A Conclusion of the Intelligent Design of Life is *Rationally Compelling*

Michael J. Behe

Lehigh University

Charles Darwin

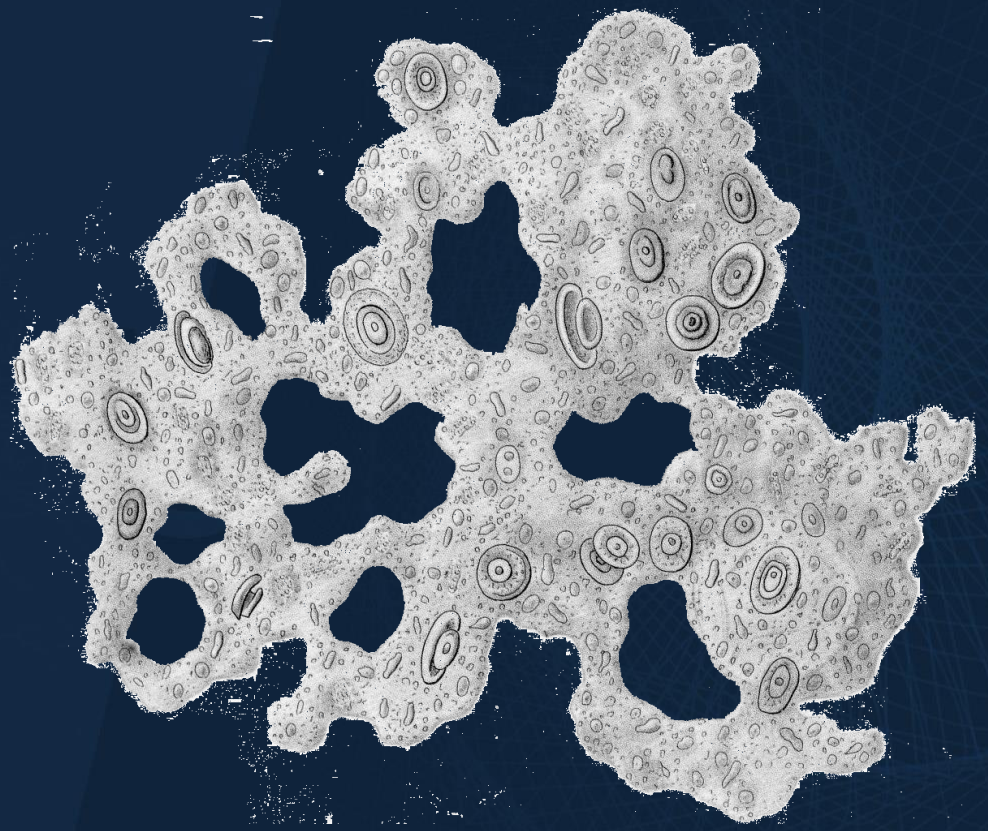
1809-1882

Karol Darwin

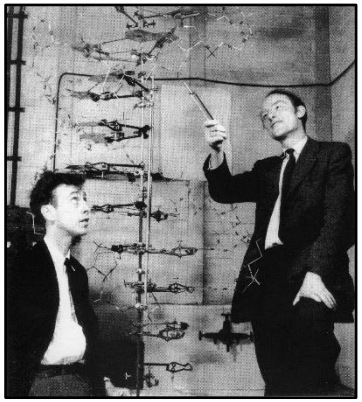
Bathybius haeckelii
1870

“Protoplasm”

“Protoplazma”



Early 1950s



Late 1950s

1960s

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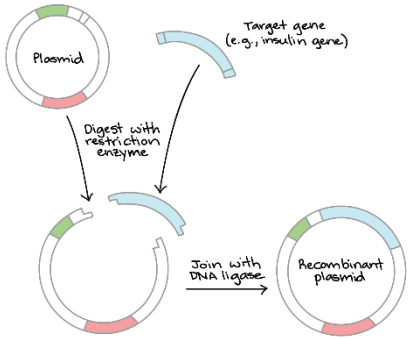
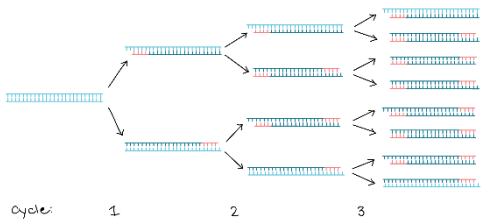
T	TTT	phe	TCT	ser	TAT	tyr	TGT	cys	T
	TTC		TCC		TAC		TGC		C
	TTA	leu	TCA		TAA	stop	TGA	stop	A
	TTG		TCG		TAG		TGG	try	G
C	CTT	leu	CCT	pro	CAT	his	CGT	arg	T
	CTC		CCC		CAC		CGC		C
	CTA		CCA		CAA	gln	CGA		A
	CTG		CCG		CAG		CGG		G
A	ATT	ile	ACT	thr	AAT	asp	AGT	ser	T
	ATC		ACC		AAC		AGC		C
	ATA	ile	ACA		AAA	lys	AGA	arg	A
	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

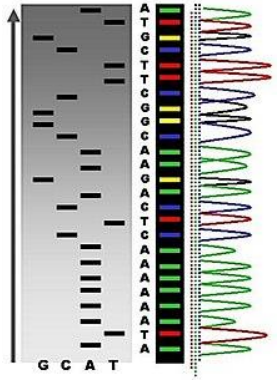
1970s



1980s



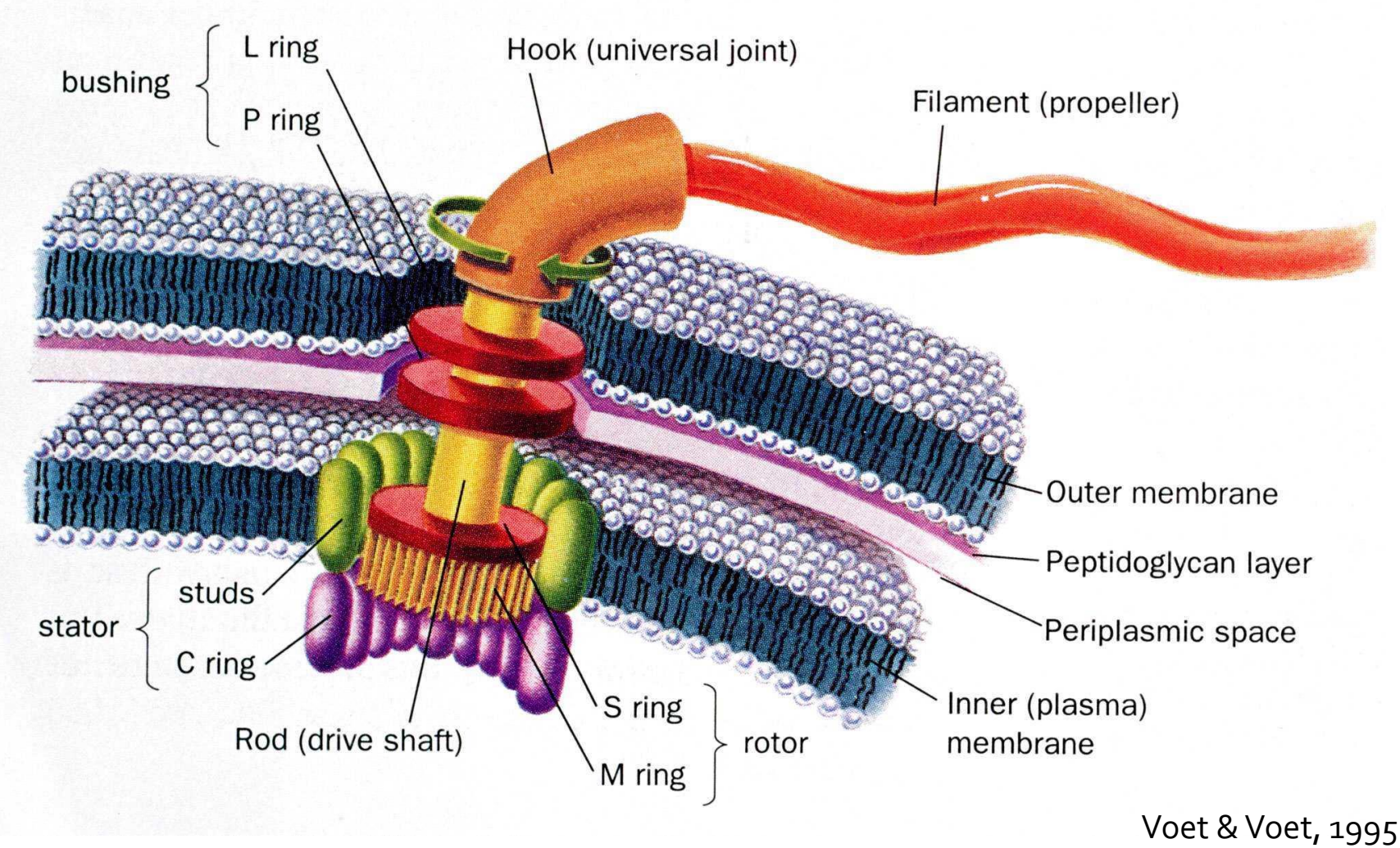
2000s



Wić bakteryjna
The Bacterial Flagellum

Wić bakteryjna

The Bacterial Flagellum



Voet & Voet, 1995

Czasopismo „Cell” (1998) **92**, spis treści

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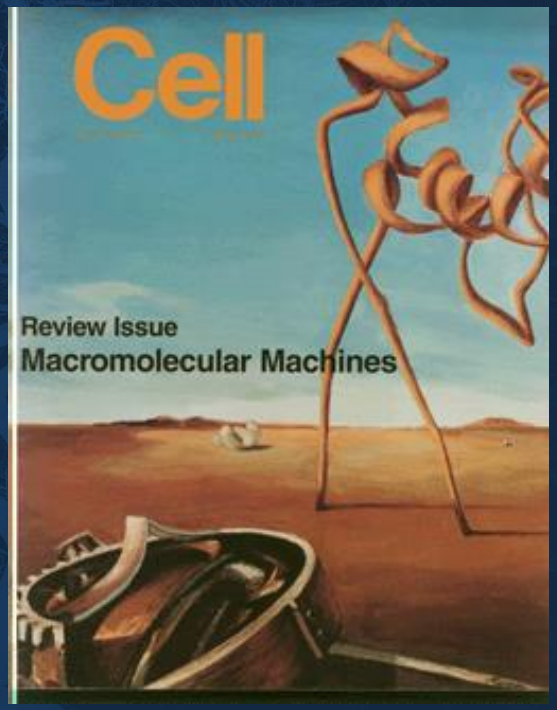

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Cryo-EM structure of the entire mammalian F-type ATP synthase

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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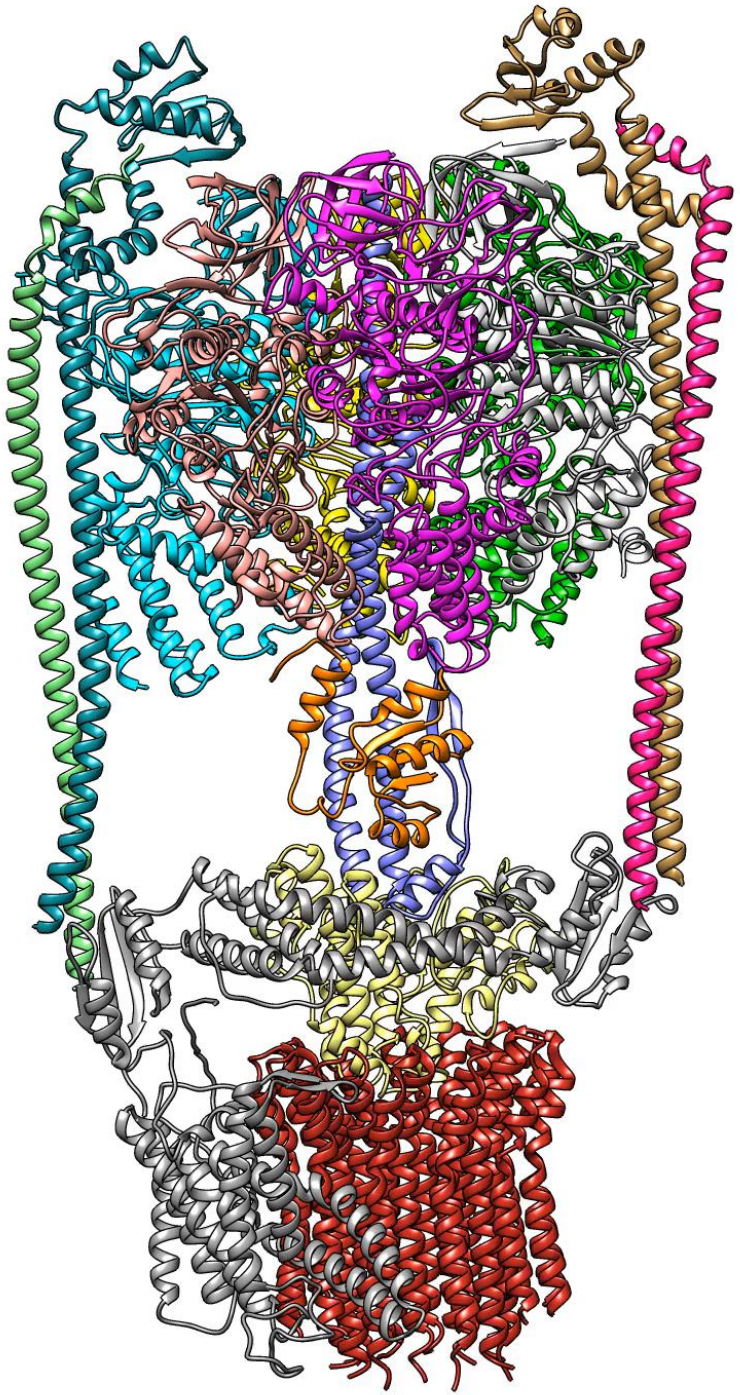
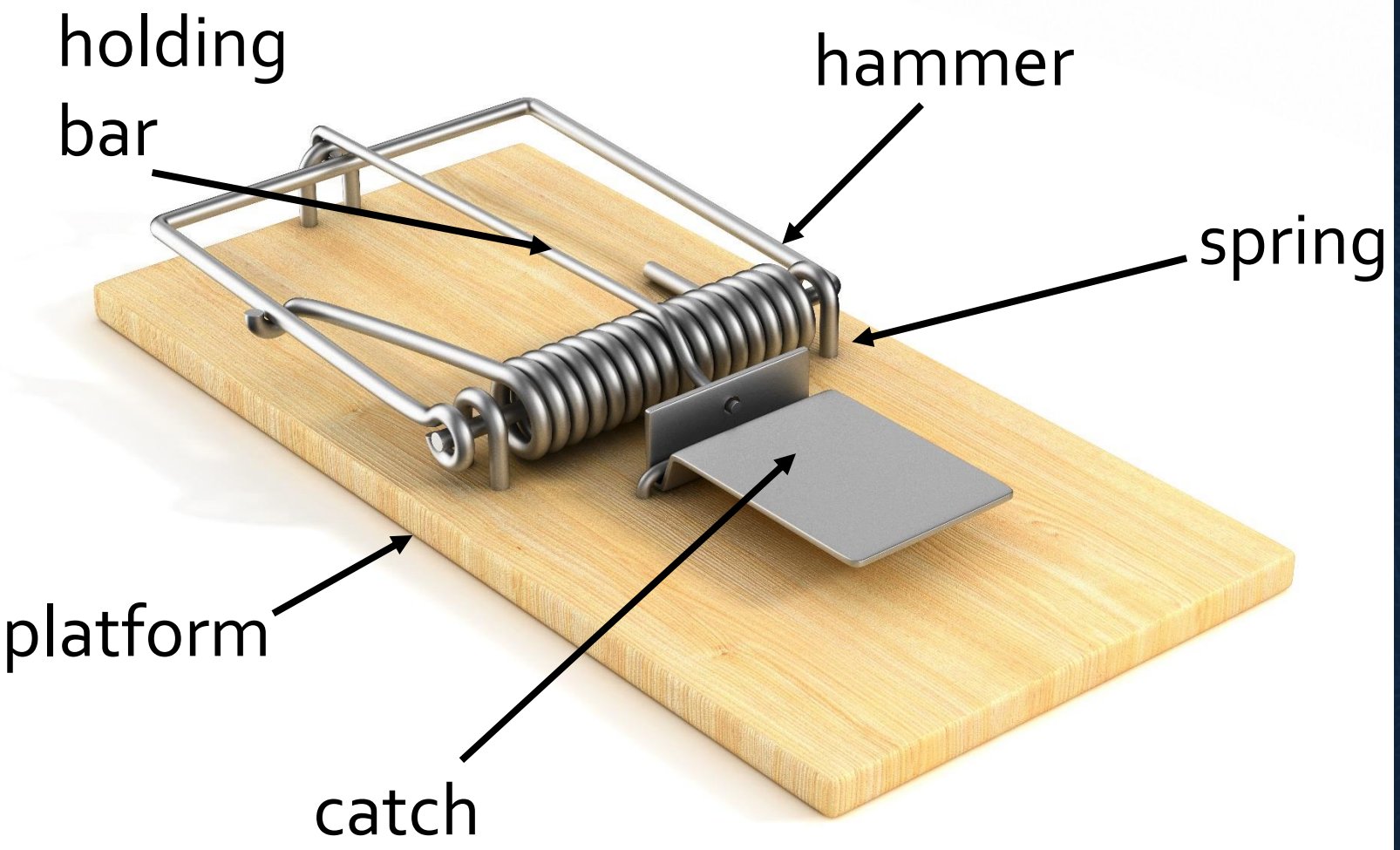
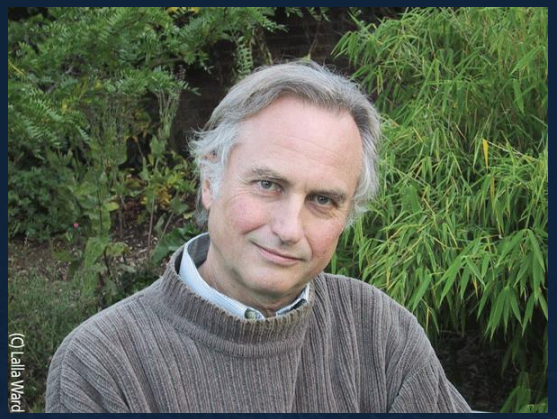


Nieredukowalna złożoność
Irreducible Complexity



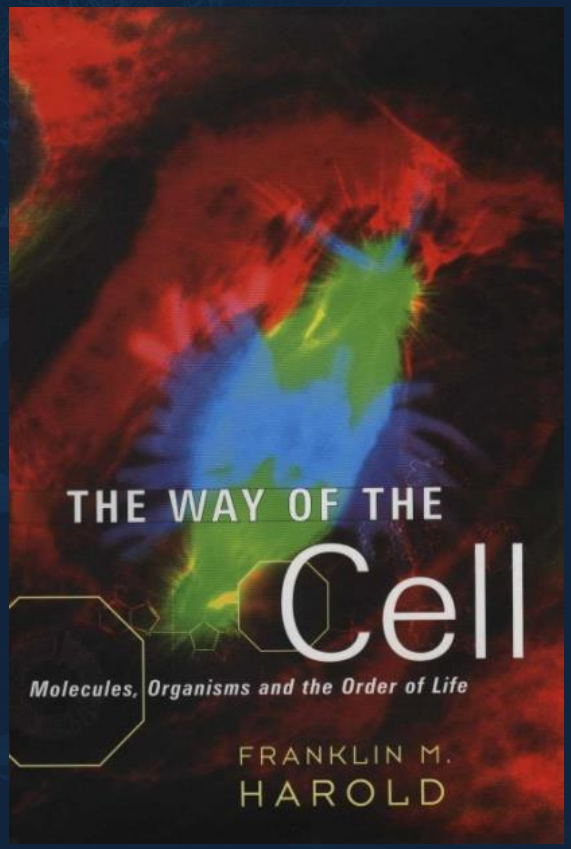
Dawkins R. 1986. *Ślepy Zegarmistrz,*
PIW Warszawa

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."

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*."


A conclusion of
intelligent design is
rationally compelling

Niesprawiedliwość

Unjust

It is UNJUST for scientists to mislead the public into thinking they know how to explain life by unintelligent means. People have a RIGHT to an unbiased appraisal.