

PURPOSIVE EXPLANATIONS

are more useful in explaining lower-level
processes in living systems
than the other way round

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Examples from Physiology

- William Harvey and the Circulation of the Blood
- The renal system and counter-current flow
- Charles Darwin and the theory of pangenesis
- Hogkin Cycles and Downward Causation

William Harvey and the Circulation of the Blood

- The function of the circulation was the object of William Harvey's *de motu cordis* (On the movement of the heart and blood in animals) in 1628. His work was the first use of quantitative calculations to answer a functional question and is therefore one of the origins of the quantitative systems biological approach. His discovery of the function of the heart as the circulation of the blood was already announced in a lecture he gave in 1616:
- “So it is proved that a continual movement of the blood in a circle is caused by the beat of the heart.” (from *Prelectiones Anatomiae Universalis*). Knowing how frequently the heart beats and what volume of blood could be pumped out during each beat he estimated how rapidly the heart could empty the entire volume of blood in the body:
- “This is also clearly to be seen by any who watch the dissection of living creatures, for not only if the great artery be cut, but, as Galen proves, even in man himself, if any artery even the smallest be cut, in the space of about half an hour, the whole mass of blood will be drained out of the whole body...”
- “By careful reckoning, of course, the quantity of blood forced up beyond the valve by a single compression may be estimated, and this multiplied by a thousand gives so much blood transmitted in this way through a single portion of the veins in a relatively short time, that without doubt you will be very easily convinced by the quickness of its passage of the circulation of the blood.”
- The answer in the case of a human is 30 minutes. Harvey then proposed an answer to the question where in the body does all this blood go?

Prediction of existence of capillaries

- Until Harvey, people thought that the blood ebbs and flows back and forth as it gets pumped into the expanding arteries, rather like the tides of the sea ebbing back and forth on the seashore. Harvey realized that this could not be true since he demonstrated one-way flow of blood through the veins taking blood to the heart. The veins have valves, so ensuring that the blood cannot travel back to the extremities. It must always flow towards the heart. He concluded:
- “It must therefore be concluded that the blood in the animal body moves around in a circle continuously, and that the action or function of the heart is to accomplish this by pumping. This is the only reason for the motion and beat of the heart.”
- Since there is continuous one-way flow the arteries and veins must somehow connect together. With the naked eye Harvey could not see how that happened so he supposed that there must be what he called porosities in the tissues through which the blood could flow from the tips of the arterial tree into the tips of the venous tree. Harvey’s achievement therefore was not only to discover the circulation of the blood, but also to make a prediction that he himself could not prove. It was in 1661 that Marcello Malpighi used a light microscope to observe the flow of blood through what we now call capillaries in the brain and other organs.

Principle of Constraint

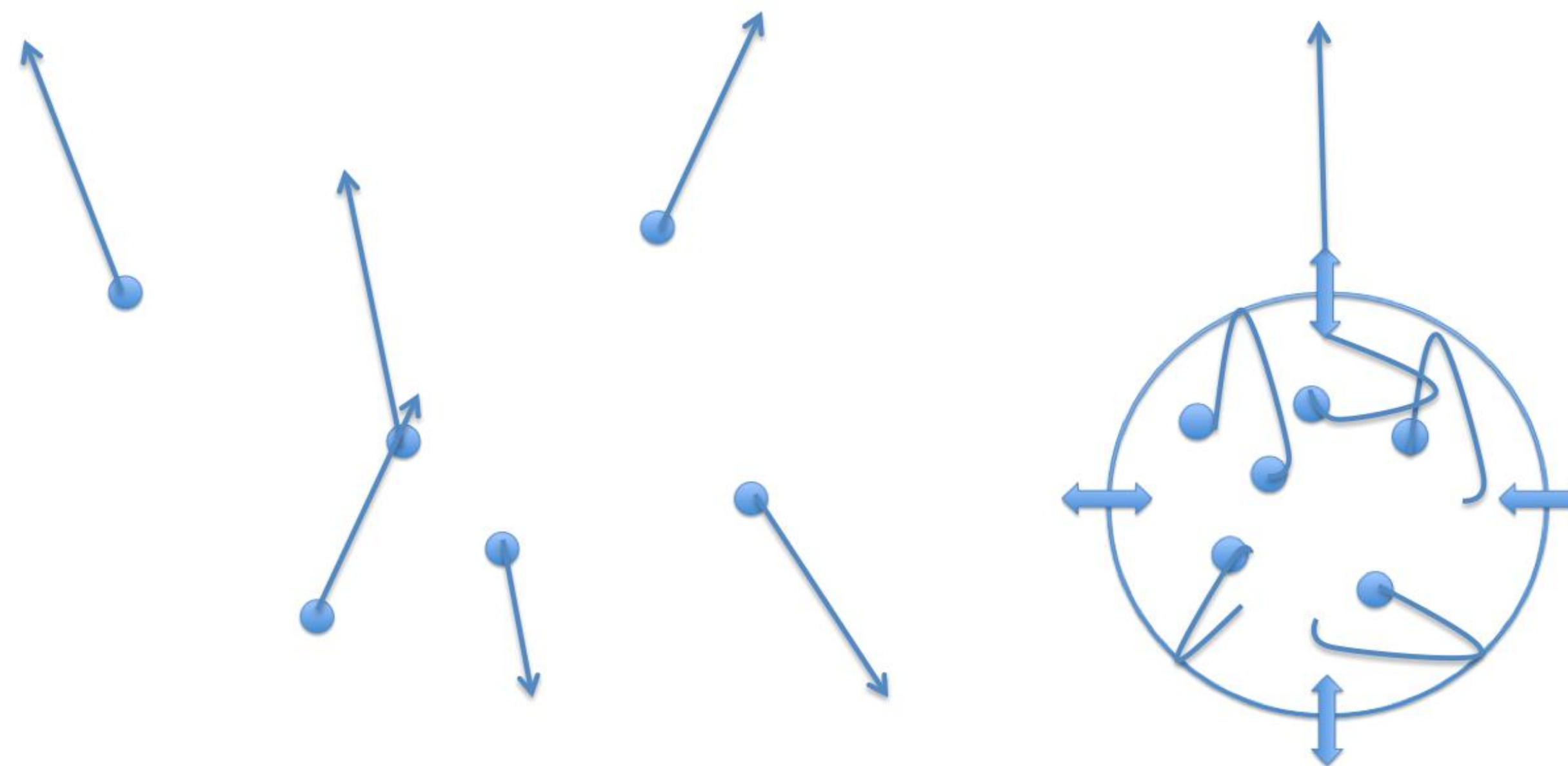
- However much we might study the particles of blood, what we now call cells, platelets, vesicles and all their associated fluids and dissolved molecules, nothing in these molecular movements would tell you that the blood circulates. This fact was realized by Benedict Spinoza, who communicated his idea in a letter to *The Royal Society* in 1665:
- “Let us imagine, with your permission, a little worm, living in the blood, able to distinguish by sight the particles of blood, lymph etc, and to reflect on the manner in which each particle, on meeting with another particle, either is repulsed, or communicates a portion of its own motion. This little worm would live in the blood, in the same way as we live in a part of the universe, and would consider each particle of blood, not as a part, but as a whole. He would be unable to determine, how all the parts are modified by the general nature of blood, and are compelled by it to adapt themselves, so as to stand in a fixed relation to one another.”
- There is an important lesson here: functional theories about the workings of the cells, tissues, organs and systems of a living organism can make micro-level predictions that can be tested experimentally. But the converse does not necessarily or even usually hold. The multitudinous directions of movement of particles will not yield conclusions about the functioning of the whole, as we know well from thermodynamics, where constraint of such movements by containers generates the high-level properties of temperature, volume and pressure, and where most of the lower-level stochasticity is ironed out. Biology has reached a similar impasse in seeking to explain physiological function in health and disease purely from measurements of gene sequences and associations in genome-wide association studies (GWAS).
- The constraint of molecular and other micro-components by membranes and other boundaries in physiological systems can be readily understood with a simple diagram (next slide). Without constraint particles will move every which way and so disperse any functional network they may form. Under constraint by boundaries, functional networks may persist. Such constraint must have developed at a very early stage in the development of life. Boundaries are highly functional in physiological systems. Their essential membranous molecules, lipids, do not depend on genes. Yet those molecules are also inherited. They are also better self-replicators than DNA. Lipids automatically insert themselves into existing membranes.

Principle of Constraint

Through random thermal motion unconstrained particles will move in all directions.

Any functional network they may form will disperse and so cease to be functional.

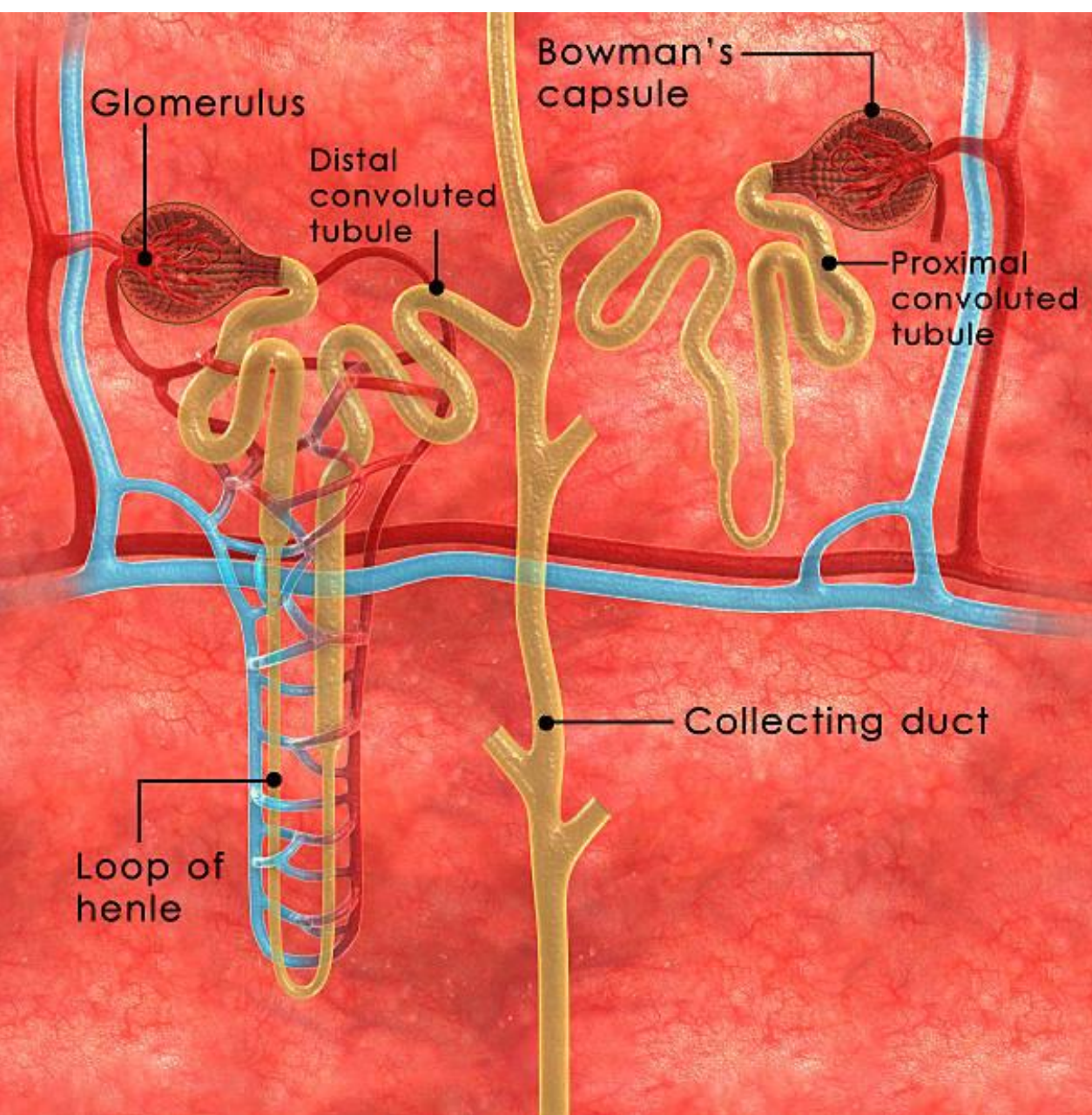
Right: Constraint, e.g. by a vesicular membrane, or a circulatory system of vessels, will keep most particles contained. A functional network may then survive



Unconstrained

Constrained

The renal system and counter-current flow

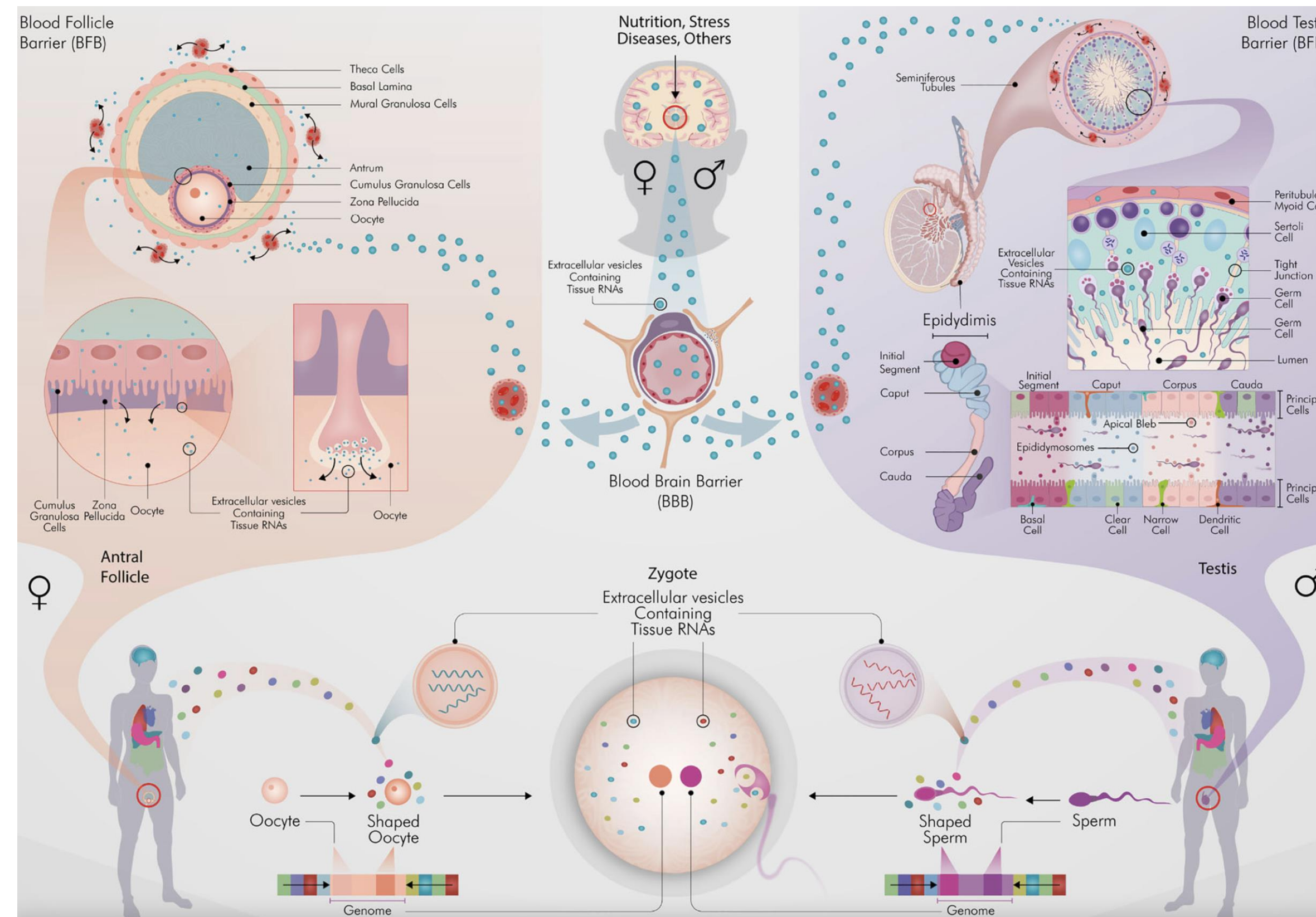


- Physiological studies of the kidney and renal system illustrate the same kind of functional analysis leading to successful predictions of micro-level components and processes.
- The structure of the kidney is a compact maze, with tiny tubes interweaving with each other, forming pathways bending back on themselves to run to where they came from. From a molecular-level viewpoint this all seems pointless. Why carry fluids and molecules dissolved in them back and forth through such long tortuosities? Calculations using physiological high-level insight provide the answer. From an engineering point of view the arrangement of the renal tubules uses the principle of counter-current flow, which was first proposed in the kidney by Werner Kuhn in 1951, and confirmed by Carl Goeschalk in 1998. Engineers frequently use this principle to construct heat exchangers and to concentrate chemical compounds.
- This principle is of functional use all over the body. It is amazingly simple but also deeply explanatory. In the limb extremities arteries and veins run together side by side. The hot blood emerging from the heart warms the cool blood coming back through the veins. This heat exchange system conserves heat in the body as a whole, so enabling warm-blooded organisms to keep heat balance more easily. This balance in turn optimises metabolic processes, such as enzyme reactions, so that they run at optimum levels.
- These functional insights predict the existence of the required selective protein transporters in the cells lining the kidney tubules. Many of those have now been found.

Charles Darwin and the theory of pangenesis

- In Charles Darwin's book, *The variation of animals and plants under domestication* (Darwin, 1868), he outlined a theory for how physiological changes in organisms during their lifeFme could influence future generations through their effects on the germ-line cells, the future eggs and sperm. So convinced was he that he treated his theory of pangenesis as a "beloved child" This was no passing fancy. He very much wished it to be true. At the same time, he realized its speculative nature, since no-one had any evidence that transmission of material, which he called gemmules, from the soma to the germ-line could occur. He wrote:
- "Physiologists maintain, as we have seen, that each cell, though to a large extent dependent on others, is to a certain extent, independent or autonomous. I go one step further, and assume that each cell casts off a free gemmule, which is capable of reproducing a similar cell." (Darwin, 1868, vol 2, p 377).
- "The existence of free gemmules is a gratuitous assumption, yet it can hardly be seen as very improbable, seeing that cells have the power of multiplication through the self-division of their contents." (Darwin, 1868, vol 2, p 378)
- He therefore imagined his gemmules as rather like spores. He was wrong to suppose that they were capable of "reproducing a similar cell", but correct to see cells as "casting off a free gemmule". His text only needs revising to read "capable of influencing other cells" for his gemmules to become the extracellular vesicles of today. His theory did not need them to reproduce, only to influence characteristics.

Bubbling Beyond the Barrier



Schematic of the emerging role of extracellular vesicles (EVs) RNA in short- and long-range soma–germline communication

Lifetime factors including nutrition, stress, and disease induce the production and release of EVs containing various RNAs into the circulatory system, including from the brain after surpassing the blood brain–barrier (BBB). Tissue EVs migrate through the blood–follicle barrier (BFB) and blood–testis barrier (BTB) and enter the antral follicle (left) and seminiferous tubules (right), respectively. In the antral follicle, EVs travel inside trans-zonal projections extending from the cumulus granulosa cells through the zona pellucida and into the maturing oocyte. In the testis, EVs interacting with developing sperm cells in the seminiferous tubules. EVs are also produced by different segments of the epididymis and interact with sperm prior to ejaculation. Modified gametes produce a fertilised zygote with influenced by lifetime factors of one or both parents (Phillips & Noble, 2023. *Journal of Physiology*, in press).

Darwin's gemmules become EVs, exosomes

- When, after Darwin's death, Weismann proclaimed the 'all-sufficiency' (*allmacht*) of natural selection and the necessity for a barrier (Weismann, 1892, 1893), it was difficult, if not impossible, for defenders of Darwin's idea to resist Weismann's exclusion of the inheritance of acquired characteristics.
- Yet, in retrospect, we can now see that Darwin was using a similar logic to that of William Harvey and his 'porosities'. The fact that we can't directly see something postulated by a valid scientific theory does not, in itself, disprove the theory. It may simply mean that the resolution with which we can see things is not sufficiently high. Harvey's porosities appeared just three decades later in the light microscope detection of capillaries. Darwin's gemmules have had to wait much more than a century, but we have nevertheless found them. The evidence that DNAs, RNAs and other molecules get transmitted from the soma to the germ-line is now clear from work in many laboratories. Darwin's gemmules have become the extracellular vesicles detected by an order of magnitude increase in the resolution of light microscopy, brought about by detecting light directly emitted from vesicles by fluorescent labelling of molecules contained in the vesicles, which also means that we know precisely what the molecules are. Notably, they include DNAs, RNAs and transcription factor proteins.

Hodgkin Cycles and Downward Causation

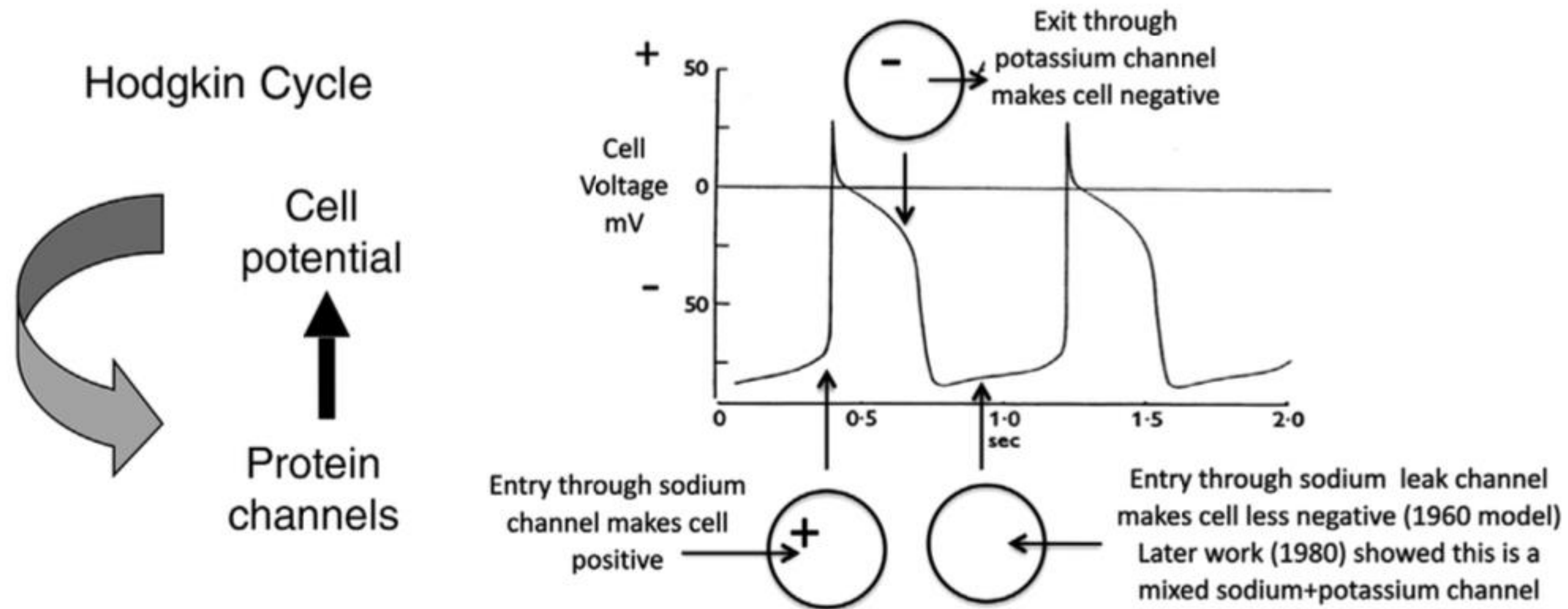
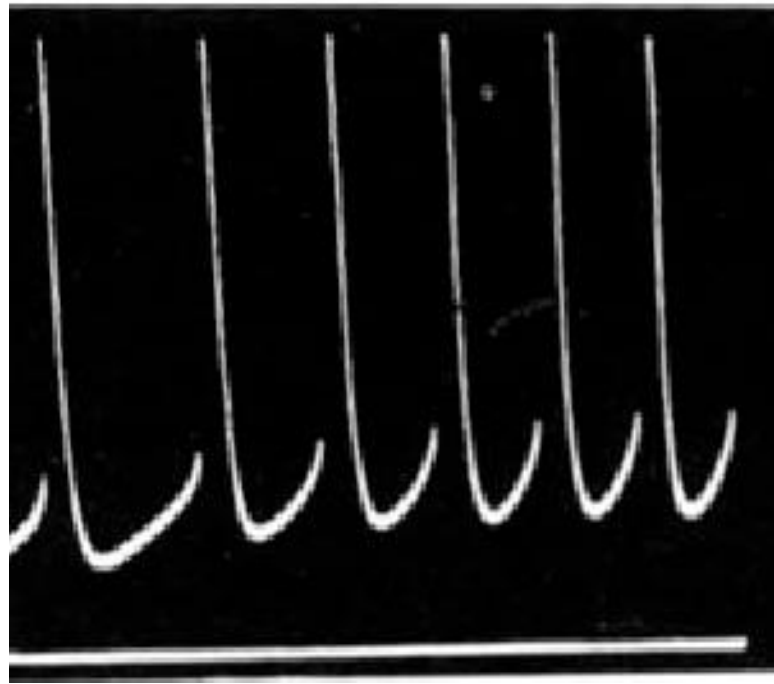
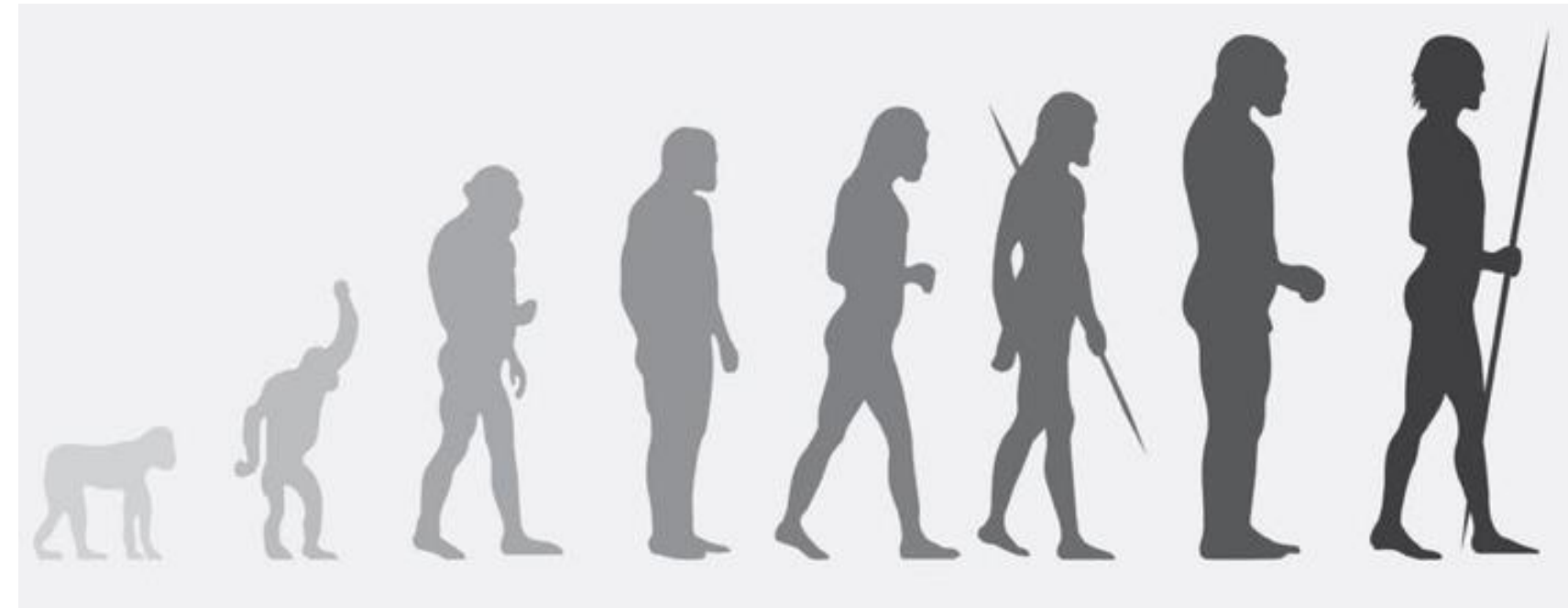


Figure 2. The Hodgkin cycle and the 1960/62 model of Purkinje fibre action and pacemaker potentials
Left: The Hodgkin cycle. Right: The 1960/62 model of Purkinje fibre action and pacemaker potentials. Exit of K^+ ions through the delayed rectifier channel made the model cell negative, while its subsequent decay allowed sodium ions to make the cell become positive again, so forming a complete cycle.

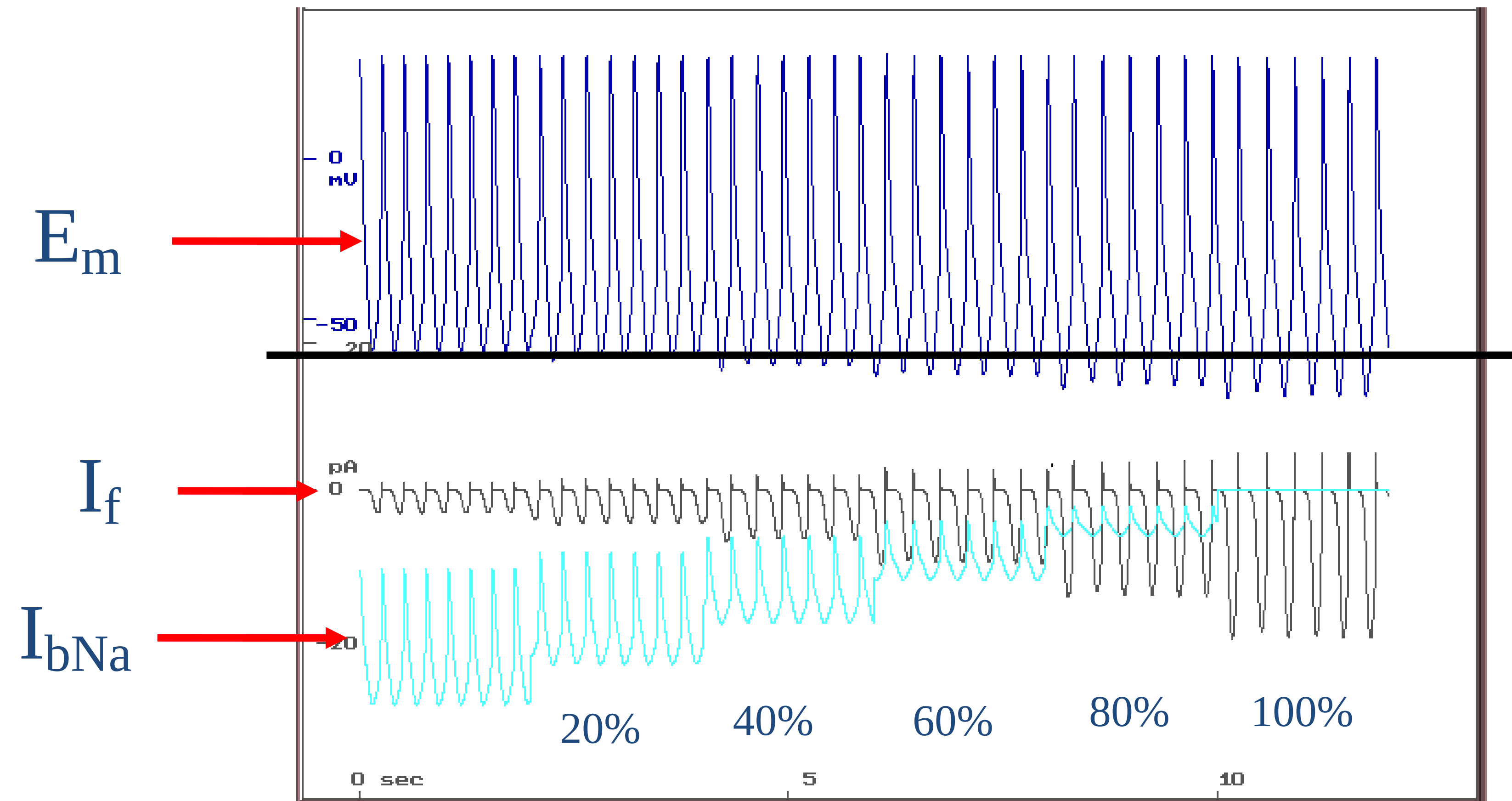
From: Pacing the Heart To: The Pace of Evolution



- Heart rhythm is an example of the difference between association and causation.
- HCN gene protein contributes around 80% of electric current
- But knockout or block produces only 10-15% association score.

Model of sinus node – i_{bNa} & i_f

Example of robust reaction to ‘gene knock-out’



Noble, D., J. C. Denyer, H.F. Brown. & D DiFrancesco (1992). Proc Royal Society B **250**: 199-207.

Genetic buffering: How extensive is it?

Hillenmeyer ME, Fung E, Wilentz S, Pierce SE, Hoon S, Lee W, Proctor M, St Onge RP, Koller D, Altman RB, Davis RW, Nislow C & Giaever M (2008). The chemical genomic portrait of yeast: uncovering genome-wide drug dependencies for all genes. *Science* **320**, 362-365.

80% of knockouts are silent!

The Omnigenic hypothesis 2017

already over 1000 citations!

[Cell. 2017 Jun 15; 169\(7\): 1177–1186.](#)

PMID: [28622505](#)

doi: [10.1016/j.cell.2017.05.038](#)

An expanded view of complex traits: from polygenic to omnigenic

[Evan A. Boyle](#),^{1,†} [Yang I. Li](#),^{1,†} and [Jonathan K. Pritchard](#)^{1,2,3,†}

- All genes contribute to many or even all functions
- Many genes show very low association data
- Linear addition of such data invalid
- Gene-centric views of development & evolution need revising

“We propose that gene regulatory networks are sufficiently interconnected that all genes expressed in disease- relevant cells are liable to affect the functions of core disease-related genes and that most heritability can be explained by effects on genes outside core pathways.”

The Failure of Upward Causation

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ORIGINAL RESEARCH

bmjmedicine

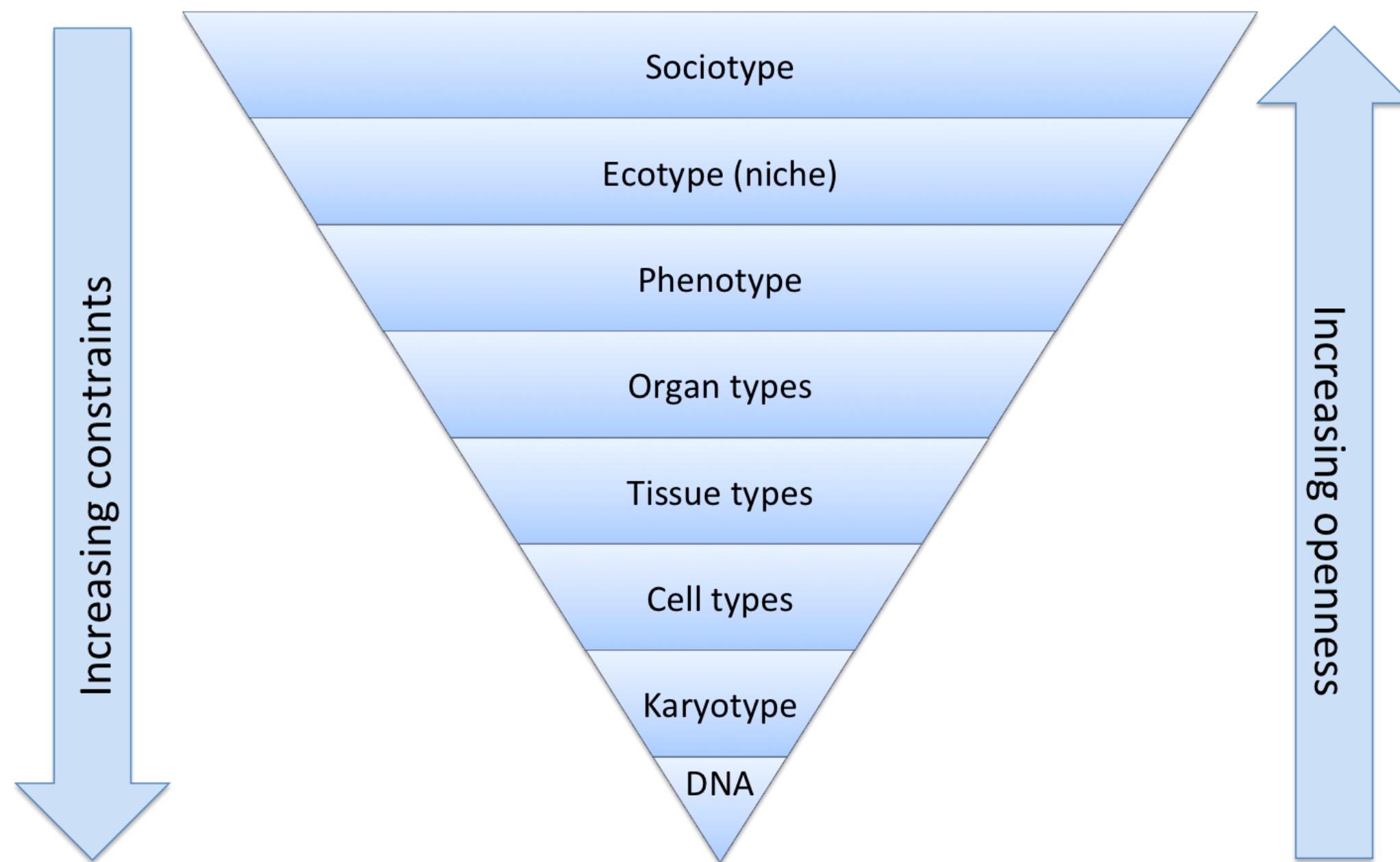


Performance of polygenic risk scores in screening, prediction, and risk stratification: secondary analysis of data in the Polygenic Score Catalog

Aroon D Hingorani,^{1,2,3,4} Jasmine Gratton ^{1,2}, Chris Finan,^{1,2,3,4} A Floriaan Schmidt,^{1,3,4,5} Riyaz Patel,^{1,2,3,4} Reecha Sofat,^{4,6} Valerie Kuan,^{1,2,3} Claudia Langenberg,^{7,8,9} Harry Hemingway,^{2,3,4,10} Joan K Morris,¹¹ Nicholas J Wald^{10,11}

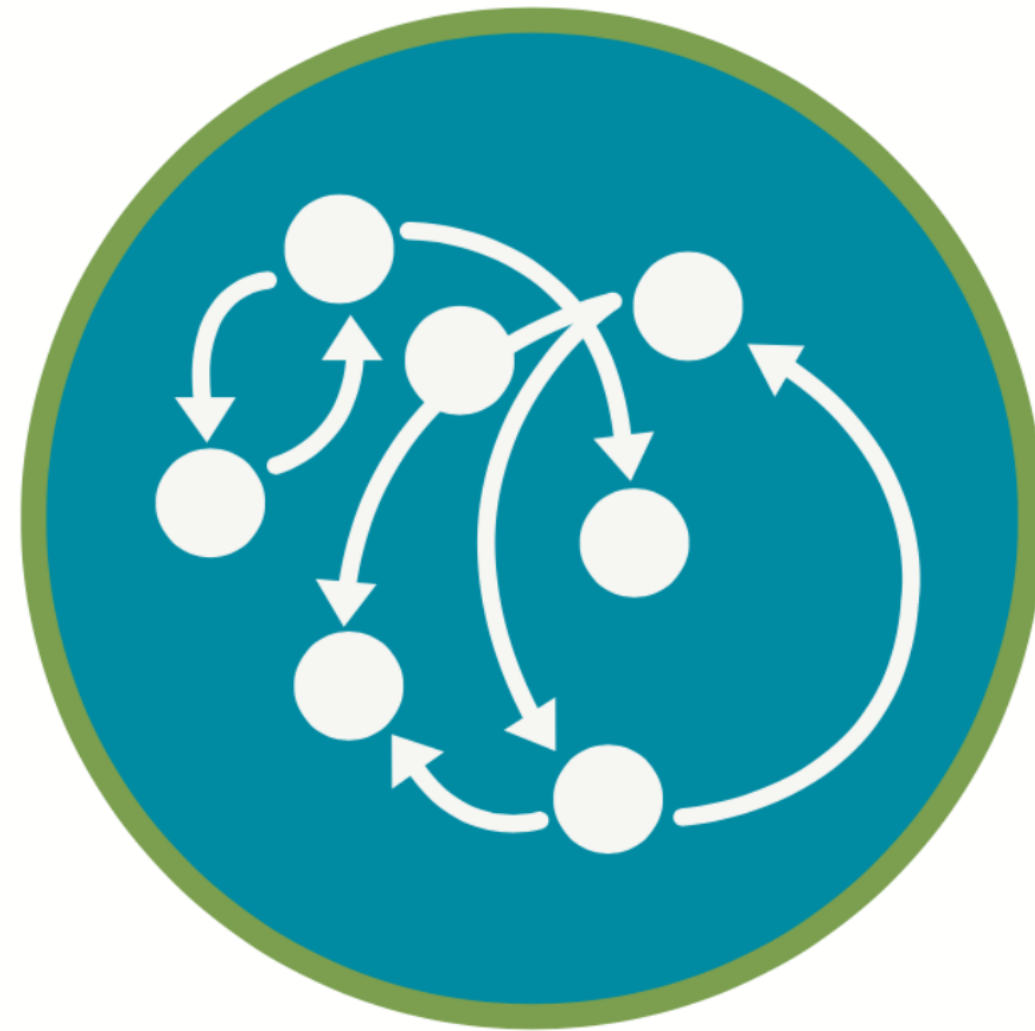
Our results showed the poor performance of polygenic risk scores in population screening, individual disease prediction, and population risk stratification. This finding is not obvious from the metrics reported in the Polygenic Score Catalog but is clear based on the appropriate metrics used in this study. Our conclusion is consistent with that of others, but is insufficiently recognised.

Where do purposes come from?



- They can arise as forms of causation at all levels of the organism, except the molecular level.
- Molecules, such as DNA, must simply do what their chemistry makes them do.
- DNA is constrained by the living processes that control it DNA is therefore the most constrained level of organisation.
- The sociotype is the most open level.

UNDERSTANDING LIVING SYSTEMS



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or Amazon

It will require creative ingenuity to shift the culture of biology away from the misunderstandings of the twentieth century. It will be for a new generation to discover and create their own culture fit for the challenges of the twenty-first century.

They will have plenty of looming signposts to warn them what went wrong. Theirs will be a generation that must take responsibility for the way in which the earth's ecosystems need rescuing, even for our own species to survive.

Theirs will be the generation that faces the challenge of ageing societies, requiring medical science to find solutions to diseases of old age that do not readily yield to reductionist gene-centric solutions since those diseases are multifactorial. Only an integrative approach that understands those multifactorial interactions can possibly hope to address those diseases.

Theirs will be a generation that can try to recover from the damage to society that results from reductionist models of physiology and evolution that have metaphorically shaped ideas and models in fields as diverse as economics, sociology, philosophy, ethics, politics ... the list goes on because no aspect of today's society can have escaped dogmas like 'we are born selfish', 'they [genes] created us body and mind', 'it's in their DNA', and the myriad of other tropes of related types that we now use almost without thinking.

Those future generations will also need to rewrite the textbooks, not only because they see the virtue of 'let us therefore teach our children', but also because their politicians, economists, sociologists and philosophers will also need to find new strategies, in collaboration with biologists who can lead them out of the gene-centric impasse.

It is arguably a challenge the scale of which human society has never faced before.

We wish them all well.

Read all about it

Noble D. & Phillips, D. 2023. Speciation via Physiological Selection of Environmentally-Acquired Traits. *Journal of Physiology*. In press.

PHYSIOLOGY LEADS SPECIATION

Noble, D. 2022. Physiology Vindicates Darwin's Dream. *Experimental Physiology*, 107, 1015-1028.
Phillips, D. & Noble, D. 2023. Bubbling Beyond the Barrier. *Journal of Physiology*, In Press

DARWIN'S GEMMULE THEORY VINDICATED

Noble, D. 2023. Physiology returns to the centre of biology. *Интегративная физиология (Integrative Physiology)* 4 (1), 8-17.

CHALLENGE TO PHYSIOLOGISTS TO FIND ELECTRO-GENE-EDITING COUPLING

Noble, R. & Noble, D. 2023. *Understanding Living Systems*. Cambridge University Press.

EVERYTHING IN LAY LANGUAGE