

Maths justifies Metaphysics in Biology

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Is Metaphysics not Science?

Dawkins: “I am not a philosopher.” (1976, at Holywell Manor, Oxford, repeated many times since)

Coyne: “The Illusion of Agency is so powerful....we have no choice in this matter....” (2014)

Watson: “I do not like to suffer at all from what I call the German disease, an interest in philosophy.”

Yanai & Lercher: “A hypothesis is a liability” (*Genome Biology*, 2020)

Futuyma & KirkPatrick: “The concept of purpose plays no part in scientific explanation.” (*Evolution*, 2018)

Wolpert: “The limits of reductionism are only a reflection of our ignorance.” (*The limits of Reductionism*, 1998)

Leading to focus on measuring association scores and **ignoring or misinterpreting causation in genomics**
(causation is a metaphysical idea)

SHOCKING OUTCOME: “Polygenic risk scores performed poorly in population screening, individual risk prediction, and population risk stratification. Strong claims about the effect of polygenic risk scores on healthcare seem to be dis-proportionate to their performance.” (Hingorani et al., 2023)

CONCLUSION: theories of causation are necessary. Science is not just association scores!

That automatically involves metaphysical parameters in the mathematics.

1. Lessons from imaginary numbers

1960

Research Student at University College London

1960 Experience as a research student at UCL

Repolarisation threshold in heart muscle cells

Problem: Hodgkin-Huxley theory predicts such a threshold

Silvio Weidmann (1951) observed it in Purkinje fibres from the heart

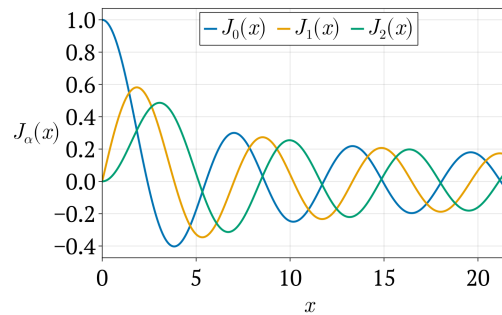
My 1960/62 model predicts it. Necessarily so.

But Johnson and Tille (1961) showed that it is absent using point polarisation of a block of ventricular tissue

Point polarisation of a 2D or 3D structure requires Bessel functions

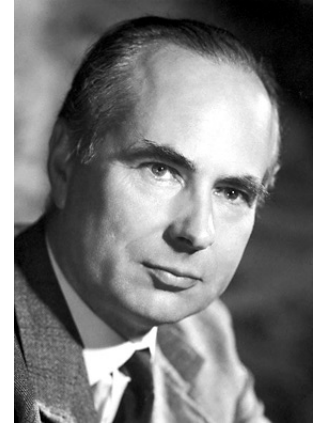
So, I tried Bessel functions in my Mercury computer program

All I got was unwanted oscillations!!!



Plot of Bessel function of the first kind, for integer orders
(From Wikipedia).

Consultation with the great **ANDREW HUXLEY**



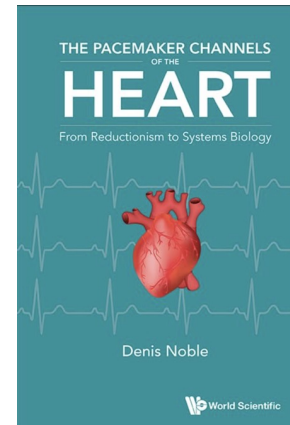
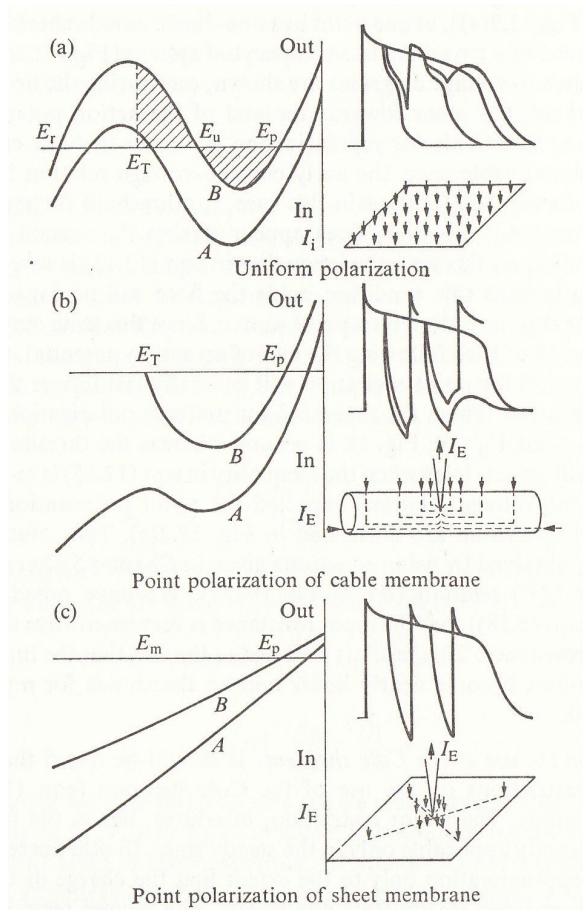
Frustrated, I showed my results to Andrew Huxley
who had become the chair of Physiology at UCL.
“Denis, you need a Bessel Function of an imaginary argument!”

“IMAGINARY!!?”

Imaginary worked!!

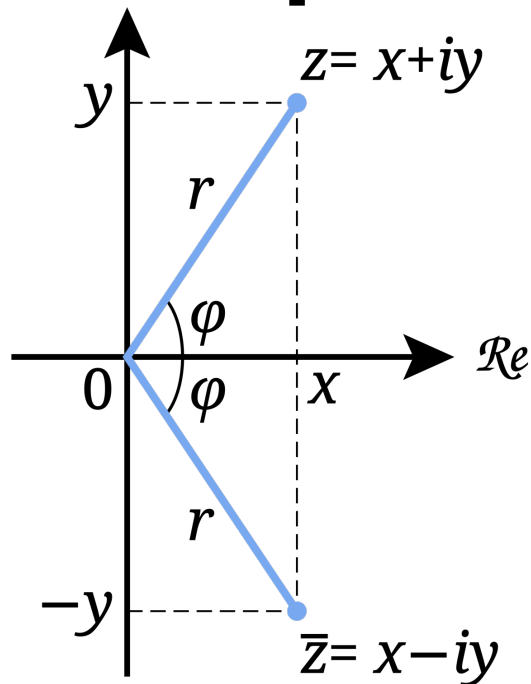
Originally from
Electric Current Flow in Excitable Cells
(Jack, Noble & Tsien, 1975)

Reproduced in
The Pacemaker Channels of the Heart
Noble 2025 (just published)



BUT WHY?

The square root of -1 does not exist!!



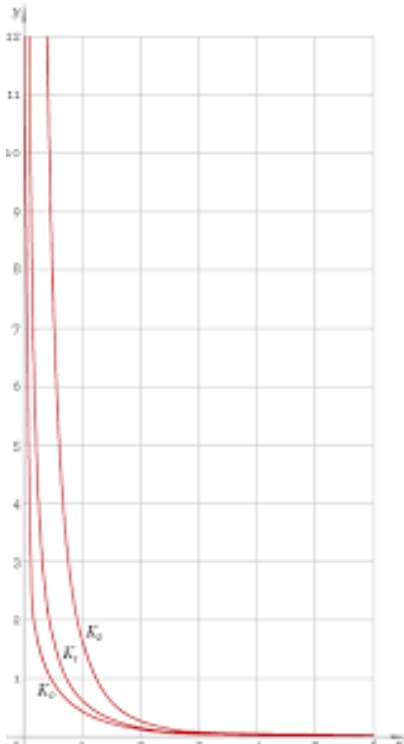
But it can be represented
as orthogonal to ordinary numbers
in a 2 dimensional plane

No-one has ever seen an imaginary number of apples!

Yet the concept is of widespread utility in mathematics

As shown by Euler, Cauchy and Gauss

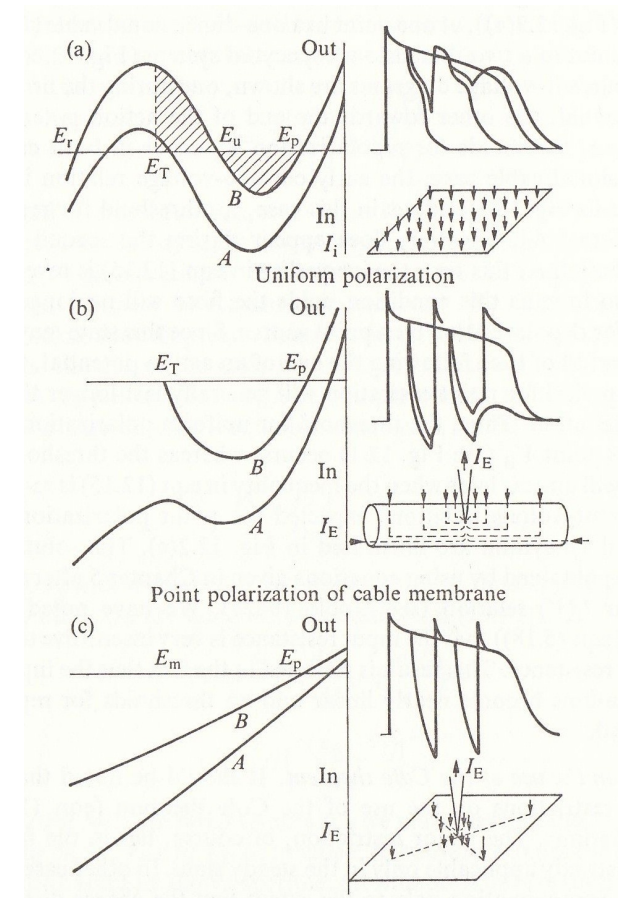
Decay in 2D and 3D



Point excitation of 2D sheets or 3D tissues shows decay from excitation point **very much steeper** than exponential.

Could this hide the non-linearities in membrane excitation properties?

Yes. Even in 2D the result is almost complete linearisation. 3D would be even worse



2. Lessons from the Gene-centric Impasse

The failure of genomics to lead to the promised cures for common complex diseases depends on total reliance on association scores

The metaphysical problem here is that association scores **do not reliably identify causation**

Because causation is a metaphysical concept that requires a hypothesis that can be modelled to identify causation

Is a hypothesis a liability in science?

Yanai & Lercher. 2020. A Hypothesis is a Liability. *Genome Biology* 21, 231

Derived from the ultra-radical view that science should focus only on what it can measure: association between one observation and another

Genomics is the ultimate outcome of this view.
Does it work?

Only when one factor (gene) is a sole and sufficient cause of a phenotype: Monogenetic diseases

They affect only 5% of the human population

The Gene-Centric Impasse

The common diseases affecting 95% of humans are strongly polygenic

Schizophrenia: 160 gene association scores

(Merikangas et al 2022 Molecular Psychiatry volume 27, 1373–1383)

Cancers: 291 associated genes

(Futreal et al Nat Rev Cancer. 2004 Mar;4(3):177–183 2025)

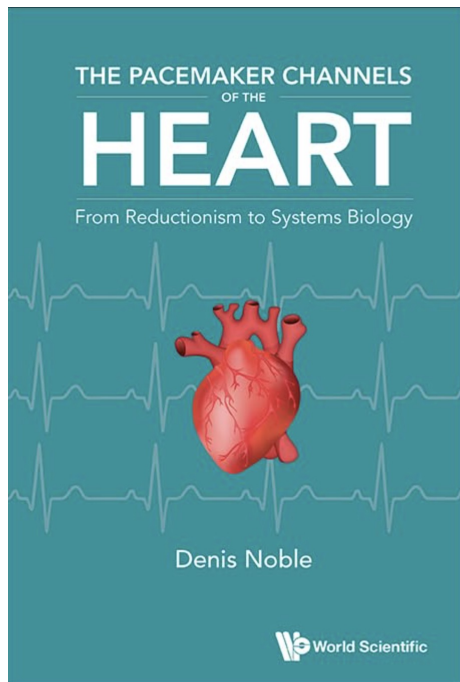
Cardiovascular diseases: 735

(Akawi et al 2024)

Alzheimer's disease 75

(Bellenguez, et al. 2022 New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nature Genetics*)

Books and articles showing how causation can be measured



Just Published 2025

Noble & Hunter, 2020. How to link genomics to physiology through epigenomics *Epigenomics* 12 285-287. doi:10.2217/epi-2020-0012

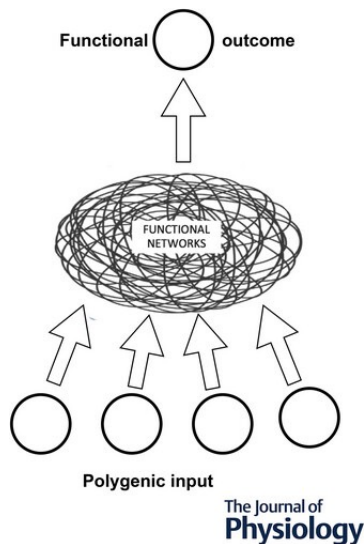
Noble, D. 2025. The cardiac pacemakers: A paradigm of robustness in evolutionary biology. *J Physiol.* <https://doi.org/10.1113/JP287139>

Method: Create experimentally-based model that includes gene products such as channels, enzymes, etc.

Check that association scores with genes are low
Then measure active causation within the model by each gene component or product.

Measuring causation is metaphysical

since it depends on measuring something beyond association



Example: *Heart pacemaker channels*. 4 genetic/protein components any one of which is sufficient for networks to generate rhythm. Each is a back-up for the others. Low association score can then be compatible with strong causation.

“Polygenic risk scores performed poorly in population screening, individual risk prediction, and population risk stratification. Strong claims about the effect of polygenic risk scores on healthcare seem to be dis-proportionate to their performance.” (Hingorani et al., 2023)

To reveal this difference we need to build a quantitative hypothesis, preferably a detailed model of the biological processes involved, Reverse engineering of a validated model can then lead us to quantify causation.

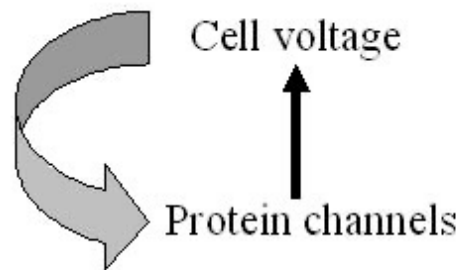
Noble, D. 2025. The cardiac pacemakers: A paradigm of robustness in evolutionary biology. *Journal of Physiology*, <https://doi.org/10.1113/JP287139>

3. Hodgkin Cycles and Conditioned arising

Two-way interaction is fundamental to the general principle of Relativity, the basis of Einstein's Theory of General Relativity, and of its extension to the Principle of Biological Relativity.

In Theory of General Relativity, objects in space-time distort space-time (a field) and so influence the movements of objects within it. In Biological Relativity, the form of higher levels necessarily influences the movements of elements at lower levels of the organism.

Downward causation in the Hodgkin Cycle



A necessary two-way interaction between molecular events (opening and closing of protein channels) and a **field property** dependent on an integrative outcome of those molecular events. The field is created across the cell membrane and is huge: of the order of **10 million Volts per metre**

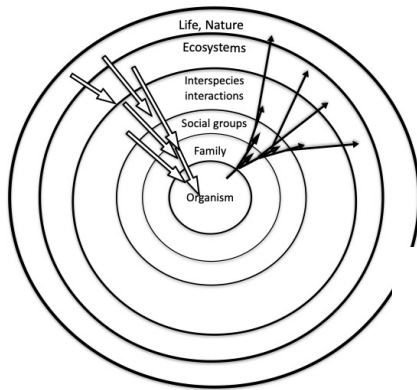
In the integration procedures it acts as a boundary condition in each step. It is therefore causation by form, even though varying between steps. All levels of organisation form boundary conditions for the molecular events. Hodgkin-type cycles therefore from the basis of biological relativity: no privileged level of causation.

Daoist/Buddhist conditioned arising

States that nothing exists in and of itself. All existence depends on two-way interaction. This is the sense of the No-Self (anatman) concept in Buddhism.

A 'gene' is just such a 'no-self'. It is only functional as a DNA sequence by being read by the living organism. DNA is a passive, not an efficient cause. It can do nothing functional outside a living cell to read its sequence. Then it is just another chemical.

4. Orthogonal Causation: Social context interactions

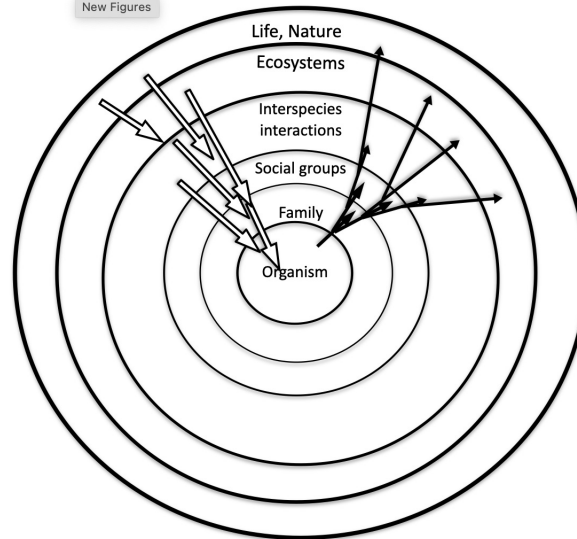


⁴⁻³ ence of non-material (social interactions and ethical/moral judgements) on human behaviour, including underlying cultural routines with actions consistent with those non-material influences.

[Values influence action: how might intentional agency work physiologically?](#) Journal for the General Philosophy of Science. 51-09525-3

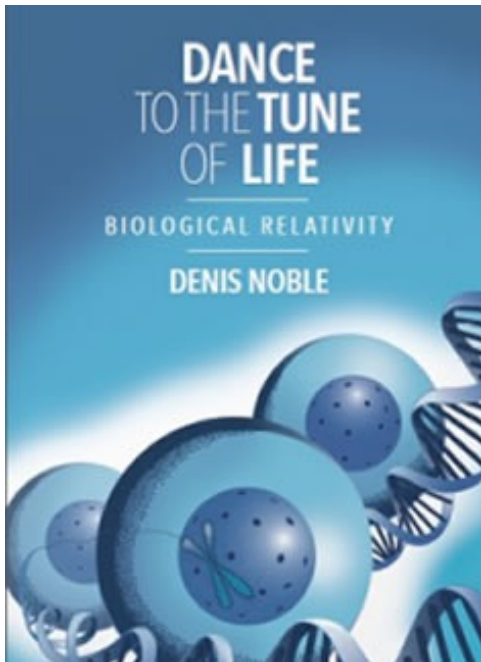
cited: the pre-eminent role of values. *Theoretical Biology Forum*: 115, 1/2, 2022. pp. 277-295

New Figures



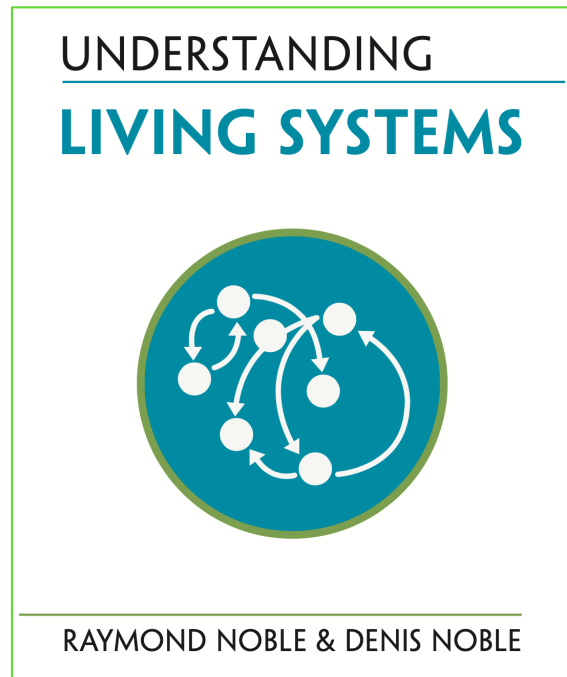
› hint from mathematics. Like the square root of -1 they can be

Relevant Publications



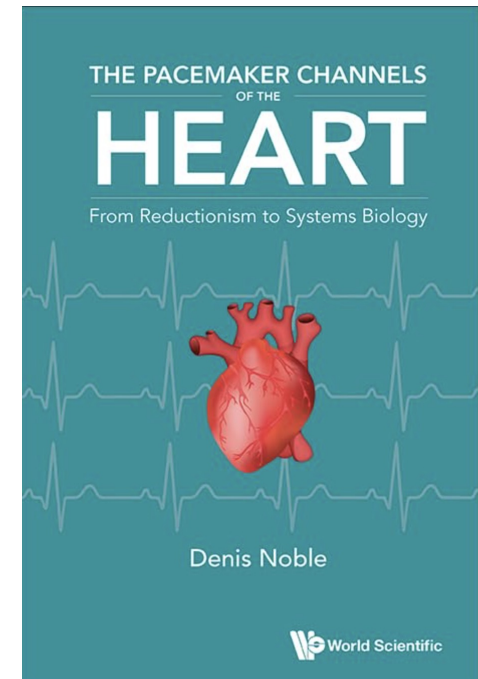
Published by CUP in 2016

Chapter 10: The Relativity of Epistemology.



Published by CUP in 2023

Chapter 4: Purpose in Life



Published by World Scientific in 2025

Chapter 10: 65 Years On

Thank you for listening