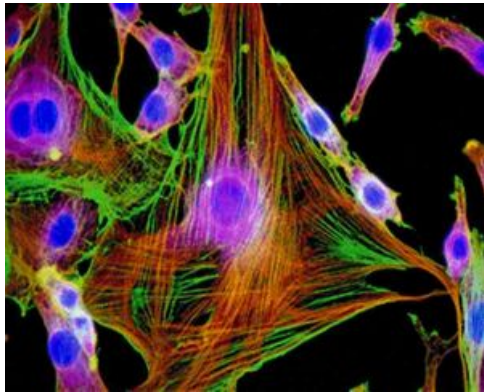


lecture 1

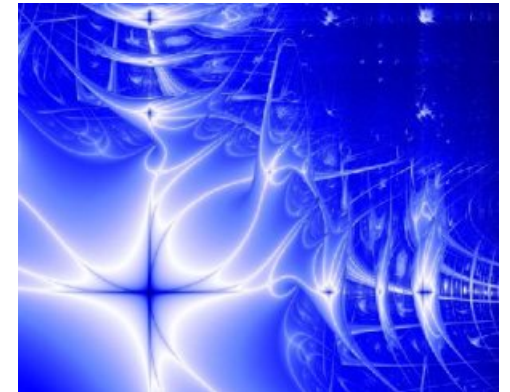
the role of mathematics in biology

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<http://vcp.med.harvard.edu/>



“A Systems Approach to Biology”, UBA Buenos Aires, 11-22 June 2018

0. what is systems biology?

the usual answers

“X-omics”

it is about using high-throughput technologies to acquire data on all X molecules and using computational algorithms to infer causality from correlation

“modelling”

it is about constructing mathematical models of biological systems so that biology becomes a predictive science like physics and engineering

but what are the questions

to which “omics” and “modelling” seek the answers?

systems biology

how do we get from dead molecules to living organisms?

how do the collective interactions of molecular components give rise to the phenotype of the organism?

1. the role of mathematics in biology has been a source of confusion

what the biologists say

Chapter 5 - Diseases of the Will

*Contemplators. Bibliophiles and Polyglots.
Instrument addicts. Misfits. Theorists.*

Santiago Ramon y Cajal,
Advice for a Young Investigator,
MIT Press, 1999 (first published 1897)

"If ... you are a bit short in mathematical training, even very short, relax. You are far from alone ... many of the most successful scientists in the world today are mathematically no more than semiliterate."

Edward Wilson
Letters to a Young Scientist
W W Norton, 2013

"I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics ... for men thus endowed seem to have an extra sense."

Charles Darwin, **Autobiography**
W W Norton, 1958 (written in 1876)

what the mathematicians say

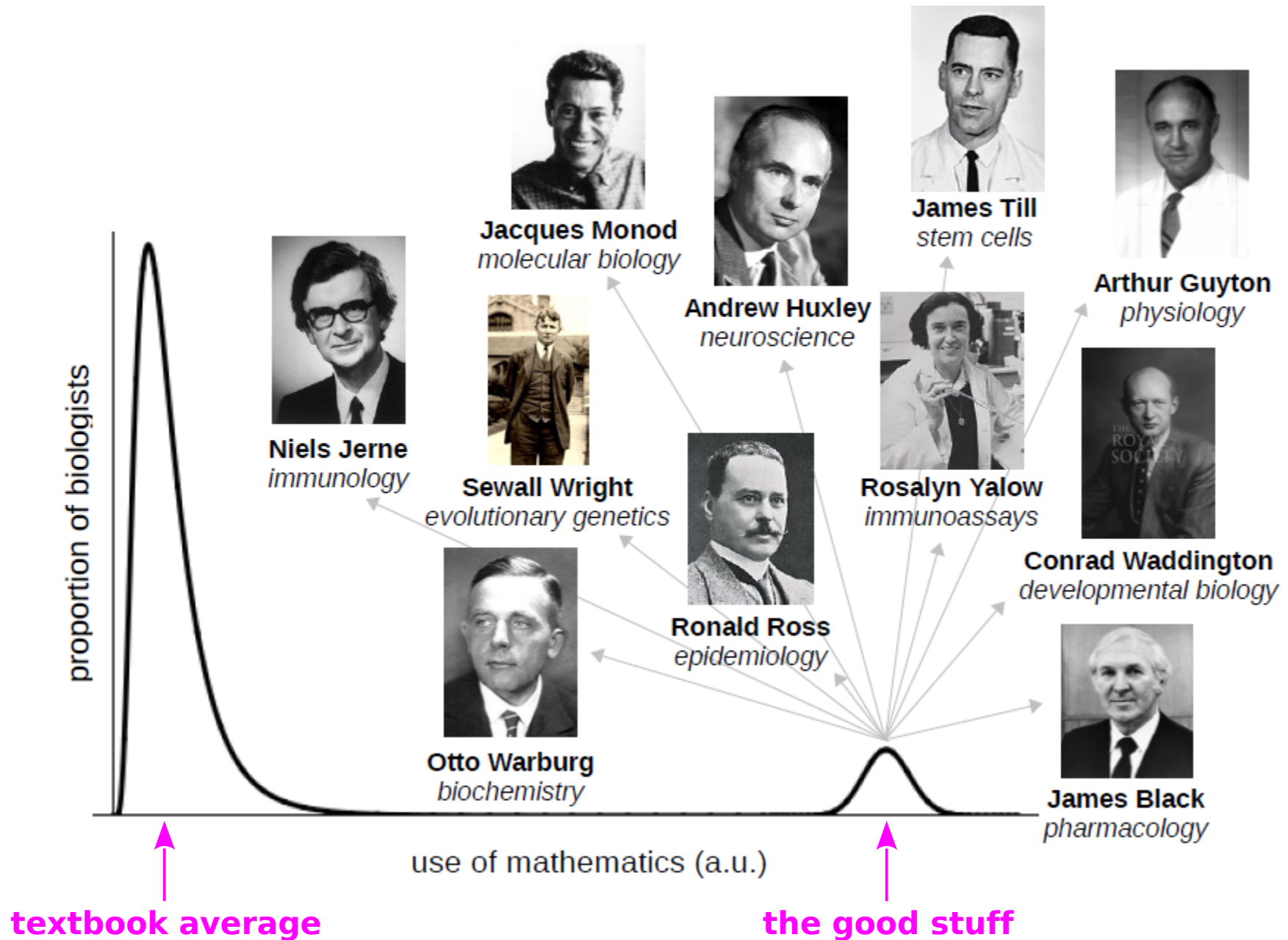
“Eugene Wigner wrote a famous essay on the unreasonable effectiveness of mathematics in natural sciences. He meant physics, of course. There is only one thing which is more unreasonable than the unreasonable effectiveness of mathematics in physics, and this is the unreasonable ineffectiveness of mathematics in biology.”

Israel Gelfand, as quoted in Alexandre Borovik, **Mathematics Under the Microscope: Notes on Cognitive Aspects of Mathematical Practice**, online version, 3 January 2007.

“The lack of real contact between mathematics and biology is either a tragedy, a scandal, or a challenge, it is hard to decide which.”

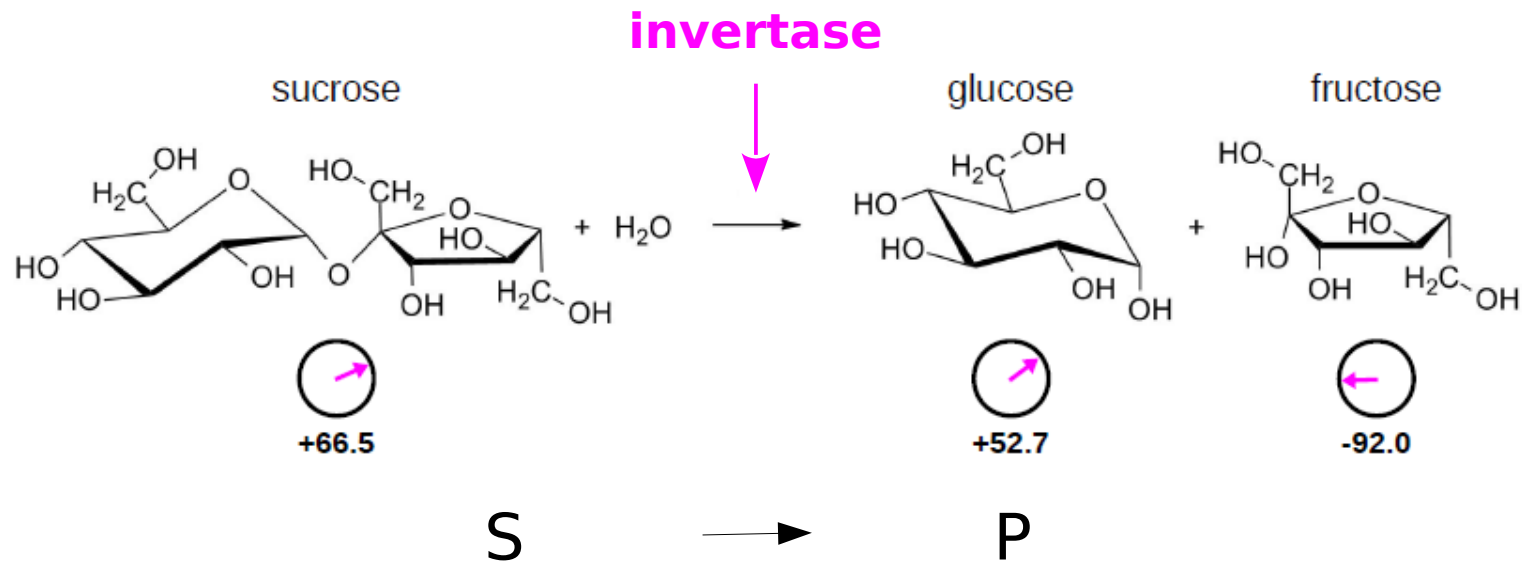
Marc Kac, Gian-Carlo-Rota & Jacob Schwartz, **Discrete Thoughts: Essays on Mathematics, Science and Philosophy**, Birkhauser, 1993

a revisionist view



2. learning from an example

the michaelis-menten formula



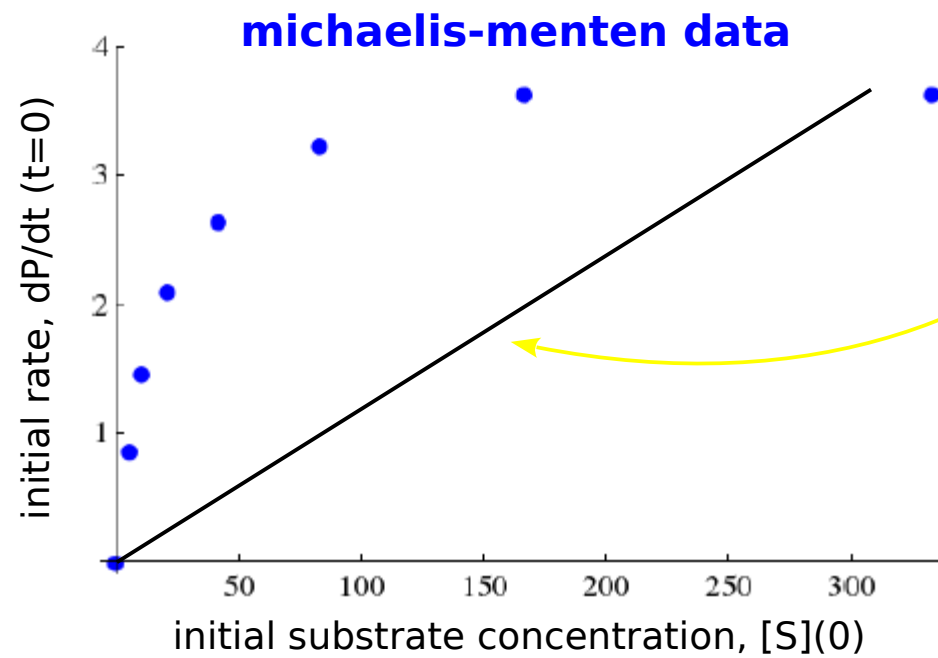
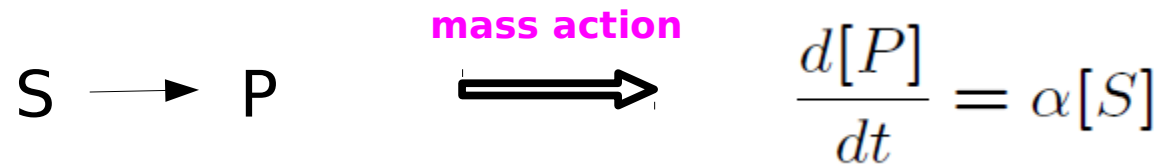
$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

Michaelis & Menten, "Die kinetik der Invertinwirkung", *Biochem Z*, **49**:333-69, 1913

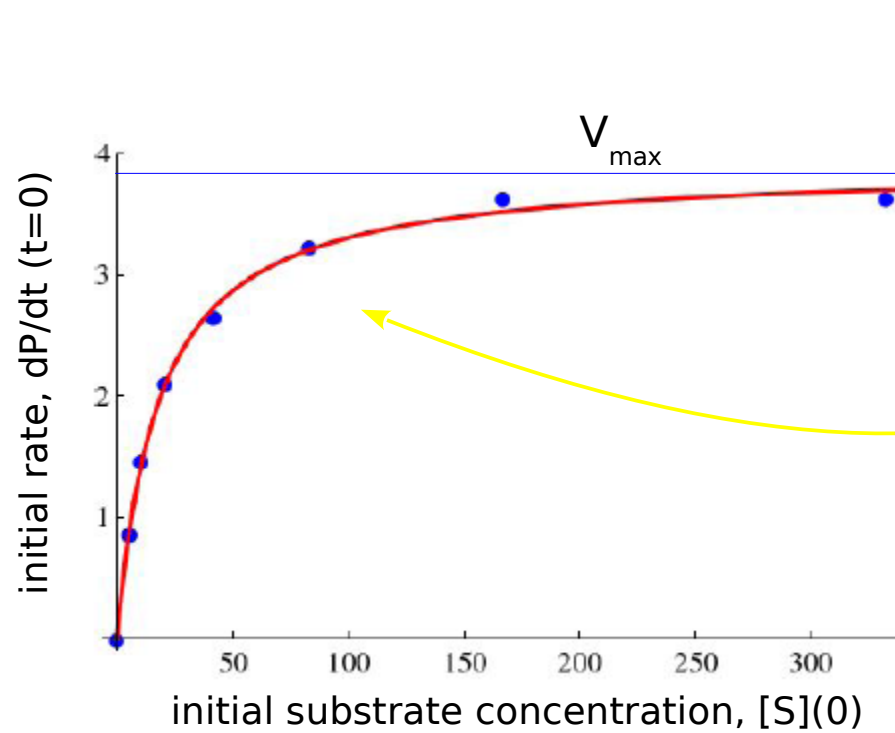
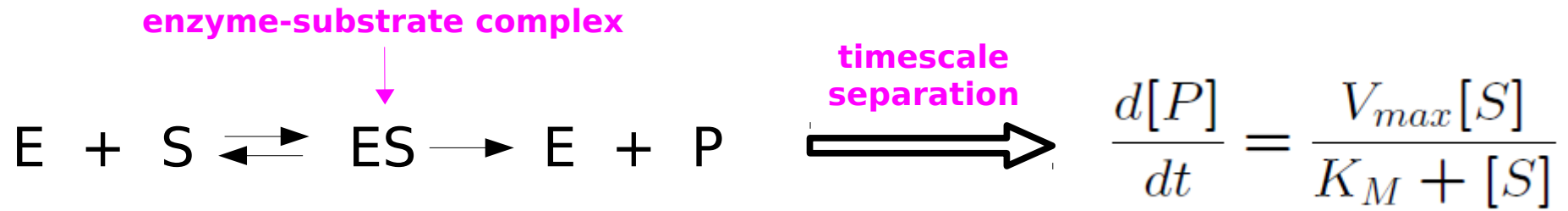
Johnson & Goody, "The original Michaelis constant: translation of the 1913 Michaelis-Menten paper", *Biochemistry*, **50**:8264-9 2011



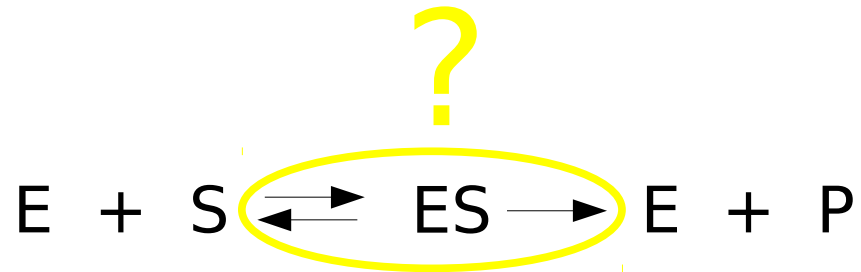
data do not support direct conversion



the enzyme-substrate complex



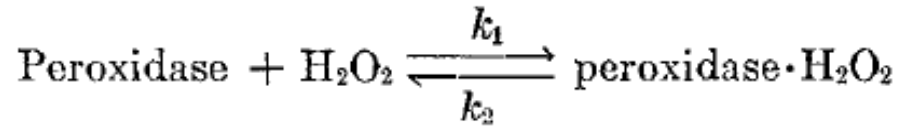
a theoretical entity



michaelis and menten did not identify the enzyme-substrate complex.

it was a hypothetical concept which, if it existed, could explain a great deal of experimental data (with the help of mathematics).

which remained theoretical for 30 years



“The reaction velocity constants are, however, lumped into one term, the Michaelis constant, and are not separately determined. It is the purpose of this research to determine these constants separately, and to show whether the Michaelis theory is an adequate explanation of enzyme mechanism. Moreover, studies on the over-all enzyme activity do not permit a determination of whether the enzyme-substrate compound exists in fact and, if it exists, whether such a compound is responsible for the enzyme activity”



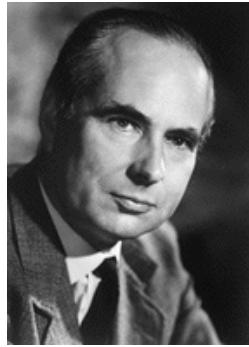
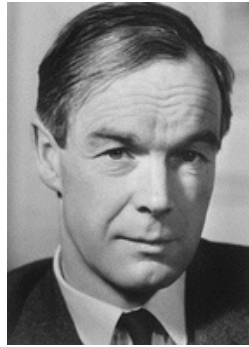
1913-2010

$$k_1 = 1.2 \times 10^7 \text{ M}^{-1} \text{ sec}^{-1} \quad k_2 = 0.2 \text{ sec}^{-1}$$

B Chance, *“The kinetics of the enzyme-substrate compound of peroxidase”*, J Biol Chem, **151**:553-77 1943

mathematics provides evidence for things unseen

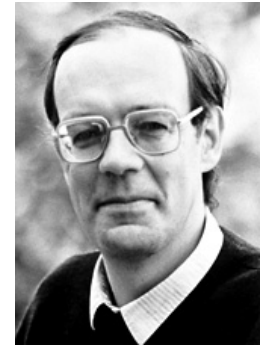
“ion channels”



1952

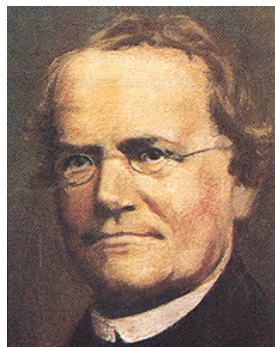


1970

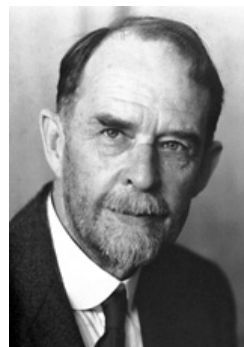


1976

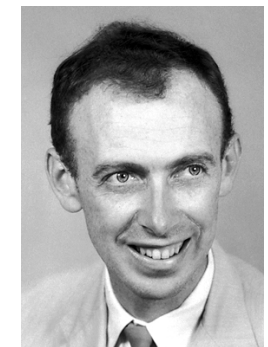
“genes”



1866



1915



1953

Biology is more theoretical than physics

Jeremy Gunawardena

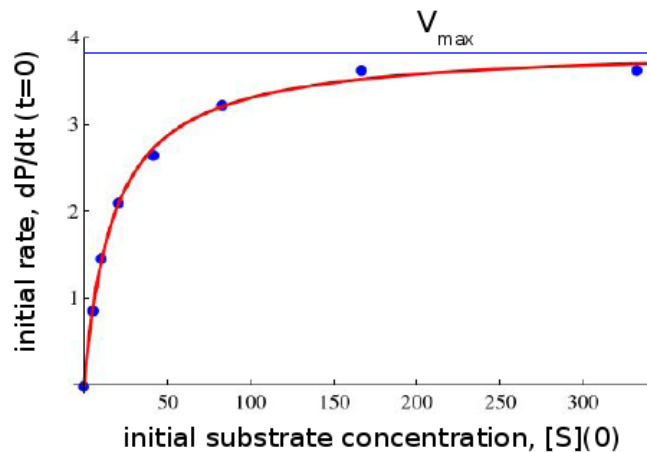
Department of Systems Biology, Harvard Medical School, Boston, MA 02115

ABSTRACT The word “theory” is used in at least two senses—to denote a body of widely accepted laws or principles, as in “Darwinian theory” or “quantum theory,” and to suggest a speculative hypothesis, often relying on mathematical analysis, that has not been experimentally confirmed. It is often said that there is no place for the second kind of theory in biology and that biology is not theoretical but based on interpretation of data. Here, ideas from a previous essay are expanded upon to suggest, to the contrary, that the second kind of theory has always played a critical role and that biology, therefore, is a good deal more theoretical than physics.

Mol Biol Cell, **24**:1827-9, 2013

models are not descriptions of reality

michaelis & menten's data was so convincing because they used an acetate buffer to control pH (*)



but ... there is no pH dependence in their mathematical model

$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

~~pH~~

(*) L Michaelis, **Die Wasserstoffionen-Konzentration: Ihre Bedeutung Fur Die Biologie Und Die Methoden Ihrer Messung.** 1914.

they describe our assumptions about reality

REVIEW

Models in biology: 'accurate descriptions of our pathetic thinking'

Jeremy Gunawardena

Gunawardena *BMC Biology* 2014, 12:29

<http://www.biomedcentral.com/1741-7007/12/29>



"Models in (systems biology) are not meant to be descriptions, pathetic descriptions of nature; they are designed to be accurate descriptions of our pathetic thinking about nature."



1924-2010

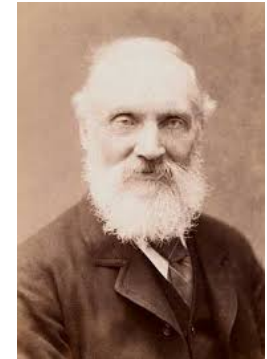
James Black, *"Drugs from emasculated hormones: the principles of syntopic antagonism"*, Nobel Lecture, 1988

Rob Phillips, *"Theory in biology: Figure 1 or Figure 7"*, *TICB* **25**:723-9 2015.

the dark side of the model

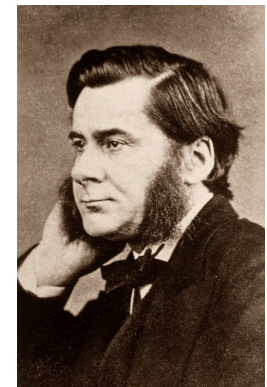
the most serious objection to darwin's theory of natural selection came from physics

in 1863 william thomson calculated that the age of the earth was no more than 100,000,000 years.



1824-1907

"I desire to point out that this seems to be one of the many cases in which the admitted accuracy of mathematical processes is allowed to throw a wholly inadmissible appearance of authority over the results obtained by them. Mathematics may be compared to a mill of exquisite workmanship, which grinds you stuff of any degree of fineness; but, nevertheless, what you get out depends on what you put in".



1825-1895

Thomson, *"On the secular cooling of the Earth"*, Phil Mag **25** :1-14 1863

Huxley, *"Geological reform"*, Q J Geol Soc Lond **25**:38-53 1869

Scott Gilbert, *"Achilles and the tortoise: some caveats to mathematical modeling in biology"*, Prog Biophys Mol Biol doi: 10.1016/j.pbiomolbio.2018.01.005

in summary

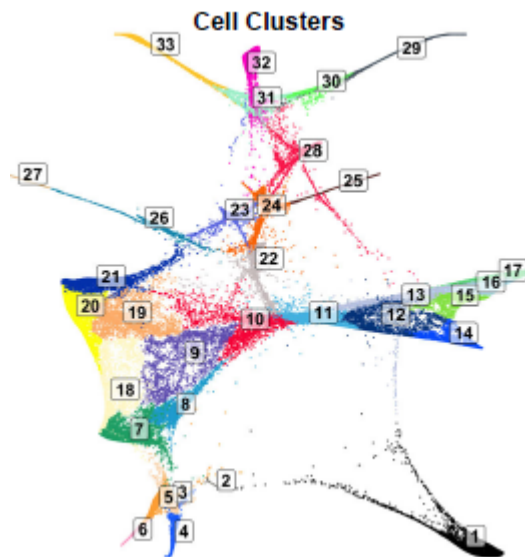
1. models can provide evidence for things unseen
2. biology is more theoretical than physics
3. models describe our pathetic assumptions, not reality
4. models can make good tools but they are bad masters

"The guiding motto in the life of every natural philosopher should be, "Seek simplicity and distrust it."

3. mathematics in modern biology

a taxonomy of models

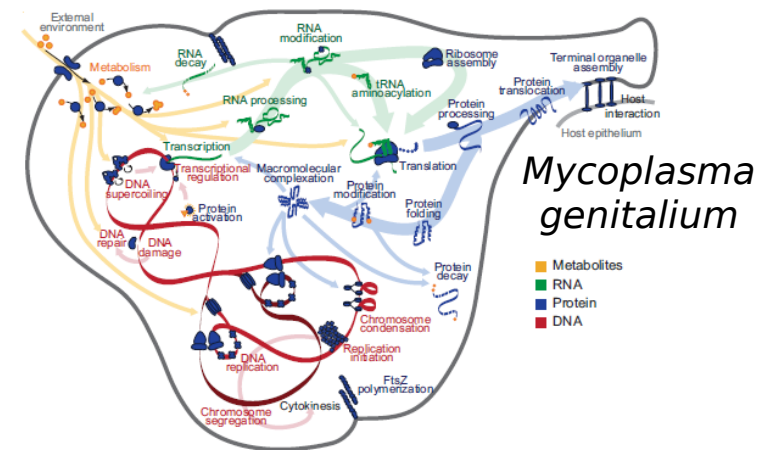
REVERSE MODELS
starting from data



Schiebinger et al, bioRxiv,
<https://doi.org/10.1101/191056>

FORWARD MODELS
starting from mechanism

THICK MODELS
"all" the details

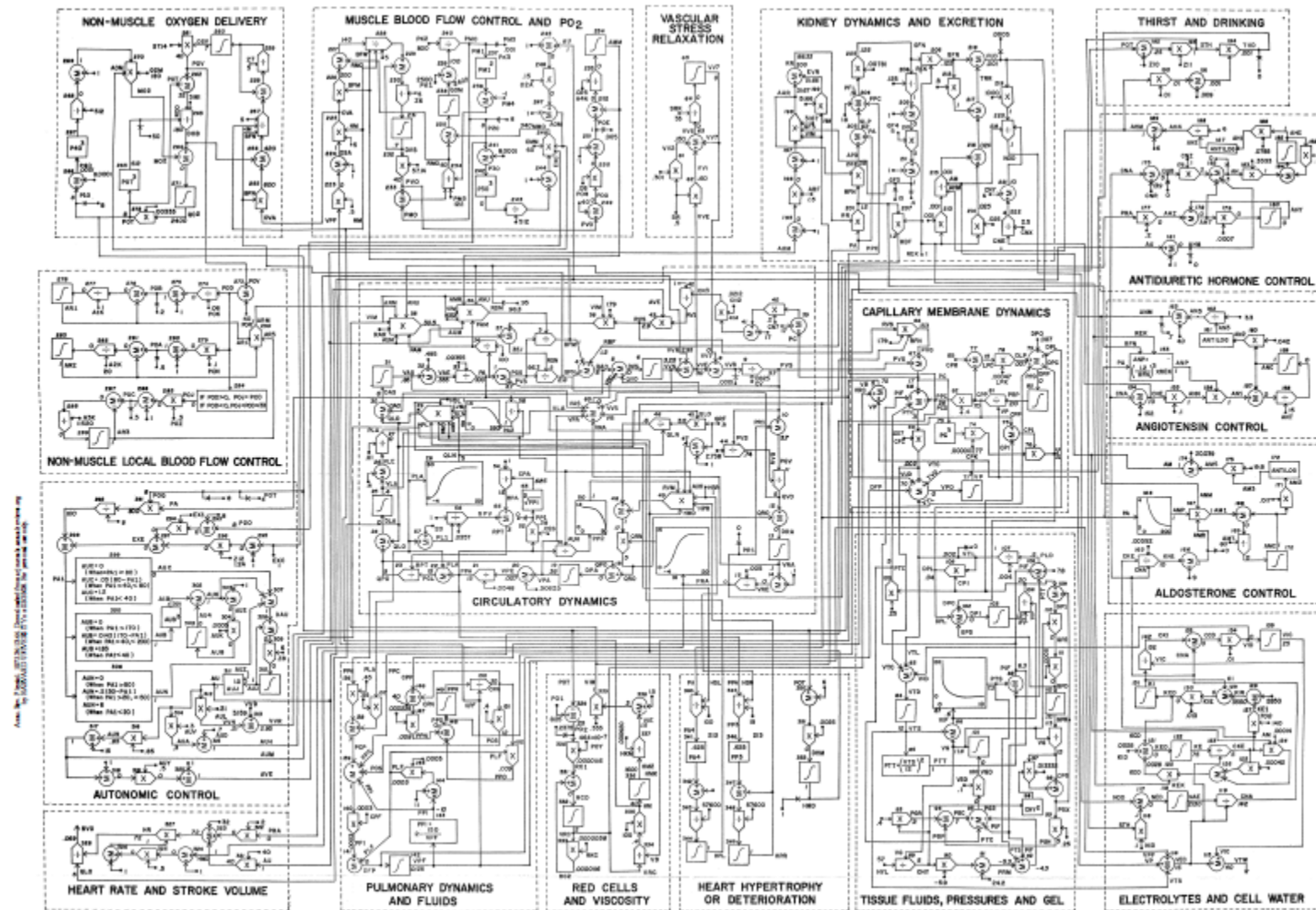


Covert et al, Cell **150**:389-401 2012

THIN MODELS
answering a question

$$\frac{d[P]}{dt} = \frac{V_{max}[S]}{K_M + [S]}$$

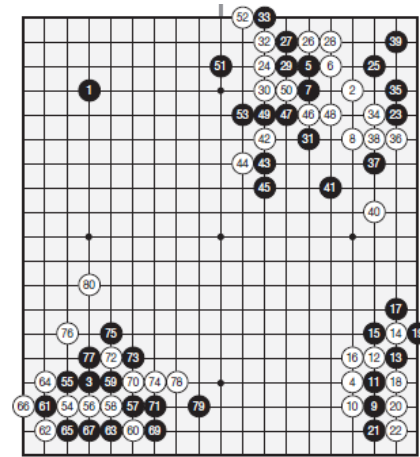
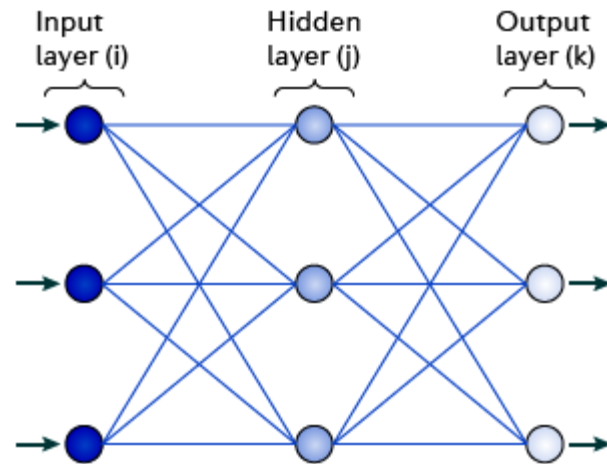
guyton's thick model for blood pressure regulation



Guyton, Coleman, Granger, "Circulation: overall regulation", Annu Rev Physiol **34**:13-44 1972

the rise of the machines

deep learning in artificial neural networks (ANNs) – a paradigm change



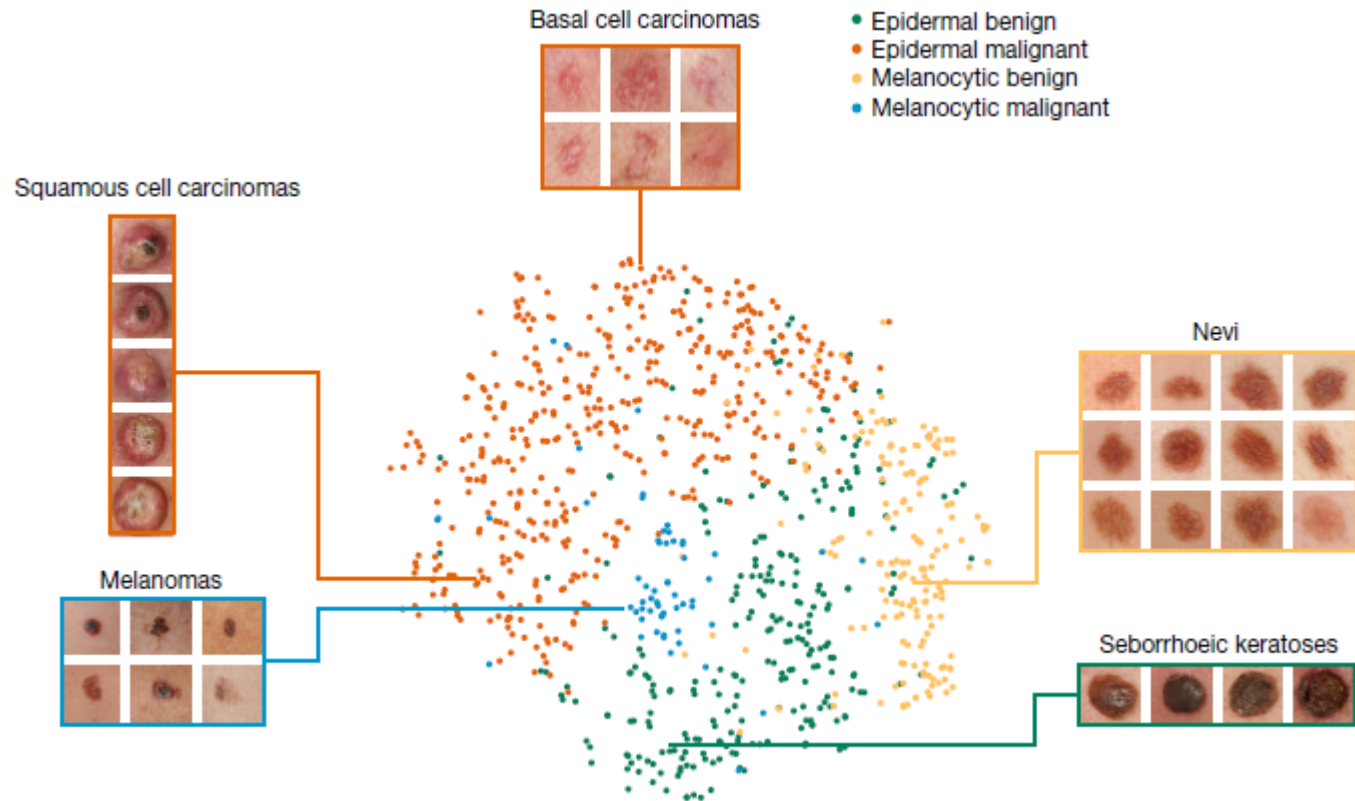
“Humankind has accumulated Go knowledge from millions of games played over thousands of years, collectively distilled into patterns, proverbs and books. In the space of a few days, starting tabula rasa, AlphaGoZero was able to rediscover much of this Go knowledge, as well as novel strategies that provide new insights into the oldest of games.”

Silver et al, “*Mastering the game of Go without human knowledge*”, Nature **550**:354-9 2017

LeCun, Bengio, Hinton, “*Deep learning*”, Nature **521**:436-44 2015

<https://www.tensorflow.org/>

ANNs are reverse models



“The CNN achieves performance on par with all tested experts across both tasks, demonstrating an artificial intelligence capable of classifying skin cancer with a level of competence comparable to dermatologists.”

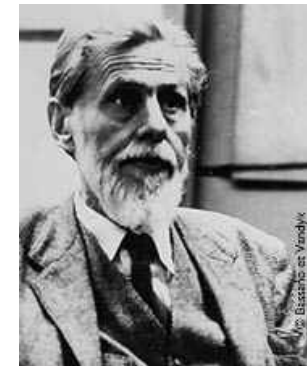
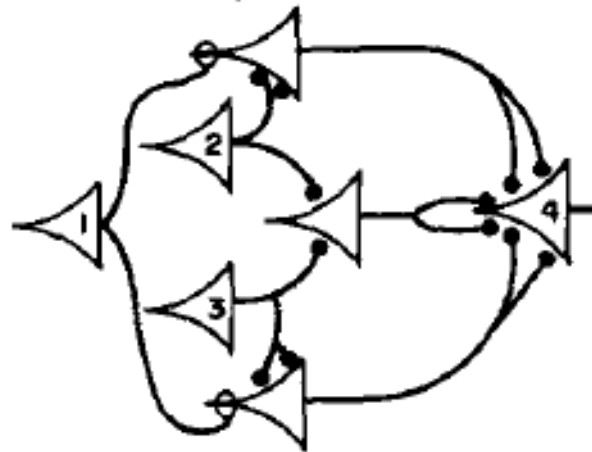
convolutional neural network

Esteva, Kuprel, Novoa, Ko, Swetter, Blau, Thrun, “Dermatologist-level classification of skin cancer with deep neural networks”, Nature **542**:115-8 2017

ANNs are forward models

A LOGICAL CALCULUS OF THE IDEAS IMMANENT IN NERVOUS ACTIVITY*

■ WARREN S. McCULLOCH AND WALTER PITTS



1898-1969



1923-1969

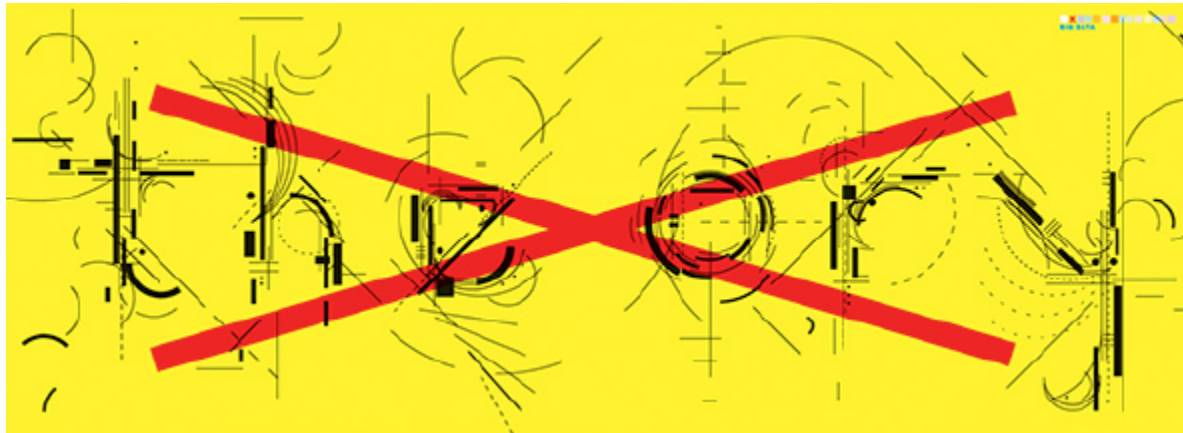
McCulloch & Pitts, Bull Math Biophys **5**:115-33 1943

Frank Rosenblatt, *"The perceptron: a probabilistic model for information storage and organization in the brain"*, Psychol Rev **65**:386-408 1958

fake news of World Domination

The End of Theory: The Data Deluge Makes the Scientific Method Obsolete

By Chris Anderson 06.23.08

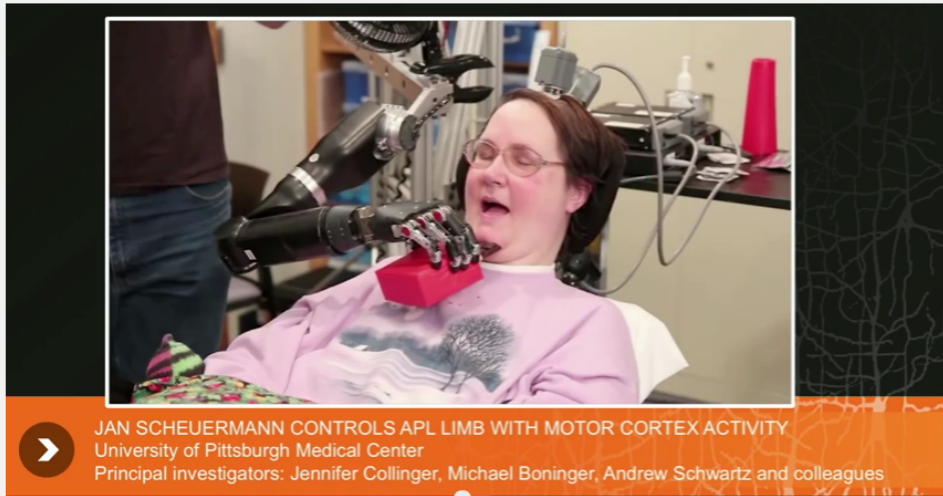


Wired Magazine, 16.07.

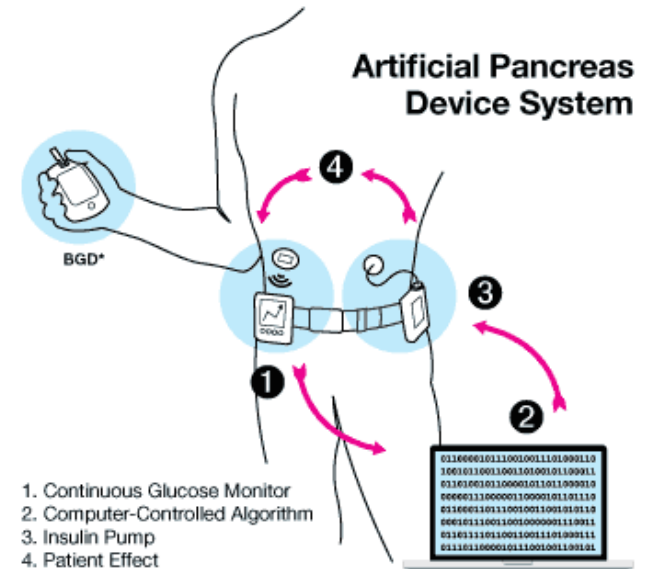
4. challenges for the future

progress

neuroscience



physiology



Collinger et al “*High-performance neuroprosthetic control by an individual with tetraplegia*”, *Lancet* **381**:557-64 2013; <https://www.youtube.com/watch?v=WV0bjkk86pw>

FDA, “*Premarket Approval Applications for Artificial Pancreas Device Systems*”, US DHHS Guidance for Industry document issued 9 Nov 2012.

levels of representation

the brain should be understood as a hierarchy of three levels of understanding

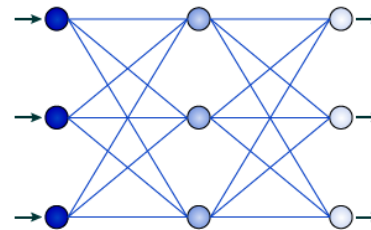
- computational behaviour, learning

$$Q^*(s,a) = \max_{\pi} \mathbb{E}[r_t + \gamma r_{t+1} + \gamma^2 r_{t+2} + \dots | s_t = s, a_t = a, \pi],$$



1945-1980

- algorithmic neural network



- implementation neuron, spikes



$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

Marr, **Vision**, W H Freeman, 1982; Reichardt, Poggio, Quart Rev Biophys **3**:311-75 1976.

Willshaw, Dayan, Morris, Phil Trans Roy Soc B **370**: 20140383 2015

what are the levels of representation in systems biology?