

**Magari fosse frode !**  
(..storia della colonna infame)

Alessandro Giuliani



Il pregiudizio più comune è pensare di non avere pregiudizi.

La scienza inganna in tre modi: trasformando le sue proposizioni in norme, divulgando i suoi risultati più che i suoi metodi, tacendo le sue limitazioni epistemologiche

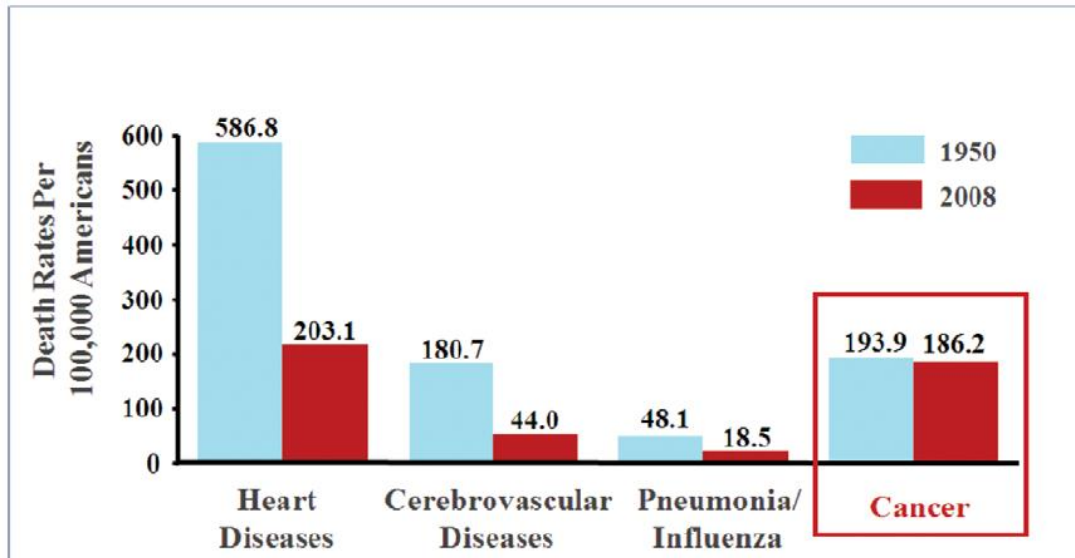
Nicolas Gomez Davila (In margine a un testo implicito)



EDITORIAL

Fear of Failure: Why American Science  
Is Not Winning the War on Cancer

Behind many stereotypes there is a truth. The stereotypical FEAR OF



Mortality rates (years 1950-2008) for infectious, heart, cerebrovascular diseases (From American Cancer Society (ACS) 2010 Cancer Facts & Figures; Atlanta, USA, 2008).

## Essay

# Why Most Published Research Findings Are False

John P. A. Ioannidis

**Table 4.** PPV of Research Findings for Various Combinations of Power ( $1 - \beta$ ), Ratio of True to Not-True Relationships ( $R$ ), and Bias ( $u$ )

$1 - \beta$	$R$	$u$	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

**19th century  
scientist**

I must find the  
explanation for this  
phenomenon in order  
to truly understand  
Nature...



**21st century  
scientist**

I must get the  
result that fits my  
narrative so I can  
get my paper into  
Nature..



# STATISTICAL ERRORS

P values, the 'gold standard' of statistical validity, are not as reliable as many scientists assume.

BY REGINA NOZZO

## PROBABLE CAUSE

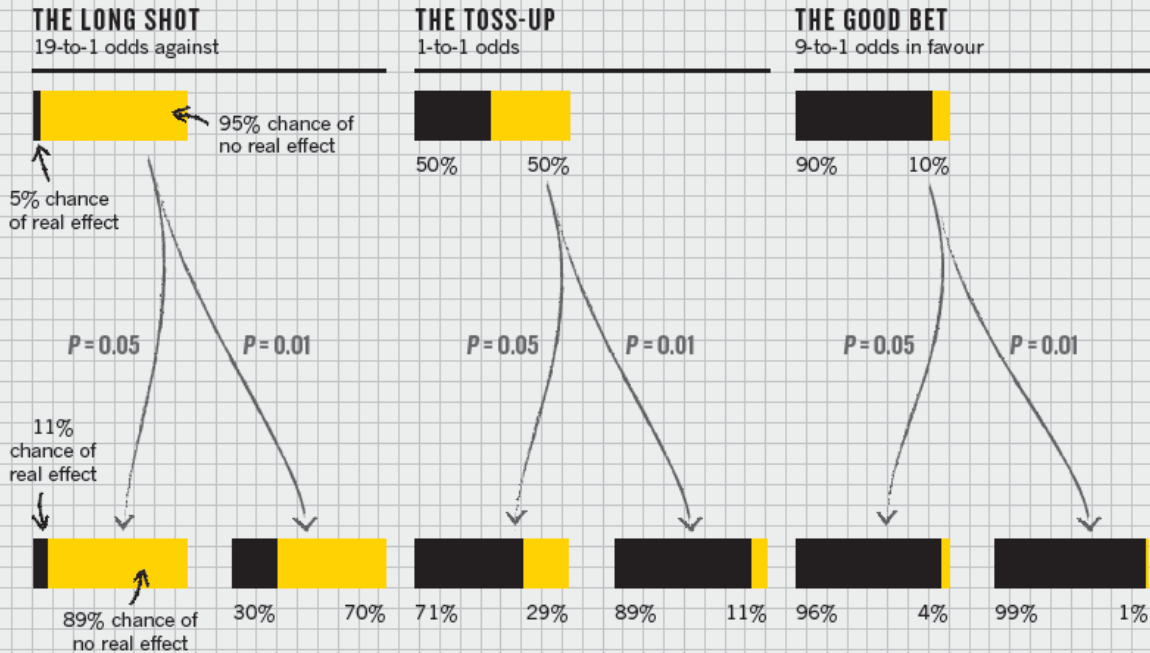
A P value measures whether an observed result can be attributed to chance. But it cannot answer a researcher's real question: what are the odds that a hypothesis is correct? Those odds depend on how strong the result was and, most importantly, on how plausible the hypothesis is in the first place.

■ Chance of real effect  
■ Chance of no real effect

**Before the experiment**  
The plausibility of the hypothesis — the odds of it being true — can be estimated from previous experiments, conjectured mechanisms and other expert knowledge. Three examples are shown here.

**The measured P value**  
A value of 0.05 is conventionally deemed 'statistically significant'; a value of 0.01 is considered 'very significant'.

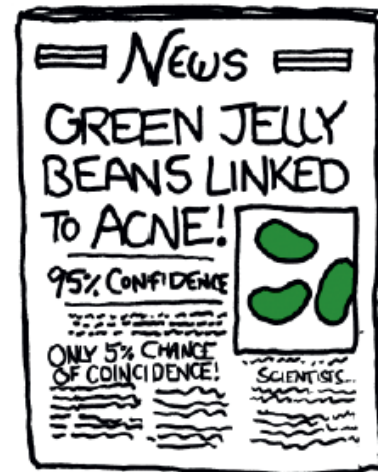
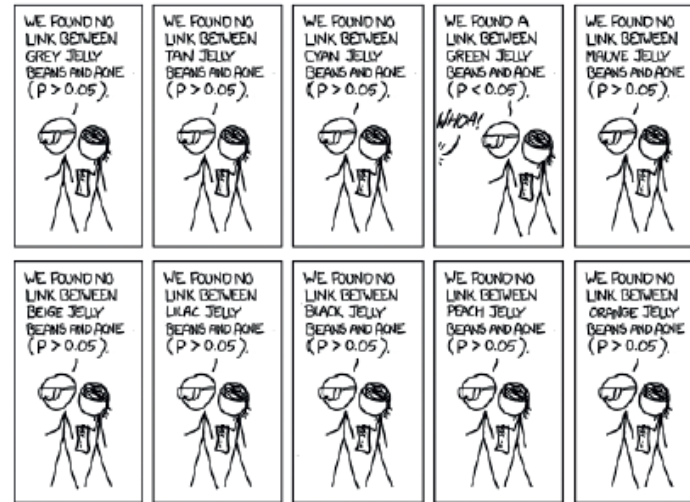
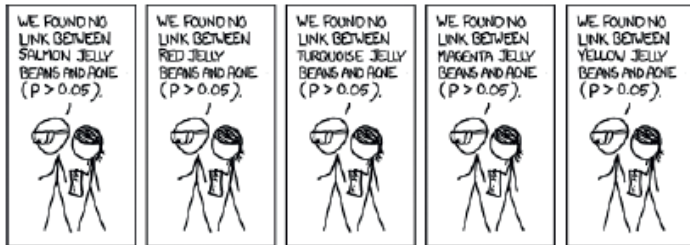
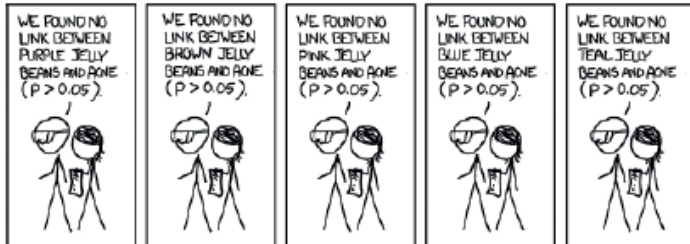
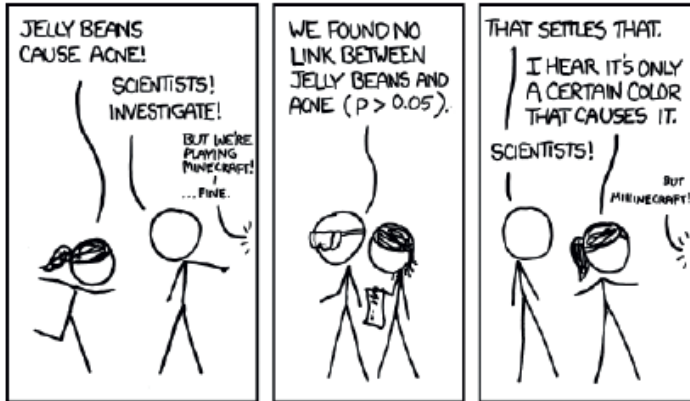
**After the experiment**  
A small P value can make a hypothesis more plausible, but the difference may not be dramatic.



# Deming, data and observational studies

A process out of control and needing fixing

“Any claim coming from an observational study is most likely to be wrong.” Startling, but true. Coffee causes pancreatic cancer. Type A personality causes heart attacks. Trans-fat is a killer. Women who eat breakfast cereal give birth to more boys. All these claims come from observational studies; yet when the studies are carefully examined, the claimed links appear to be incorrect. What is going wrong? Some have suggested that the scientific method is failing, that nature itself is playing tricks on us. But it is our way of studying nature that is broken and that urgently needs mending, say **S. Stanley Young** and **Alan Karr**; and they propose a strategy to fix it.







Deer in Headlights. A deer caught in the headlights will freeze, much like an author or reader seeing a p-value < 0.05, and think there must be a real effect. Authors can exploit this phenomenon intentionally or fool both themselves and the reader. Illustration: Tom Boulton

March 16, 2015

## Amid a Sea of False Findings, the NIH Tries Reform

By Paul Voosen

How do you change an entire scientific culture?

It may sound grandiose, but that is the loaded question now facing the National Institutes of Health, the federal agency that oversees and finances U.S. biomedical research.

**Volume 526 Number 7572 pp164-286**

8 October 2015



# A manifesto for reproducible science

Marcus R. Munafò<sup>1,2\*</sup>, Brian A. Nosek<sup>3,4</sup>, Dorothy V. M. Bishop<sup>5</sup>, Katherine S. Button<sup>6</sup>,  
Christopher D. Chambers<sup>7</sup>, Nathalie Percie du Sert<sup>8</sup>, Uri Simonsohn<sup>9</sup>, Eric-Jan Wagenmakers<sup>10</sup>,  
Jennifer J. Ware<sup>11</sup> and John P. A. Ioannidis<sup>12,13,14</sup>

**Improving the reliability and efficiency of scientific research will increase the credibility of the published scientific literature and accelerate discovery. Here we argue for the adoption of measures to optimize key elements of the scientific process: methods, reporting and dissemination, reproducibility, evaluation and incentives. There is some evidence from both simulations and empirical studies supporting the likely effectiveness of these measures, but their broad adoption by researchers, institutions, funders and journals will require iterative evaluation and improvement. We discuss the goals of these measures, and how they can be implemented, in the hope that this will facilitate action toward improving the transparency, reproducibility and efficiency of scientific research.**

GENOMICS

# Deflating the Genomic Bubble

James P. Evans,<sup>1\*</sup> Eric M. Meslin,<sup>2</sup> Theresa M. Marteau,<sup>3</sup> Timothy Caulfield<sup>4</sup>

Unrealistic expectations and uncritical translation of genetic discoveries may undermine other promising approaches to preventing disease and improving health.



www.sciencemag.org **SCIENCE** VOL 331 18 FEBRUARY 2011

Michael J. Joyner, MD  
Laboratory of Human Integrative Physiology and Department of Anesthesiology, Mayo Clinic, Rochester, Minnesota.

Nigel Paneth, MD, MPH  
Departments of Epidemiology and Biostatistics and Pediatrics and Human Development, College of Human Medicine, Michigan State University, East Lansing.

John P. A. Ioannidis, MD, DSc  
Stanford Prevention Research Center, Department of Medicine and Meta-Research Innovation Center at Stanford, Stanford University, Stanford, California.

Opinion

VIEWPOINT

## What Happens When Underperforming Big Ideas in Research Become Entrenched?

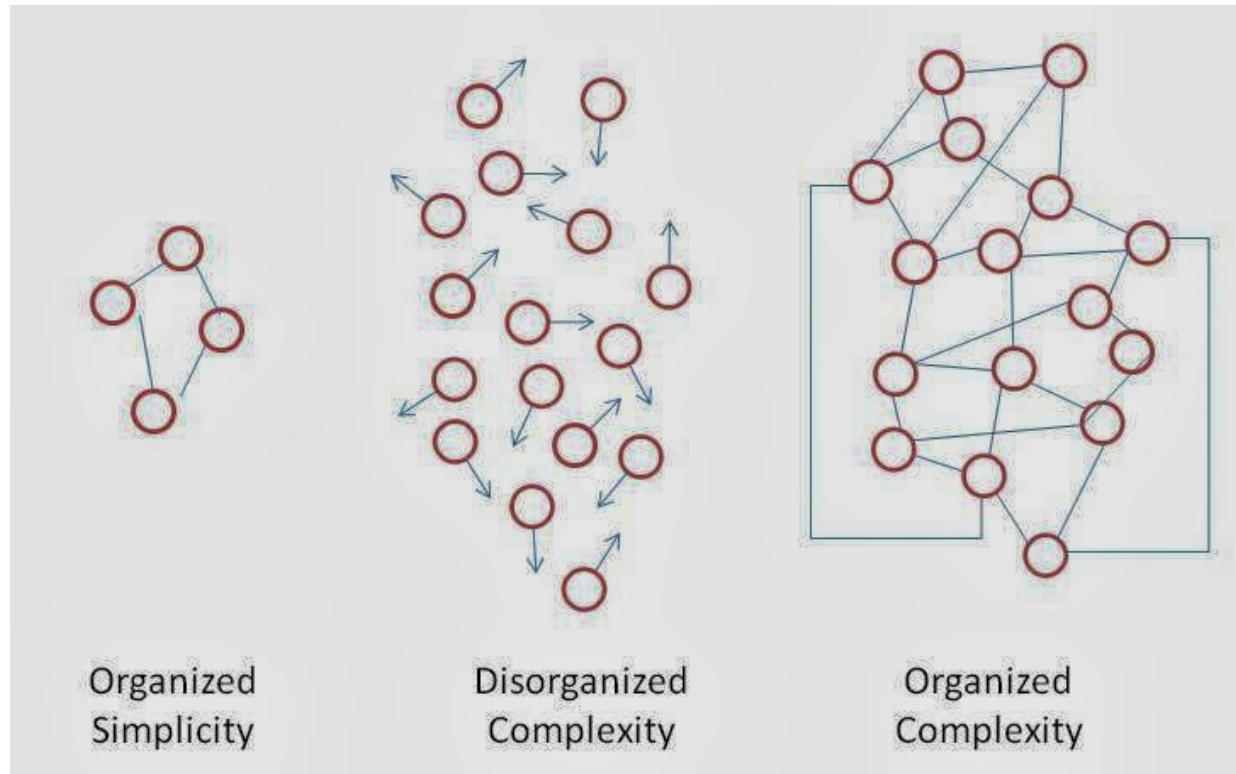
JAMA Published online July 28, 2016

# SCIENCE AND COMPLEXITY

By WARREN WEAVER  
Rockefeller Foundation, New York City

"Science and Complexity", *American Scientist*, 36: 536 (1948).

*Based upon material presented in Chapter 1 "The Scientists Speak," Boni & Gaer Inc., 1947. All rights reserved.*





## Perspective: Sloppiness and emergent theories in physics, biology, and beyond

Mark K. Transtrum,<sup>1</sup> Benjamin B. Machta,<sup>2</sup> Kevin S. Brown,<sup>3,4</sup> Bryan C. Daniels,<sup>5</sup> Christopher R. Myers,<sup>6,7</sup> and James P. Sethna<sup>6</sup>

<sup>1</sup>*Department of Physics and Astronomy, Brigham Young University, Provo, Utah 84602, USA*

<sup>2</sup>*Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, New Jersey 08544, USA*

<sup>3</sup>*Departments of Biomedical Engineering, Physics, Chemical and Biomolecular Engineering, and Marine Sciences, University of Connecticut, Storrs, Connecticut 06269, USA*

<sup>4</sup>*Institute for Systems Genomics, University of Connecticut, Storrs, Connecticut 06030-1912, USA*

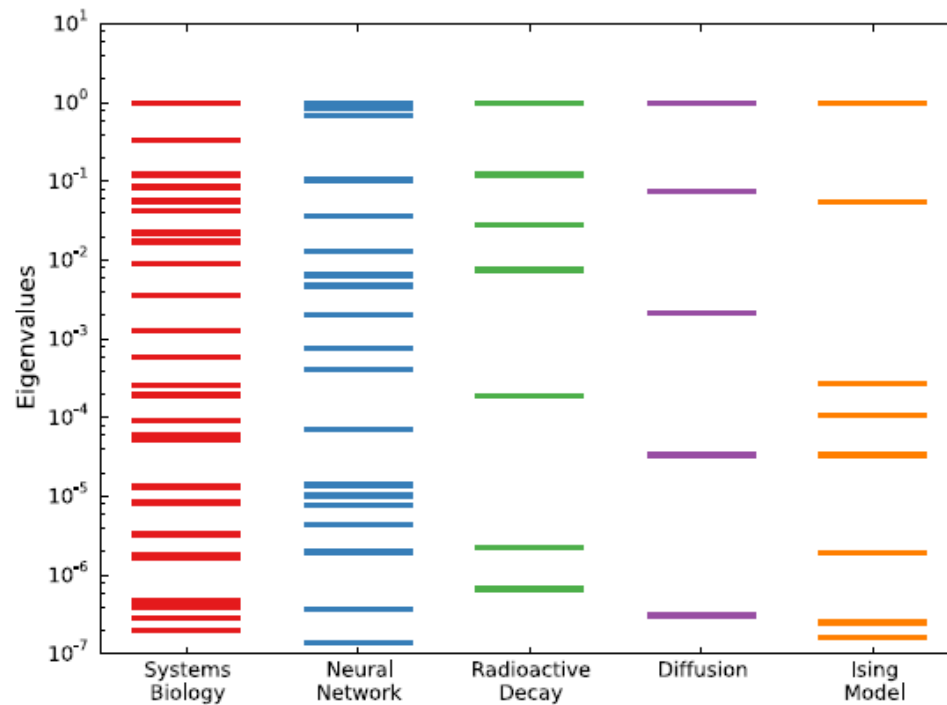
<sup>5</sup>*Center for Complexity and Collective Computation, Wisconsin Institute for Discovery, University of Wisconsin, Madison, Wisconsin 53715, USA*

<sup>6</sup>*Laboratory of Atomic and Solid State Physics, Cornell University, Ithaca, New York 14853, USA*

<sup>7</sup>*Institute of Biotechnology, Cornell University, Ithaca, New York 14853, USA*

(Received 2 February 2015; accepted 4 June 2015; published online 1 July 2015)

As a young physicist, Dyson paid a visit to Enrico Fermi<sup>1</sup> (recounted in Ditley, Mayer, and Loew<sup>2</sup>). Dyson wanted to tell Fermi about a set of calculations that he was quite excited about. Fermi asked Dyson how many parameters needed to be tuned in the theory to match experimental data. When Dyson replied there were four, Fermi shared with Dyson a favorite adage of his that he had learned from Von Neumann: “with four parameters I can fit an elephant, and with five I can make him wiggle his trunk.” Dejected, Dyson took the next bus back to Ithaca.

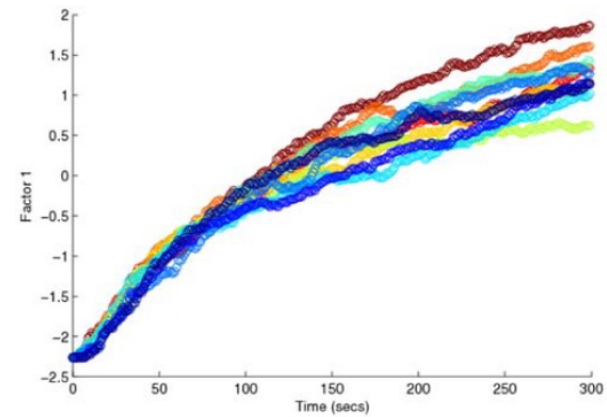
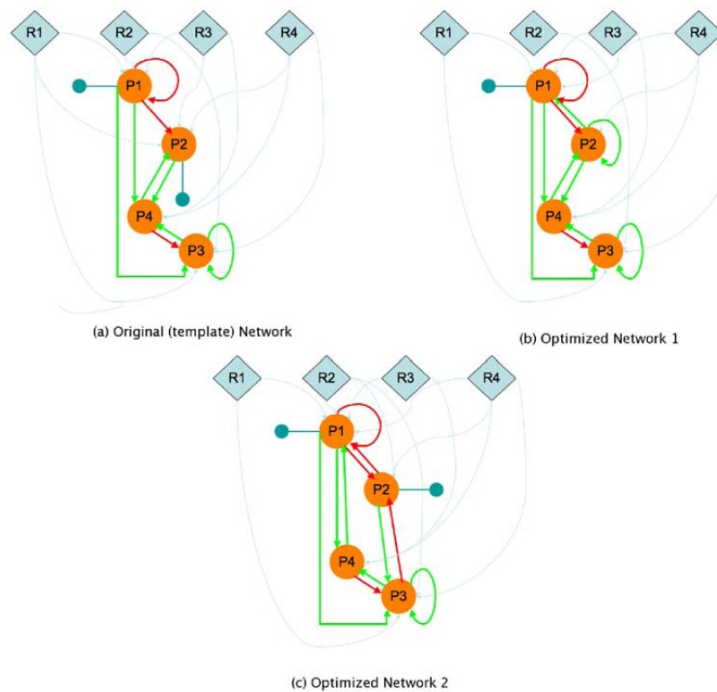


We noted previously that the characteristic eigenvalue spectrum of the FIM suggests a simpler, lower-dimensional “theory” embedded within larger, more complex “models,” and in this section, we make this notion explicit. We will see that

# Indeterminacy of Reverse Engineering of Gene Regulatory Networks: The Curse of Gene Elasticity

Arun Krishnan<sup>1\*</sup>, Alessandro Giuliani<sup>2</sup>, Masaru Tomita<sup>1</sup>

<sup>1</sup> Institute for Advanced Biosciences, Keio University, Tsuruoka, Japan, <sup>2</sup> Istituto Superiore di Sanità, Environment and Health Department, Rome, Italy





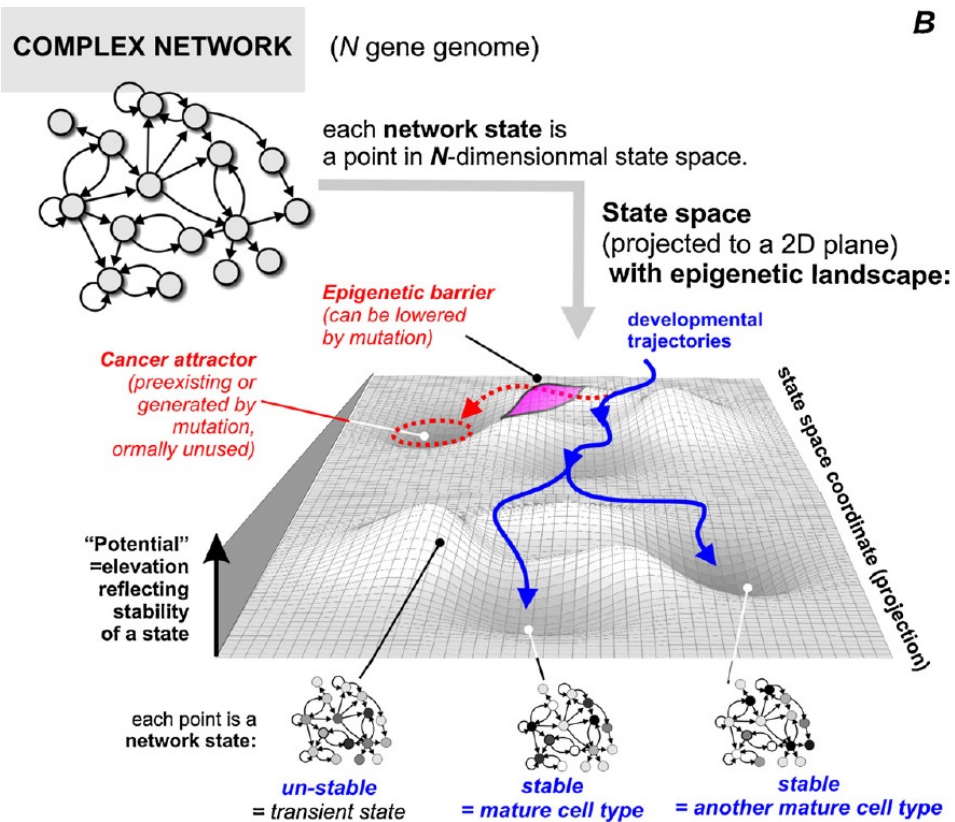
Review

## Cancer attractors: A systems view of tumors from a gene network dynamics and developmental perspective

Sui Huang<sup>a,\*</sup>, Ingemar Ernberg<sup>b</sup>, Stuart Kauffman<sup>a</sup>

<sup>a</sup> Institute for Biocomplexity and Informatics, Biological Sciences Bldg, University of Calgary, 2500 University Drive, Calgary AB, Canada

<sup>b</sup> Dept of Microbiology, Tumor and Cell Biology (MTC) Karolinska Institutet, Box 280, 171 77 Stockholm, Sweden



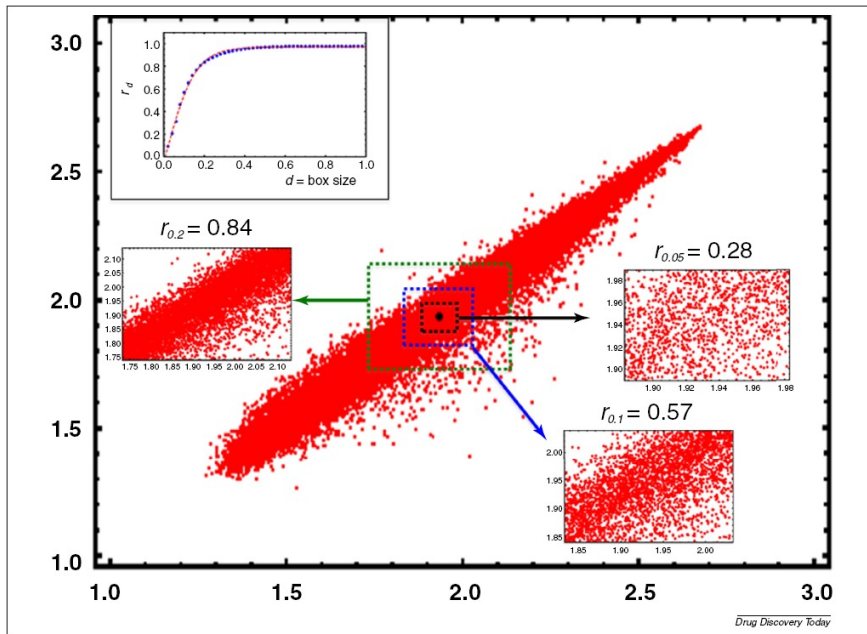
Physical and genetic/biochemical cues at the bifurcation points (hills) may drive the system toward different fate commitment (attractors-valleys)

RESEARCH ARTICLE

# Cell Fate Decision as High-Dimensional Critical State Transition

Mitra Mojtabedi<sup>1,2\*</sup>, Alexander Skupin<sup>2,3\*</sup>, Joseph Zhou<sup>2</sup>, Ivan G. Castaño<sup>1,4</sup>, Rebecca Y. Y. Leong-Quong<sup>1</sup>, Hannah Chang<sup>5</sup>, Kalliopi Trachana<sup>2</sup>, Alessandro Giuliani<sup>6</sup>, Sui Huang<sup>1,2\*</sup>

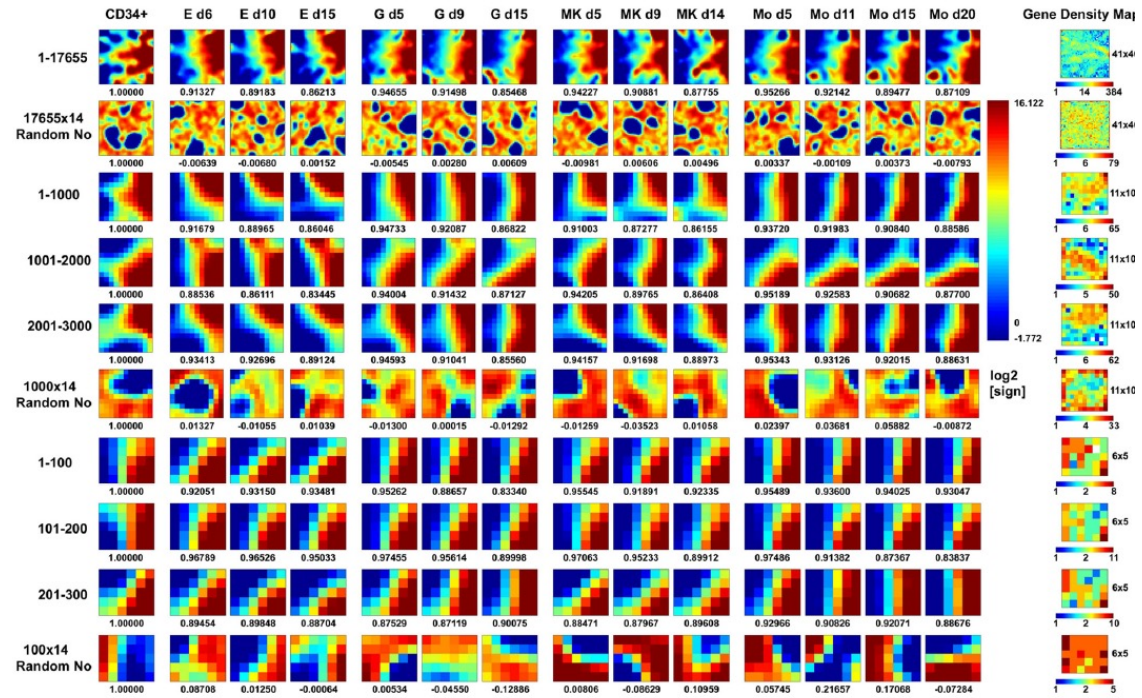
1 Department of Biological Sciences, University of Calgary, Calgary, Alberta, Canada, 2 Institute for Systems Biology, Seattle, Washington, United States of America, 3 Luxembourg Centre for Systems Biomedicine, Esch-sur Alzette, Luxembourg, 4 Corporación Parque Explora, Department of innovation and design, Medellín, Colombia, 5 5AM Ventures, Menlo Park, California, United States of America, 6 Environment and Health Department, Istituto Superiore di Sanità, Roma, Italy



A

SEQUENCES SIGNAL	SEQUENCES SIGNAL	SEQUENCES SIGNAL	SEQUENCES RATIO	SEQUENCES RATIO
54630 0-71337 All	17655 >500 Expressed	3019 >5000 High Expression	7642 >3x Changed	3561 >8x High Change
		14636 500-5000 Medium Expression		4081 3-6x Medium Change
36975 <500 No/Low Expression				

B



‘Del rigor en la ciencia’

Jorge Luis Borges

*In quell'impero, l'Arte della Cartografia raggiunse una tale Perfezione che la mappa di una sola provincia occupava tutta una Città e la mappa dell'Impero tutta una Provincia. Col tempo codeste Mappe Smisurate non soddisfecero e i Collegi dei Cartografi eressero una mappa dell'Impero che uguagliava in grandezza l'Impero e coincideva puntualmente con esso. Meno Dedite allo studio della cartografia, le Generazioni Successive compresero che quella vasta Mappa era inutile e non senza Empietà la abbandonarono alle Inclemenze del Sole e degl'Inverni. Nei deserti dell'Ovest rimangono lacere rovine della mappa, abitate da Animali e Mendichi; in tutto il paese non è altra reliquia delle Discipline Geografiche. (Suarez Miranda, Viaggi di uomini prudenti, libro quarto, cap. XLV, Lérida, 1658)*