Confronting complexity: cancer at the intersection of physics and biology

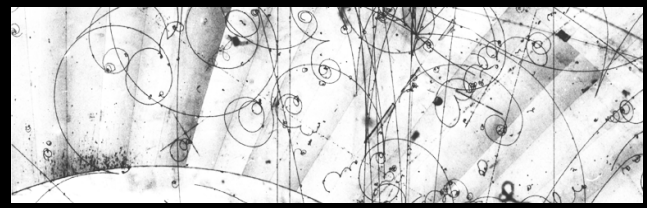
Paul Davies

BEYOND
Institute for Fundamental Concepts in Science

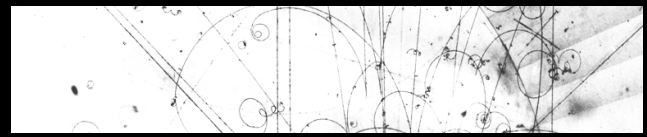
Arizona State University

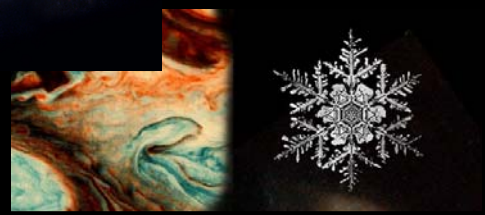
The Three Frontiers

The very large

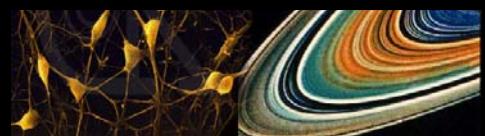


The very small



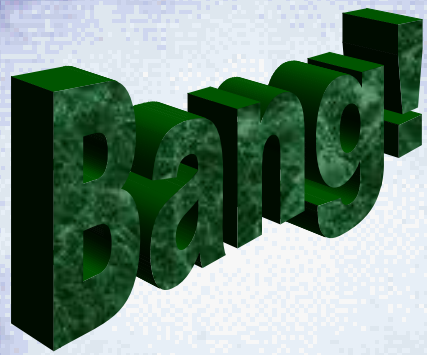


The very complex



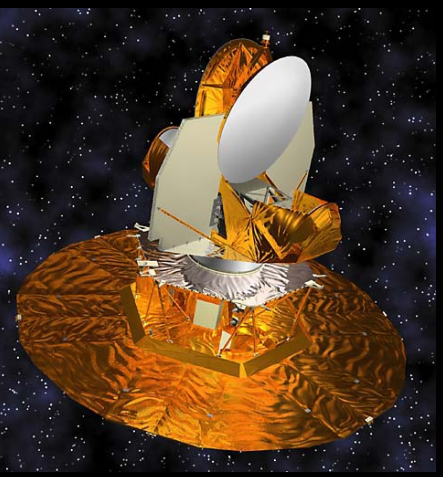

The very
large

The Big

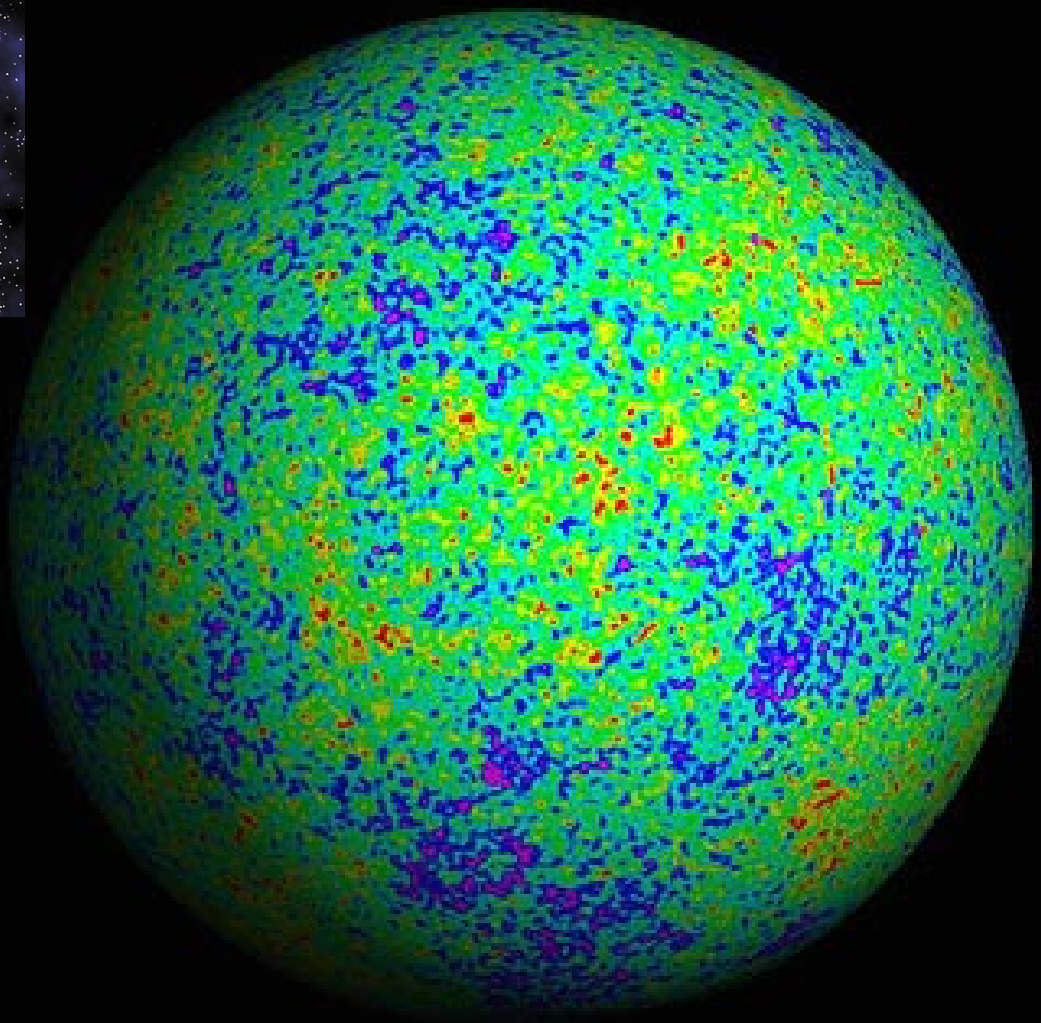


13.7 billion years ago

Ripples at the dawn of time (380,000 years)

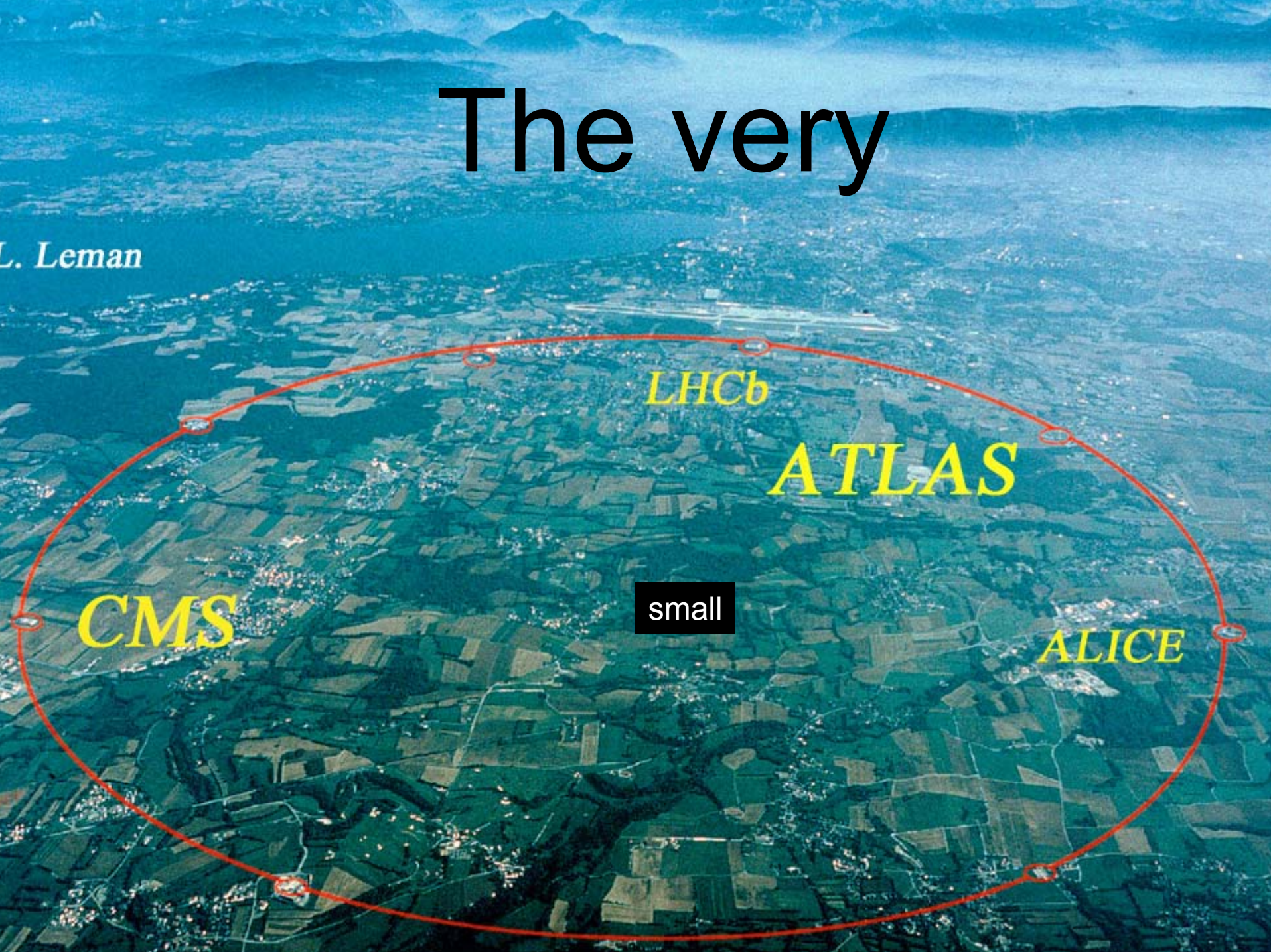


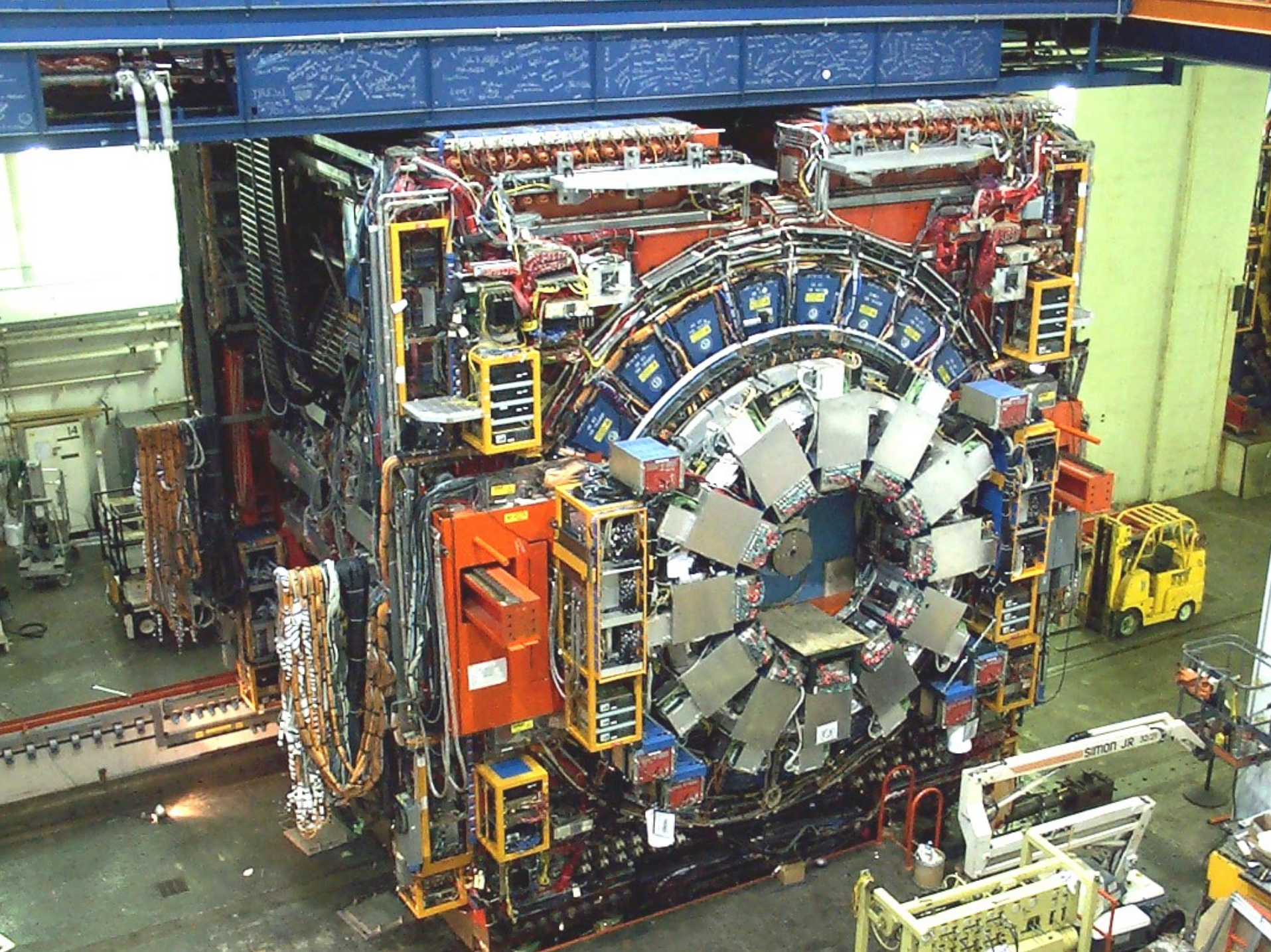
WMAP



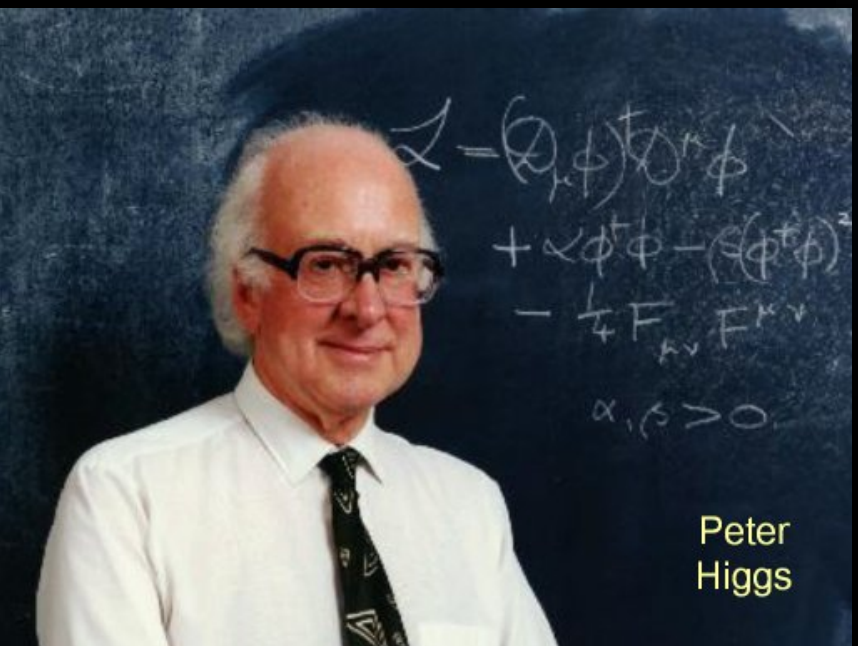
Gravitational waves

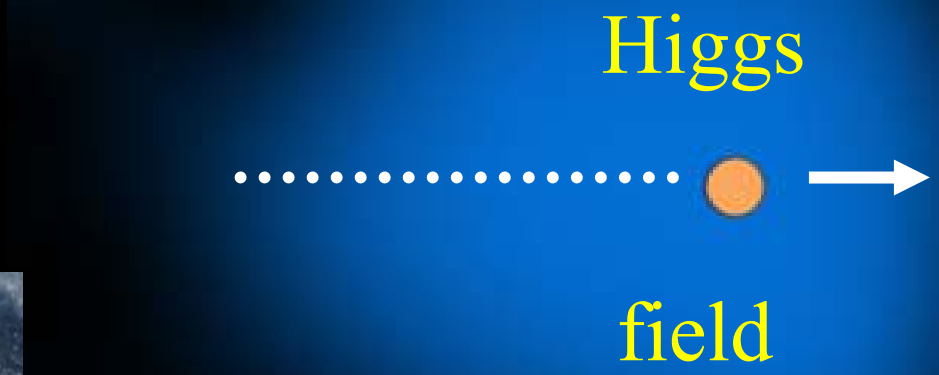
10^{-23}

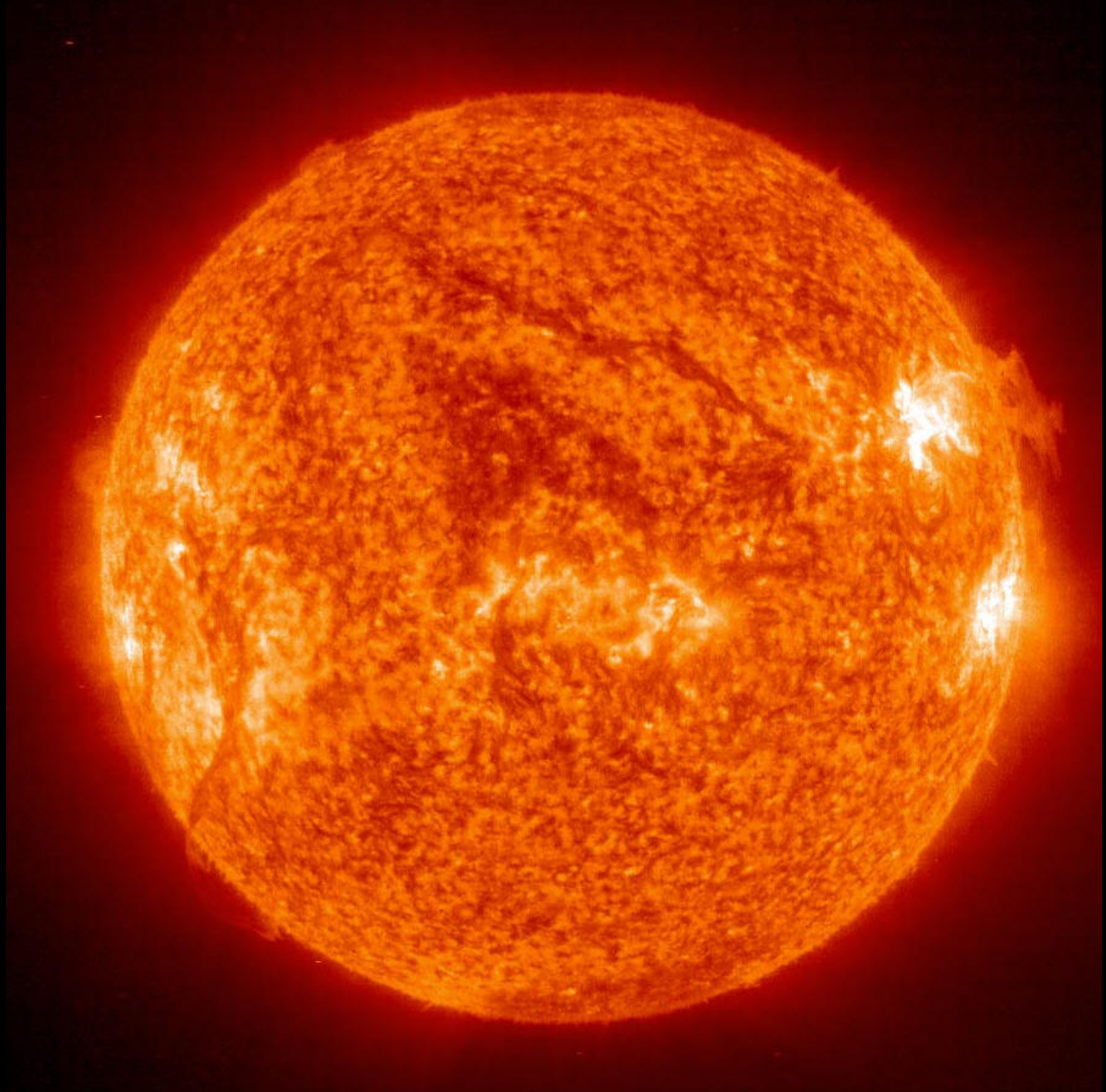

The very
L. Leman
LHCb
ATLAS
CMS
small
ALICE


SIMON JR

The origin of mass?

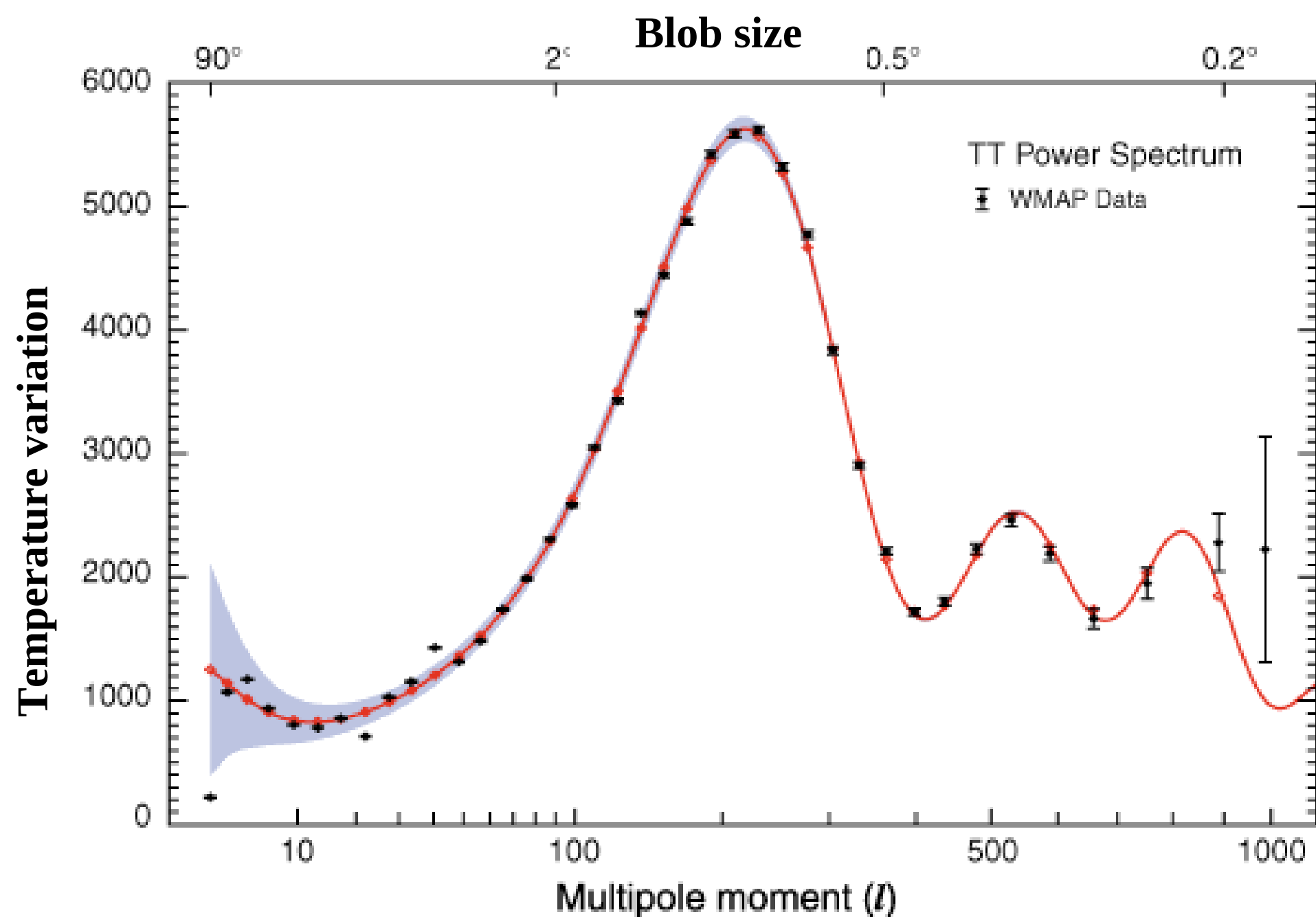






Black hole

$$\begin{aligned} \mathrm{d}s^2 = {} & \rho^{-2}\chi^{-4}(\Delta_\theta a^2 \sin^2\theta - \Delta)\,\mathrm{d}t^2 + \rho^2\Delta^{-1}\,\mathrm{d}r^2 + \rho^2\Delta_\theta^{-1}\,\mathrm{d}\theta^2 \\ & + \rho^{-2}\chi^{-4}[\Delta_\theta(r^2+a^2)^2\sin^2\theta - \Delta a^2\sin^4\theta]\,\mathrm{d}\phi^2 \\ & - 2\rho^{-2}\chi^{-4}a\sin^2\theta[\Delta_\theta(r^2+a^2) - \Delta]\,\mathrm{d}t\,\mathrm{d}\phi \end{aligned}$$


Blob size
90°
2°
0.5°
0.2°
6000
5000
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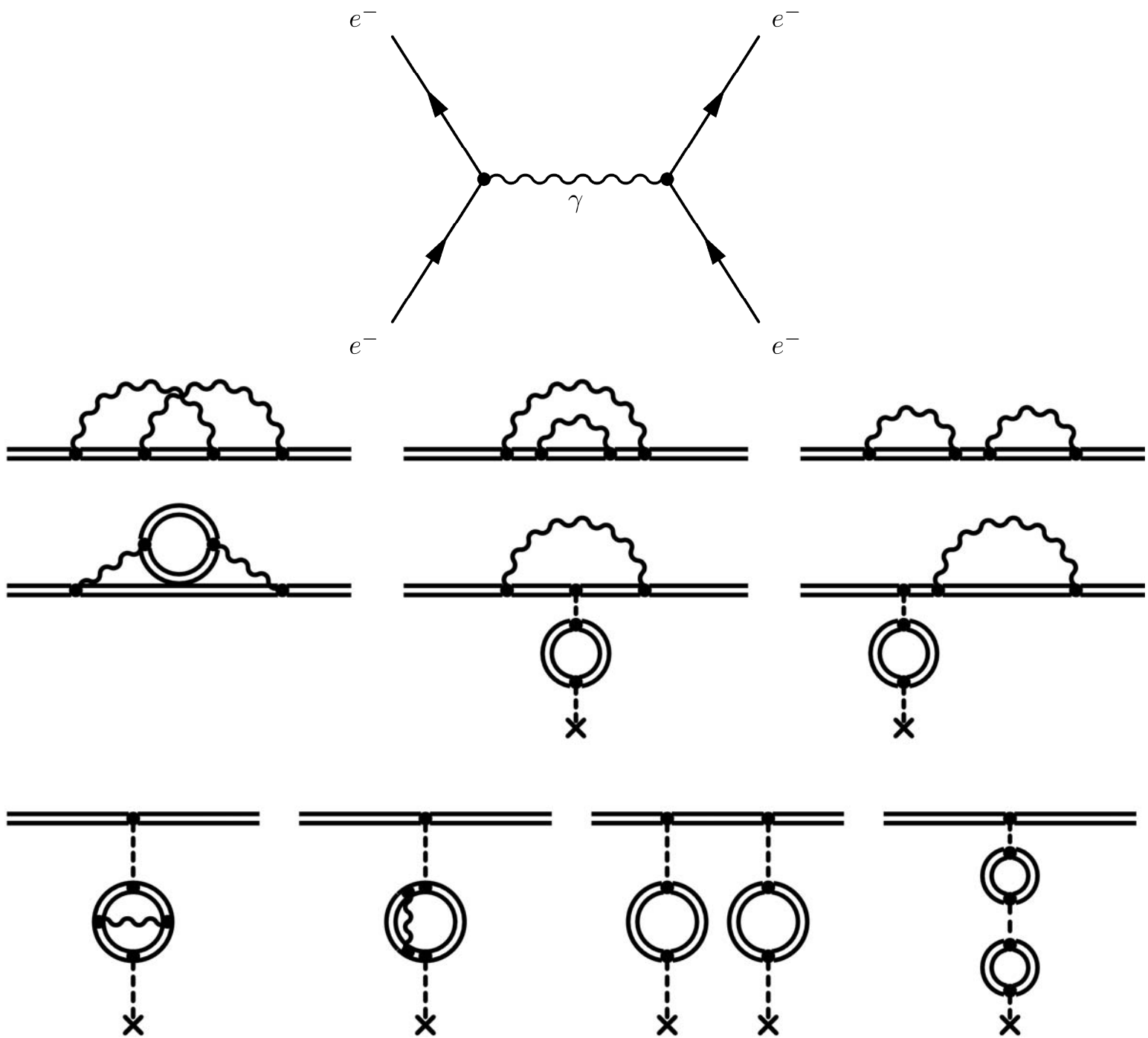
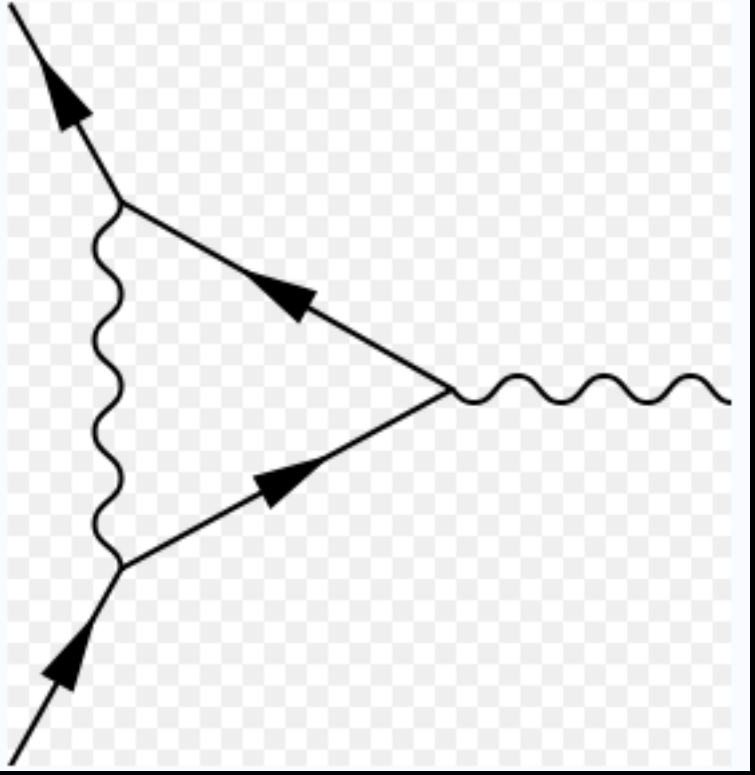
3000
2000
1000
0
Temperature variation
TT Power Spectrum
WMAP Data
10
100
500
1000
Multipole moment (l)


e^-
e^-
γ
e^-
e^-



Anomalous magnetic moment of the electron

Experiment g/2 = 1.001 159 652 180

Theory g/2 = 1.001 159 652 173

Simplicity at the heart of complexity

Intrinsic complexity

Not merely the complicated conjunction of many simple things

Chaos theory

Self-organization

Information theory

Fractals

Cellular automata

Nonlinear dynamics

Systems theory

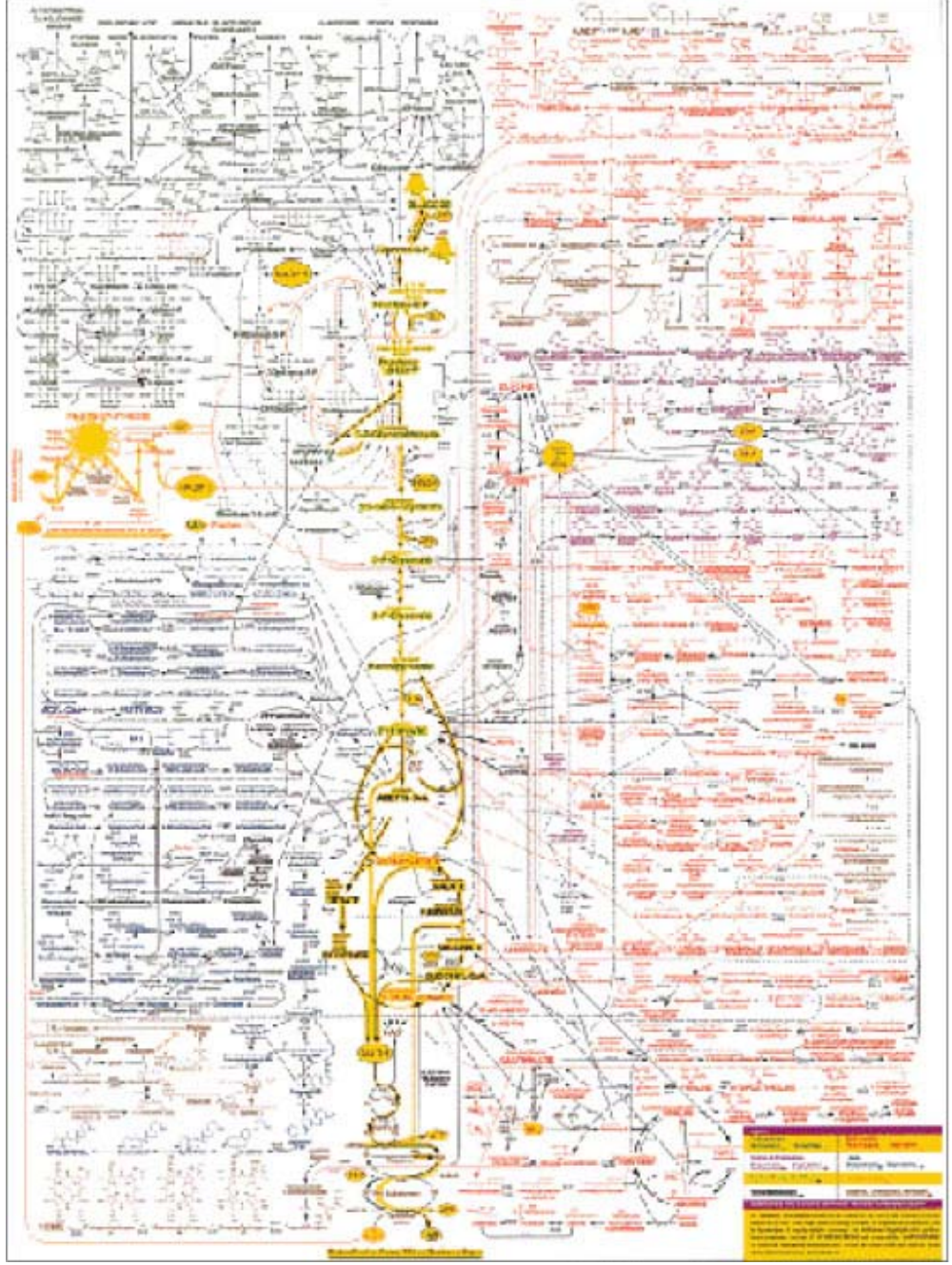
Network theory

Ecosystems

Bioinformatics

Life

- ***What is it?***
- ***How did it begin?***
- ***Can we make it?***
- ***What makes it tick?***



Metabolic map

Scientists & Research

ISB Faculty Member

Lee Hood

Area of Expertise: Adaptive immunity, genomics and biotechnology

ISB Faculty Member

Aimee Dudley

Area of Expertise: Genetics, Gene regulatory networks, Technology development

Complete Faculty Listing

Affiliations

Senior Research Scientist

Greg Carter

Area of Expertise: Computational Biology and Genetics

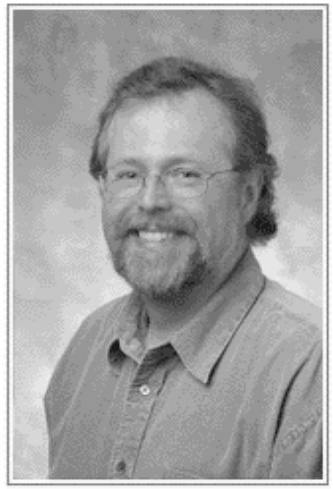
Complete Senior Research Scientists Listing

P4 Medicine™

Welcome to the Institute for Systems Biology

Bill Gates and Nathan Myhrvold to Keynote Institute for Systems Biology´s 2008 Annual Symposium

The Institute for Systems Biology announces that Bill Gates, co-chair of the Bill & Melinda Gates Foundation and chairman of Microsoft Corporation and Nathan Myhrvold, PhD, president and CEO of Intellectual Ventures, will serve as keynote speakers for the 7th Annual Institute for Systems Biology International Symposium. Read full release



Weekly Podcasts from the GENcast Network

ISB Associate Professor Nitin Baliga, PhD featured in a Genetic Engineering and Biotechnology News Podcast
NEW MODEL FOR PREDICTING THE MOLECULAR RESPONSE OF LIVING CELLS TO GENETIC OR ENVIRONMENTAL CHANGE
Genetic Engineering and Biotechnology, Jan. 10, 2008 Listen

Systems Biology Alters Drug Development

This article in Genetic Engineering and Biotechnology News

Major Grant Research

Center for Systems Biology

Innate Immunity-Systems Biology

National Center for Dynamic Interactome Research (NCDIR)

The self-organization of cells into complex interacting systems can be described using a branch of mathematics called nonlinear dynamics, which includes the study of chaos. Here, Donald Coffey explains how analysis of complex biological systems using nonlinear dynamics sheds light on the events leading to disorders as varied as epilepsy, heart disease and cancer.

Self-organization, complexity and chaos: The new biology for medicine

DONALD S. COFFEY

The immortal molecule within our body is DNA, and as such could represent the reductionist answer to the old question "Where were you before your grandmother was born?" The continuity and capability of a DNA sequence to cycle on through subsequent human generations and to adapt and evolve into a complex human system, which is able to build skyscrapers and travel in space, represents a spectacular feat of molecular management. Yet only a minute amount of DNA triggers the process of molecular self-organization that results in such biological complexity.

Many complex biological properties such as human creativity do not seem to have developed during evolution in a continuous or linear manner but rather exhibit a restricted 'all or none' development that can be explained best by a branch of mathematics called nonlinear dynamics (which includes the study of chaos). For example, there are astounding differences in the degree of creativity between species that are physiologically very similar, such as the chimpanzee and the human, who share over 90% homology in their DNA sequence. Even though chimpanzees evolved for many millions of years longer than did humans they still cannot even construct a simple box whereas the late developing human can invent and produce the great diversity of items available in a shopping mall. What types of enzymes or protein molecules are found only in a human that could possibly account for this great difference? Small changes in the human DNA sequence may have produced this profound transition in creative traits, a transition that is nonlinear when compared with overall evolutionary time.

The abrupt changes that characterize nonlinear systems are termed 'emergent properties'. In nonlinear systems, small effects can have very large and unexpected consequences. This is also one of the hallmarks of chaotic systems, which are extremely sensitive to initial conditions. Indeed, human brain recordings exhibit nonlinear dynamics: billions of neurons interact by cell–cell communication to form a collective system that emerges as more than the sum of its individual neurons[1]. These self-organized neuronal interactions within the brain respond to their external environment and form dynamic neural networks that collectively store, process and rapidly retrieve vast amounts of information, which is displayed as consciousness and stunning creativity. What type of analysis is required to explain the development of a unique biological property such as creativity? Knowing the sequence of the human genome is only one part of this understanding and certainly will not be complete without some additional analysis of self-organization. Nonlinear dynamics, including chaos theory, is emerging as the new form of analysis for studying complex biological systems such as the brain, the heart, bacteria, epidemics and cancer.

Self-organization and emerging complexity

Insights into these nonlinear emergent biological properties are provided by a mathematical description of how individual units that are relatively independent can join together and alter their state of interaction with other units. These interactions result in self-organization into an adaptive interactive network that possesses new collective properties not possessed by the sum of the individual components. Such a dynamic collective system is exemplified by a flock of birds, a school of fish, an ant hill, a biofilm of bacteria or by the interactions between people on the streets of New York City (Fig. 1). If the interactions between the individual units are too strong, the network is ordered and rigid and contains little diversity in its ability to respond to changing states and to the environment. If the interactions are too weak, the system tends to disperse and becomes disorganized in behavior because of the lack of feedback between the units. Dynamic variations in the degree of interaction between the individual units gives diversity to the collective network, which in turn provides the system with the plasticity to rapidly adapt to changing environmental situations. This plas-

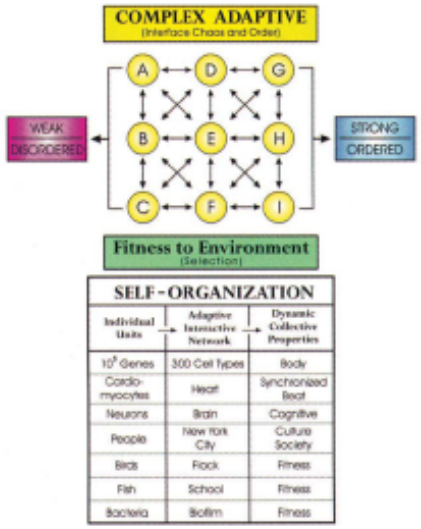
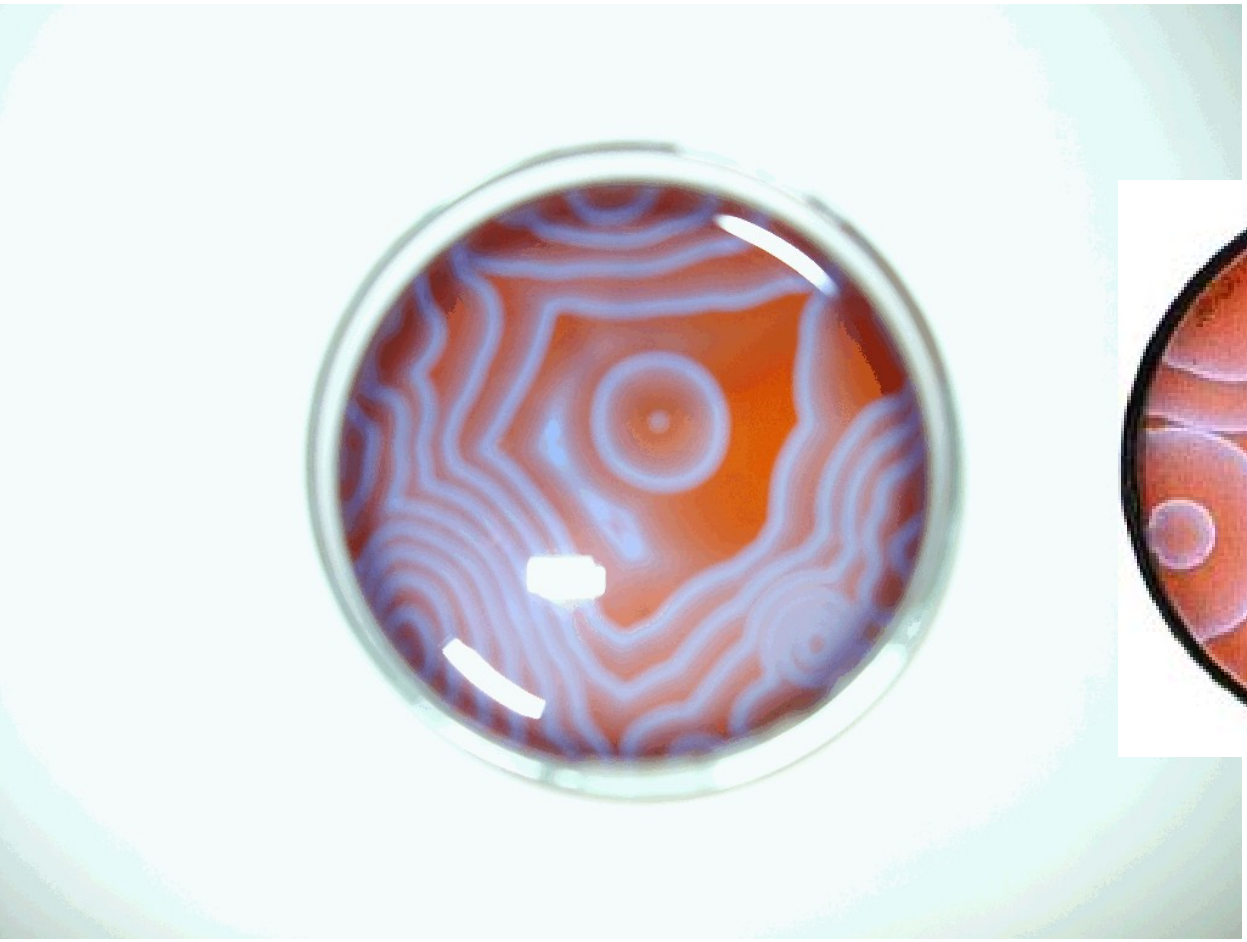


Fig. 1 Examples of self-organizing units that form an interactive network with new collective properties. Each unit interacts with neighboring elements in the system by direct linkage and the interactions obey a simple set of rules that are defined by nonlinear dynamics.

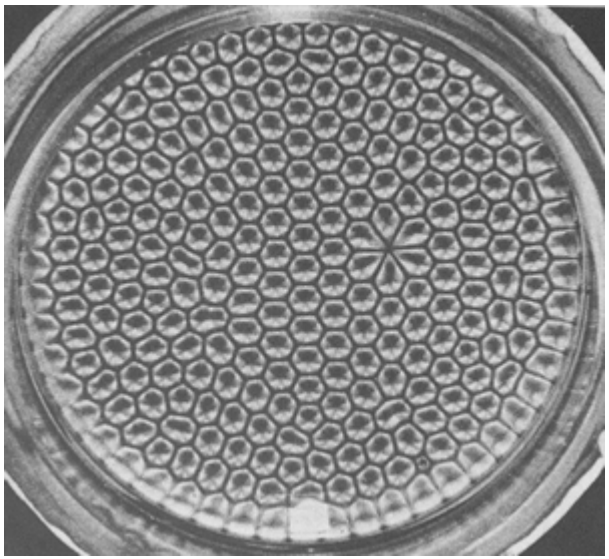
Clues from non-living coherent complex systems

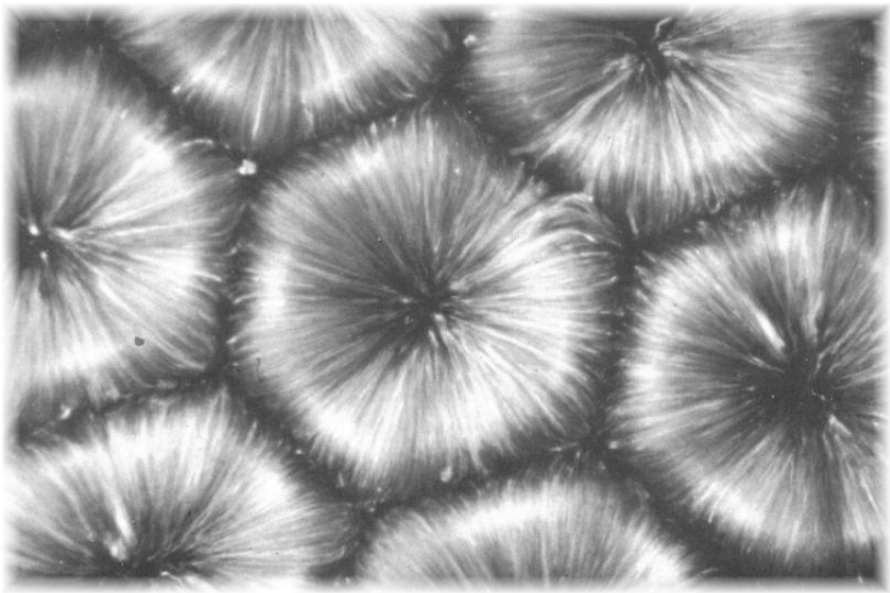
- Nonlinear
- Self-organizing
- Far from thermodynamic equilibrium
- Adaptive and robust

Belousov-Zhabotinsky reaction



Convection cells

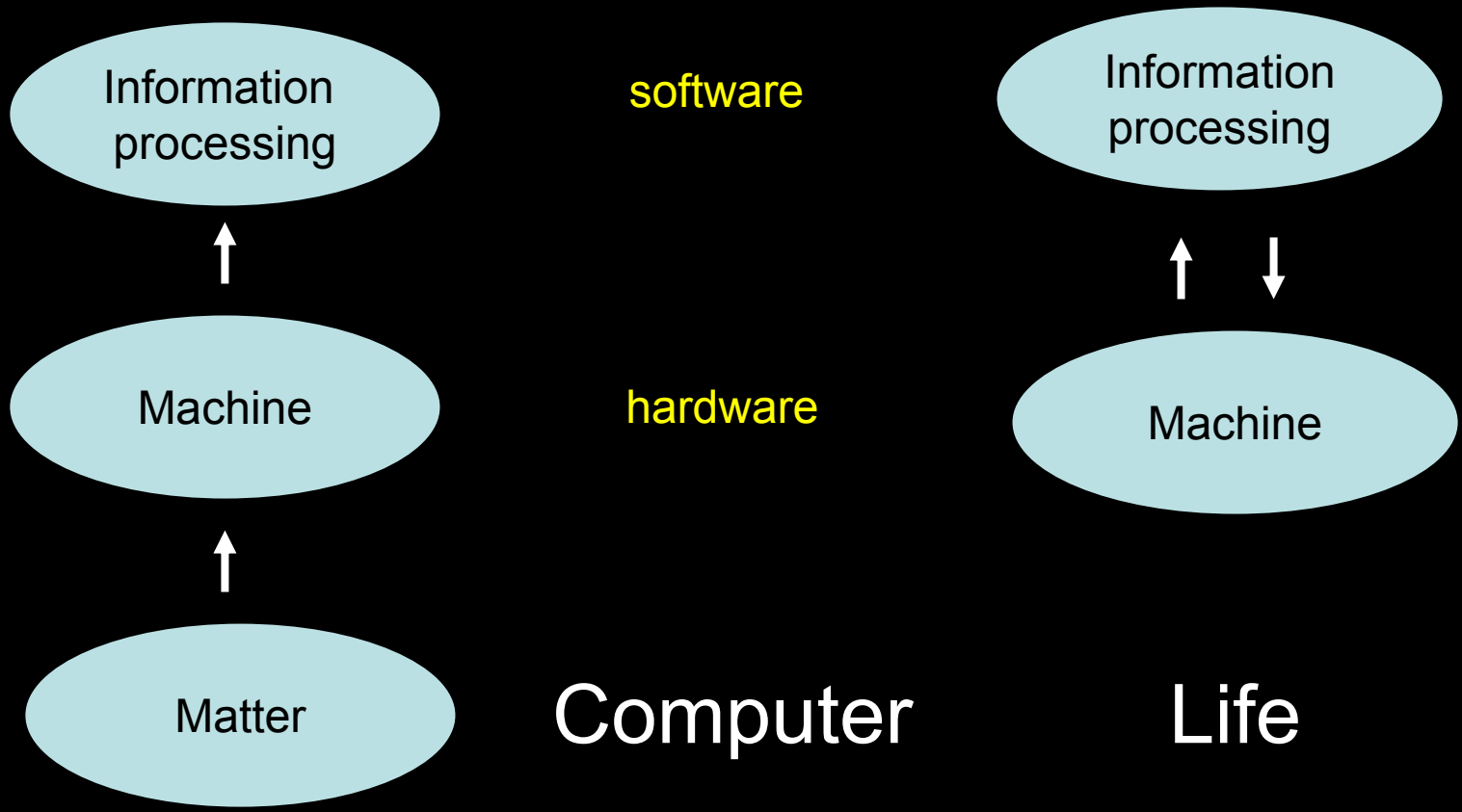


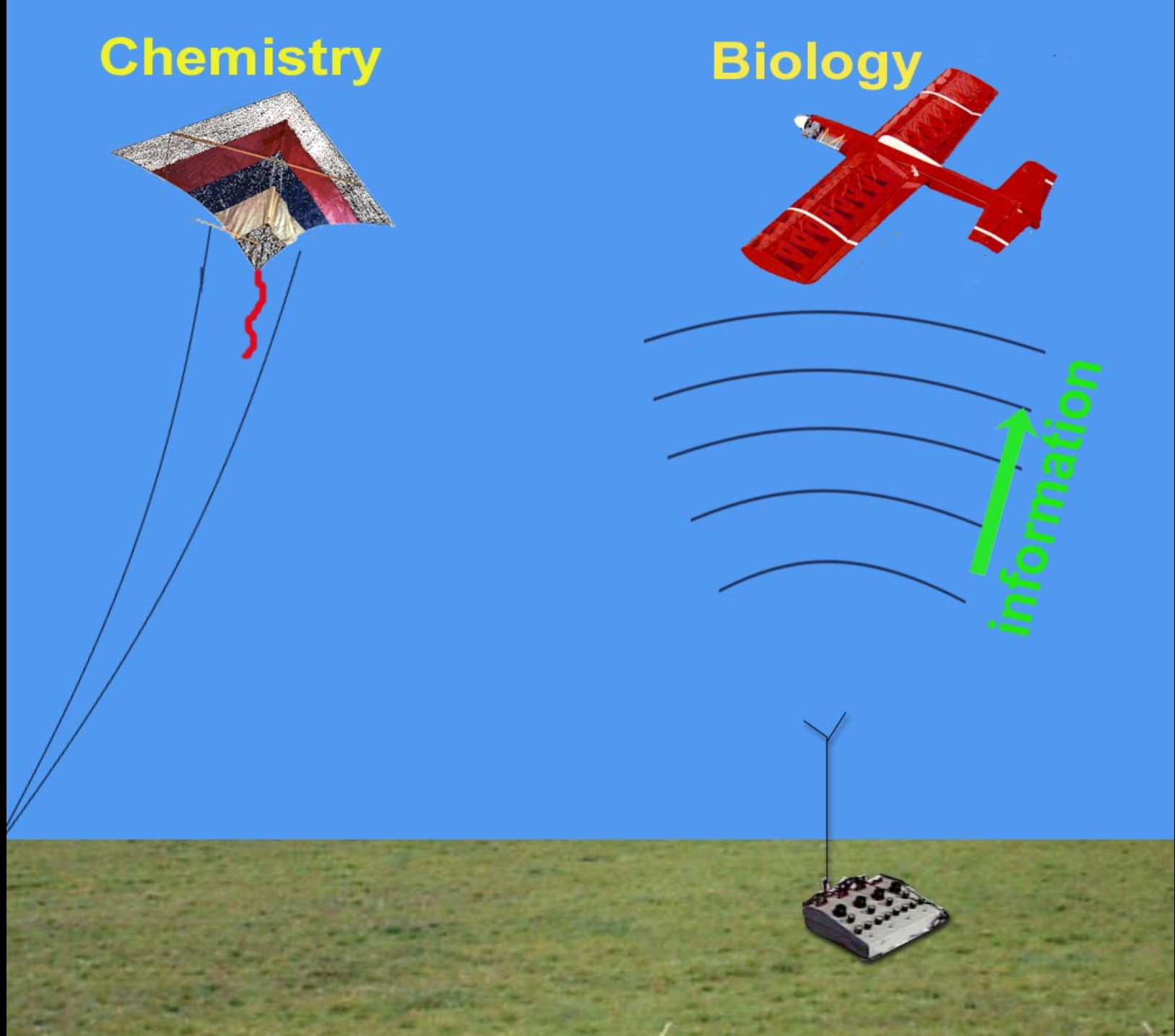


Self-organization a clue?

- Caution: life is *not* a self-organizing system. It is a *supervised* organizing system, under software control.
- When the supervision is flawed, life "goes wrong."
- Life involves a web of information flow, but the information is not just "bits" – it depends on the *context*. Contextual information is closely related to semantic information: genes are coded instructions that need "interpretation" by a molecular milieu.

Life as hardware-software entanglement




Chemistry
Biology
information

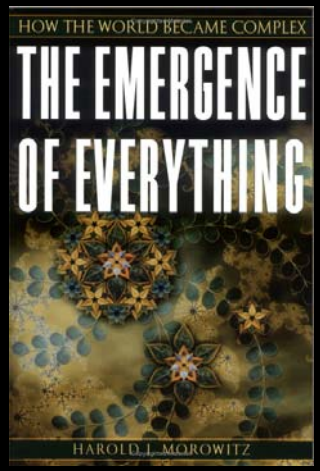
Emergence

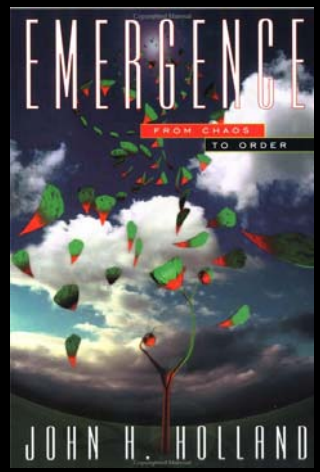
The whole is greater than the sum of its parts

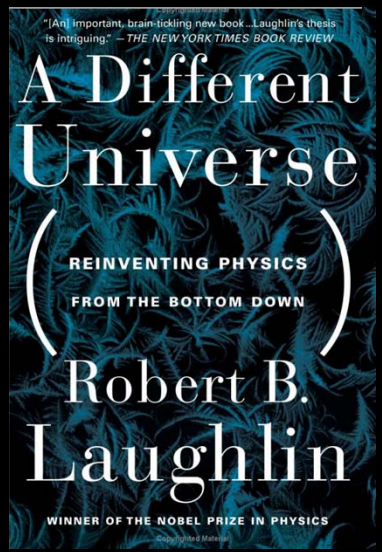
Murray Gell-Mann

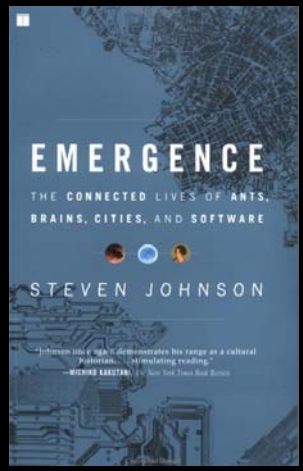
“You don’t need something more
to get something more”

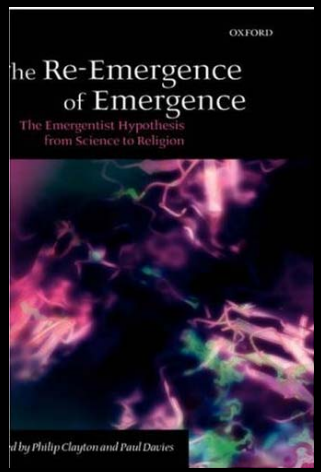
Emergent literature











Tackling computational complexity

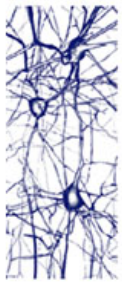
ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

anglais seulement

BLUE BRAIN PROJECT

SCHOOL OF LIFE SCIENCES - BBP

EPFL > FSV > BMI > Blue Brain Project



Blue Brain Project

- About the Blue Brain Project
- News & Media information
- Gallery
- People
- Frequently Asked Questions
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The Blue Brain project is the first comprehensive attempt to reverse-engineer the mammalian brain, in order to understand brain function and dysfunction through detailed simulations.

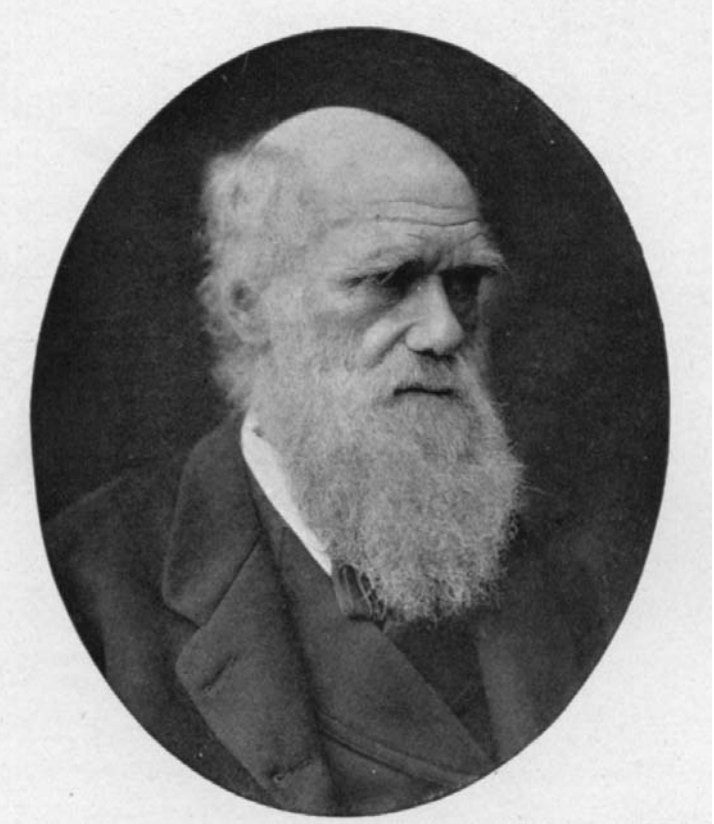
In July 2005, EPFL and IBM announced an exciting new research initiative - a project to create a biologically accurate, functional model of the brain using IBM's Blue Gene supercomputer. Analogous in scope to the Genome Project, the Blue Brain will provide a huge leap in our understanding of brain function and dysfunction and help us explore solutions to intractable problems in mental health and neurological disease.

At the end of 2006, the Blue Brain project had created a model of the basic functional unit of the brain, the neocortical column. At the push of a button, the model could reconstruct biologically accurate neurons based on detailed experimental data, and automatically connect them in a biological manner, a task that involves positioning around 30 million synapses in precise 3D locations.

In November, 2007, the Blue Brain project reached an important milestone and the conclusion of its first Phase, with the announcement of an entirely new data-driven process for creating, validating, and researching the neocortical column.

More detailed information and a glimpse into the future of the Blue Brain Project.

Henry Markram



Cancer is a phenomenon of the basic life process itself

What is life?

How did cancer evolve as part of life?

Origin of life (3.8 Gyr)

Evolution of eukaryotic cell (2.5 Gyr)

Evolution of multi-cellularity (600 Myr)

Evolution of aging

J. Theoret. Biol. (1966) **12,** 12–45

The Moulding of Senescence by Natural Selection

W. D. HAMILTON

Imperial College Field Station, Silwood Park,
Sunninghill, Berks., England

(*Received* 16 *October* 1965)

The consequences to fitness of several types of small age-specific effects on mortality are formulated mathematically. An effect of given form always has a larger consequence, or at least one as large, when it occurs earlier. By reference to a model in which mortality is constant it is shown that this implication cannot be avoided by any conceivable organism. A basis for the theory that senescence is an inevitable outcome of evolution is thus established.

The simple theory cannot explain specially high infant mortalities. Fisher's "reproductive value", the form of which gave rise to an erroneous opinion on this point, is shown to be not directly relevant to the situation. Infant mortality may evolve when the early death of one infant makes more likely the creation or survival of a close relative. Similarly, post-reproductive life-spans may evolve when the old animal still benefits its younger relatives.

The model shows that higher fertility will be a primary factor leading to the evolution of higher rates of senescence unless the resulting extra mortality is confined to the immature period. Some more general analytical notes on the consequences of modifications to the reproductive schedule are given.

Applications to species with populations in continual fluctuation are briefly discussed. Such species apart, it is argued that general stationarity of population can be assumed, in which case the measurement of consequences to fitness in terms of consequences to numerical expectation of offspring is justified.

All the age-functions discussed are illustrated by graphs derived from the life-table of the Taiwanese about 1906, and the method of computation is shown.

Force of selection is *age-specific*

Malthusian parameter defines Darwinian fitness. He derived the first partial derivative for the proportional effect on fitness of age-specific changes in survival probability. This effect is given by $s(x)/T$, where T is a measure of generation length and

$$s(x) = \sum_{y=x+1} e^{-ry} l(y)\, m(y), \qquad (1)$$

where r is the Malthusian parameter, or the growth rate of the population, associated with the specified $l(y)$ survivorship and $m(y)$ fecundity functions. The dummy variable y is used to sum up the net expected reproduction over all ages after age x. Ultimately, the $s(x)$ function represents the fitness impact of an individual's future reproduction. Note that, before the first age of reproduction, s is always equal to 1; once reproduction has ended, s is equal to zero; and during the reproductive period, $s(x)$ progressively falls.

Like mortality, the age-specific force of natural selection acting on fecundity has a scaling function

$$s'(x) = e^{-rx} l(x). \qquad (2)$$

An interesting difference between these scaling functions is that the force of natural selection acting on survival only decreases

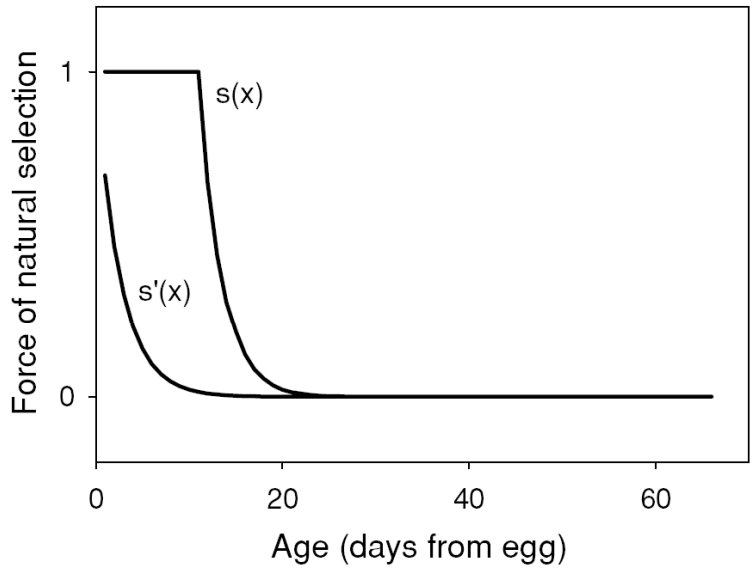


Figure 1. Hamilton's Forces of Natural Selection scaling functions with respect to somatic age: ***s(x)*** the scaling function for the force of natural selection acting on proportionally uniform changes in age-specific survival probability; and ***s′(x)*** the scaling function for the force of natural selection acting on changes in age-specific fecundity. Age-specific survival and fecundity values used to calculate these functions were derived from a cohort of 1111 female *Drosophila melanogaster* from population CO_1 of Rauser et al. (2006b).

doi:10.1111/j.1558-5646.2007.00120.x

HAMILTON'S FORCES OF NATURAL SELECTION AFTER FORTY YEARS

Michael R. Rose,[1] Casandra L. Rauser,[1] Gregory Benford,[2] Margarida Matos,[3] and Laurence D. Mueller[1]

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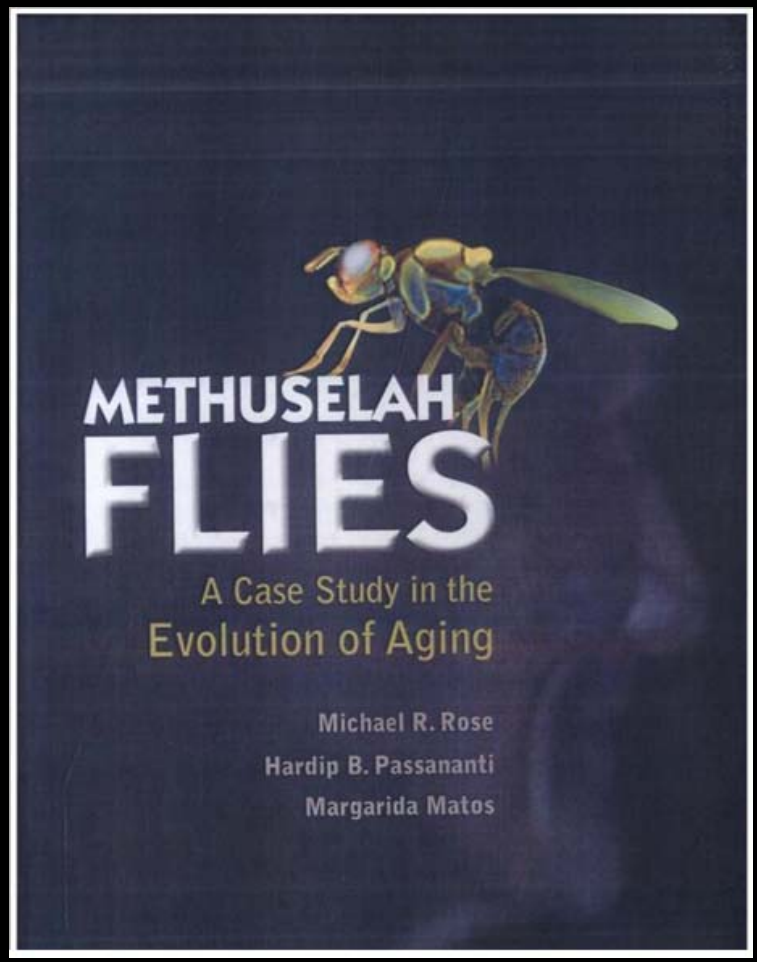
In 1966, William D. Hamilton published a landmark paper in evolutionary biology: "The Moulding of Senescence by Natural Selection." It is now apparent that this article is as important as his better-known 1964 articles on kin selection. Not only did the 1966 article explain aging, it also supplied the basic scaling forces for natural selection over the entire life history. Like the Lorentz transformations of relativistic physics, Hamilton's Forces of Natural Selection provide an overarching framework for understanding the power of natural selection at early ages, the existence of aging, the timing of aging, the cessation of aging, and the timing of the cessation of aging. His twin Forces show that natural selection shapes survival and fecundity in different ways, so their evolution can be somewhat distinct. Hamilton's Forces also define the context in which genetic variation is shaped. The Forces of Natural Selection are readily manipulable using experimental evolution, allowing the deceleration or acceleration of aging, and the shifting of the transition ages between development, aging, and late life. For these reasons, evolutionary research on the demographic features of life history should be referred to as "Hamiltonian."

KEY WORDS: **Aging, demography, experimental evolution, forces of natural selection, late life, senescence, William D. Hamilton.**

In 1966, William D. Hamilton published "The Moulding of Senescence by Natural Selection" in *Journal of Theoretical Biology*. At the time, the paper was hardly noticed. Forty years later, as of this writing, it is clear that this paper was another milestone in Hamilton's miraculous decade of the 1960s. His best-known articles from this period are his two 1964 articles on kin selection (Hamilton 1964a,b) and his 1967 article on evolutionary strategies of sex-ratio manipulation. In those three articles, he laid foundations for contemporary research in behavioral ecology and cognate fields, including research on inclusive fitness and frequency-dependent strategies. These three publications are among the most heavily cited in the evolutionary literature, broadly construed. Here we will argue that Hamilton's 1966 article is at least as important as those three articles.

Hamilton was an avid disciple of R.A. Fisher (see the marginalia of Hamilton's 1996 volume), whose 1930 book *The Genetical Theory of Natural Selection* contained elliptical remarks on the parallels between age-specific reproductive value and age-specific survival probabilities, particularly the parallel between the decline of reproductive value and the decline of age-specific survival probability with increasing age. Haldane (1941), Medawar (1946, 1952), and Williams (1957) took up the same theme, although, like Fisher, none supplied a useful formal analysis. It was Medawar, especially in his 1952 publication, who popularized the term "force of natural selection." But there was no quantitatively explicit and cogent analysis of this evolutionary concept before Hamilton's 1966 analysis.

Like his other 1960s publications, Hamilton's 1966 analysis of the forces of natural selection contains obscure wording and inelegant mathematical notation. But he finally made the verbal hints and circumlocutions of his predecessors mathematically explicit. Hamilton's assumption, taken from Fisher, was that the



Flies don’t get cancer!

Cells on a knife-edge

- Multicellularity: joining a union means giving up freedom to pursue a “selfish cell” agenda
- In vertibrates, adult cells need to proliferate, but in a “unionized”, i.e. regulated, manner
- With aging, the delicate controls may fail due to lack of selective pressure on the regulatory systems (Hamilton)
- Cells revert to pre-multicellular “selfish cell” anarchy
- Cancer is a “fine-tuning” problem

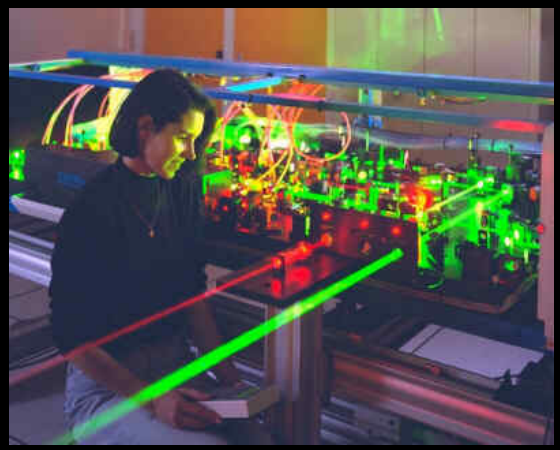
Control mechanisms in networks

- Kauffman: gene networks have a critical threshold at which internal cycles scale like a power law
- Healthy cells operate at the critical threshold, “on the edge of chaos”
- Slip beyond the threshold, and chaos reigns

How can physics help tame cancer?

- New scanning and diagnostic techniques

T rays (teraherz radiation)



C.A.R.S. – coherent anti-Stokes Raman scattering

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Abstract

Biophoton detection as a novel technique for cancer imaging

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Abstract

Biophoton emission is defined as extremely weak light that is radiated from any living system due to its metabolic activities, without excitation or enhancement. We measured biophoton images of tumors transplanted in mice with a highly sensitive and ultra-low noise CCD camera system. Cell lines employed for this study were AH109A, TE4 and TE9. Biophoton images of each tumor were measured 1 week after carcinoma cell transplantation to estimate the tumor size at week 1 and the biophoton intensity. Some were also measured at 2 and 3 weeks to compare the biophoton distribution with histological findings. We achieved sequential biophoton imaging during tumor growth for the first time. Comparison of microscopic findings and biophoton intensity suggested that the intensity of biophoton emission reflects the viability of the tumor tissue. The size at week 1 differed between cell lines, and the biophoton intensity of the tumor was correlated with the tumor size at week 1 (correlation coefficient 0.73). This

Theoretical physics

- New conceptual insights into complex systems
- Experience with modeling computational complexity
- Ability to extract a signal from confusing noise
- Ability to “stand back” and see the system as a whole
- Tendency to ask really dumb questions, seemingly without embarrassment
- Salamander limb regeneration
- How do cells stick together, and why do metastasized cells come unstuck?
- Tolerance of “wild ideas”

Example of a wild idea:

Life at the quantum edge

Cells as bags of quantum nanostructures

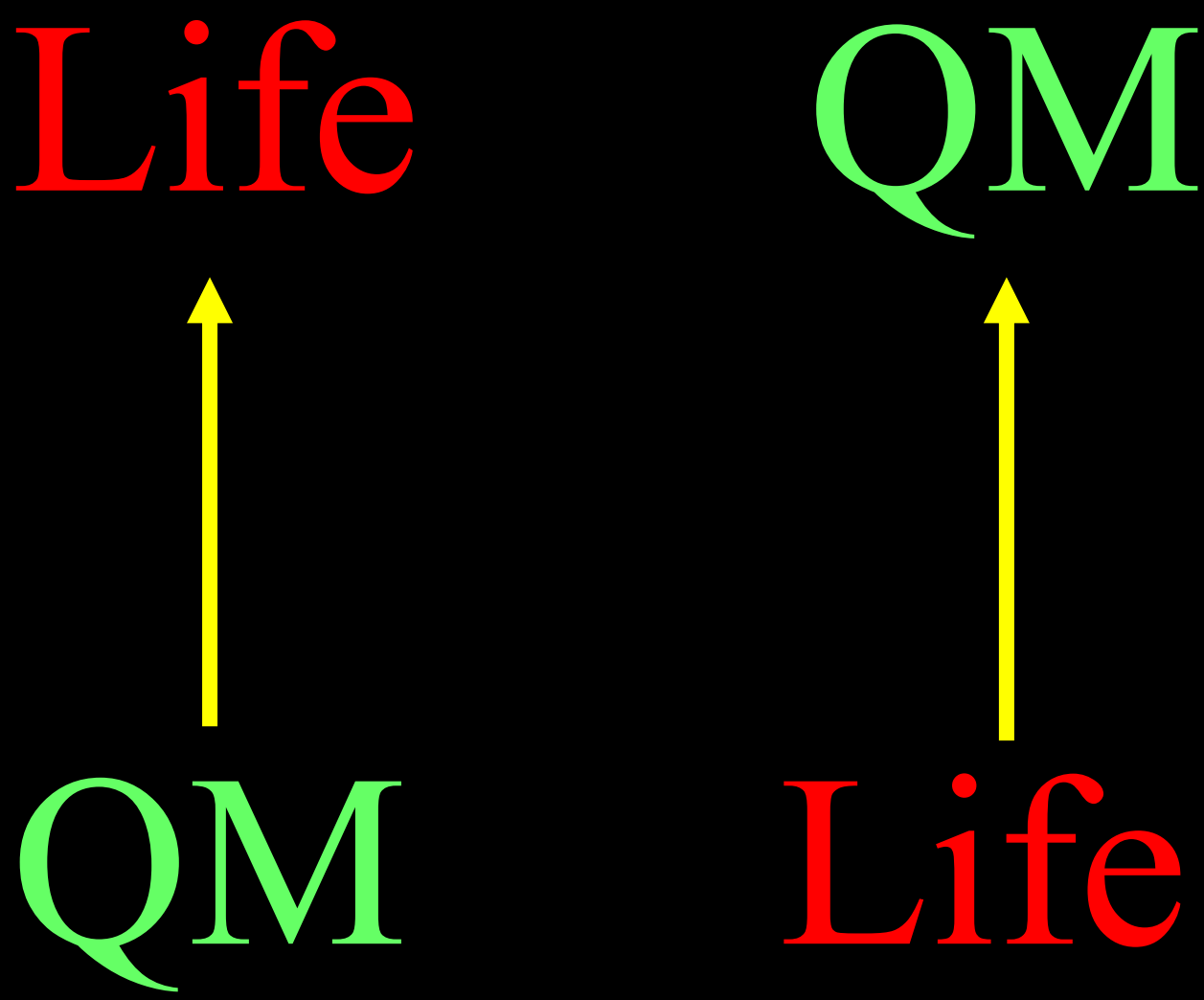
Two ways that QM may play a role in life

1. **Negative effect**

Life's efficiency is limited by quantum mechanics, so perhaps life tends to evolve to the 'quantum edge.'

2. **Positive effect**

Life (or pre-life) *harnesses* quantum effects to improve its performance or to accomplish unusual tasks.


Life
QM
QM
Life

‘Non-trivial’ quantum effects

Superposition

Entanglement

Tunneling

System/environment interaction, e.g. watchdog

Wigner inequalities

(Peter Pešić, John Barrow)

Quantum clock, mass m, size l:

$$T < ml^2/\hbar$$

Smallest autonomous organism - *Mycoplasma*

$m \sim 8 \times 10^{-14}$ g $l \sim 0.3\mu$m

$T \sim 100$ min

Typical nanostructure in cell

$m \sim 10^3$ daltons $l \sim 100$Å

$T \sim$ milliseconds

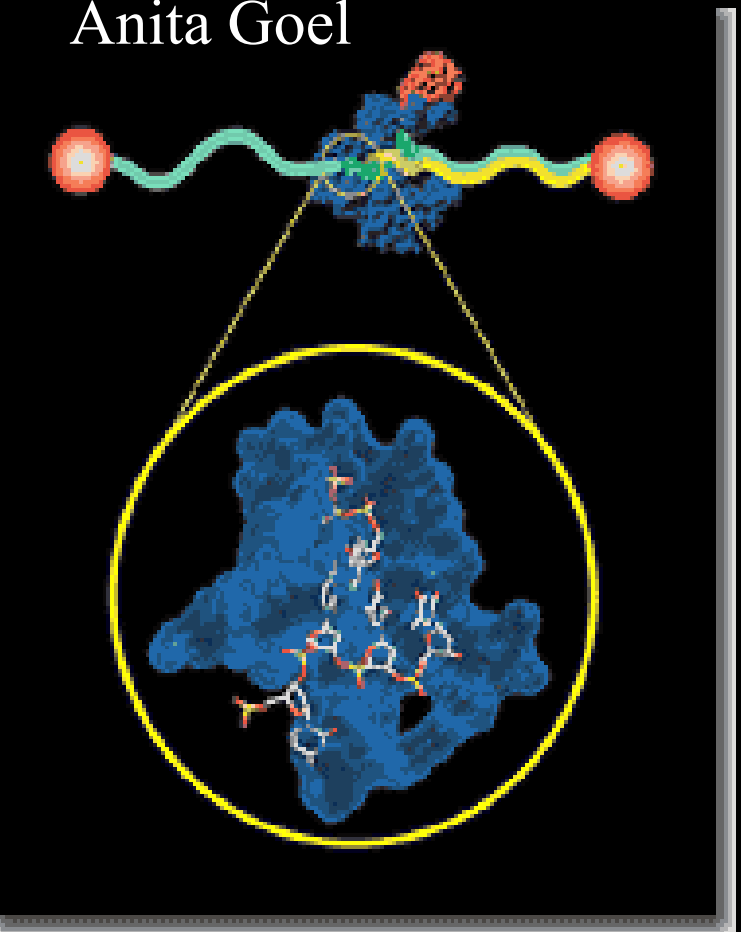
Anita Goel

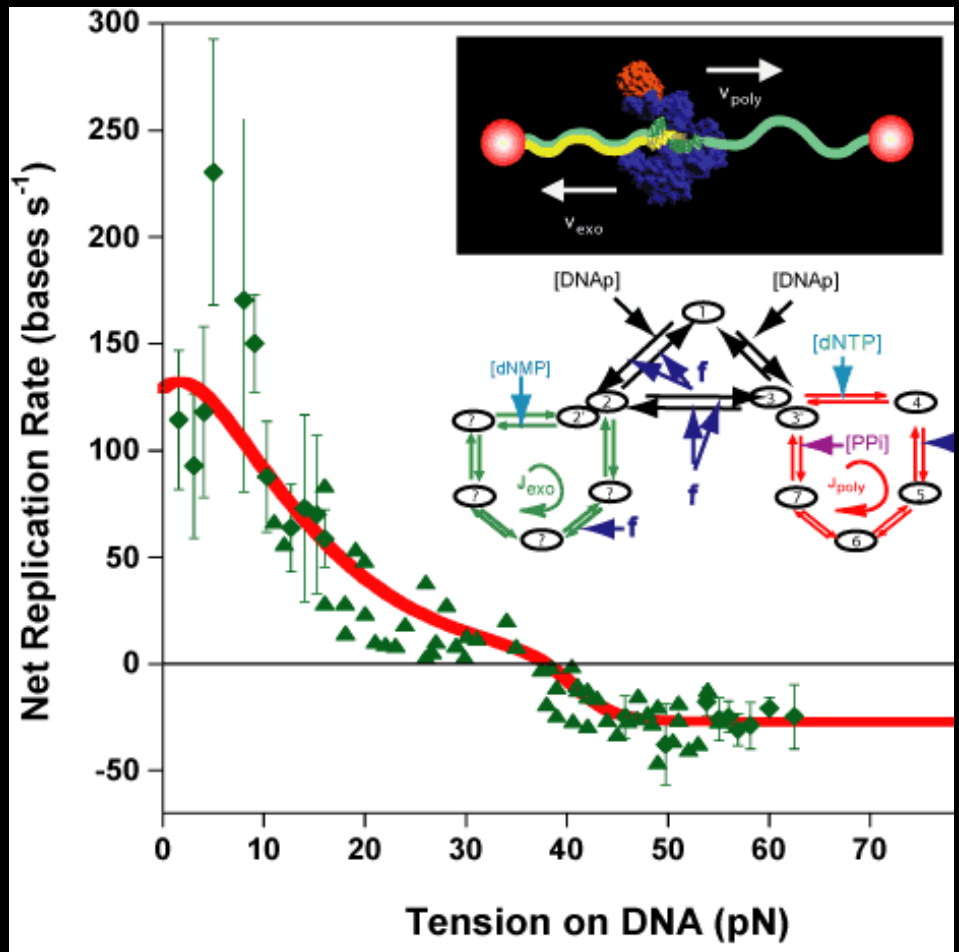
Polymerase motor

$v > \hbar/ml$

$m \approx 10^{-19}$ g, $l \approx 10^{-3}$ cm

$v > 10^{-5}$ cm/s ~ 100 bp/s





Quantum algorithms and the genetic code

Apoorva Patel

Grover's algorithm for searching an unsorted database of N objects

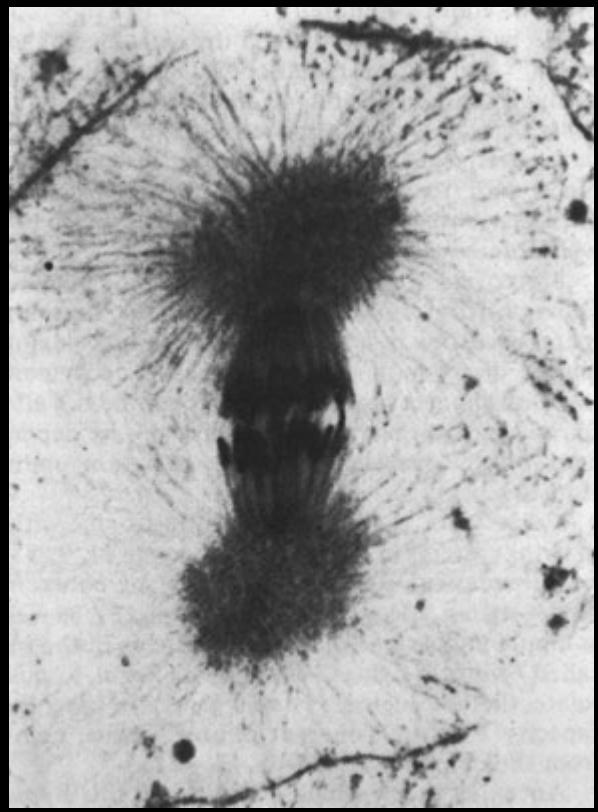
$\sqrt{N}$ improvement

Q queries: $(2Q + 1) \sin^{-1}(1/\sqrt{N}) = \pi/2$

Unique integer solution: $Q = 1, N = 4$

For $Q = 3, N = 20.2$

Popp, Hameroff, Penrose "quantum mitosis"



A thermodynamic interpretation of malignancy: do the genes come later?

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Summary Current theories on cancer development focus on 'unlucky' mutations affecting oncogenes suppressor genes. In this article a theory will be developed which interprets cancer as an adaptive phen response to cellular stress induced by an energetic overload which would ultimately lead to an increase in One of these adaptive mechanisms is paneuploid polyploidization, a phenomenon frequently described tumours. This inherent property of the genome to multiply with limited sequence variability may be involv new proteins which are more appropriate to manage the harmful situation of energetic overload. Anothe mechanism to prevent increasing entropy is the change in chirality of proteins and carbon hydrates bec enantiomers with higher intrinsic energy ultimately reduces entropy of the cell. These chiral alterations i molecular structures of proteins and DNA, resulting in abnormal function of the former and disturbances transcription and repair of the latter. Moreover, the altered proteins may – as a secondary step – induce changes of the DNA. Because changes in chirality affect the structure of a cell randomly, one can expe multiple genes or proteins, and this is exactly what has been described in the literature. Therefore, this help to clarify confusing findings of tumour genetics accumulated over the last two decades. Cancer cou

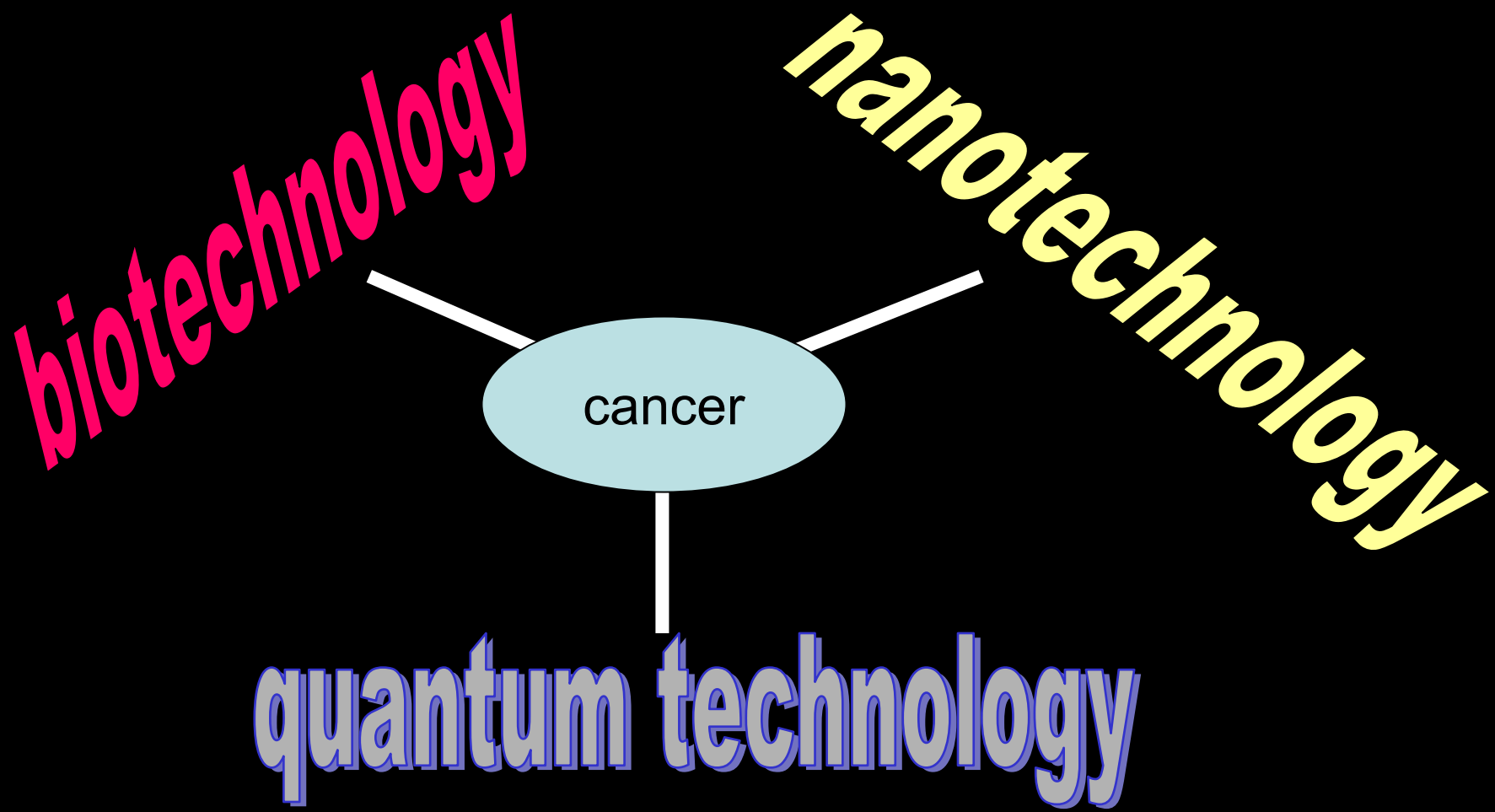
Elena Pikuta

Richard Hoover

NASA Marshall
Spaceflight Center

Anaerovirgula multivorans

The technology of the complex future



Conclusion

- Physicists have plucked most of the low-hanging fruit ("simple" systems)
- There exists a class of problems that are computationally challenging but not intractable, which should soon yield to Moore's law: *cancer may be one of them*
- Cancer – like life – can be understood only within the context of evolutionary biology as well as cell biology