Is the Cell *Really* a Machine?

Daniel J. Nicholson

GEORGE MASON UNIVERSITY

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The Hallmarks of Cancer

Review

Douglas Hanahan* and Robert A. Weinberg†
*Department of Biochemistry and Biophysics and Hormone Research Institute
University of California at San Francisco
San Francisco, California 94143
†Whitehead Institute for Biomedical Research and Department of Biology
Massachusetts Institute of Technology
Cambridge, Massachusetts 02142

After a quarter century of rapid advances, cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The foundation has been set in the discovery of mutations that produce oncogenes with dominant gain of function and tumor suppressor genes with recessive loss of function; both classes of cancer genes have been identified through their alteration in human and animal cancer cells and by their elicitation of cancer phenotypes in experimental models (Bishop and Weinberg, 1996).

Some would argue that the search for the origin and treatment of this disease will continue over the next quarter century in much the same manner as it has in the recent past, by adding further layers of complexity evolve progressively from normalcy via a series of premalignant states into invasive cancers (Foulds, 1954).

These observations have been rendered more concrete by a large body of work indicating that the genomes of tumor cells are invariably altered at multiple sites, having suffered disruption through lesions as subtle as point mutations and as obvious as changes in chromosome complement (e.g., Kinzler and Vogelstein, 1996). Transformation of cultured cells is itself a multistep process: rodent cells require at least two introduced genetic changes before they acquire tumorigenic competence, while their human counterparts are more difficult to transform (Hahn et al., 1999). Transgenic models of tumorigenesis have repeatedly supported the conclusion that tumorigenesis in mice involves multiple rate-limiting steps (Bergers et al., 1998; see *Oncogene*, 1999, R. DePinho and T. E. Jacks, volume 18[38], pp. 5248–5362). Taken together, observations of human cancers and animal models argue that tumor development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells (Foulds, 1954; Nowell, 1976).

[HTML] The **hallmarks** of **cancer**

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After a quarter century of rapid advances, **cancer** research has generated a rich and complex body of knowledge, revealing **cancer** to be a disease involving dynamic changes in the …

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Cell

Leading Edge
Review

Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
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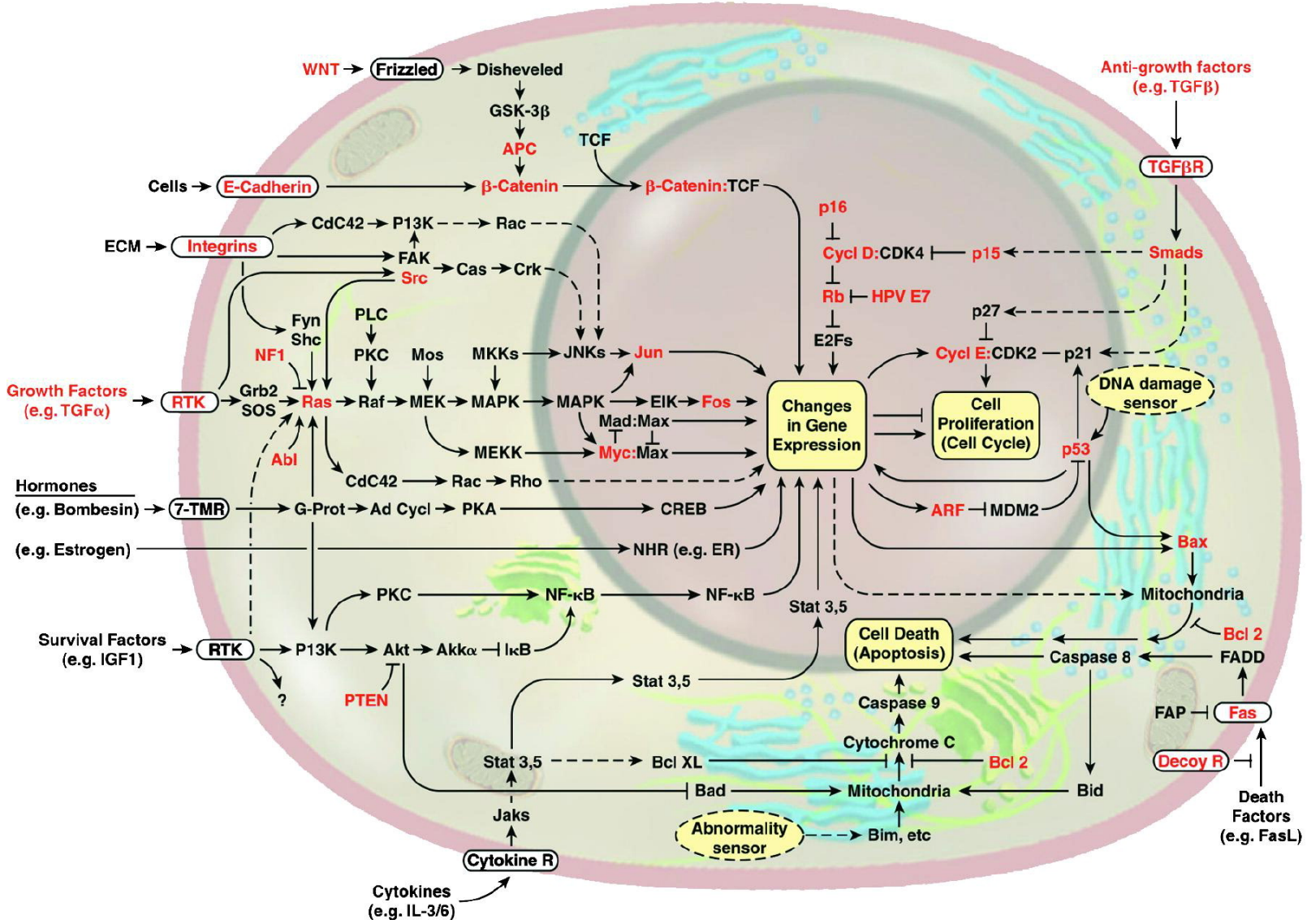
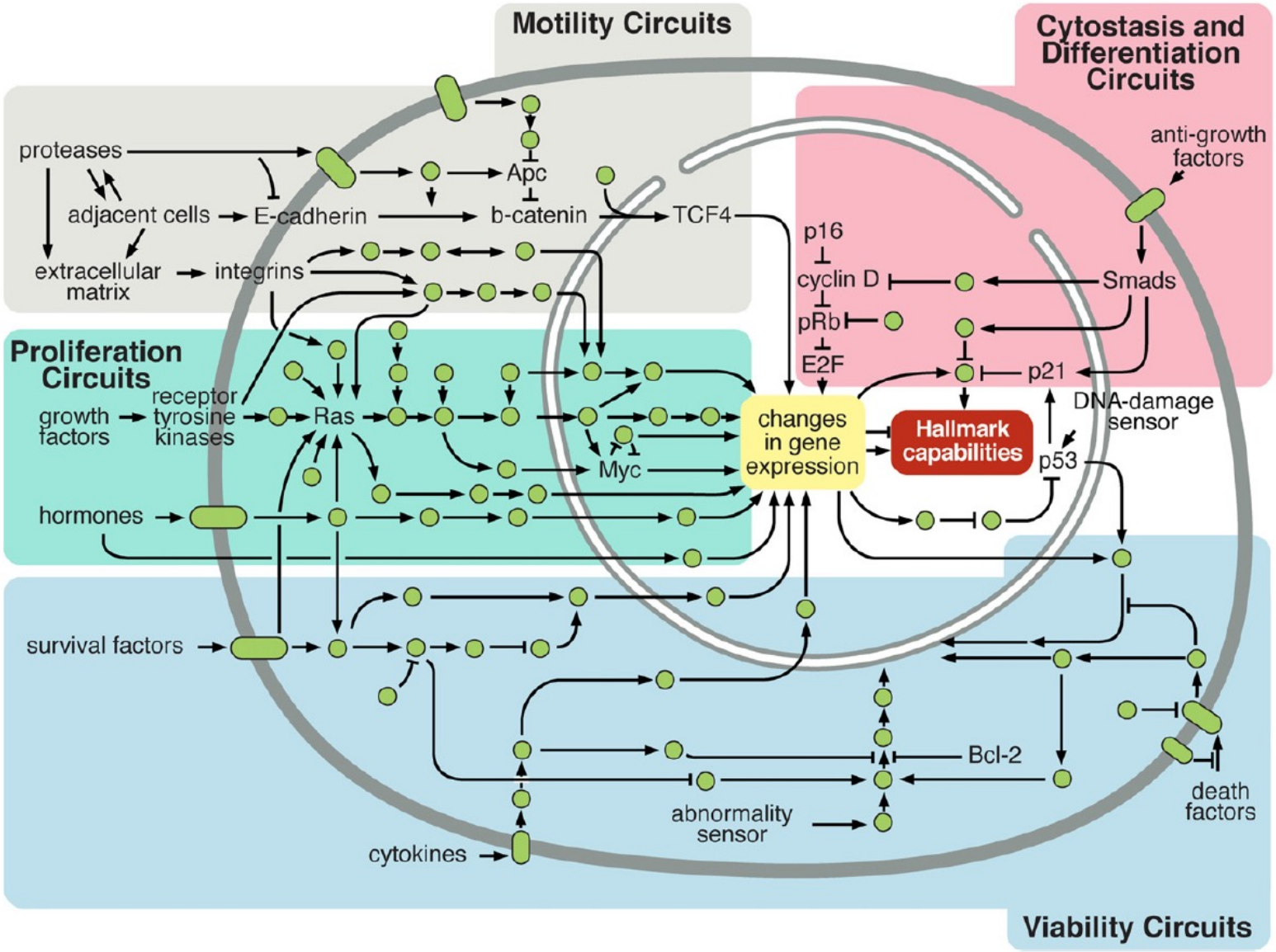
The hallmarks of cancer comprise six biological capabilities acquired during the multistep development of human tumors. The hallmarks constitute an organizing principle for rationalizing the complexities of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. Underlying these hallmarks are genome instability, which generates the genetic diversity that expedites their acquisition, and inflammation, which fosters multiple hallmark functions. Conceptual progress in the last decade has added two emerging hallmarks of potential generality to this list—reprogramming of energy metabolism and evading immune destruction. In addition to cancer cells, tumors exhibit another dimension of complexity: they contain a repertoire of recruited, ostensibly normal cells that contribute to the acquisition of hallmark traits by creating the "tumor microenvironment." Recognition of the widespread applicability of these concepts will increasingly affect the development of new means to treat human cancer.

Hallmarks of Cancer I (2000)



Hallmarks of Cancer II (2011)



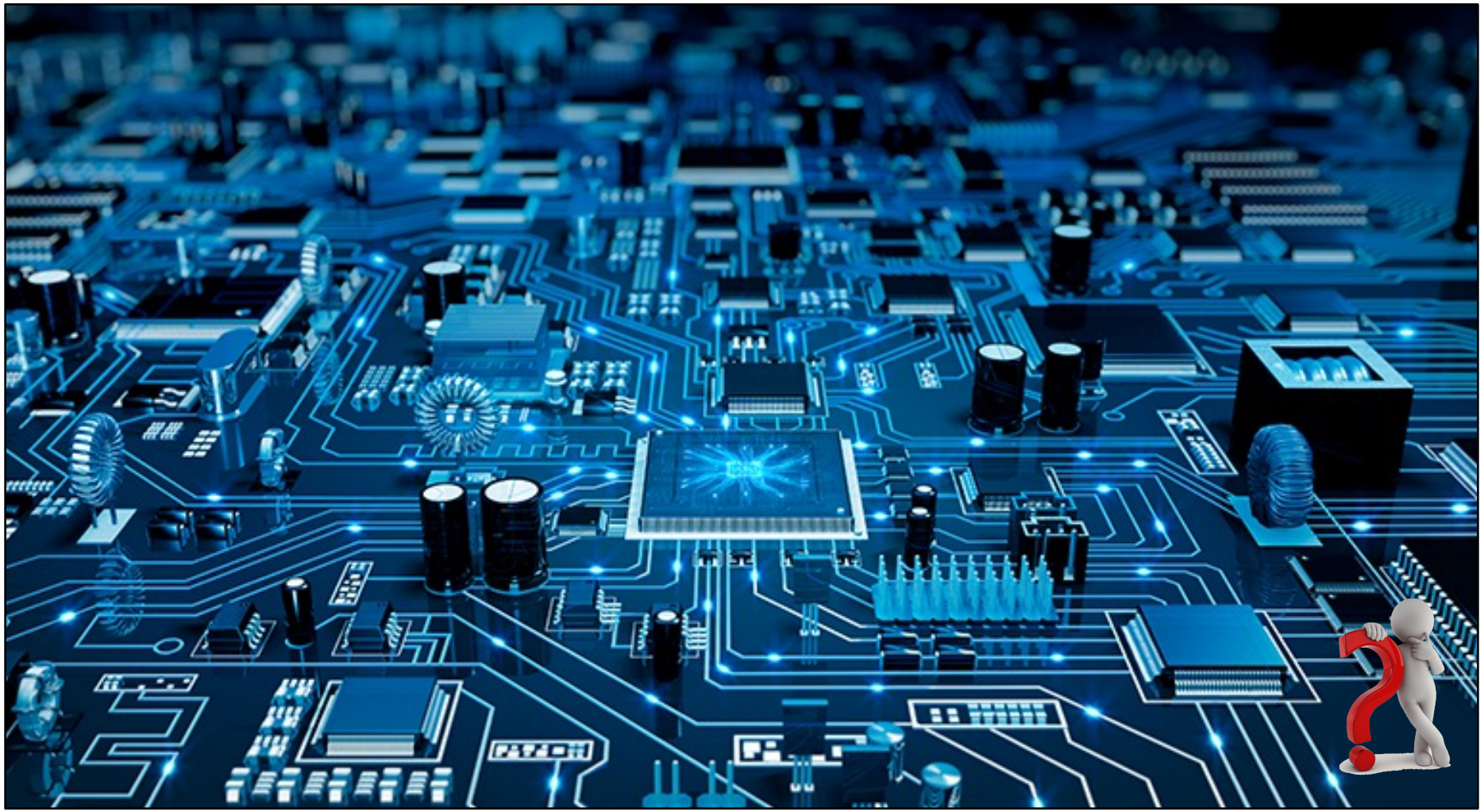
‘The Integrated Circuit of the Cell’

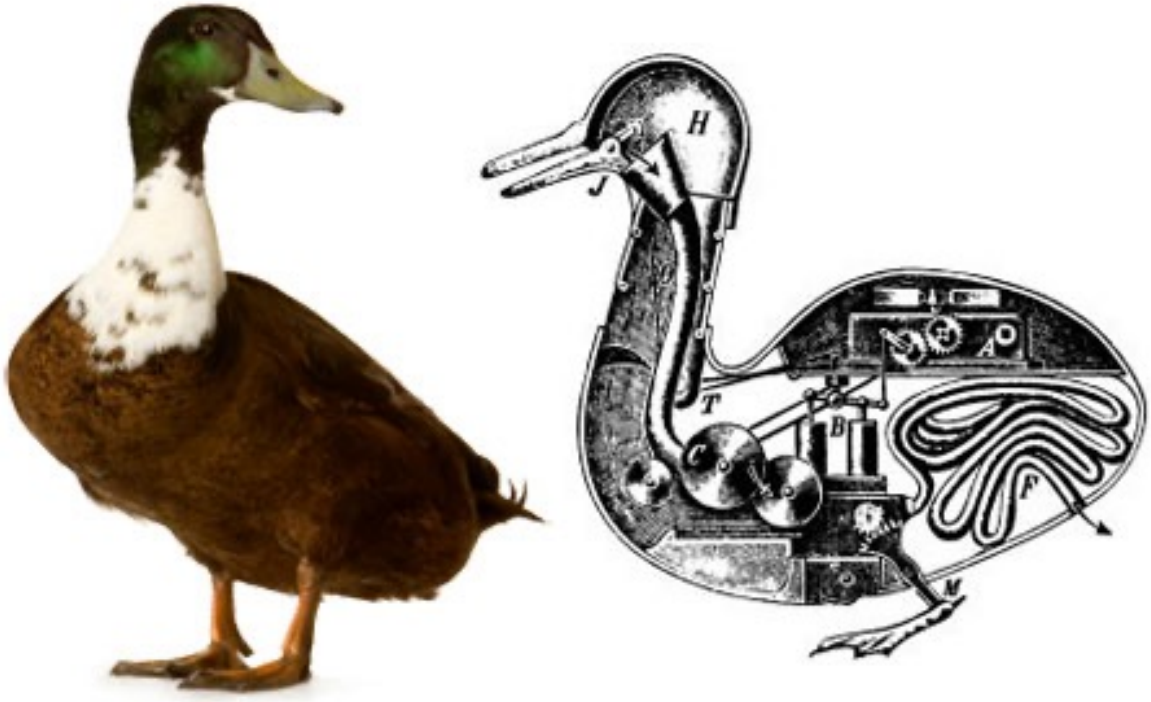
“Progress in dissecting signaling pathways has begun to lay out a circuitry that will likely mimic electronic integrated circuits in complexity and finesse, where transistors are replaced by proteins (e.g., kinases and phosphatases) and the electrons by phosphates and lipids. […]

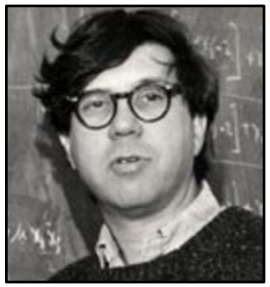
Two decades from now, having fully charted the wiring diagrams of every cellular signaling pathway, it will be possible to lay out the complete ‘integrated circuit of the cell’ upon its current outline.

We will then be able to apply the tools of mathematical modeling to explain how specific genetic lesions serve to reprogram this integrated circuit in each of the constituent cell types so as to manifest cancer.” (Hanahan & Weinberg 2000)

‘The Integrated Circuit of the Cell’

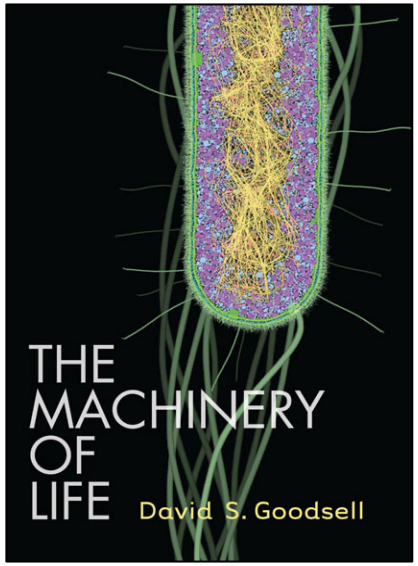






"Present day biology is the realization of the famous metaphor of the organism as a *bête-machine* elaborated by Descartes in Part V of the *Discours*" (**Lewontin** 2009)

"We animals are the most complicated and perfectly-designed pieces of machinery in the known universe" (**Dawkins** 1976)



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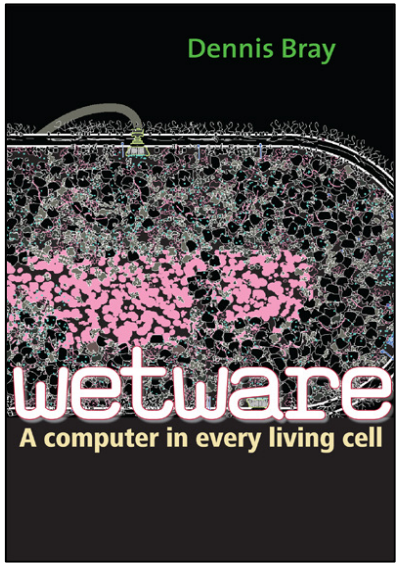
The Cell as a Collection of Protein Machines: Preparing the Next Generation of Molecular Biologists

Biological machines: from mills to molecules

Marco Piccolino



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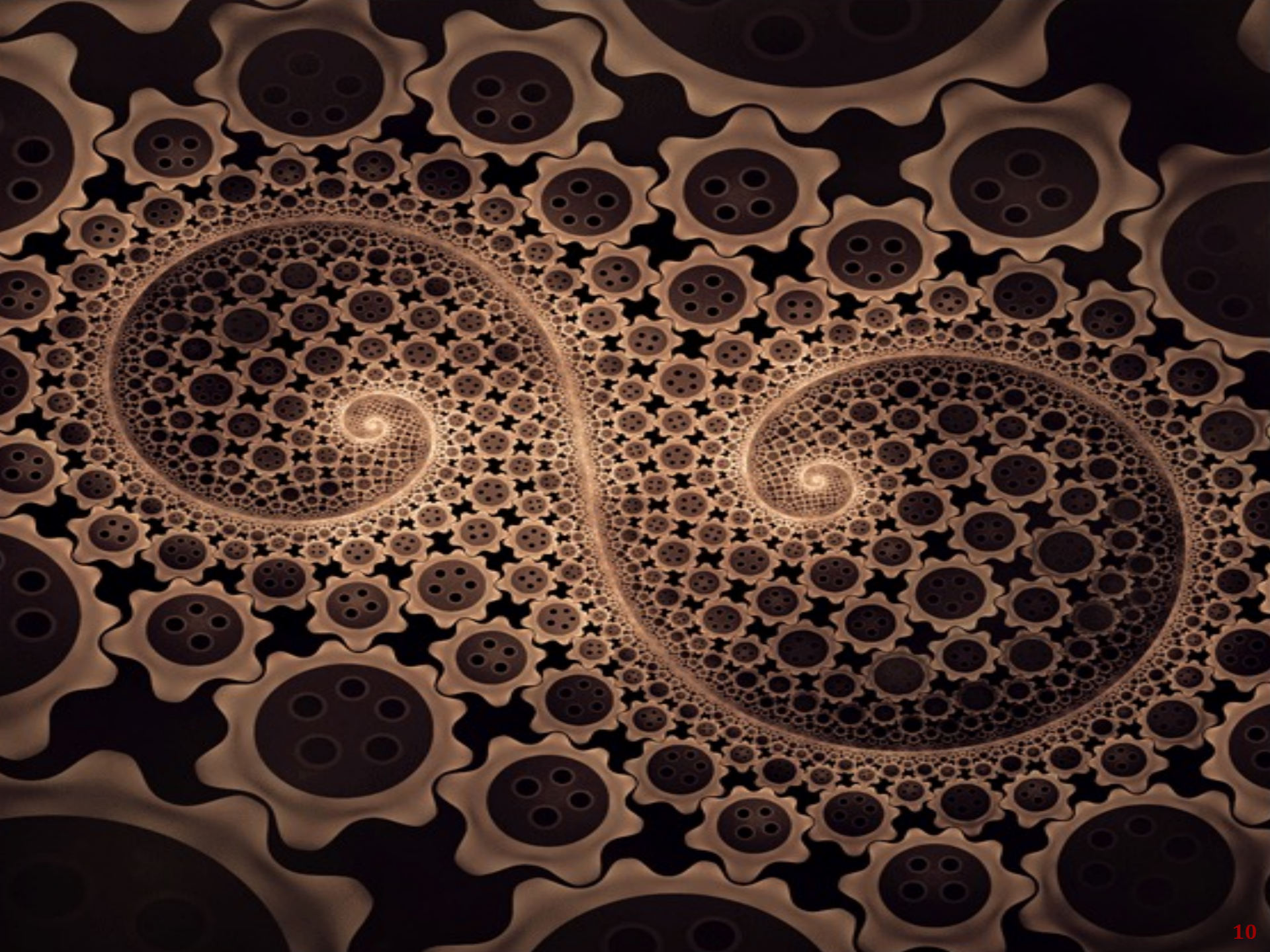
Unscrambling the Puzzle of Biological Machines: The Importance of the Details

Structural biology of cellular machines

Wah Chiu[1], Matthew L. Baker[1] and Steven C. Almo[2]

[1]National Center for Macromolecular Imaging and Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX 77030, USA
[2]Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY 10461, USA

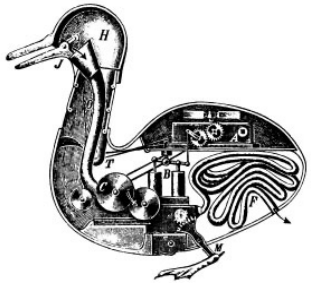


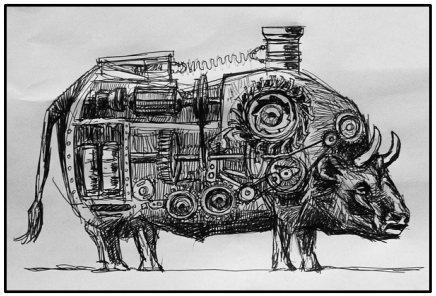
Mechanicism as a Philosophy of Nature

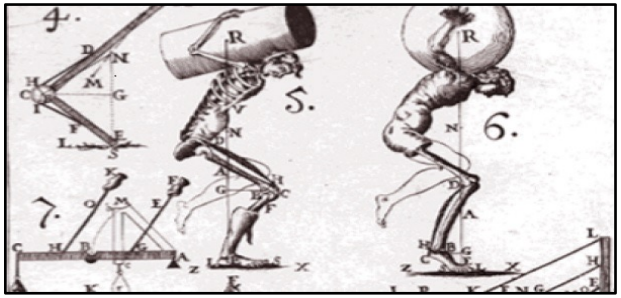
Machine Ontology

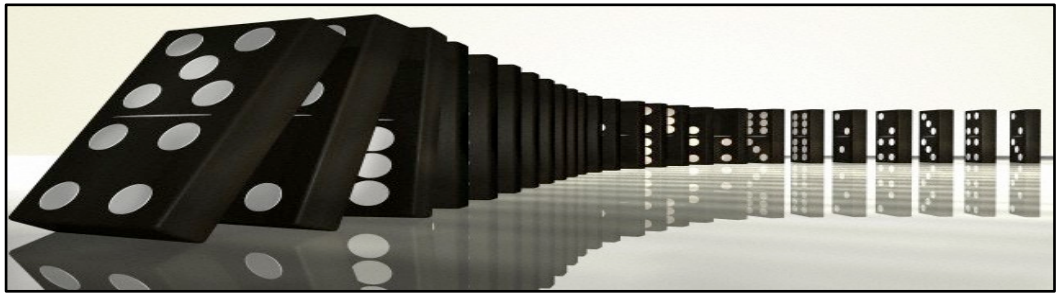
Reductionism

Determinism





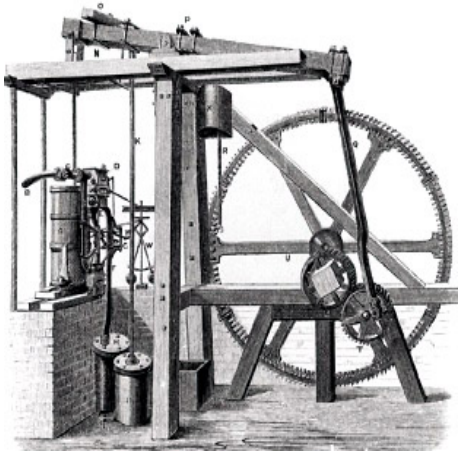




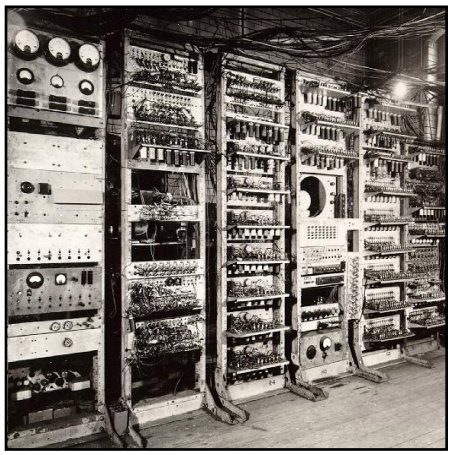
The Development of the Machine Conception of the Organism

17th Century

18th Century



20th Century

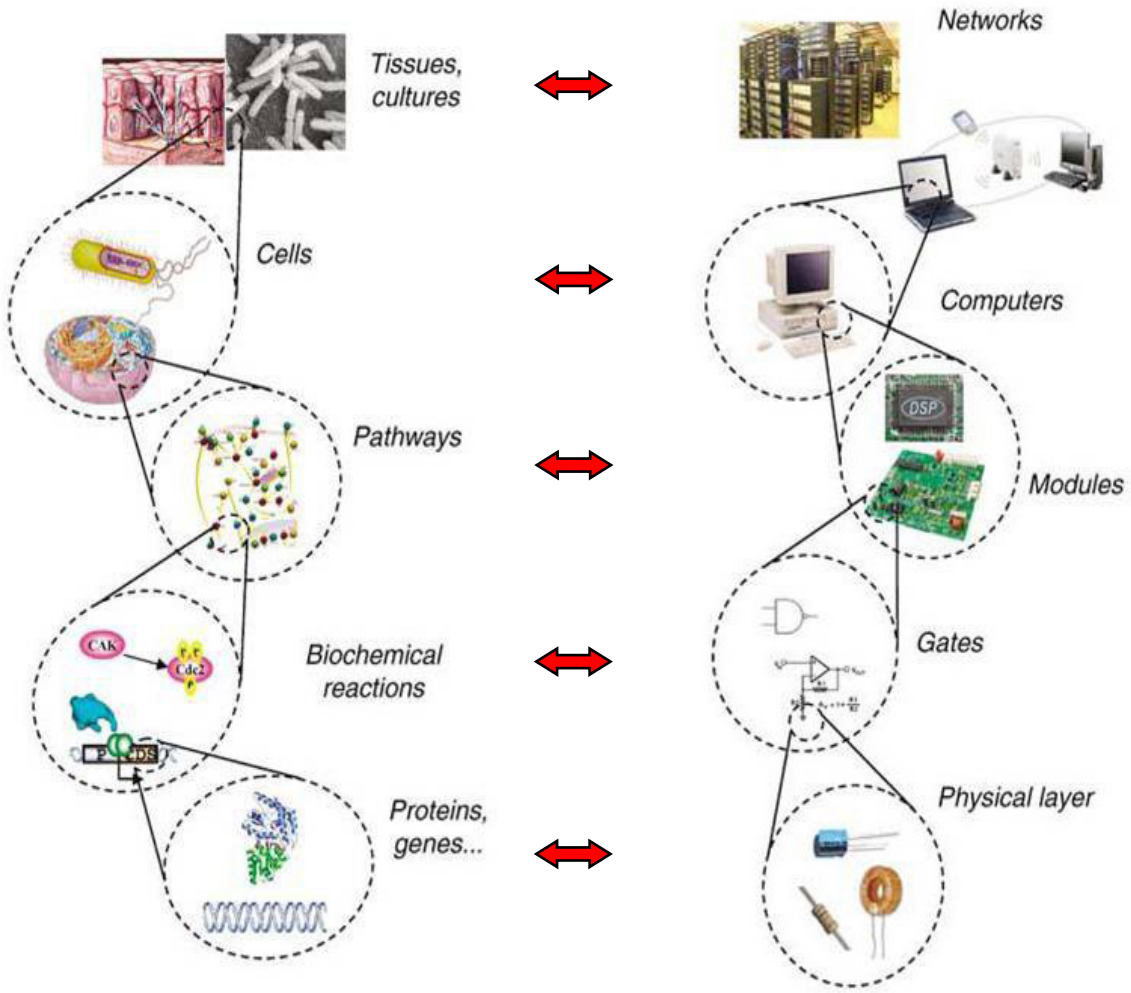


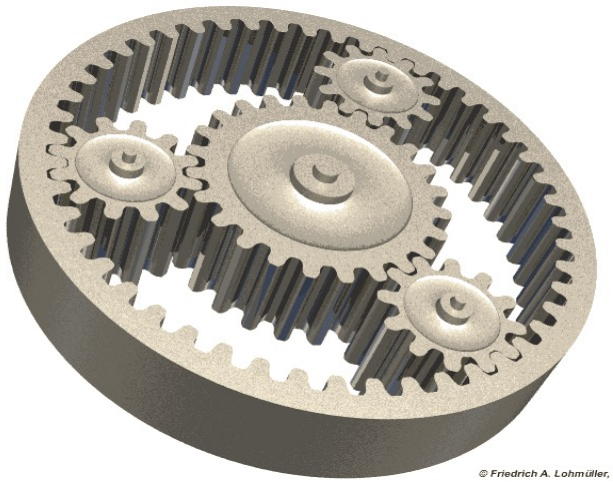
Descartes

Lavoisier

Jacob

"The analogy between an organism and a machine holds true to a remarkable extent at all levels at which it is investigated" (**Changeux** 1965)





Mechanicism in Molecular Biology

- Molecular biology is committed to the basic tenets of mechanicism:

  - **Machine ontology**

    "By the microscopic clockwork function that establishes between DNA and protein, this system is thoroughly Cartesian: **the cell is indeed a machine**" (**Monod** 1972)

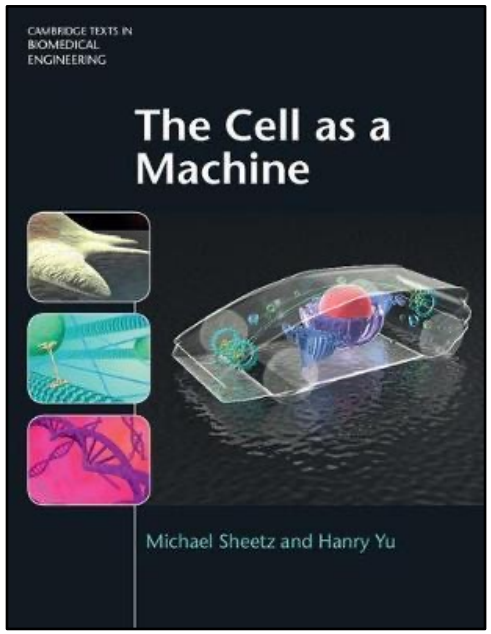
  - **Reductionism**

    "The ultimate aim of the modern movement in biology is to explain all of biology in terms of physics and chemistry" (**Crick** 1966)

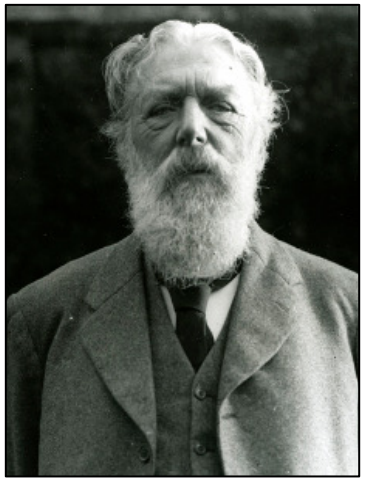
  - **Determinism**

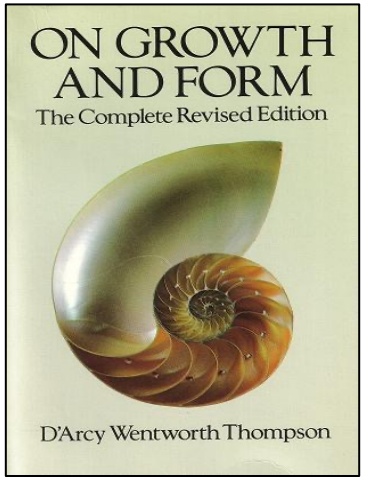
    "If I had the complete sequence of DNA of an organism and a large enough computer, I would be able to compute the organism" (**Brenner**, in Lewontin 2000)

So What is Wrong with Machine Conception of the Cell?



Cells ≠ Machines: The Argument from Scale





"The **world** where bacillus lives, gravitation is forgotten, and the viscosity of the liquid, the resistance defined by Stokes' law, the molecular shocks of the Brownian movement, also the electric charges of the ionized medium, make up the physical environment and have their potent and immediate influence on the organism.
The predominant factors are no longer those of our scale; we have come to the edge of a **world** of which we have no experience, and where all our preconceptions must be recast" (**Thompson** 1917)

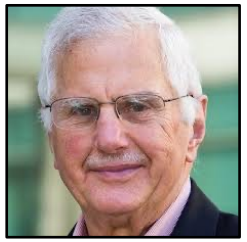
Cells ≠ Machines: The Argument from Scale

- Differences of size and in the physical scale in which organisms live are of overwhelming importance in determining their structure and behaviour
- By virtue of their microscopic size, cells and their molecular components are subject to very different physical forces than macroscopic organisms
- Microscopic and macroscopic organisms inhabit different '**worlds**'. Whereas the macroscopic world is ruled by gravity and inertia, the microscopic world is dominated by Brownian motion and diffusion
- Our intuition, based as it is on our experience of the macroscopic world, fails when judging the adaptive problems that cells have to overcome

Cells ≠ Machines: The Argument from Scale

- Thus, we should be extremely sceptical of analogies that seek to explain microscopic entities by appealing to the properties of macroscopic ones
- Yet this is *precisely* what the metaphorical appeals to machines in the explanation of cellular phenomena attempt to do
- We draw on machines to explain features of cells because they are familiar and intuitively intelligible macroscopic objects of our everyday experience
- But if machines *were* the size of cells they would not be able to function, as their physical environment would be entirely different. We should avoid distorting the reality of cells by conceiving them as machines

The Rise of the (Molecular) Machines



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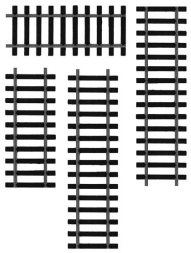
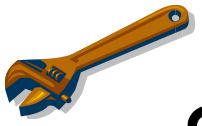
The Cell as a Collection of Protein Machines: Preparing the Next Generation of Molecular Biologists

Bruce Alberts
President, National Academy of Sciences
2101 Constitution Avenue NW
Washington, D.C. 20418
Professor, Department of Biochemistry and Biophysics
University of California, San Francisco
San Francisco, California 94143

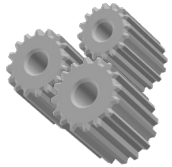
Subcellular assembly	Sample of 'molecular machine' language	Source reference
Ribosome	"probably the most sophisticated machine ever made"	Garrett 1999
Proteasome	"a molecular machine designed for controlled proteolysis"	Voges et al. 1999
Bacteriorhodopsin	"a deceptively simple molecular machine"	Kühlbrandt 2000
Apoptosome	"a seven-spoked death machine"	Salvesen et al. 2002
Glideosome	"a molecular machine powering motility"	Keeley et al. 2003
Spliceosome	"the most complex macromolecular machine known"	Nilsen 2003
Blood clotting system	"a typical example of a molecular machine"	Spronk et al. 2003
Condensin	"the key molecular machine of chromosome condensation"	Strunnikov 2003
Photosynthetic system	"the most elaborate nanoscale biological machine in nature"	Imahori 2004
Bacterial flagellum	"an exquisitely engineered chemi-osmotic nanomachine"	Pallen et al. 2005
Myosin filament	"a complicated machine of many moving parts"	Ohki et al. 2006
RNA degradasome	"a supramolecular machine dedicated to RNA processing"	Marcaida et al. 2006
Cyclosome	"a machine designed to destroy"	Peters 2006
RNA Polymerase	"a multifunctional molecular machine"	Haag et al. 2007

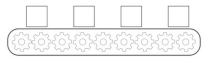
The Diversity of Molecular Machines

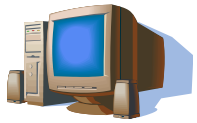


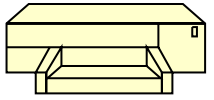


Maromolecular Assembly	Machine Analogy
Cilium / Flagellum	Propeller
ATP synthase	Generator
Ribosome	Factory assembly line
Ion channel / Nuclear pore	Gate / key / pass
Actin filament network	Train tracks
Polymerase	Copy machine
Ligase	Chain coupler
Polymerase	Copy machine
Spliceosome	Film editing machine
Protein sorting mechanism	Mail sorting machine
Protease / proteasome	Bulldozer / destroyer
Magnetosome	Compass





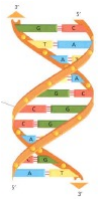




The Rationale of the Molecular Machine Concept

- Viewing proteins as molecular machines unifies two schools of molecular biology:

‘Structural school’ (**STRUCTURE**)



‘Informational school’ (**SPECIFICITY**)

As means of ascertaining function

Central dogma of structural biology

Highly coordinated operation

Context-independent activity

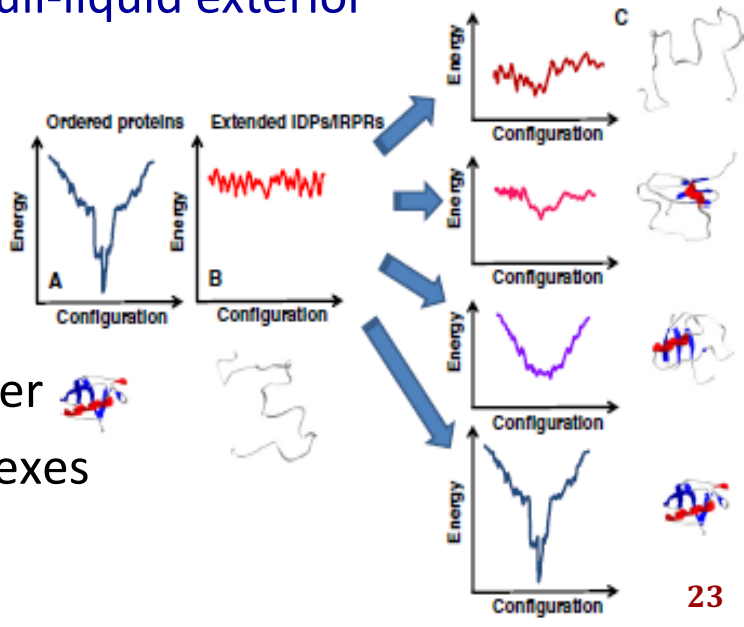
“Why do we call large protein assemblies underlying cell function protein *machines*? Precisely because, like the machines invented by humans to deal efficiently with the macroscopic world, these protein assemblies contain highly coordinated moving parts. Within each protein assembly, intermolecular collisions are not only restricted to a small set of possibilities, but reaction C depends on reaction B, which in turn depends on reaction A—just as it would in a machine” (**Alberts** 1998)

The Problem With the Molecular Machine Concept

- Due to their tiny size, macromolecular assemblies cannot possibly operate in the orderly, reproducible manner that is characteristic of machines
- In a machine, the motions of the various parts are perfectly orchestrated. For example, when a gear rotates, the shaft to which it is connected rotates in synchrony, a spring is compressed, a latch is released, etc.
- These movements are purposeful, predictable, and are always precisely executed in exactly the same temporal sequence
- In contrast, macromolecules are subject to continuous Brownian motion, which means that the majority of conformational changes they undergo are the result of 'random walks' that have nothing to do with their function

How the Molecular Machine Concept Overemphasizes Structural Rigidity

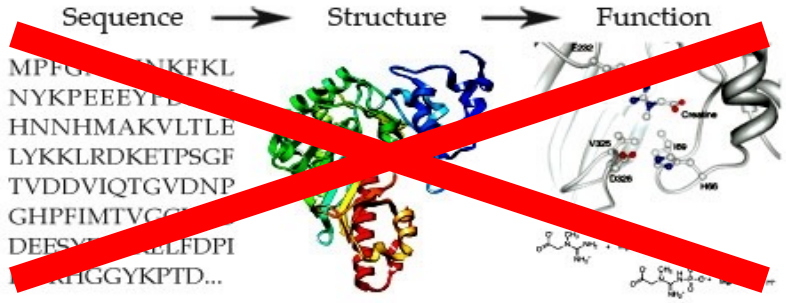
- By virtue of their size, proteins cannot exhibit the sort of rigidity and specificity that characterizes the structure and operation of machines
- In vivo, proteins behave more like liquids than solids; they are 'dense liquids' or 'melted solids' with a 'near-solid interior' and a 'full-liquid exterior'
- Most proteins do not have a single conformation, but rather stochastically sample a suite of possible configurations depending on context
- Some proteins lack an ordered structure altogether (IDPs), forming fluid, ever-flickering 'fuzzy' complexes



How the Molecular Machine Concept Overemphasizes Functional Specificity

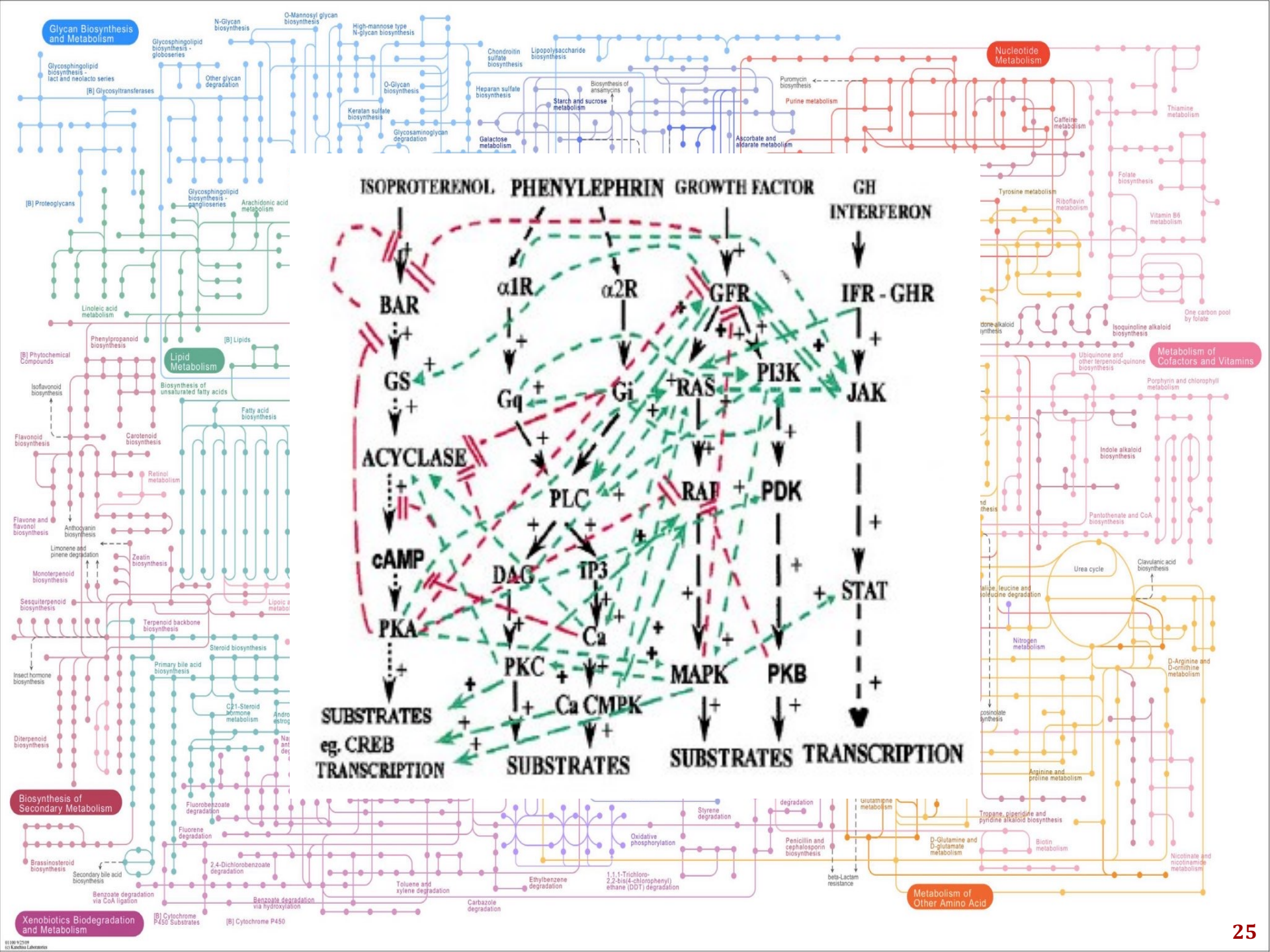
- In proteins, structure does not unilaterally determine function. Proteins exhibit behavioural repertoires, 'moonlighting' according to the needs of the cell

- Most protein-protein interactions are non-specific. Interactions are short and caused by stochastic events. Associations are transitory & contingent



- Proteins exist in a dynamic environment and rely on probabilistic collision events with appropriate partners to reliably perform cellular functions

- This is all a consequence of the fact that, **by virtue of being so small**, most proteins are constantly being knocked about by stochastic forces


ISOPROTERENOL
PHENYLEPHRIN
GROWTH FACTOR
GH
INTERFERON
BAR
α1R
α2R
GFR
IFR - GHR
GS
Gq
Gi
RAS
PI3K
JAK
ACYCLASE
PLC
RAF
PDK
cAMP
DAG
IP3
STAT
PKA
Ca
PKC
MAPK
PKB
Ca CMPK
SUBSTRATES
eg. CREB
TRANSCRIPTION
SUBSTRATES
SUBSTRATES
TRANSCRIPTION
Glycan Biosynthesis and Metabolism
Nucleotide Metabolism
Lipid Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolism
Xenobiotics Biodegradation and Metabolism
Metabolism of Other Amino Acid

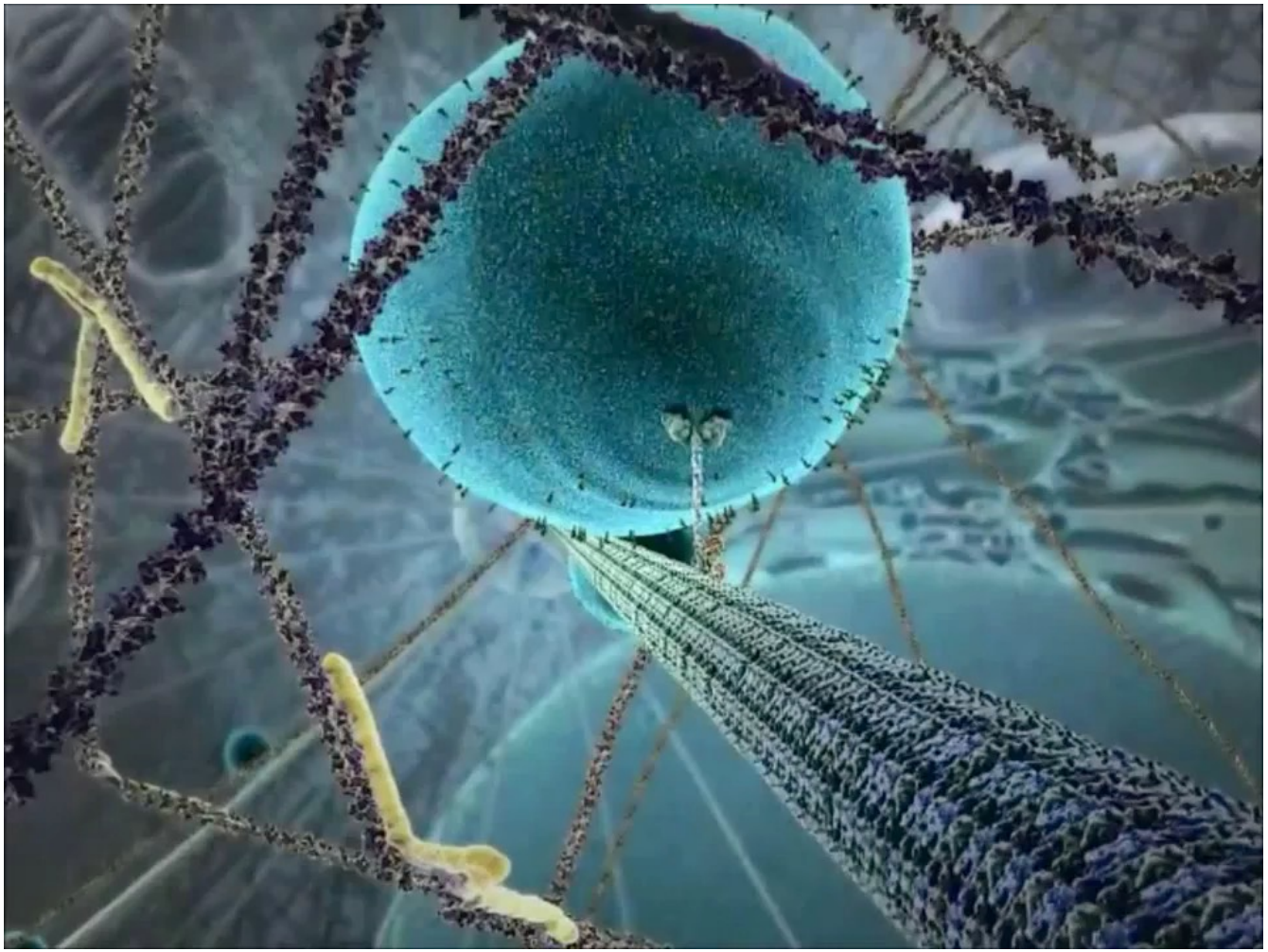
Molecular Motors: A Mechanicist Interpretation

- Molecular motors (e.g. kinesin, myosin) are viewed as 'ingenious' nano-machines, efficiently converting chemical energy into mechanical work

- It is argued that repetitive power strokes resulting from periodic conformational rearrangements driven by cycles of ATP hydrolysis move the protein forward

- Molecular motors move by 'walking' along the cytoskeleton. The 'walking' is enabled by the formation of dimers between motor domains (the 'feet') and microtubules or actin filaments ('tracks')

The Power-Stroke Model: A Well-Known Illustration



Problems with Power-Stroke Model: The Importance of Scale (Again)

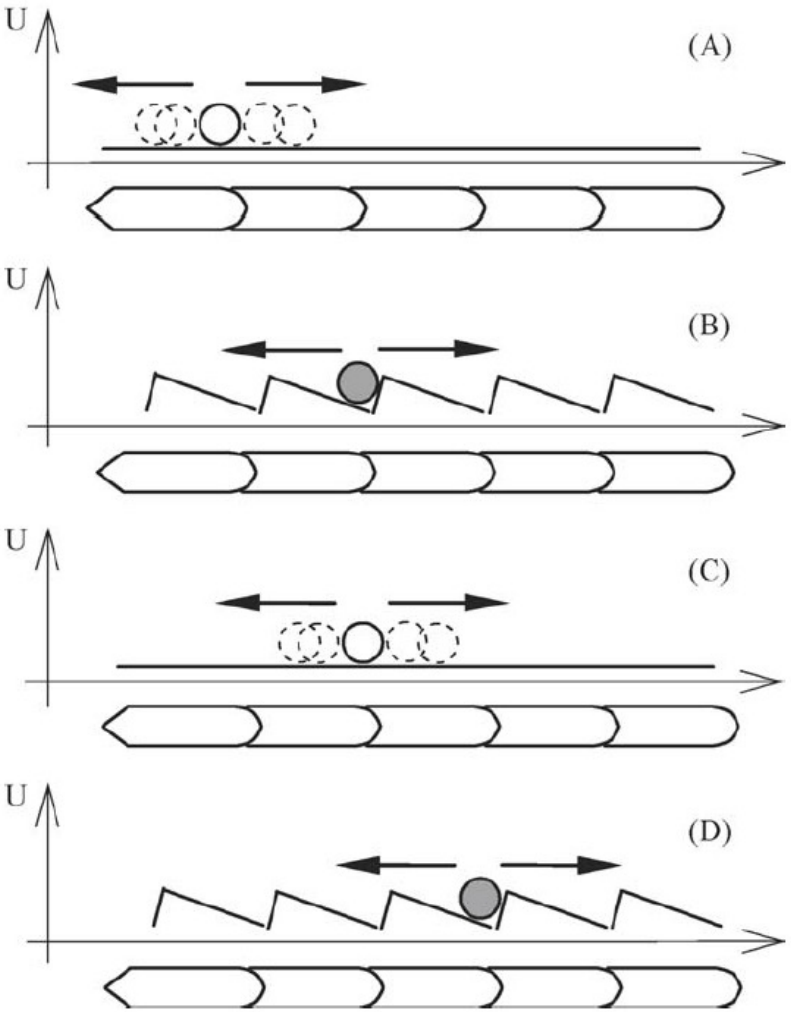
"For molecules, moving deterministically is like trying to walk in a hurricane: the forces propelling it along the desired path are puny compared to the random forces exerted by its environment"

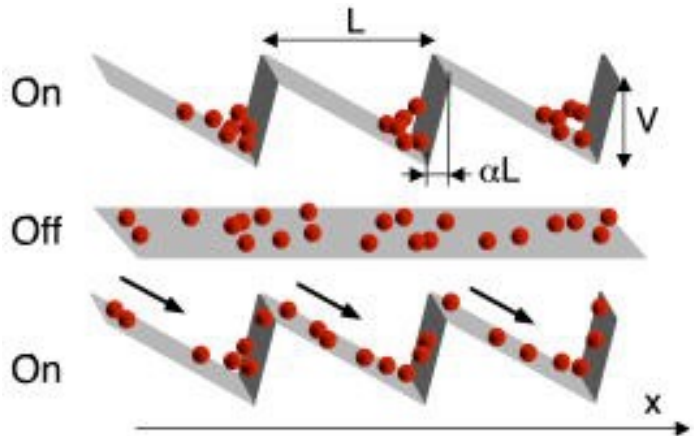
"When considering the operation of a molecular motor, the forces that control the movement of macroscopic objects—in particular gravity—have little relevance. In the molecular world, Brownian storms rage relentlessly"

"Molecular motors are tiny and operate on a physical scale that makes them very different from the man-made, macroscopic objects we normally imagine when we hear the word 'machine'"

"A macroscopic motor must either work with Brownian motion or fight against it, and the former seems far more preferable"

The Brownian Ratchet Model





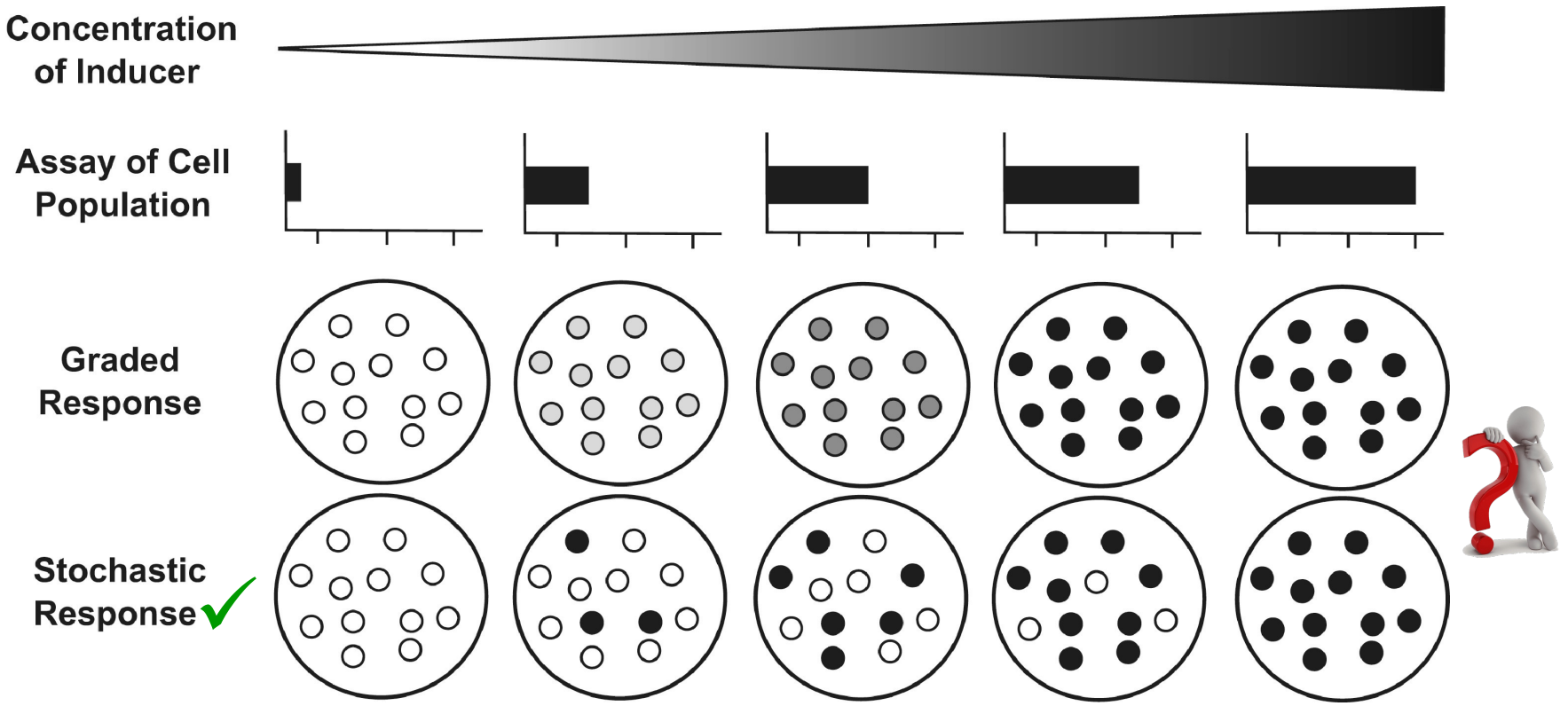
How Size Complicates the Predictability of Cellular Behaviour

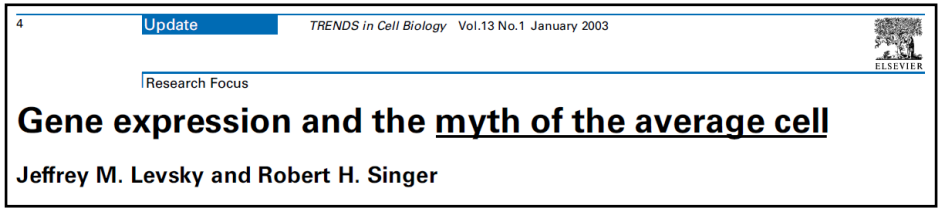
- The machine conception of the cell has led to the view that its behavioural patterns are predictable because they result from the execution of set programs of gene expression or signal transduction, in which a precise sequence of steps is followed and a pre-determined response is produced

- In fact, most response patterns of individual cells are unpredictable. The variation in cellular responses results from random fluctuations in the probability of occurrence of a critical, all-or-nothing step in the cell that requires the action of individual molecules subject to stochasticity

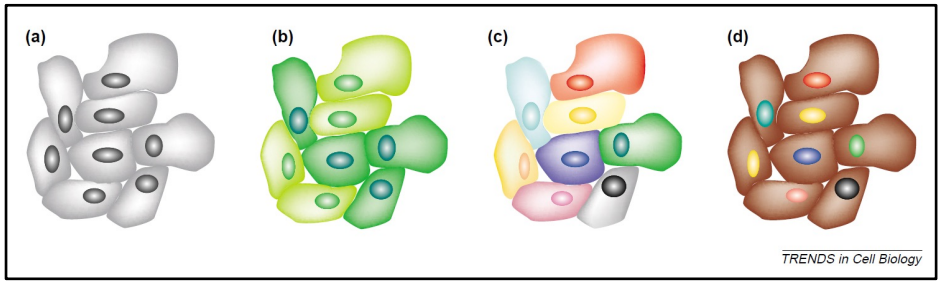
- The predictability of the overall process of development overall arises because millions of molecules have an extremely low probability of all "misbehaving" together. But the smaller the number of molecules involved in a process, the harder it becomes to predict its behaviour

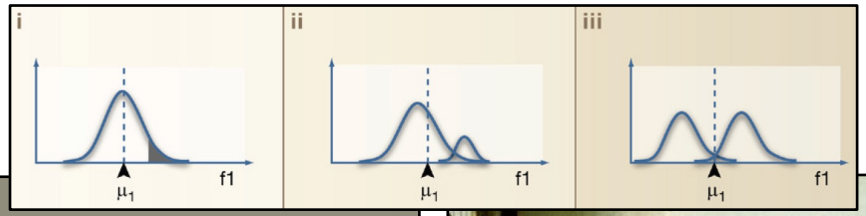
Non-Genetic Cell Heterogeneity: The Case of Gene Expression

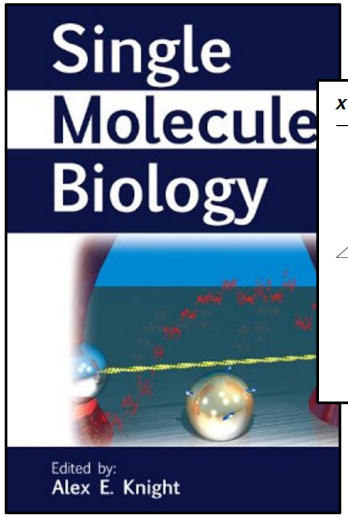


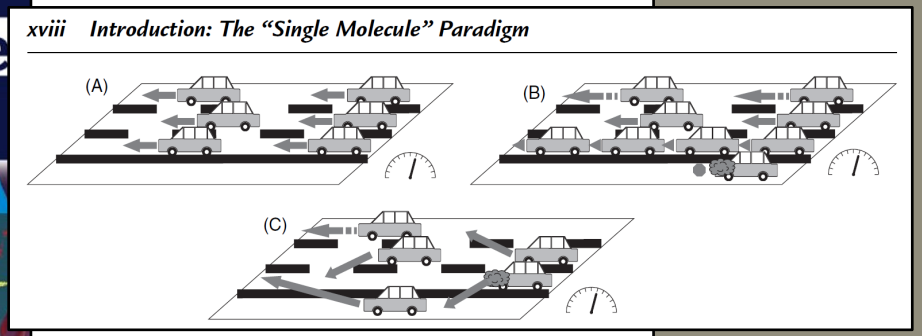


No two cells are the same, even if genetically identical. Our reliance on ensemble methods has resulted in the 'myth of the average cell': a statistical contrivance for representing our knowledge beyond the limits of detection









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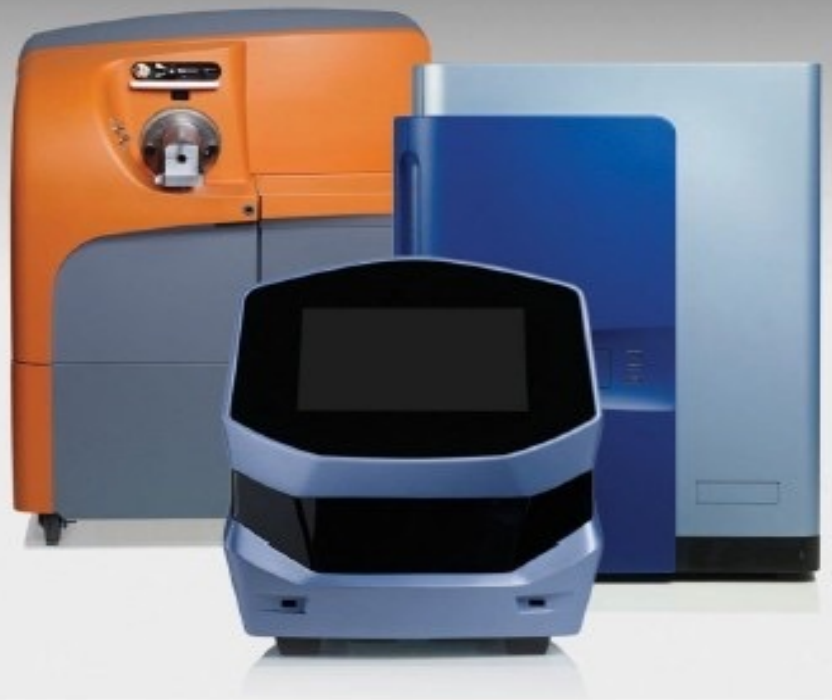
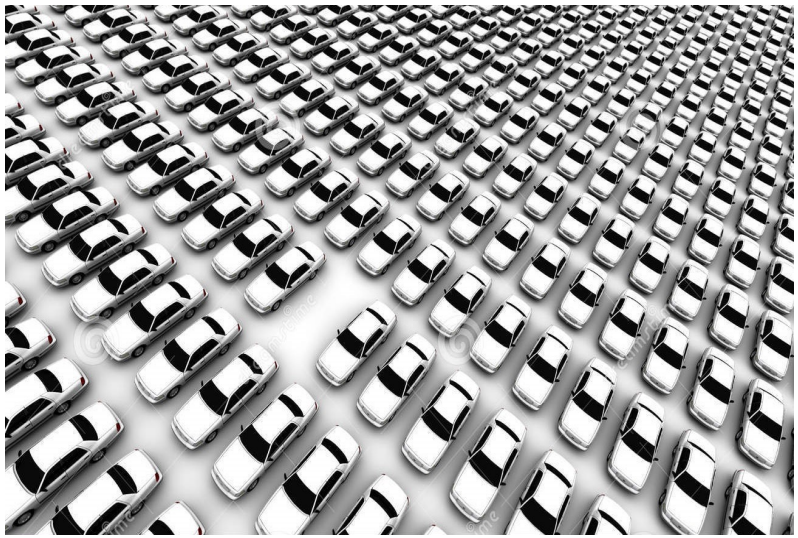


EVERY CELL IS UNIQUE

Tell its story with single-cell biology

Every Cell is Unique



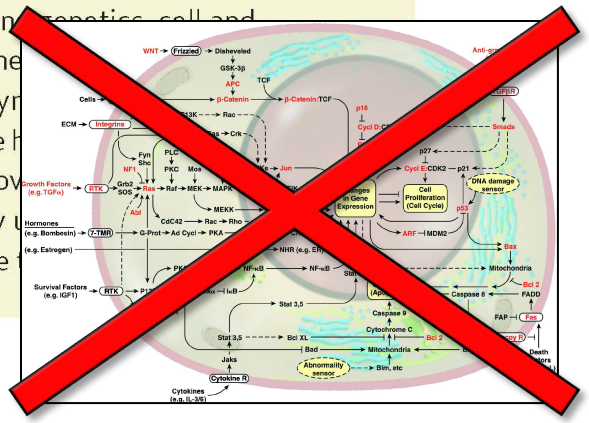
REVIEW

Hallmarks of Cancer: New Dimensions

Douglas Hanahan

ABSTRACT The hallmarks of cancer conceptualization is a heuristic tool for distilling the vast complexity of cancer phenotypes and genotypes into a provisional set of underlying principles. As knowledge of cancer mechanisms has progressed, other facets of the disease have emerged as potential refinements. Herein, the prospect is raised that phenotypic plasticity and disrupted differentiation is a discrete hallmark capability, and that nonmutational epigenetic reprogramming and polymorphic microbiomes both constitute distinctive enabling characteristics that facilitate the acquisition of hallmark capabilities. Additionally, senescent cells, of varying origins, may be added to the roster of functionally important cell types in the tumor microenvironment.

Significance: Cancer is daunting in the breadth and scope of its diversity, spanning genetics, cell and tissue biology, pathology, and response to therapy. Ever more powerful experimental tools and technologies are providing an avalanche of "big data" about the myriad of the diseases that cancer encompasses. The integrative concept embodied in the hallmarks is helping to distill this complexity into an increasingly logical science, and the provisions presented in this perspective may add value to that endeavor, to more fully understand mechanisms of cancer development and malignant progression, and apply that knowledge



Number of Times ‘Circuit’ Is Used

- **Hallmarks of Cancer I (2000) ⟶ 28**
- **Hallmarks of Cancer II (2011) ⟶ 34**
- **Hallmarks of Cancer III (2022) ⟶ 4**

General Conclusions: Why Does This Matter?

- The acceptance of the machine conception of the cell is what justifies in the mind of biologists their appeal to reductionistic, gene-centric, and deterministic approaches in dealing with a wide range of problems, including cancer

- If we want to convince our experimental colleagues of the shortcomings of their approaches, it can be helpful to show them: (a) where these approaches come from; (b) what conceptions justify them; and (c) what alternatives might be available to them