"Re-Analysis of Variance, Re-Analysis of Cause": Lewontin (1974), 50 years later

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Rest in Power, Dick

Santa Fe Institute

RESEARCH NEWS + EVENTS EDUCATION APPLIED COMPLEXIT

The Harvard Crimson

Distinguished Harvard Geneticist Richard C. Lewontin '50, A 'Fantastic Mentor,' and 'Polymath,' Dies at 92

Richard C. Lewontin '50, a renowned population geneticist and organismic and evolutionary biology professor at Harvard, died on July 4 at the age of 92. Though he retired in 2003, he remained involved with Harvard until shortly before his death.

BY LEAH J. TEICHHOLTZ July 18, 2021

Richard C. Lewontin '50 — a prolific scientist who developed new methods for analyzing genetic variance — in the lab, manually scoring a DNA sequence. By Courtesy of Andrew Berry

chard Lewontin

SFI Stanislaw Ulam Memorial Lectures

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GRACE HUCKINS SCIENCE SEP 3, 2021 8:00 AM

Richard Lewontin Leaves a Legacy of Fighting Racism in Science

The late evolutionary biologist made a reputation—and enemies—by speaking out against the idea that genes are destiny. Science still needs people like him.

theguardian.com/science/2021/jul/28/richard-lewontin-obituary

Genetics

Richard Lewontin obituary

Pioneering biologist and geneticist whose research showed the emptiness of traditional biological concepts of race

Andrew Brown *and* Steven Rose

Wed 28 Jul 2021 18.07 BST

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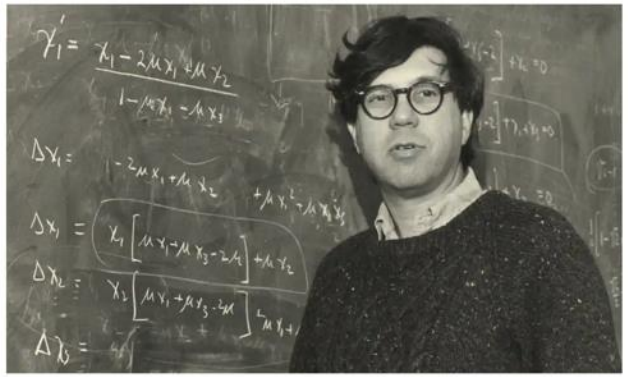

Richard Lewontin at Harvard, where his analysis of the proteins that genes code demonstrated more genetic diversity within 'races' than between them. Photograph: from the Ernst Mayr library and archives of the Museum of Comparative Zoology, Harvard University

The American scientist Richard Lewontin, who has died aged 92, was intimately involved in some of the most important discoveries, and feuds, of evolutionary biology during the decades in which it passed from knowing that genes existed to specifying them in precise molecular terms.

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OBITUARY | 13 July 2021

Richard C. Lewontin (1929–2021)

Pioneer of molecular evolution who campaigned against biological racism.

Michael R. Dietrich

SEP

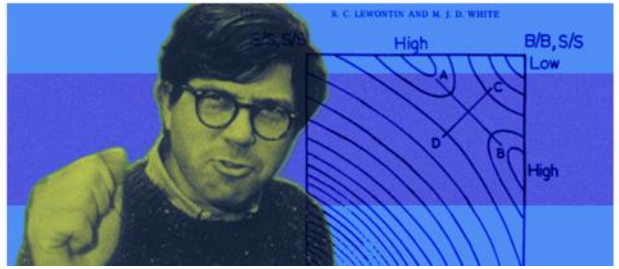
November 23, 2021

Richard Lewontin as Master Dialectician

Rest in Power, Dick

By Rasmus Grønfeldt Winther

Lewontin Memorial Collection



Lewontin's Globe

By: Rasmus Grønfeldt Winther
and Pablo Carlos Budassi
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Lewontin's Globe

"Context and interaction are of the essence."

By: Rasmus Grønfeldt Winther and Pablo Carlos Budassi
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JOURNAL ARTICLE

A MOLECULAR APPROACH TO THE STUDY OF GENIC HETEROZYGOSITY IN NATURAL POPULATIONS. I. THE NUMBER OF ALLELES AT DIFFERENT LOCI IN *DROSOPHILA PSEUDOOBSCURA*

FREE

J L Hubby, R C Lewontin

Genetics, Volume 54, Issue 2, 30 August 1966, Pages 577–594, https://doi.org/10.1093/genetics/54.2.577
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Volume 14, Issue 4
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JOURNAL ARTICLE

THE EVOLUTIONARY DYNAMICS OF COMPLEX POLYMORPHISMS[1,2,3]

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R. C. Lewontin, Ken-ichi Kojima Author Notes

Evolution, Volume 14, Issue 4, 1 December 1960, Pages 458–472, https://doi.org/10.1111/j.1558-5646.1960.tb03113.x
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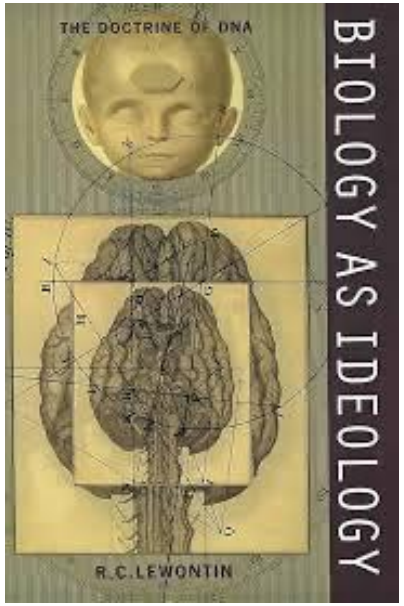

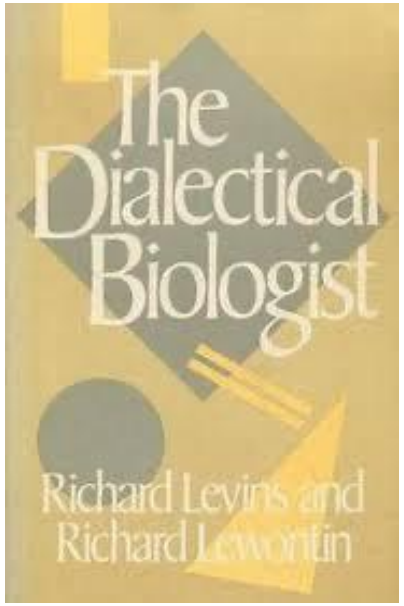

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1 March 2022

JOURNAL ARTICLE

Dawkins or Lewontin or both? Review of The Gene's-Eye View of Evolution, by J. Arvid Ågren, Oxford, U.K: Oxford University Press.

Rasmus Grønfeldt Winther

Evolution, Volume 76, Issue 3, 1 March 2022, Pages 685–687, https://doi.org/10.1111/evo.14439
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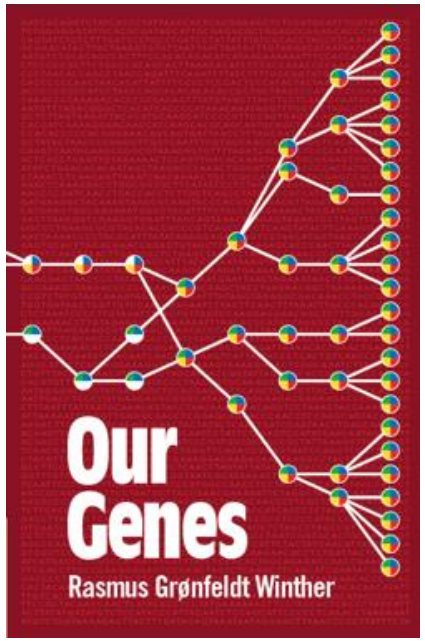


PNAS PERSPECTIVE OPEN ACCESS

Wilson and Sarich (1969): The birth of a molecular evolution research paradigm

Rasmus Grønfeldt Winther [a,b,1] and Eske Willerslev [b,c]

Edited by Dolores R. Piperno, Smithsonian Institution, Washington, DC; received January 23, 2023; accepted January 23, 2023

March 9, 2023 | 120 (11) e2220473120 | https://doi.org/10.1073/pnas.2220473120

1. Introduction

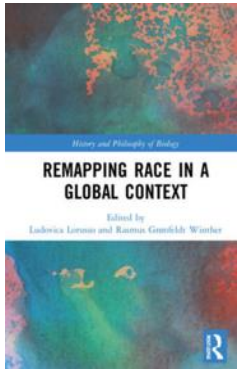
Science sometimes progresses through the emergence of a research paradigm leveraging an innovative experimental technique to tackle age-old questions in unexpected, theoretically clever, and ultimately correct manners. Wilson and Sarich's classic 1969 paper made just this sort of progress by integrating several kinds of molecular evidence of protein differences among humans, apes, Old World monkeys, and New World monkeys—especially evidence gathered using the novel immunological technique of micro-complement fixation (MC'F) (1). Their achievement was twofold: i) to effectively pinpoint a relatively early divergence of humans and African apes approximately 4 to 5 Mya and ii) to provide proof of concept of the power and validity of an "evolutionary clock" approach. Both results were surprising: Standard morphological and paleontological approaches had placed the human–African ape divergence at 15 to 30 Mya, while emphasizing the irregularity of character change in evolution.

Allan C. Wilson and Vincent M. Sarich's research paradigm at University of California, Berkeley, elegantly combined immunological protocol, evolutionary theory, and statistical reasoning to address deep human evolution. Although ref. 1 stands as perhaps the pinnacle

Chapter 1

Lewontin (1972)

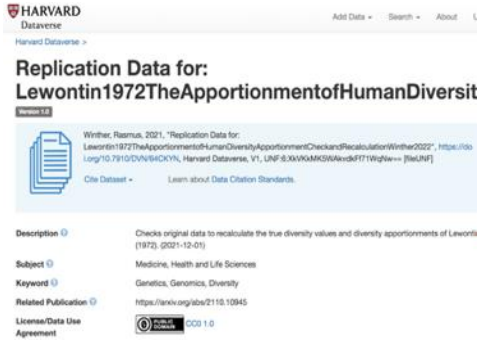
Rasmus Grønfeldt Winther

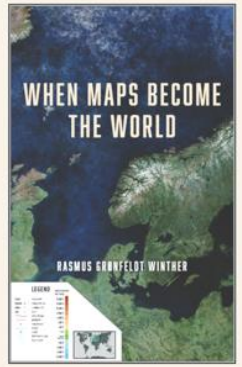


Introduction

Richard C. Lewontin is arguably the most influential evolutionary biologist of the second half of the 20th century. A PhD student of Theodosius Dobzhansky—one of the architects of the neo-Darwinian modern synthesis along with R. A. Fisher, Sewall Wright, J. B. S. Haldane, Ernst Mayr, and George Gaylord Simpson—Lewontin has dazzled us with his experimental and mathematical prowess, conceptual sharpness, and inspirational qualities as a teacher, mentor, public speaker, and writer.

Of particular note for *Remapping Race in a Global Context* is his classic 1972 article, titled "The Apportionment of Human Diversity," especially the 85.4%/8.3%/6.3% distribution of genetic diversity components that Lewontin posits (1972, Table 4, p. 396) at three levels (within populations, among populations but within races, and among races). "Lewontin's distribution," as we could call it (see Winther, 2022), has been subject to wildly





Lewontin (1974) [L74]: An Anatomy

1. Introduction
2. Discrimination of Causes and Analysis of Causes
3. Quantitative Analysis of Causes
4. Norm of Reaction
5. Effect of Additivity
6. Purposes of Analysis

Am J Hum Genet 26:400–411, 1974

Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. LEWONTIN[1]

This issue of the *American Journal of Human Genetics* contains two articles by Newton Morton and his colleagues [1, 2] that provide a detailed analytic critique of various estimates of heritability and components of variance for human phenotypes. They make especially illuminating remarks on the problems of partitioning variances and covariances between groups such as social classes and races. The most important point of all, at least from the standpoint of the practical, social, and political applications of human population genetics, occurs at the conclusion of the first paper [1] in which Morton points out explicitly the chief programmatic

1. Introduction

• This issue of the *American Journal of Human Genetics* contains two articles by Newton Morton and his colleagues [1, 2] that provide a detailed analytic critique of various estimates of heritability and components of variance for human phenotypes.

• The fallacy is that a knowledge of the heritability of some trait in a population provides an index of the efficacy of environmental or clinical intervention in altering the trait either in individuals or in the population as a whole.

• I would like in what follows to look rather closely at the problem of the analysis of causes in human genetics and to try to understand how the underlying model of this analysis molds our view of the real world. (p. 400)

Annotation:

The Analysis of Variance and the Analysis of Causes

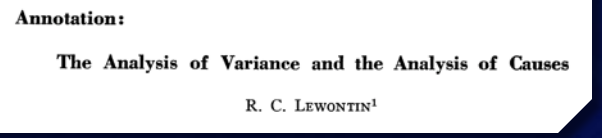
R. C. Lewontin[1]

2. Discrimination of Causes and Analysis of Causes

- We must first separate two quite distinct problems about causation that are discussed by Morton. One is to discriminate which of two alternative and mutually exclusive causes lies at the basis of some observed phenotype.

- This is the old problem of distinguishing major gene effects from "polygenic" effects. … the discrimination between two *alternative* causes of a human disorder is worth making if it can be done.

- The second problem of causation is quite different. It is the problem of the *analysis* into separate elements of a number of causes that are interacting to produce a single result. In particular, it is the problem of analyzing into separate components the interaction between environment and genotype in the determination of phenotype. (p. 401)


Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

3. Quantitative Analysis of Causes

• If an event is the result of the joint operation of a number of causative chains and if these causes "interact" in any generally accepted meaning of the word, it becomes conceptually impossible to assign quantitative values to the causes of that individual event. Only if the causes are utterly independent could we do so. For example, if two men lay bricks to build a wall, we may quite fairly measure their contributions by counting the number laid by each; but if one mixes the mortar and the other lays the bricks, it would be absurd to measure their relative quantitative contributions by measuring the volumes of bricks and of mortar.

• That is, if we cannot ask how much of an individual's height is the result of his genes and how much a result of his environment, we will ask what proportion of the deviation of his height from the population mean can be ascribed to deviation of his environment from the average environment and how much to the deviation of this genetic value from the mean genetic value. (p. 402)

$$Y - \mu_Y = (G - \mu_Y) + (E - \mu_Y) + (GE) + e,$$

Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

4. Norm of Reaction I.

• the amount of *environmental* variance that appears depends upon the *genotypic* distribution, while the amount of *genetic* variance depends upon the *environmental* distribution. Thus the appearance of the separation of causes is a pure illusion. (p. 406)

• the linear model does not really effect a separation of causes of variation and that it is a purely local description with no predictive reliability. (p. 406)

• But there is no question of sampling here, and the relation of sample to universe in statistical procedures is not the same as the relation of variation in spatiotemporally defined populations to causal and functional variation summed up in the norm of reaction. (p. 407)

Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

4. Norm of Reaction II.

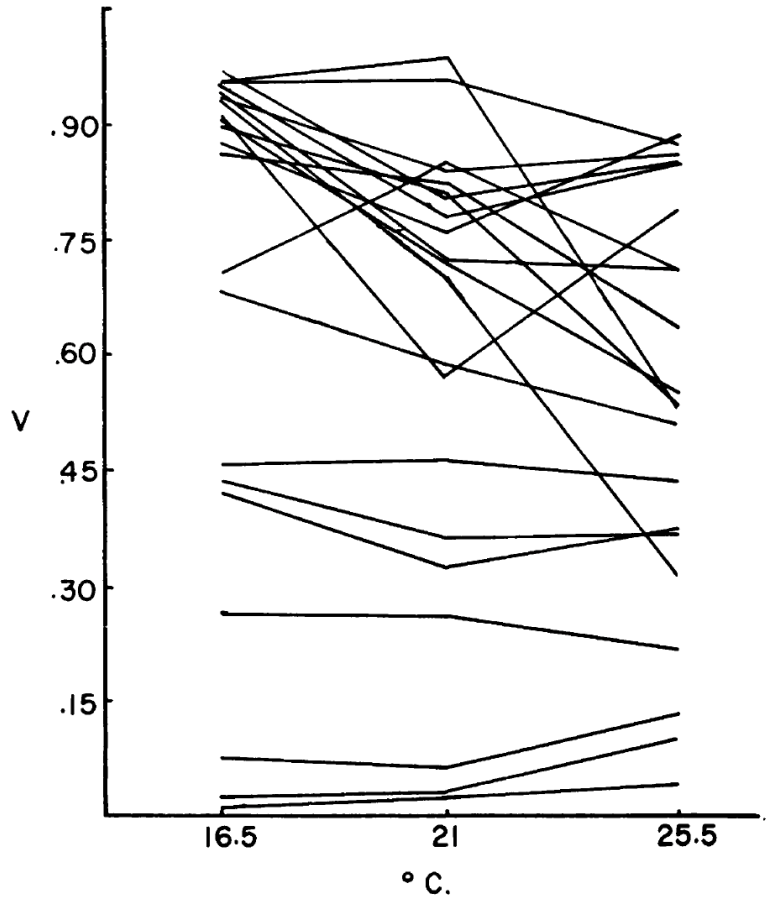


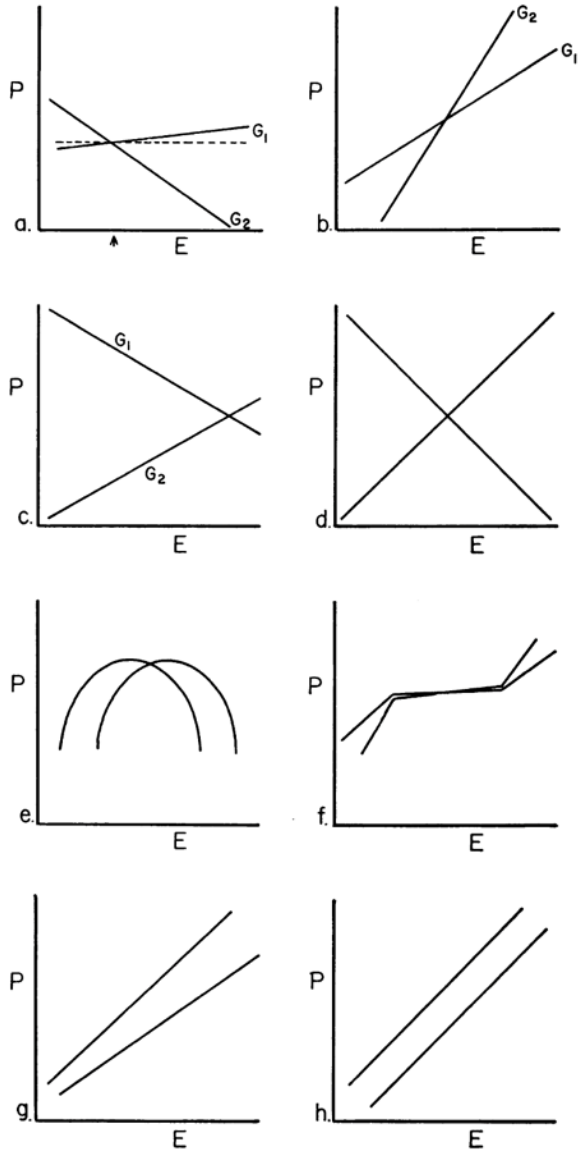
FIG. 2.—Actual reaction norms for viability of fourth chromosome homoyzgotes of *Drosophila pseudoobscura*. Data from Dobzhansky and Spassky [7].

Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. LEWONTIN[1]

4. Norm of Reaction III.



p. 405

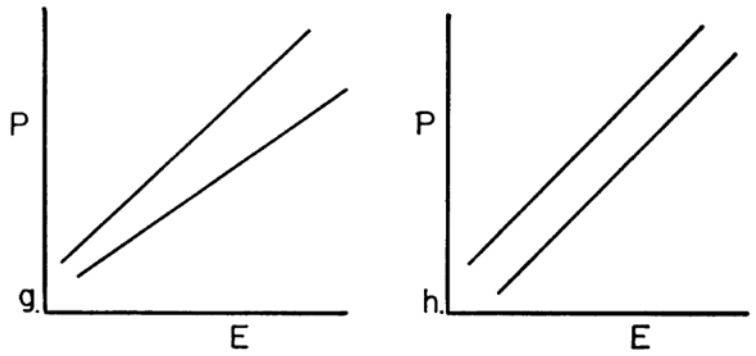
Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

5. Effect of Additivity

• There is one circumstance in which the analysis of variance can, in fact, estimate functional relationships. This is illustrated exactly in figure 1*h* and approximately in figure *1g*. In these cases there is perfect or nearly perfect additivity between genotypic and environmental effects so that the differences among genotypes are the same in all environments and the differences between environments are the same for all genotypes. Then the historical and immediate circumstances that alter genotypic and environmental distributions are irrelevant. It is not surprising that the assumption of additivity is so often made, since this assumption is necessary to make the analysis of variance anything more than a local description. (p. 408)



Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

6. Purpose of Analysis

- The purposes of these analyses are different[:] The analysis of causes in human genetics is meant to provide us with the basic knowledge we require for correct schemes of environmental modification and intervention. … knowledge of norms of reaction can also predict the demographic and public health consequences of certain massive environmental changes. Analysis of variance can do neither of these because its results are a unique function of the present distribution of environment and genotypes. (p. 409)

- The legitimate purposes of the analysis of variance in human genetics are to predict the rate at which selection may alter the genotypic composition of human populations and to reconstruct, in some cases, the past selective history of the species. (p. 410)

- In view of the terrible mischief that has been done by confusing the spatiotemporally local analysis of variance with the global analysis of causes, I suggest that we stop the endless search for better methods of estimating useless quantities. There are plenty of real problems. (p. 410)

Annotation:

The Analysis of Variance and the Analysis of Causes

R. C. Lewontin[1]

L74 Main / Global Theses: ANOVA…

1. … is local & contextual (doesn't support inferences to new contexts / new data). *No prediction!*

2. …"explains" (at best; via variance components) differences / variation rather than actual traits. *No explanation of particular cases!*

3. … fails to usefully identify (i) variance components or (ii) causes. (i) *Partitioning of the world is not pre-given;* (ii) *ANOVA (and regression, etc.) cannot, except under highly idealized assumptions, give us a "causal picture of the world"*

L74 "Smaller" / Local Theses

1. "Main effect" variance components influence / condition each other ("the amount of *genetic variance* depends on the *environmental* distribution," p. 404)

2. ANOVA can only provide a proper causal story or functional relationship when additivity holds

"The Additive Paradigm"? I. Heritability, IQ, and Race

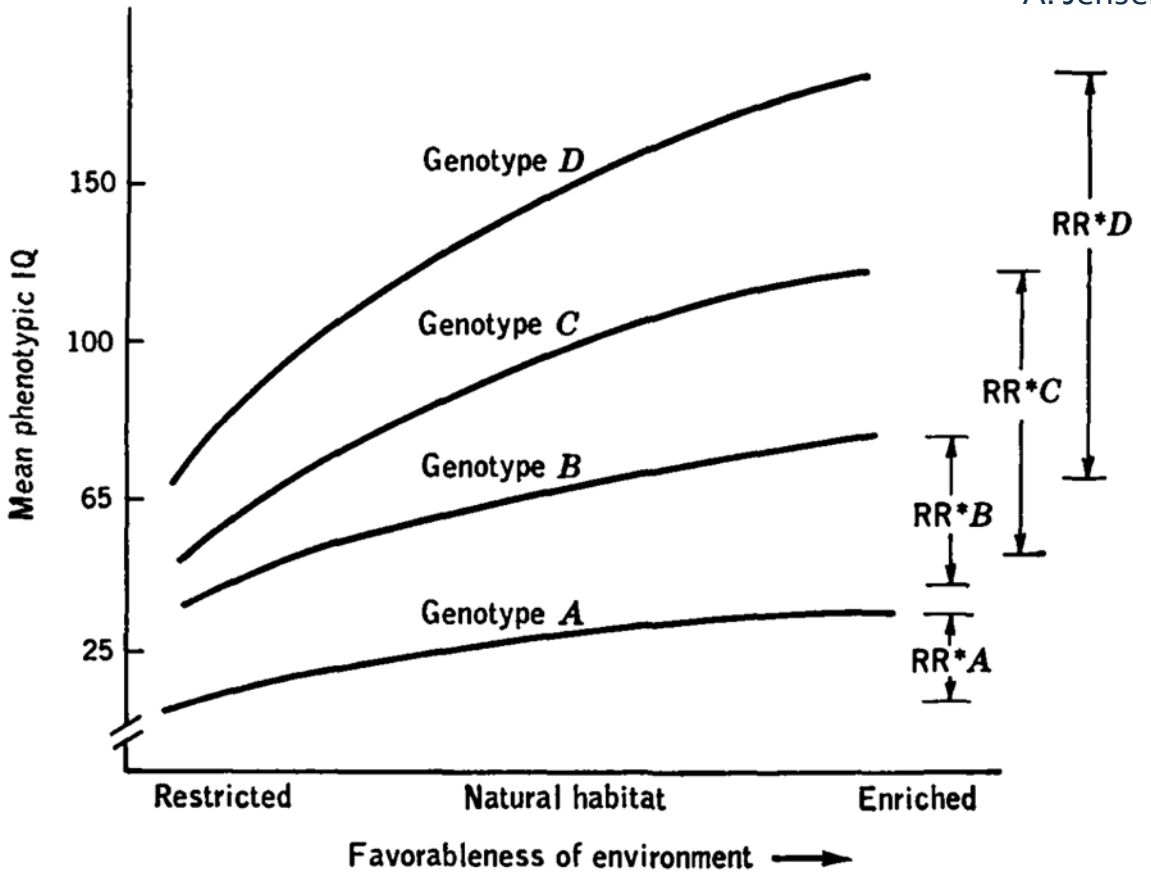
A. Jensen

How Much Can We Boost IQ and Scholastic Achievement?

ARTHUR R. JENSEN

University of California, Berkeley

Harvard Educational Review Vol. 39 No. 1 Winter 1969

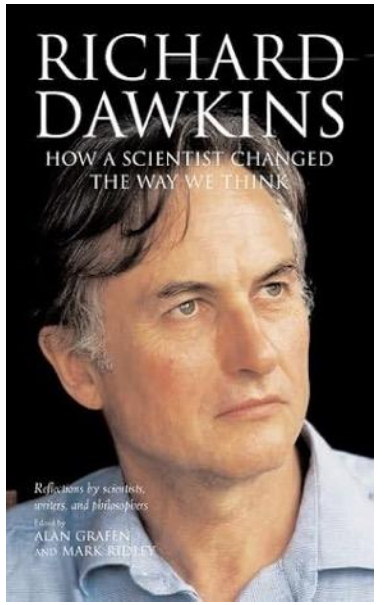


"The Additive Paradigm"? II. Statistics

R. A. Fisher

- Relation between dependent (*y*) and independent-explanatory (*x*) variable is linear
- Normal distribution of errors (or residuals) with constant variance
- Cross-variable explanatory impotence
- Ignored outliers
- **Conclusion – General Linear Models** (additivity & abstracting away from error and interaction – ceteris paribus and ceteris absentibus)

"The Additive Paradigm"? III. Genetics

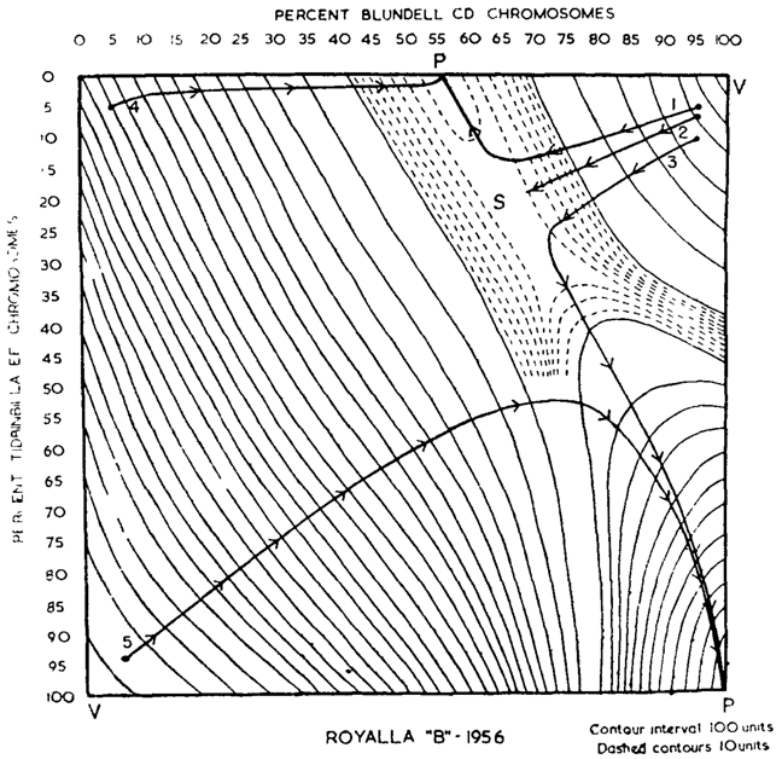


- Infinitely large populations
- Panmixia (no group structure)
- No fitness interaction (epistasis) among genes
- No/little phenotypic plasticity
- Fullness of time
- **Conclusion – Potency of Artificial & Natural Selection** (additivity & abstracting away from random genetic drift, migration, etc. – ceteris paribus and ceteris absentibus)

"Sir Ronald Fisher, the greatest biologist of the twentieth century" *The Selfish Gene*, 1976/1989, p. 124.

Lewontin "Strikes Back" I. *GBEC*

Moreover, relative selective values of substitution at a locus cannot be judged from the frequencies of the alleles in nature because *the selection of the chromosome as a whole is the overriding determinant of allelic frequencies*. (p. 307)



"Even though we may be interested in following only one segregating entity, say a third chromosome inversion in *D. persimilis*, an understanding of evolution along that one dimension requires *first* a synthetic treatment of the genotype and *then* an abstraction of the single system of interest from the complex mass. We cannot reverse the process, in general, building a theory of a complex system by the addition or aggregation of simple ones." (p. 281)

Epistasis and **Gene Interaction**!

"The fitness at a single locus ripped from its interactive context is about as relevant to real problems of evolutionary genetics as the study of the psychology of individuals isolated from their social context is to an understanding of man's sociopolitical evolution. In both cases context and interaction are not simply second-order effects to be superimposed on a primary monadic analysis. Context and interaction are of the essence." (p. 318)

Lewontin "Strikes Back"
II. "The Units of Selection"

Multi-Level Selection!

THE UNITS OF SELECTION

R. C. LEWONTIN
Department of Biology, University of Chicago, Chicago, Illinois

The principle of natural selection as the motive force for evolution was framed by Darwin in terms of a "struggle for existence" on the part of organisms living in a finite and risky environment. The logical skeleton of his argument, however, turns out to be a powerful predictive system for changes at all levels of biological organization. As seen by present-day evolutionists, Darwin's scheme embodies three principles (Lewontin 1):

1. Different individuals in a population have different morphologies, physiologies, and behaviors (phenotypic variation).
2. Different phenotypes have different rates of survival and reproduction in different environments (differential fitness).
3. There is a correlation between parents and offspring in the contribution of each to future generations (fitness is heritable).

These three principles embody the principle of evolution by natural selection. While they hold, a population will undergo evolutionary change.

While rigorous formalization of the principles of natural selection is recent, it has been obvious in a general way that other units beside the individual could be the unit of selection, and a great deal of theory-making has gone on for natural selection at other levels. While there is a superabundance of such theory, both rigorous and heuristic, and while many natural-historical observations are interpreted as arising through the agency of natural selection of molecules, cells, populations, species, and communities, there is virtually a complete absence of direct experimental or natural-historical verification of these interpretations. In view of the strong antitheoretical stance of most of biology, it is remarkable that, in the absence of much evidence, the concept of natural selection of units other than the individual is so widely accepted.

Complexity, interaction, and emergence

1. How can we best handle complexity in our statistical and genetic models?

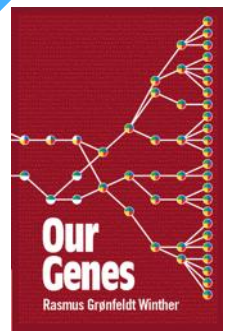
   (Many limited models; ceteris paribus/ceteris absentibus assumptions; data-rich and computation-heavy analyses; 'restart' our theory… ?)

2. What is interaction; what interacts with what; is interaction fundamental?

   (e.g., Helen Longino "Interaction: A case for ontological pluralism," 2020)

3. Is nature basically hierarchical or does it 'single out' and/or 'bottom out'?

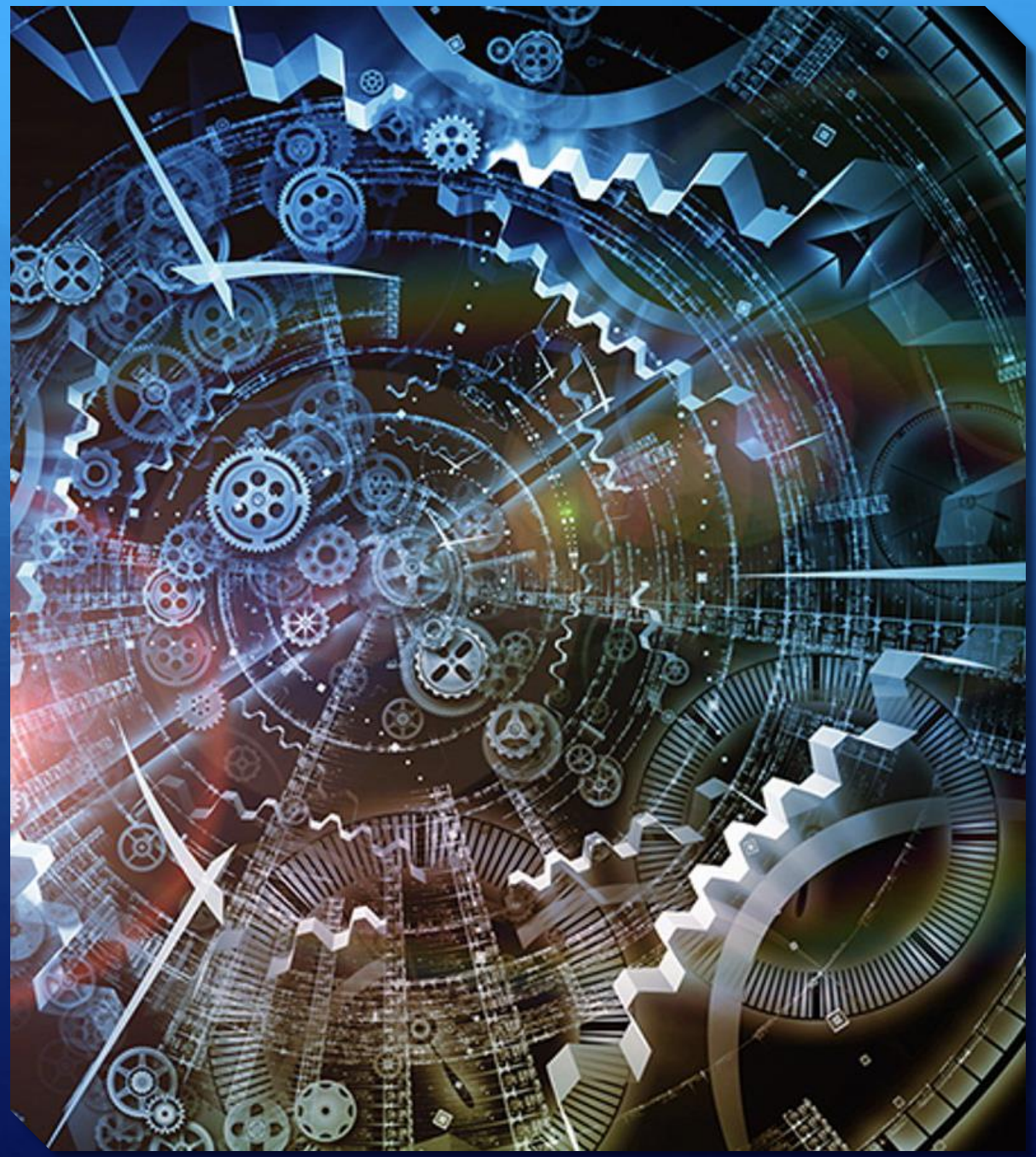
   (e.g., William Wimsatt *Re-Engineering Philosophy for Limited Beings*, 2007)

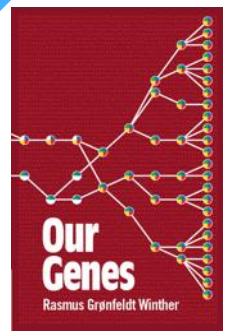


A metaphor: **Clockwork**, Soup, and Conscious Universes

In the severe clockwork universe, there are independent and inexorable laws, causal regularities, and (fundamental) kinds of objects and properties; moreover, there are relatively few such laws and causes, objects and properties.

In its essentials, a clockwork universe is taken to be deterministic; orderly and regular (across space and time); (potentially) long lasting; simple; and (potentially) totally explainable in that all causes can be postulated and identified, and their effects fully mapped out.
(Winther, *Our Genes*, pp. 286–7)

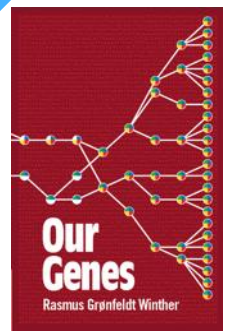




A metaphor: Clockwork, **Soup**, and Conscious Universes

To imagine a soup universe, consider a world filled with what looks like mist. We can neither measure nor assess this mist for its physical properties or chemical composition. But in it, we observe a swirling mass of sand that behaves erratically and unpredictably. It can become a perfectly shaped sphere of solid granite; at other times, it can irregularly morph into thousands of fist-sized cubes of crystals that emit sounds.

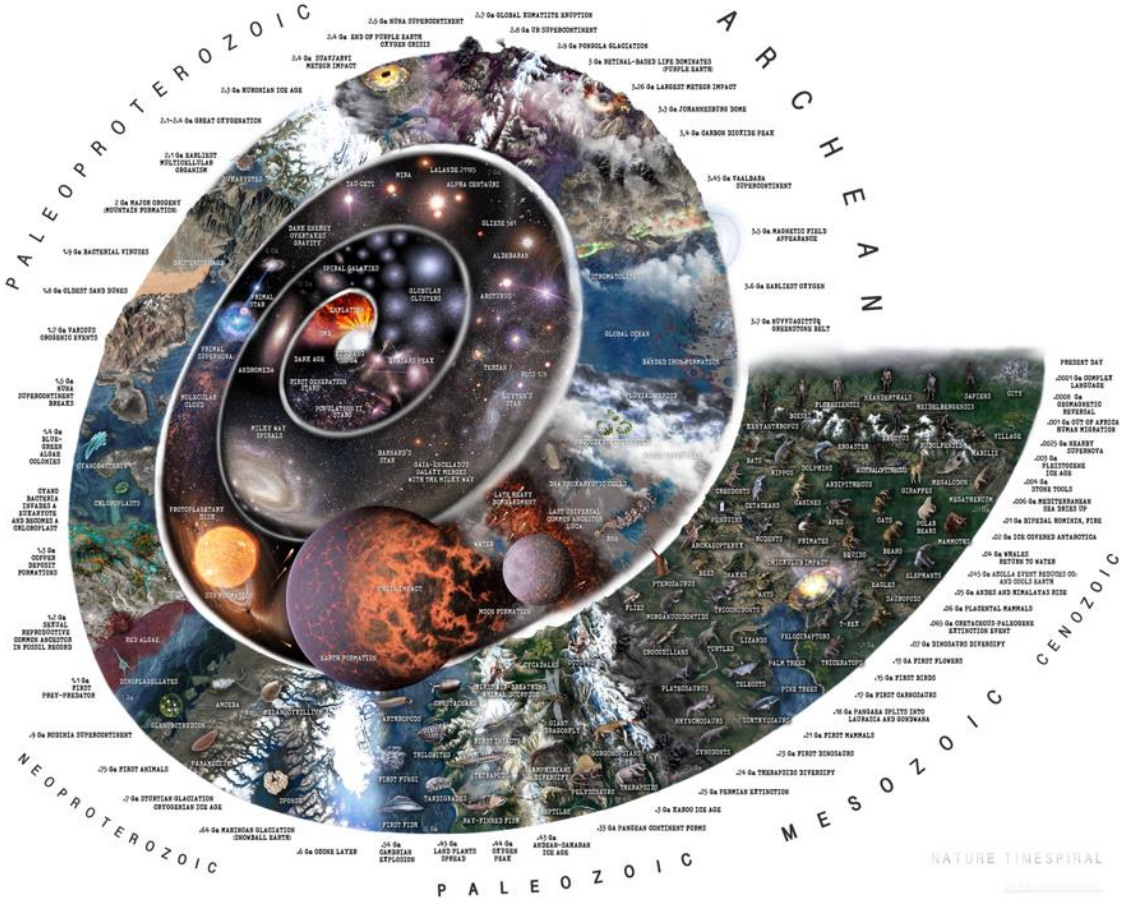
A soup universe is stochastic and chancy; disorderly; likely short-lived and unstable; so utterly complex that any instruments and measurement protocols attempting to measure it are useless; and unexplainable because regular and robust causes do not seem to exist.
(Winther, *Our Genes*, pp. 287–8)



A metaphor: Clockwork, Soup, and **Conscious** Universes

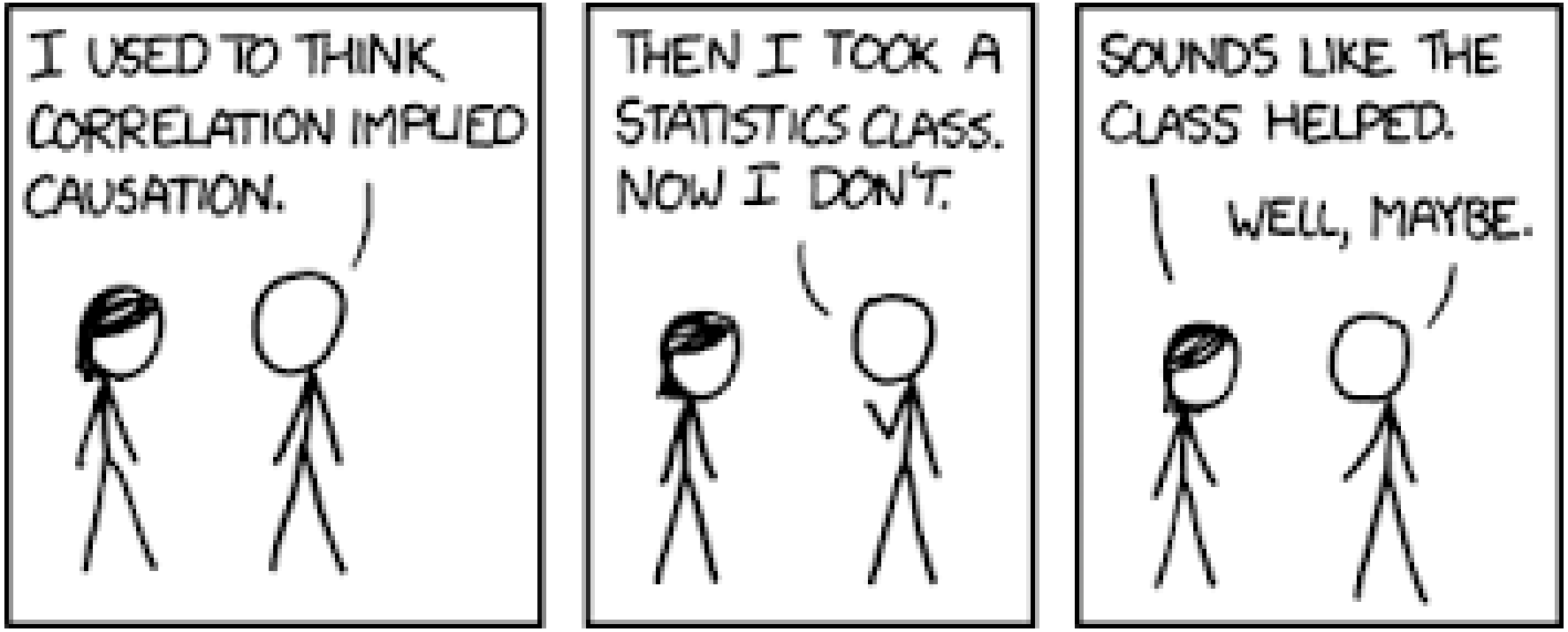
In contrast to clockwork and soup universes, a conscious universe is characterized by structure and incompletely acting laws and causes; emergent and fuzzy, yet stable, hierarchies; a (potential) long life; consciousness; complexity; and the possibility of interesting – yet incomplete and multiple – causal explanation.

In our conscious universe, however, in which both clockwork and soup elements operate, the GLM [General Linear Model] imposes elements of clockwork linear law onto soup-like chance to yield deep insights and far-reaching meanings.
(Winther, *Our Genes*, p. 294; pp. 301–2)

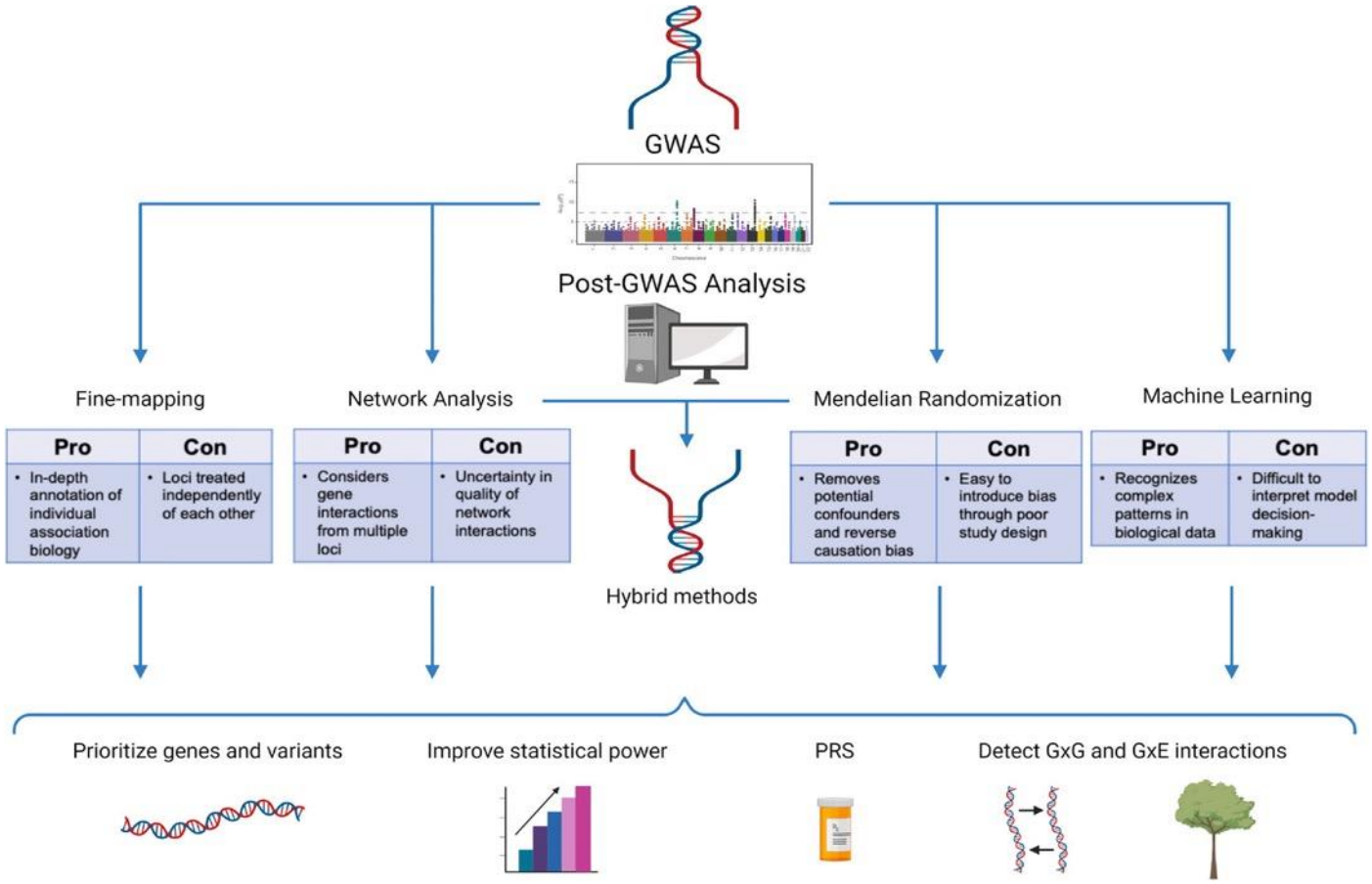


By: Pablo Carlos Budassi and Rasmus Grønfeldt Winther
https://pablocarlosbudassi.com/

Causal Analysis: XKCD

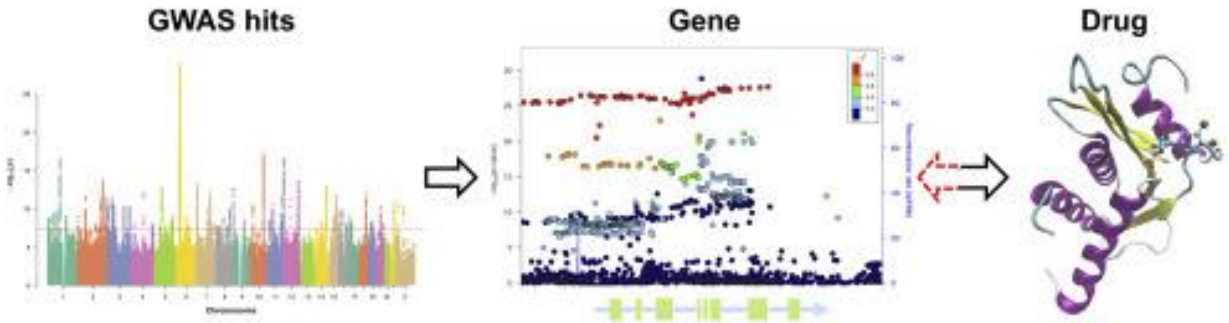


GWAS as a Solution to L74? I.



Olczak, et al. *Journal of Internal Medicine*, Volume: 290, Issue: 6, Pages: 1130-1152, First published: 24 June 2021, DOI: (10.1111/joim.13352)

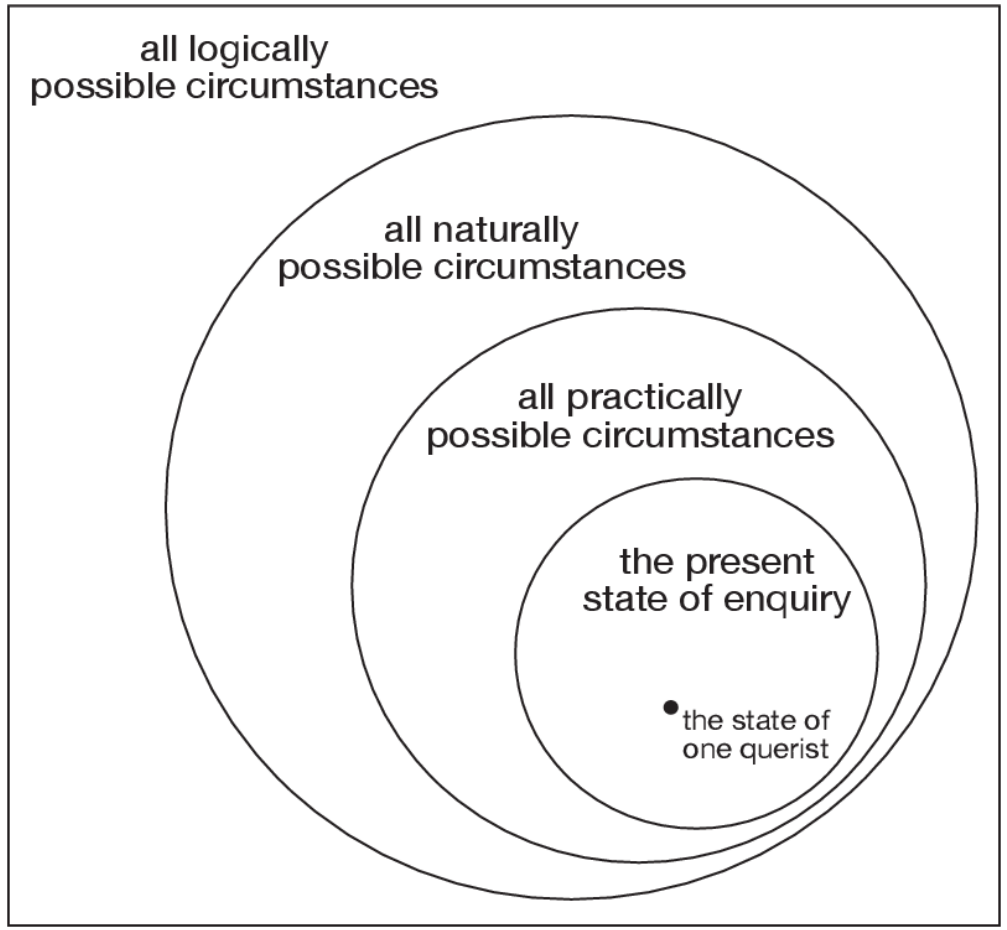
GWAS as a Solution to L74? II.



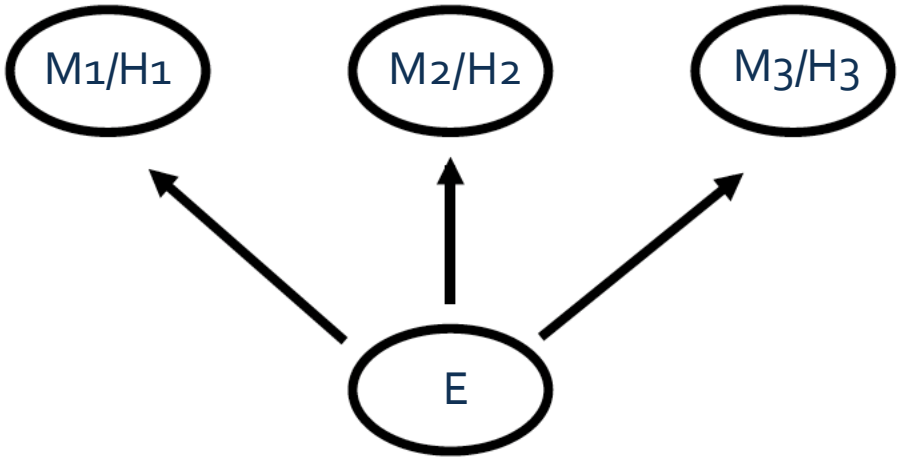
Trait	Gene with GWAS hits	Known or candidate drug
Type 2 Diabetes	*SLC30A8/KCNJ11*	ZnT-8 antagonists/Glyburide
Rheumatoid Arthritis	*PADI4/IL6R*	BB-Cl-amidine/Tocilizumab
Ankylosing Spondylitis(AS)	*TNFR1/PTGER4/TYK2*	TNF-inhibitors/NSAIDs/fostamatinib
Psoriasis(Ps)	*IL23A*	Risankizumab
Osteoporosis	*RANKL/ESR1*	Denosumab/Raloxifene and HRT
Schizophrenia	*DRD2*	Anti-psychotics
LDL cholesterol	*HMGCR*	Pravastatin
AS, Ps, Psoriatic Arthritis	*IL12B*	Ustekinumab

Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet*. 2017 Jul 6;101(1):5-22.

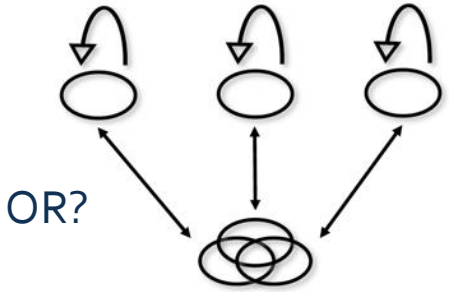
Causal Analysis? Philosophy I: Underdetermination of Theory by Evidence



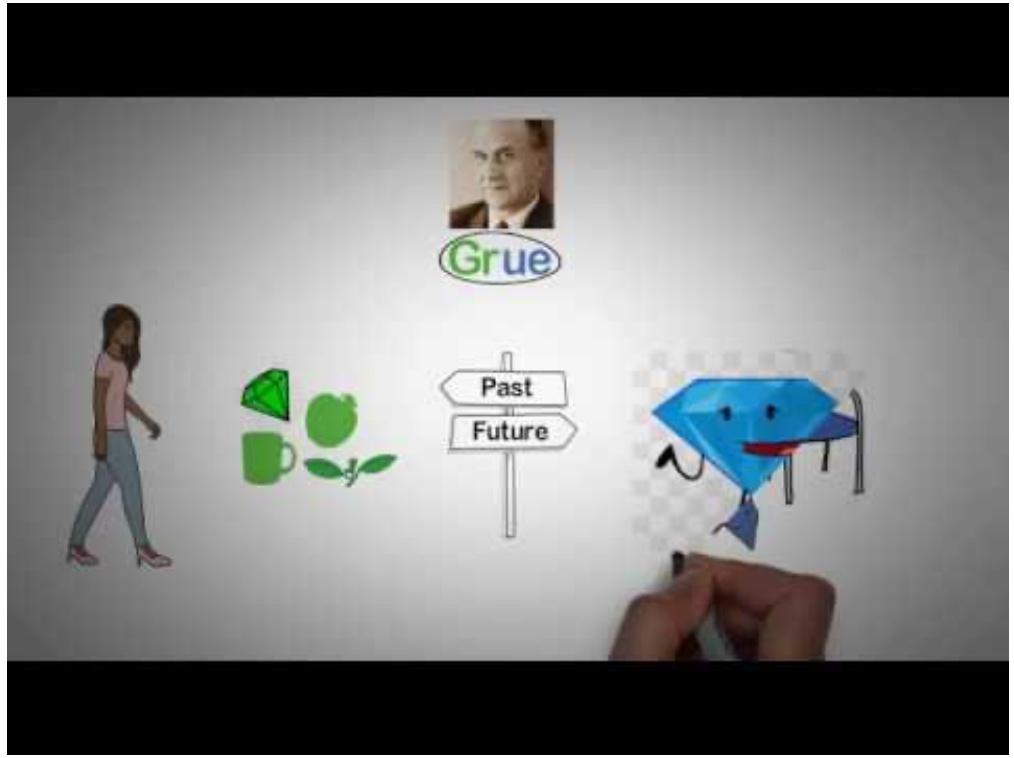
P.D. Magnus 2003. Underdetermination and the Claims of Science. PhD Thesis in Philosophy. UCSD



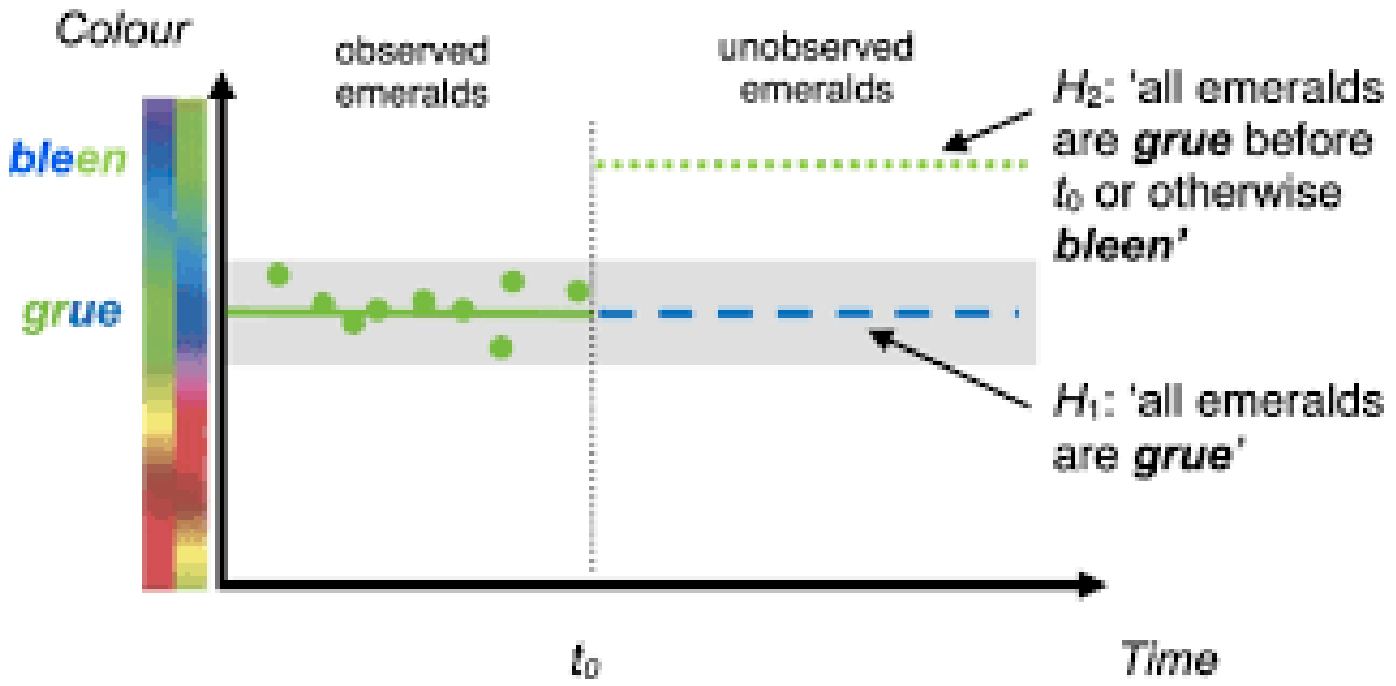
(Current; Total?)



Causal Analysis? Philosophy II: The Problem of Induction & Grue



https://www.youtube.com/watch?v=yMNqn6sdj0k



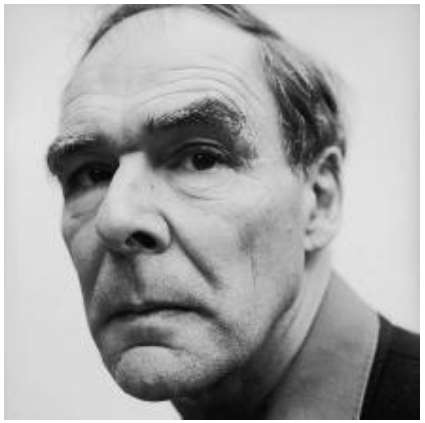
Kowalenko, R. The Putnam-Goodman-Kripke Paradox. *Acta Analytica* **37**, 575–594 (2022).

Causal Analysis? Philosophy III: Three Views

In the Mind

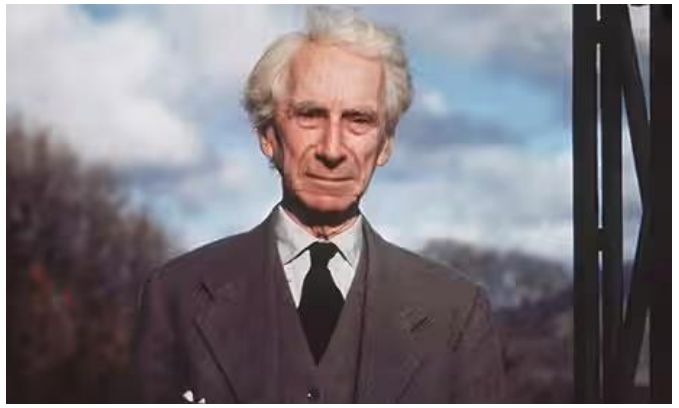
I. Kant

In the World



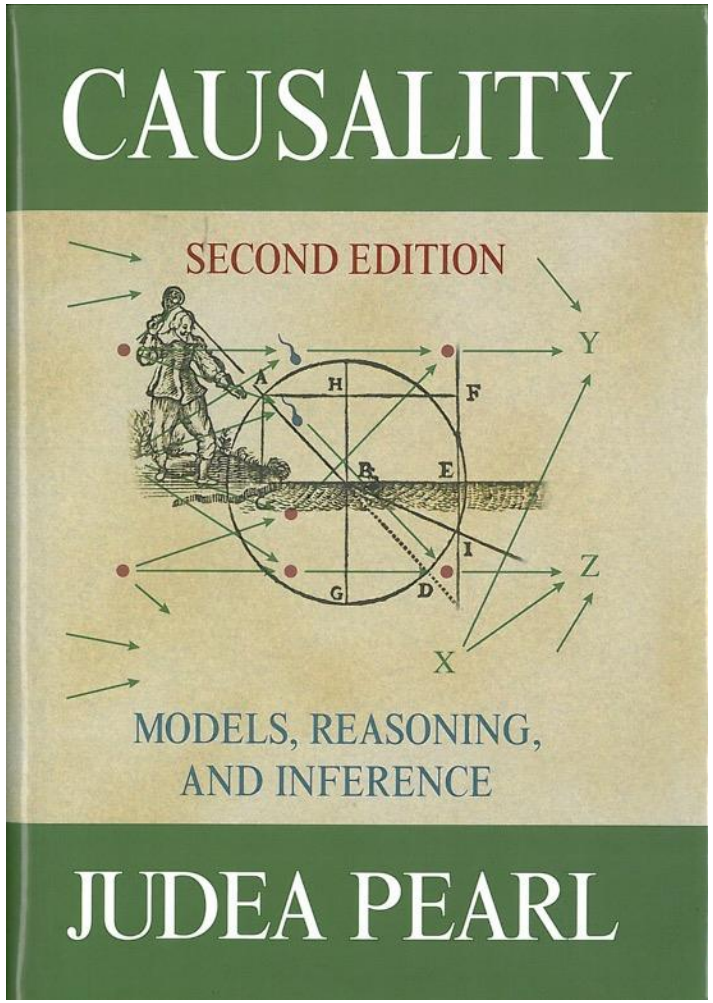
D. M. Armstrong

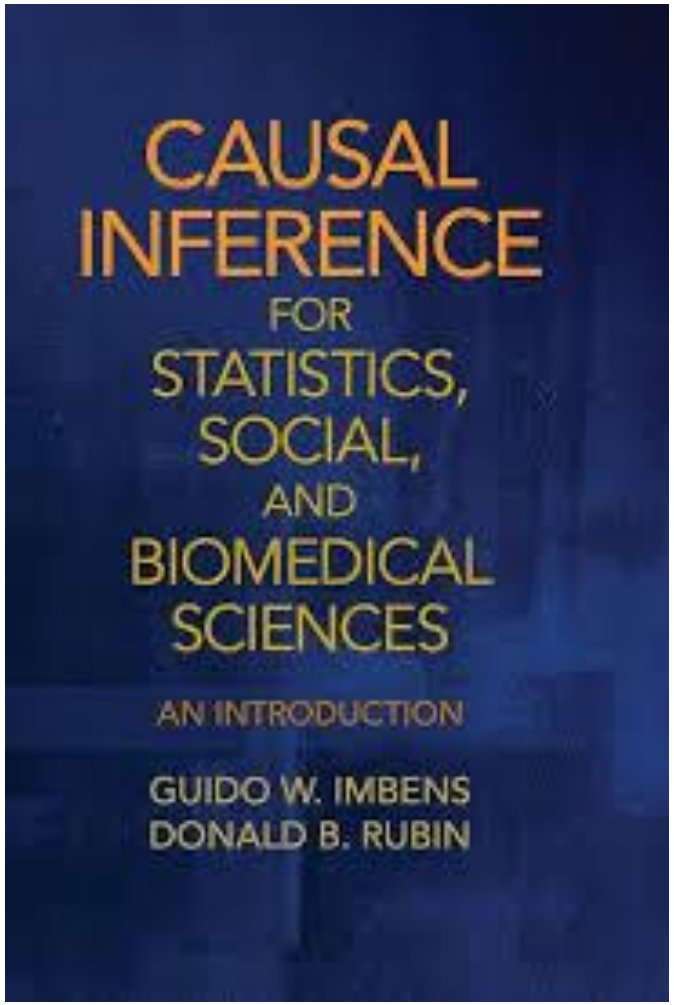
Skeptical Attitude

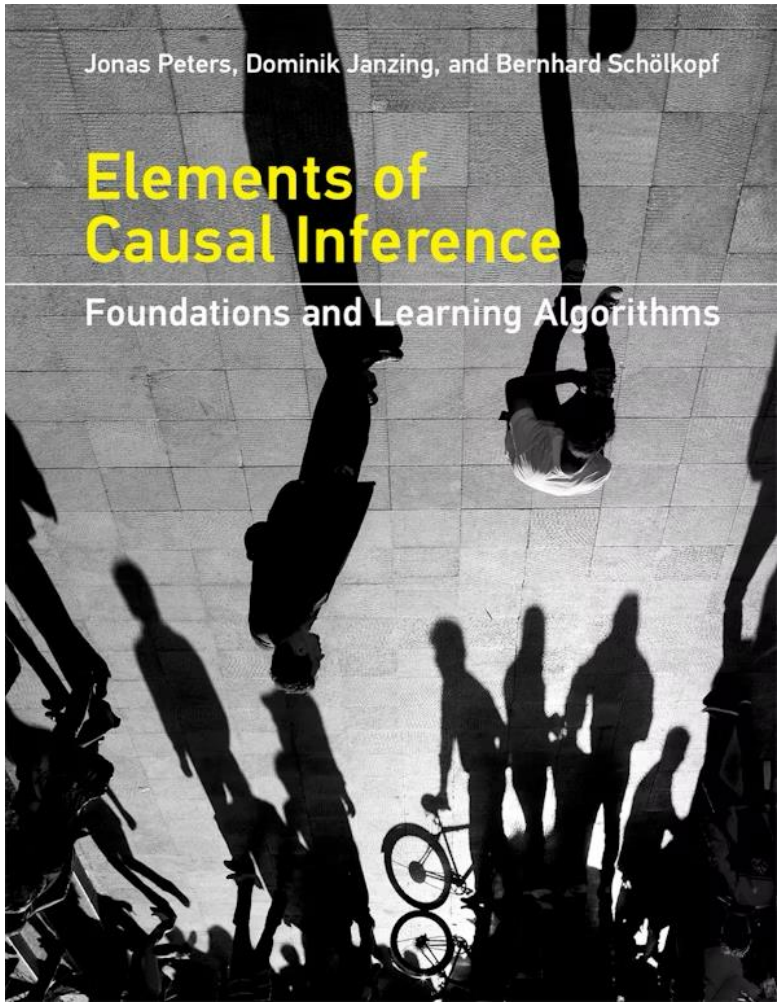


B. Russell

Causal Analysis? Statistics







Thank you

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Division of Genome Sciences

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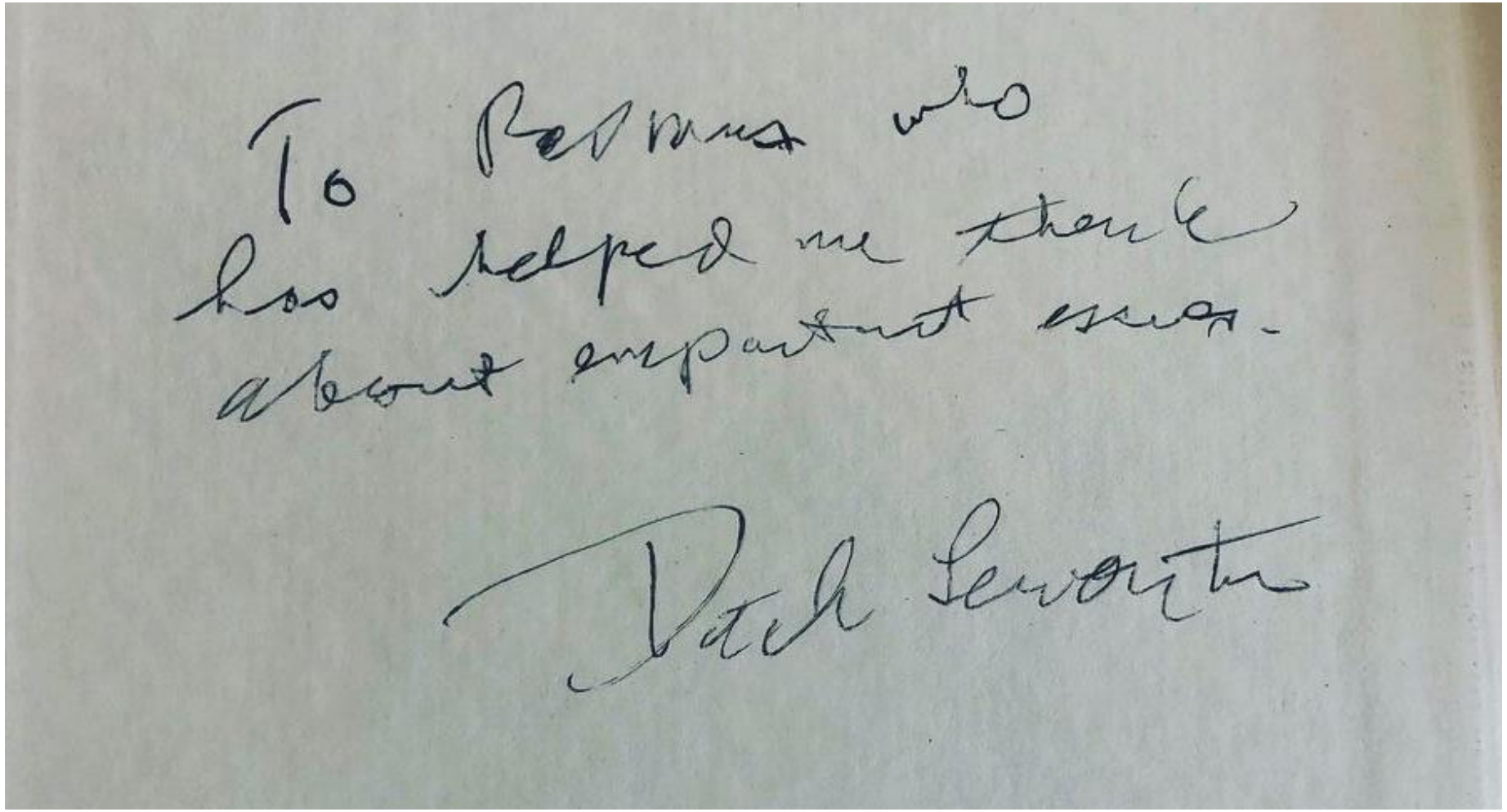
Thank you


To Barbara who
has helped me thank
about important issues.
Patch Lenworth