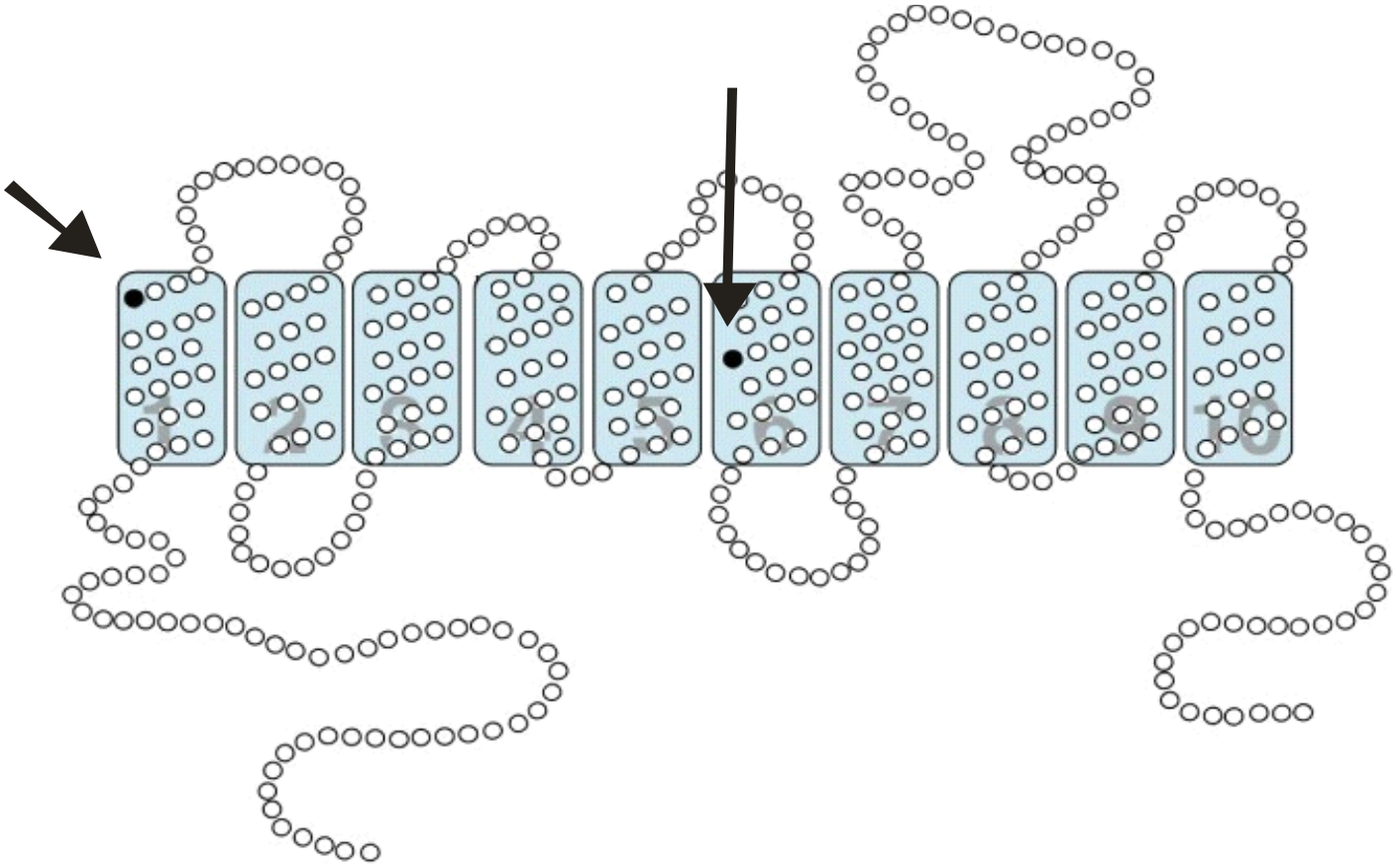
- Resistance to atovaquone arises in about every *third* patient (about 1 in 10^{12} cells)
- (Looareesuwan,S., et al. 1996. Clinical studies of atovaquone , alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am. J. Trop. Med. Hyg.* **54**:62-66)

- Resistance to chloroquine arises in about every *billionth* patient (about 1 in 10^{20} cells)
- (White NJ. 2004. Antimalarial drug resistance. *J Clin Invest 113*:1084-1092.)

Lottery: The difficulty of matching several numbers



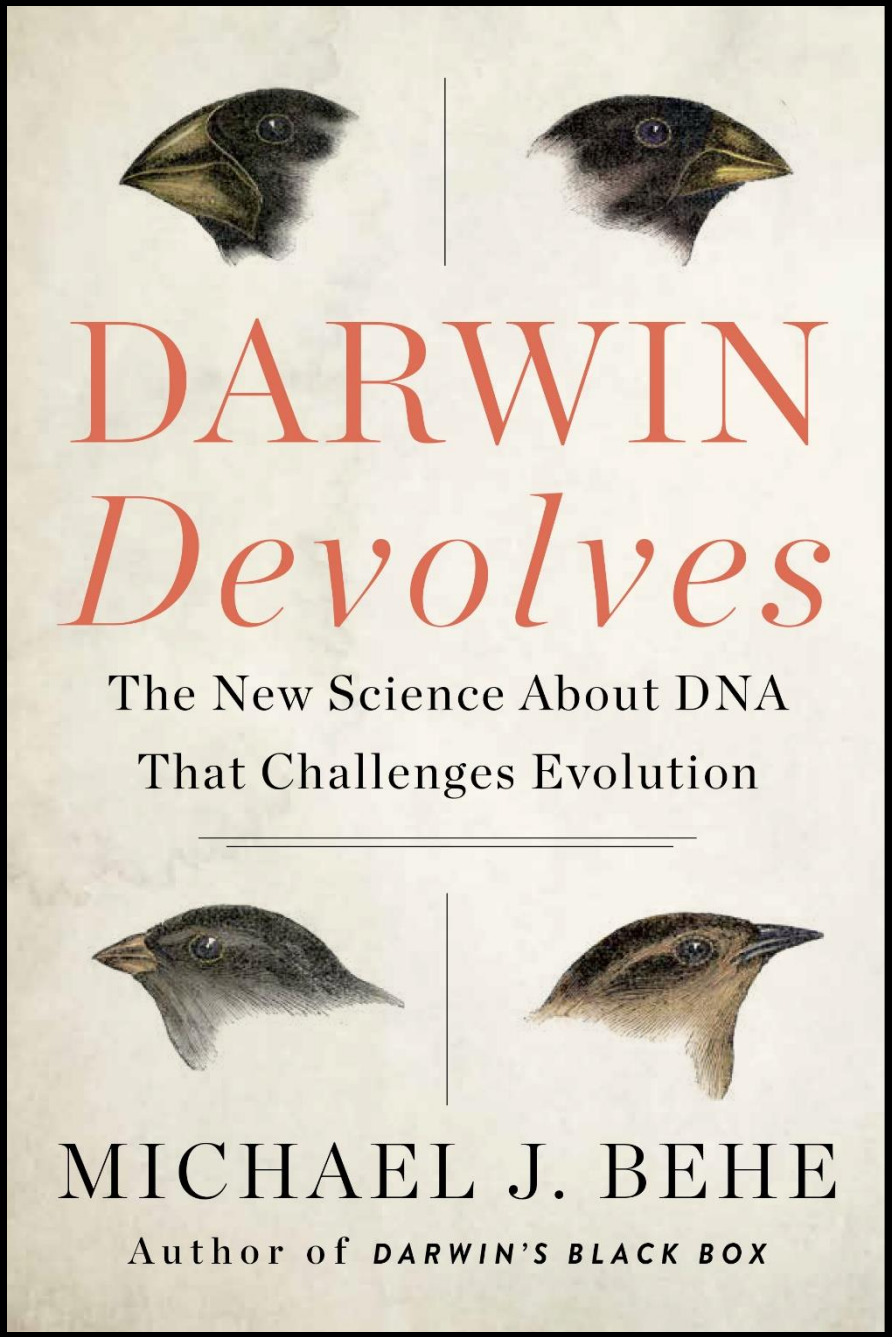
Chloroquine-resistance in malaria requires several mutations



This is not an *argument* that Darwinism *cannot* make complex functional systems; it is an *observation* that it *does not*.

No unintelligent process helped much with malarial chloroquine-resistance, including:

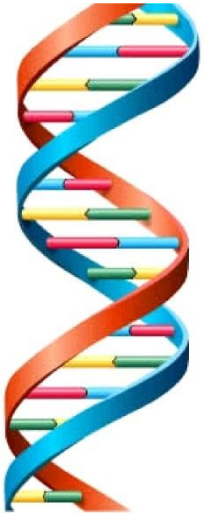
- Darwinism
- Self-organization
- Self-engineering
- Symbiosis
- *Nor any as-yet-undiscovered process*

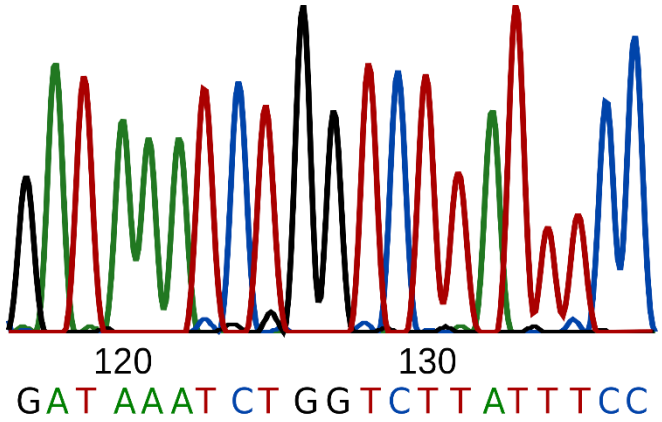

DARWIN
Devolves
The New Science About DNA
That Challenges Evolution
MICHAEL J. BEHE
Author of DARWIN'S BLACK BOX

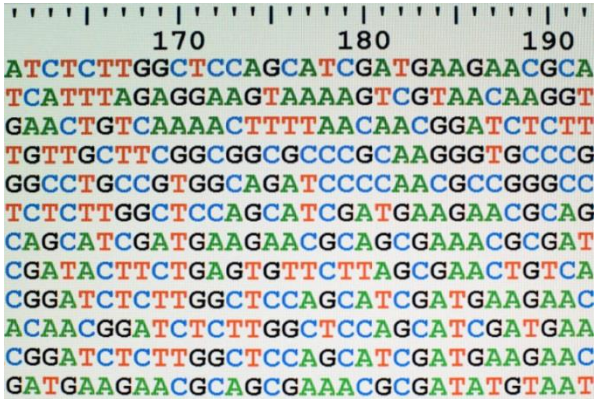
2019

Science advances with new technology

The DNA Sequencing Revolution







Key Concepts from *Darwin Devolves*

The First Rule of Adaptive Evolution

The Principle of Comparative Difficulty

The Family Line

Key Concepts from *Darwin Devolves*

The First Rule of Adaptive Evolution

The Principle of Comparative Difficulty

The Family Line

Richard Lenski

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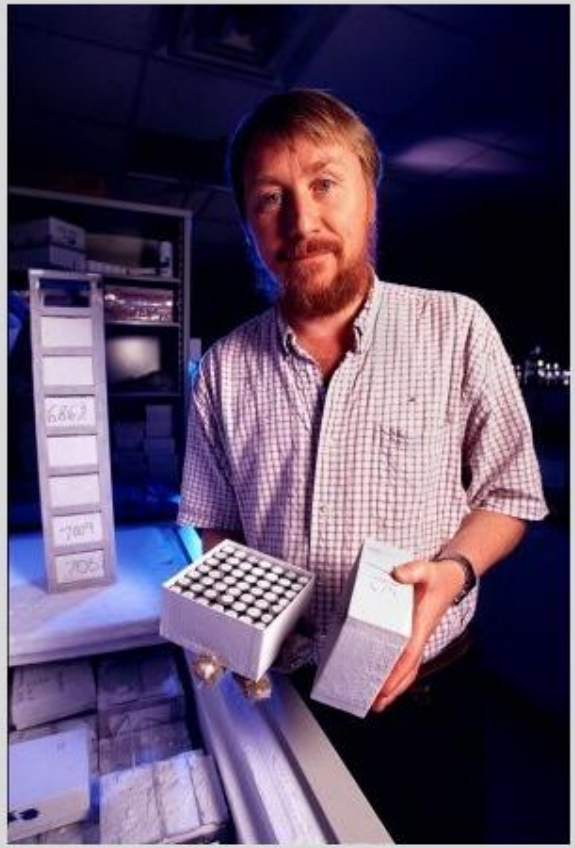

Photo courtesy of Bruce Fox, MSU

Richard E. Lenski
Hannah Distinguished Professor
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Last Updated: 7 April 2007

Feature article in Science magazine--"Test tube evolution catches time in a bottle" by Tim Appenzeller--on our research with evolving bacteria

Column on our research with digital organisms from Natural History magazine [Posted with permission of author Carl Zimmer, illustrator James Marsh, and Natural History magazine.]

Also of interest ...

- The *E. coli* long-term evolution experiment
- Some thoughts and readings on the history and philosophy of science

"expression of both the ribose operon and the maltose regulon *decreased* after 20,000 generations of experimental evolution. These changes may therefore reflect *beneficial* mutations in these regulons. Indeed, *deletions* of the *rbs* operon were found previously in all 12 of the evolved populations."

DOI: 10.1534/genetics.105.049619

Parallel Changes in Global Protein Profiles During Long-Term Experimental Evolution in *Escherichia coli*

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Manuscript received August 15, 2005
Accepted for publication May 11, 2006

ABSTRACT

Twelve populations of *Escherichia coli* evolved in and adapted to a glucose-limited environment from a common ancestor. We used two-dimensional protein electrophoresis to compare two evolved clones, isolated from independently derived populations after 20,000 generations. Exceptional parallelism was detected. We compared the observed changes in protein expression profiles with previously characterized global transcription profiles of the same clones; this is the first time such a comparison has been made in an evolutionary context where these changes are often quite subtle. The two methodologies exhibited some remarkable similarities that highlighted two different levels of parallel regulatory changes that were beneficial during the evolution experiment. First, at the higher level, both methods revealed extensive parallel changes in the same global regulatory network, reflecting the involvement of beneficial mutations in genes that control the ppGpp regulon. Second, both methods detected expression changes of identical gene sets that reflected parallel changes at a lower level of gene regulation. The protein profiles led to the discovery of beneficial mutations affecting the *malT* gene, with strong genetic parallelism across independently evolved populations. Functional and evolutionary analyses of these mutations revealed parallel phenotypic decreases in the maltose regulon expression and a high level of polymorphism at this locus in the evolved populations.

EXPERIMENTAL EVOLUTION, LOSS-OF-FUNCTION MUTATIONS, AND "THE FIRST RULE OF ADAPTIVE EVOLUTION"

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E-MAIL: MJB1@LEHIGH.EDU

KEYWORDS

experimental evolution, adaptation, mutation, loss of function, malaria, *Yersinia pestis*

ABSTRACT

Adaptive evolution can cause a species to gain, lose, or modify a function; therefore, it is of basic interest to determine whether any of these modes dominates the evolutionary process under particular circumstances. Because mutation occurs at the molecular level, it is necessary to examine the molecular changes produced by the underlying mutation in order to assess whether a given adaptation is best considered as a gain, loss, or modification of function. Although that was once impossible, the advance of molecular biology in the past half century has made it feasible. In this paper, I review molecular changes underlying some adaptations, with a particular emphasis on evolutionary experiments with microbes conducted over the past four decades. I show that by far the most common adaptive changes seen in those examples are due to the loss

Behe, M. J., 2010 Experimental Evolution, Loss-of-function Mutations, and "The First Rule of Adaptive Evolution". *Quarterly Review of Biology* 85: 1-27.

VOLUME 85, NO. 4 THE QUARTERLY REVIEW OF BIOLOGY DECEMBER 2010

EXPERIMENTAL EVOLUTION, LOSS-OF-FUNCTION MUTATIONS, AND "THE FIRST RULE OF ADAPTIVE EVOLUTION"

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KEYWORDS:
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Adaptive evolution can cause a species to gain, lose, or modify a function; therefore, it is of basic interest to determine whether any of these modes dominates the evolutionary process under particular circumstances. Because mutation occurs at the molecular level, it is necessary to examine the molecular changes produced by the underlying mutation in order to assess whether a given adaptation is best considered as a gain, loss, or modification of function. Although that was once impossible, the advance of molecular biology in the past half century has made it feasible. In this paper, I review molecular changes underlying some adaptations, with a particular emphasis on evolutionary experiments with microbes conducted over the past four decades. I show that by far the most common adaptive changes seen in those examples are due to the loss or modification of a pre-existing molecular function, and I discuss the possible reasons for the preeminence of such mutations.

ADAPTATION BY GAIN, LOSS, OR MODIFICATION OF FUNCTION

IN *THE ORIGIN OF SPECIES*, Darwin (1859) emphasized the relentlessness of natural selection:

> [N]atural selection is daily and hourly scrutinising, throughout the world, every variation, even the slightest; rejecting that which is bad, preserving and adding up all that is good; silently and insensibly working, whenever and wherever opportunity offers, at the improvement of each organic being in relation to its organic and inorganic conditions of life. (p. 84)

Yet he realized that the changes that were selected to adapt an organism to its environment did not have to be ones that conferred upon it a new ability, such as sight or flight. For instance, while observing some barnacles, Darwin discovered unexpected cases of the gross simplification of an organism (Stott 2003):

> The male is as transparent as glass . . . In the lower part we have an eye, & great testis & vesicula seminalis: in the capitulum we have nothing but a tremendously long penis coiled up & which can be exserted. There is no mouth no stomach no cirri, no

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0033-5770/2010/8504-0002$15.00

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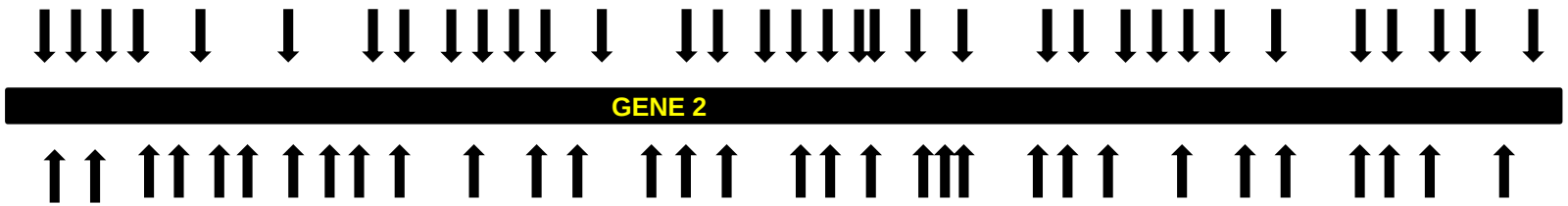
The First Rule of Adaptive Evolution:

Break or *blunt* any functional coded element whose loss would yield a net fitness gain.

Points where a gene might be improved

Points where a gene might be broken



Helpful degradation

What observation *demonstrates* about random mutations

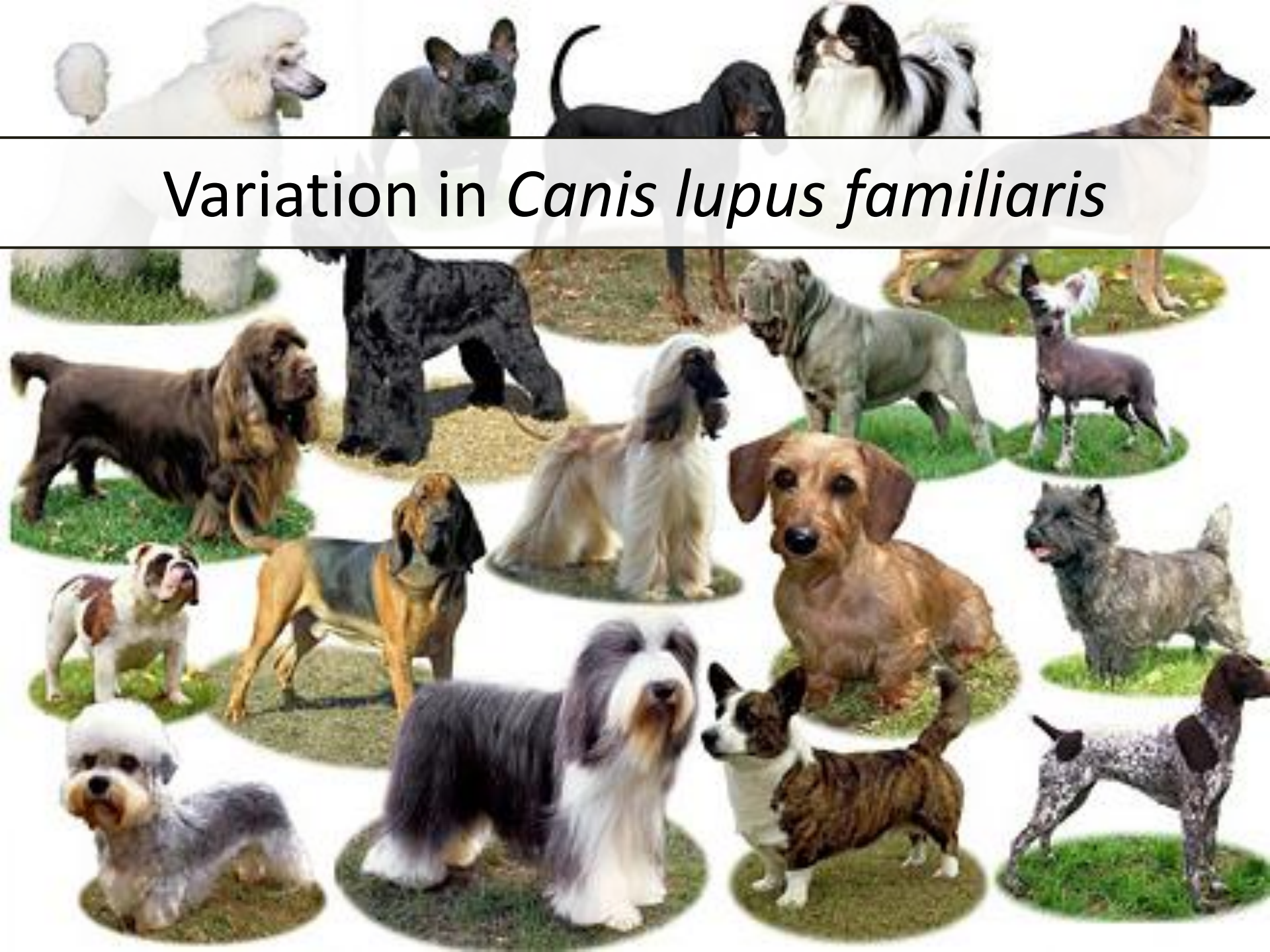
Of those mutations that affect an organism, about 99% are detrimental

Of even *beneficial* mutations, the great majority break genes or degrade function

Darwin's mechanism:

- is dominated by *"**Poison-Pill**"* mutations: positively-selected, loss-of-function mutations
- ***squanders*** genetic information for short-term gain

Variation in *Canis lupus familiaris*



Dog breed mutations

phenotype	gene	mutation	ref.
coat color, yellow	Mc1r (melanocortin 1 receptor)	LOF	1
" , black	CBD103 (ß-defensin)	ΔG23	1
coat variation ("furnishings", hair length, curl)	RSPO2 (R-spondin–2) FGF5 (fibroblast growth factor–5) KRT71 (keratin-71)	167 bp ins UTR C95→F R151→W	2
size	IGF1 (insulin-like growth factor 1)	synonymous SNP	3
short legs	FGF4 (fibroblast growth factor–4)	retroinsertion	4
short muzzle	THBS2 (thrombospondin) SMOC2	multiple SNPs "	5
muscle mass	MSTN (myostatin)	premature stop	6
white spotting	MITF (microphthalmia-assoc. TF)	SINE in reg region	7
hair ridge	FGF3,4,19 (fibroblast gfs)	133-kb duplication	8

[1] Candille,S.I. et al. 2007. A ß-defensin mutation causes black coat color in domestic dogs. Science 318:1418-1423.
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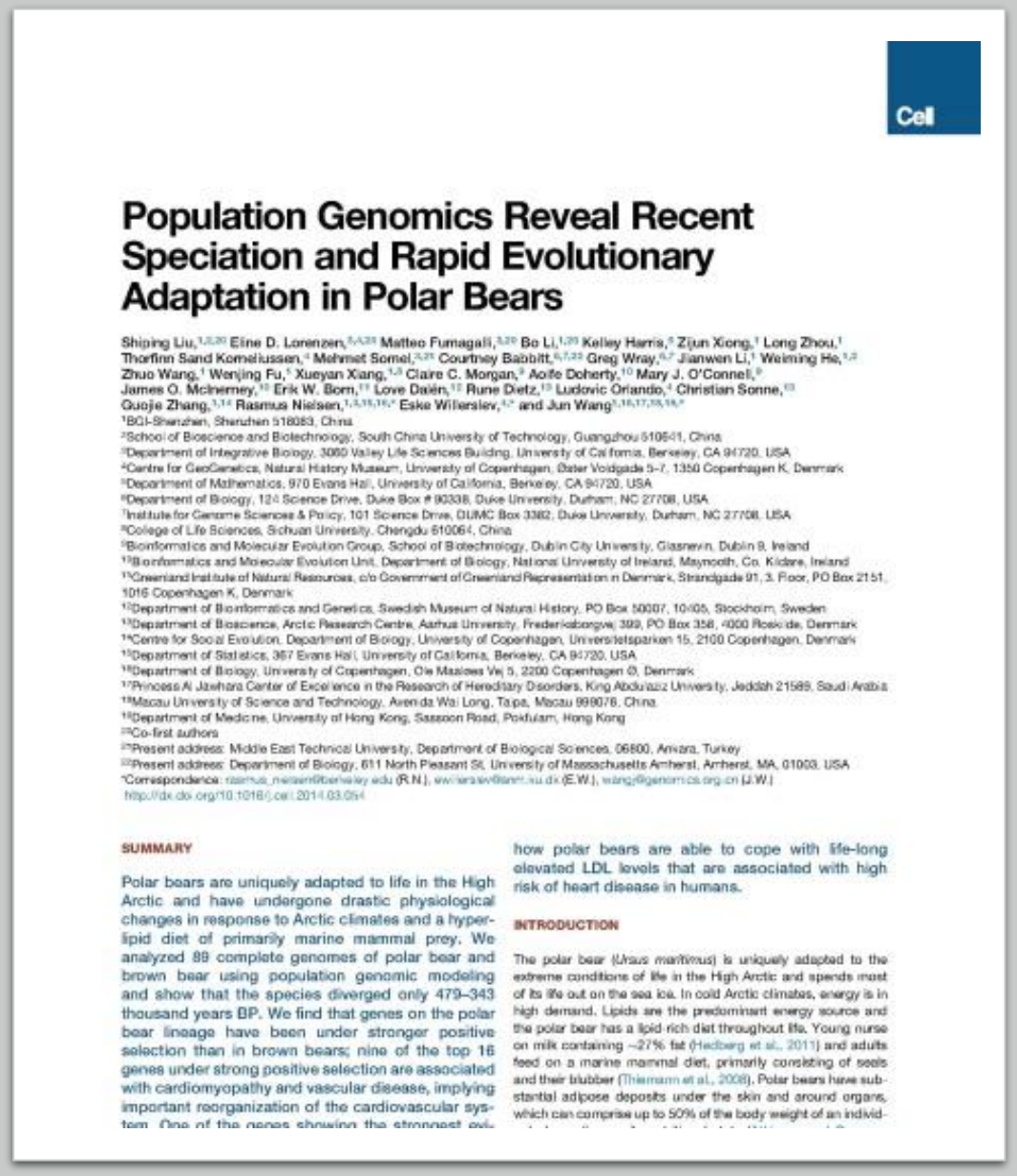
Polar bear evolution

Li, S. et al. 2014. Population Genomics Reveal Recent Speciation and Rapid Evolutionary Adaptation in Polar Bears. *Cell* **157**:785-794.

"[W]e assessed the impact of polar-bear-specific substitutions … by computational predictions: *a large proportion (ca. 50%) of mutations were predicted to be functionally damaging*."



Cell

Population Genomics Reveal Recent Speciation and Rapid Evolutionary Adaptation in Polar Bears

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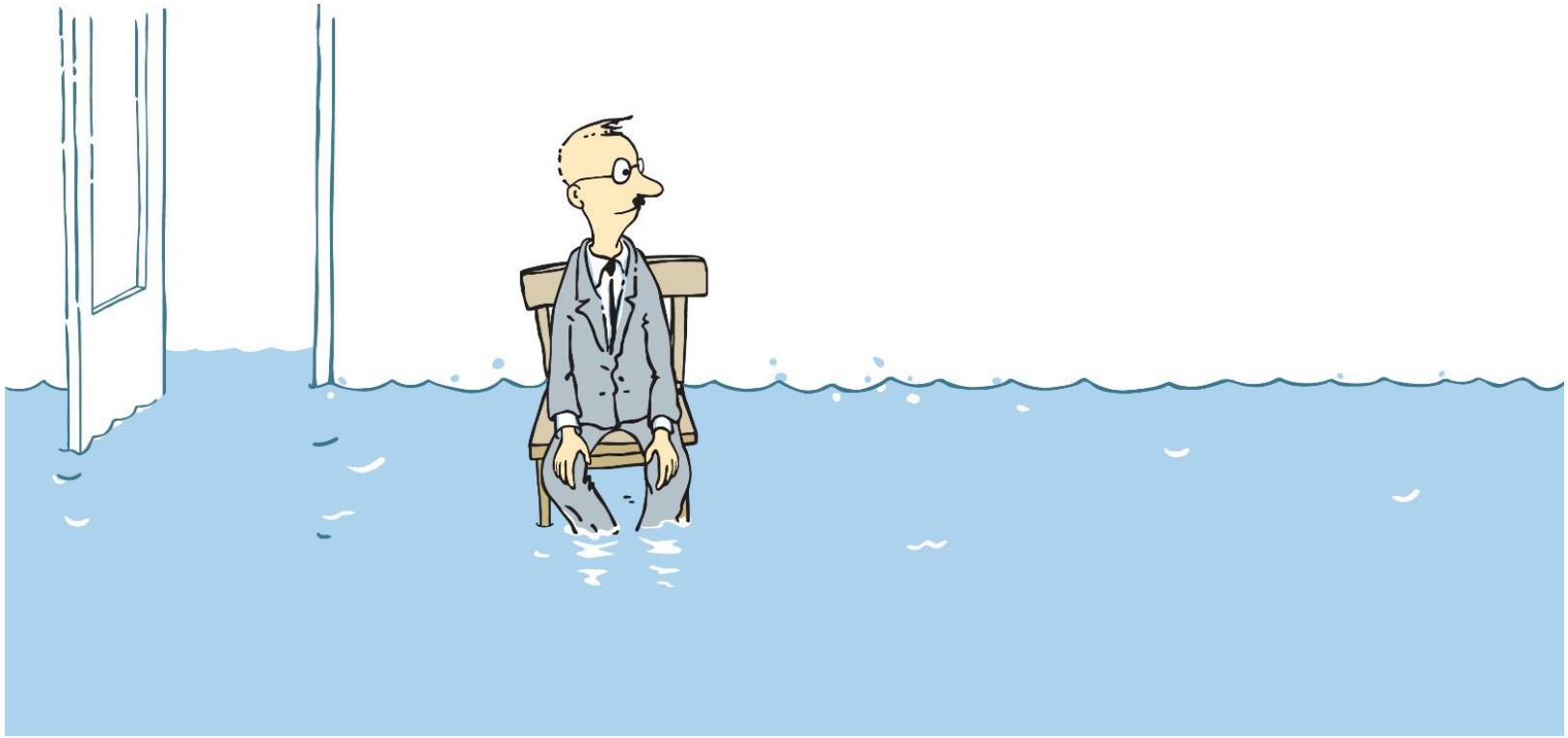
SUMMARY

Polar bears are uniquely adapted to life in the High Arctic and have undergone drastic physiological changes in response to Arctic climates and a hyper-lipid diet of primarily marine mammal prey. We analyzed 89 complete genomes of polar bear and brown bear using population genomic modeling and show that the species diverged only 479–343 thousand years BP. We find that genes on the polar bear lineage have been under stronger positive selection than in brown bears; nine of the top 16 genes under strong positive selection are associated with cardiomyopathy and vascular disease, implying important reorganization of the cardiovascular system. One of the genes showing the strongest evi-

how polar bears are able to cope with life-long elevated LDL levels that are associated with high risk of heart disease in humans.

INTRODUCTION

The polar bear (*Ursus maritimus*) is uniquely adapted to the extreme conditions of life in the High Arctic and spends most of its life out on the sea ice. In cold Arctic climates, energy is in high demand. Lipids are the predominant energy source and the polar bear has a lipid-rich diet throughout life. Young nurse on milk containing ~27% fat (Hedberg et al., 2011) and adults feed on a marine mammal diet, primarily consisting of seals and their blubber (Thiemann et al., 2008). Polar bears have substantial adipose deposits under the skin and around organs, which can comprise up to 50% of the body weight of an individ-



The water is rising quickly. Should the man wait for delivery of a complex pump that's on a ten-year backorder from the hardware store? Or should he *kick a hole in the wall* to let the water drain out?

Darwinian evolution at work

Key Concepts from *Darwin Devolves*

The First Rule of Adaptive Evolution

The Principle of Comparative Difficulty

The Family Line

Key Concepts from *Darwin Devolves*

The First Rule of Adaptive Evolution

The Principle of Comparative Difficulty

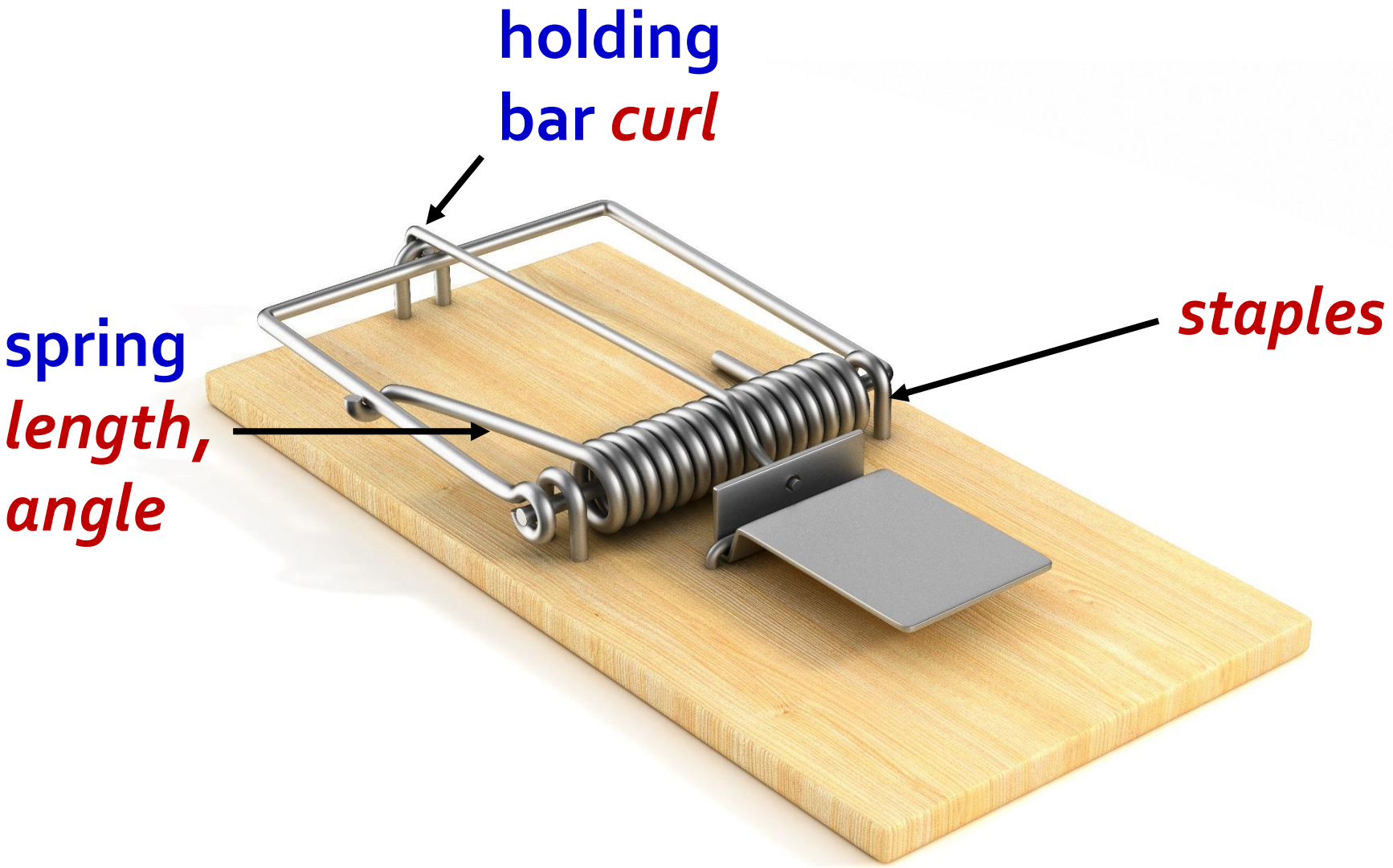
The Family Line

The Principle of Comparative Difficulty

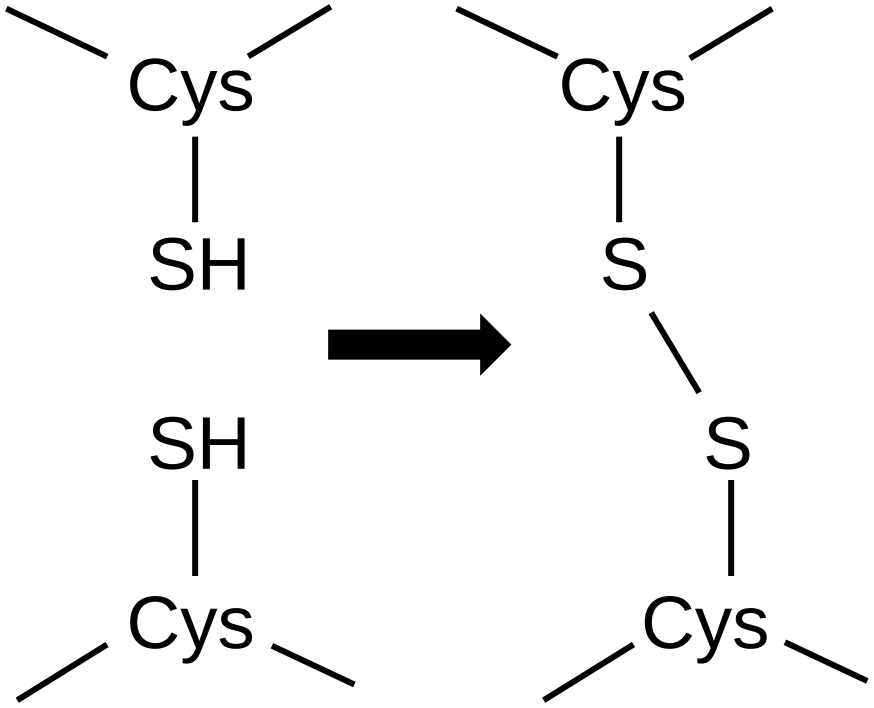
If a task that requires less effort is too difficult to achieve,

then a task that requires much more effort necessarily is too.

A common mechanical mousetrap needs multiple pieces *that are themselves complex*



mini Irreducible Complexity (mIC):



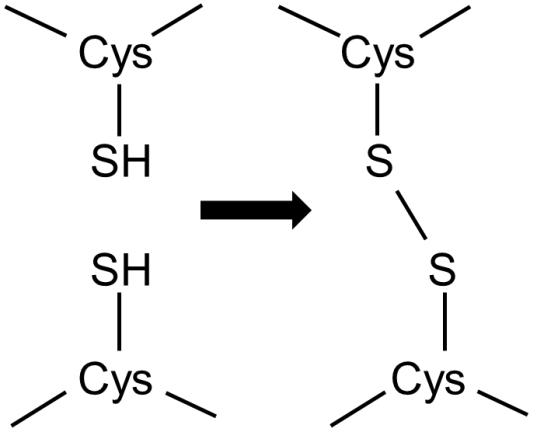
Behe, M.J., Snoke, D.W., 2004. Simulating evolution by gene duplication of protein features that require multiple amino acid residues. *Protein Sci* 13: 2651-2664.

"We conclude that, in general, to be fixed in 10^8 generations, the production of novel protein features that require the participation of two or more amino acid residues simply by multiple point mutations in duplicated genes would entail population sizes of no less than 10^9."

Darwinism is claimed to explain:

- cells
- the genetic code
- molecular machines
- genetic networks
- phyla
- literature, music
- politics, the law
- love, the universe
- ***even mind itself***

- *It just has trouble explaining a disulfide bond*



Key Concepts from *Darwin Devolves*

The First Rule of Adaptive Evolution

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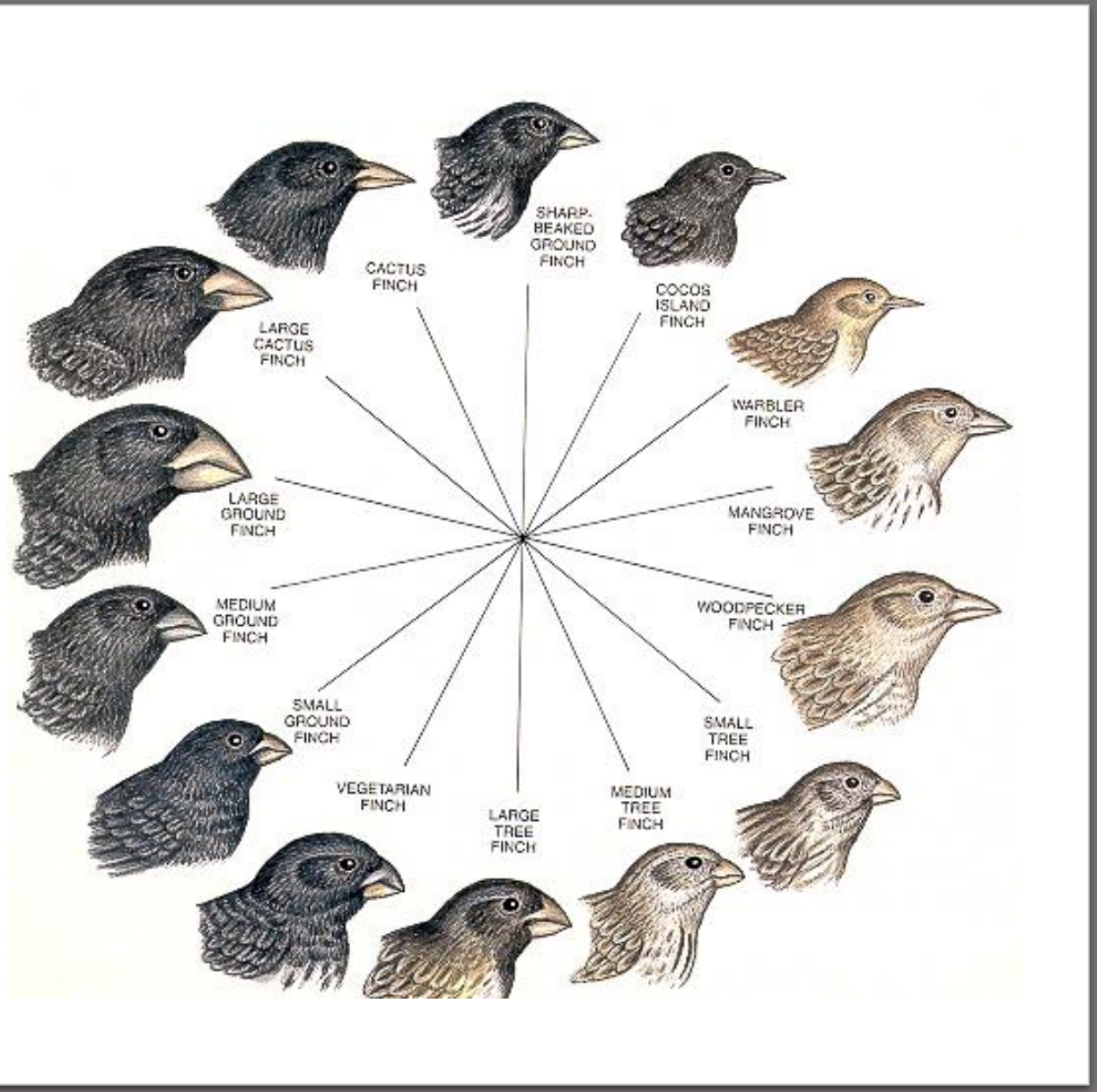
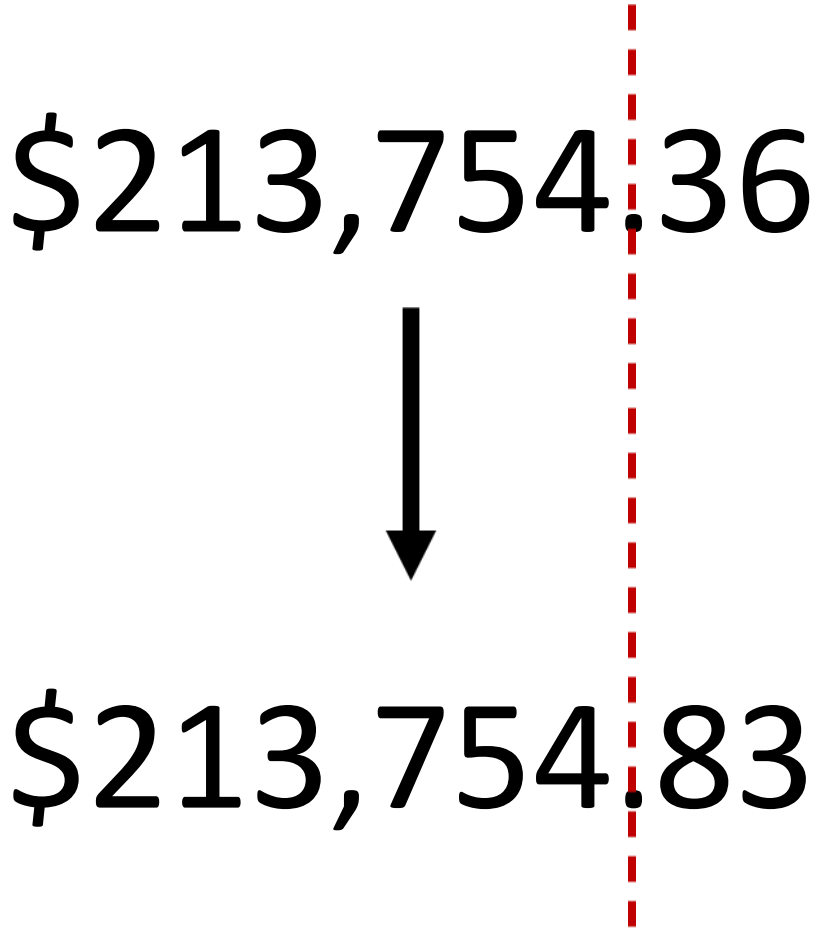


Galápagos finch species

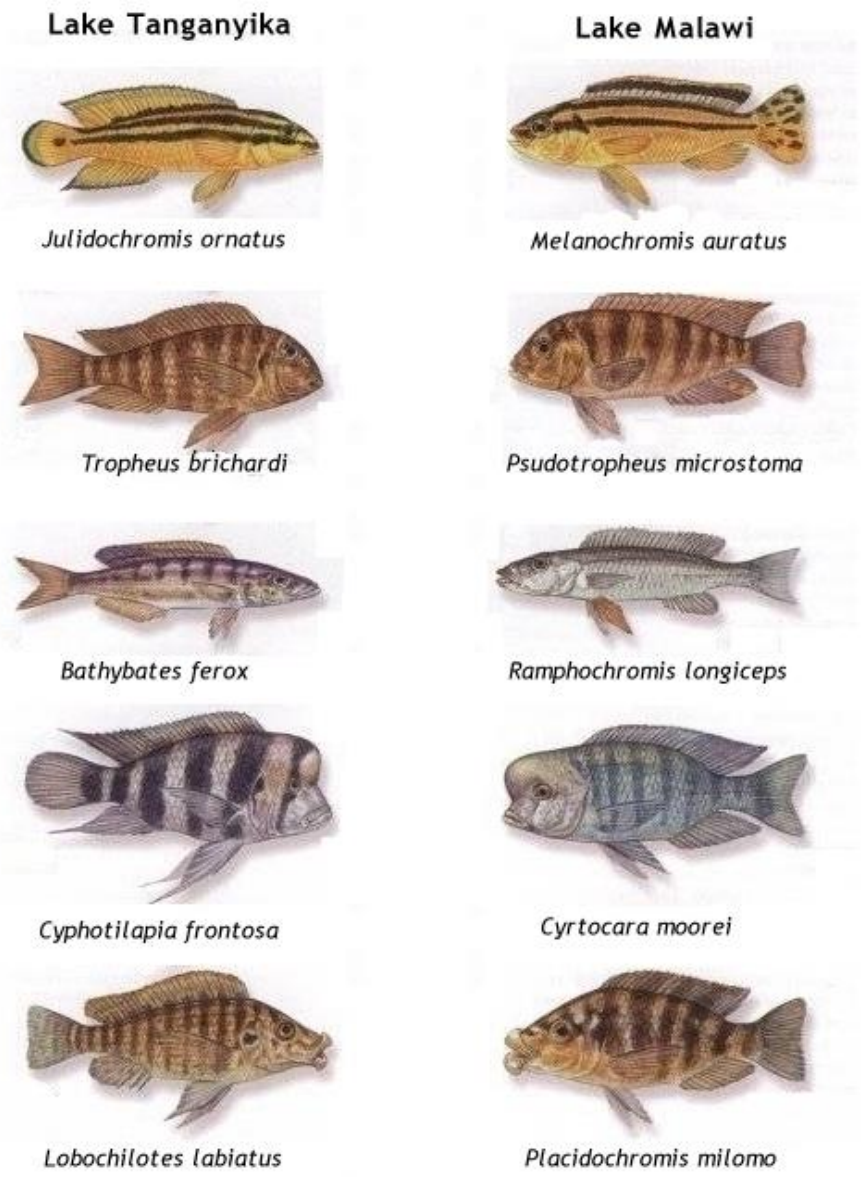
Classification of Galápagos finches and their ancestor

Level	Ancestor	Descendant
Domain	Eukaryota	Eukaryota
Kingdom	Animalia	Animalia
Phylum	Chordata	Chordata
Class	Aves	Aves
Order	Passeriformes	Passeriformes
Family	Thraupidae	Thraupidae
Genus	unknown	*Geospiza*; *Camarhynchus*; *Certhidea*; *Pinaroloxias*
Species	unknown	Various

Two million years of relentless evolution



Species of Cichlid fish



Classification of African great lake cichlids and their ancestor

Level	Ancestor	Descendant
Domain	Eukaryota	Eukaryota
Kingdom	Animalia	Animalia
Phylum	Chordata	Chordata
Class	Actinopterygii	Actinopterygii
Order	Perciformes	Perciformes
Family	Cichlidae	Cichlidae
Genus	unknown	various
Species	unknown	various

New classifications produced by luxuriantly evolving groups

group	species	genera	families	higher
finches	14	4	0	0
cichlids	~1500	~75	0	0
anoles	~300	3	0	0
honeycreepers	55	24	0	0
fruit flies	~1000	2	0	0
beetles	239	1	0	0
silverswords	50	3	0	0
lobelias	126	6	0	0

The Family Line:

Darwinian evolution is *self-limiting*

Three factors *restrict* it at the *highest* levels of biology
by *promoting* it at the *lowest* levels:

Random mutation

Natural selection

Irreducible complexity

The interaction of intelligent & unintelligent evolutionary processes

The *First Rule of Adaptive Evolution* allows organisms to quickly adapt to their environment by devolutionary processes.

Undirected evolutionary change rapidly bogs down before the *Family Line*.

Prediction: Unique information, inaccessible to unguided processes, is required at the level of family and higher.

The recognizable depth of design in animals as of **AD 2019**

The limit of Darwinian evolution now seems to be at the biological level of ***family***.

Families in the mammalian Order Carnivora



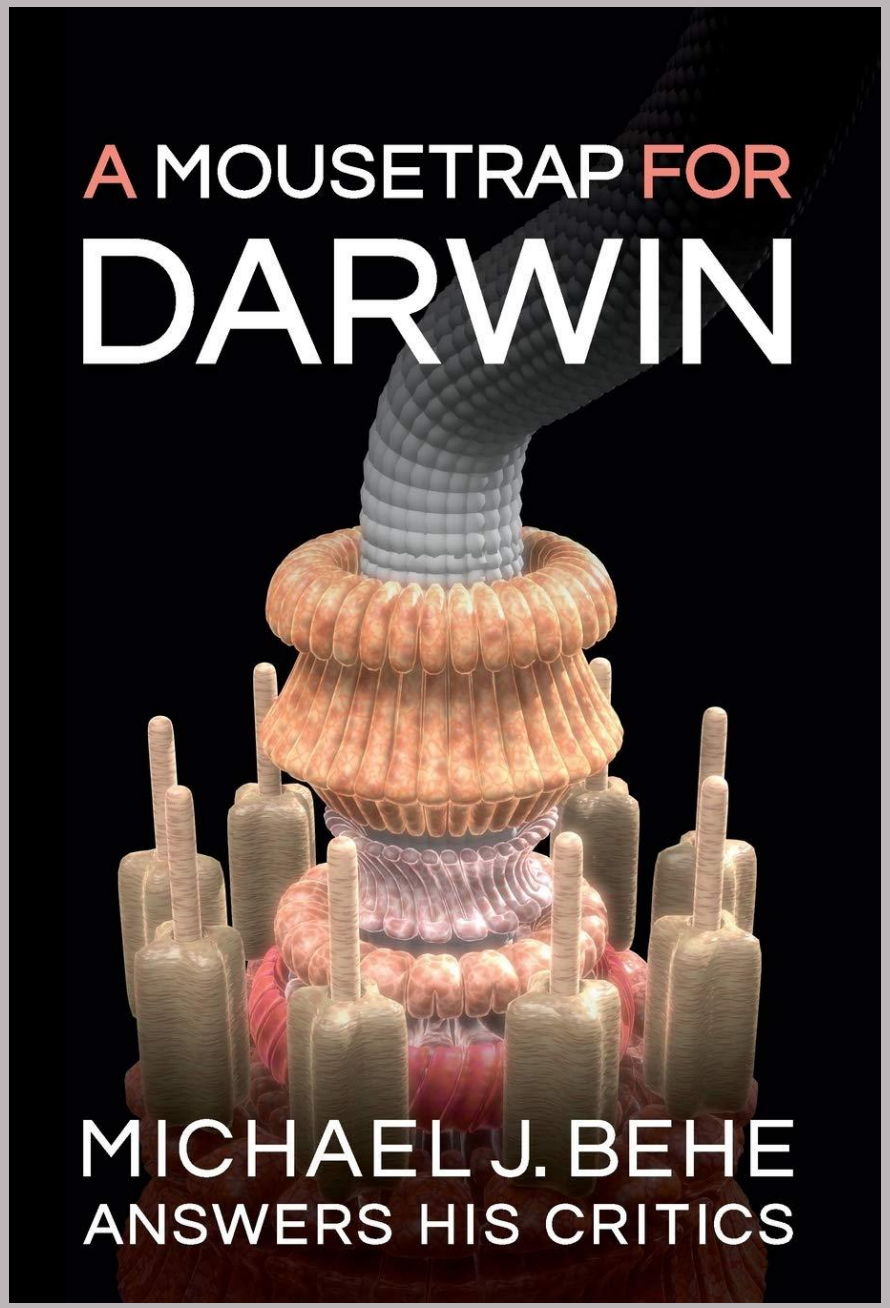


lehigh.edu/…/behe.html

discovery.org

michaelbehe.com

My responses to critics can be found at:



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