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Reflections of a conceptualist

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Scientists try to answer questions, but scientific questions do not simply appear out of thin air. It is pivital for scientists to know in detail what questions they want to answer before they attempt to do so. However, formal and conceptual thinking that allow scientists to phrase and pursue meaningful questions are – to put it mildly – not at the top of curricula anymore. Every new generation must find new tricks to access resources, which usually are distributed among the parental generation. Adding formal thinking and conceptual awareness to their experimental work would give the next generation a huge advantage.

One would think science was an objective art, but despite its multiple methods to ensure objectivity, we need to be careful. Lynn Payers' book "Medicine and Culture"[1] offers a stunning view into the large differences in medical practice across European countries and the US. For the first lecture, I was ever asked to give—I was still a biology student at the time—I chose the topic of scientific subjectivity and studied the descriptions of chicken behaviour over the previous 200 years; I demonstrated how the descriptions of hen coop behaviour changed in parallel with our own societal norms.

When I talk at trainee days, I always stress that philosophy and psychology are necessary watchdogs of even the most advanced science—alongside with statistics. I usually ask the trainees about their most important scientific instrument and how they make sure it functions flawlessly. After hearing responses that include many devices, from microscopes to PCR machines, I hint that I am looking for an even more important instrument and that they all use it irrespective of their methods and questions. Even then, I rarely get the correct answer: our own brain.

Modern biologists seem reluctant to acknowledge the contribution of their own brain in their experiments. A very successful molecular biologist once said to me: modern biologists don't need hypotheses—"give me a gene and it tells me what it does—that's all we need". Of course, this was wrong because it would have meant that modern biologists don't use their brains. They believe objectivity is secured by the way they perform their experiments.

Modern experimental science can be described as a loop that derives from a Scientific Question (Fig. 1A). The performance of a controlled experiment followed by the analyses (and interpretations) of its results leads to manipulations of either the experimental protocol (e.g., changing physical or chemical conditions) or the model organism (e.g., altering the genome) before the loop enters its next round. The purpose of this loop is to reveal mechanisms and identifying underlying components (e.g., transmitters, genes, specific cells). This is central to what I call "Implementation Biology", which is the dominant, method-driven approach in modern science.

Despite scientific progress being mainly driven by improvements in methods, science is highly territorial—entire institutes are regularly renamed according to the respectively newest methods. For example, preclinical medicine began with anatomy, which "botanized" the body and provided a taxonomy of its parts. Over time, the need to understand the function and interaction of these parts paved the way to physiology, which was defined as the scientific study of the functions and mechanisms in a living system. Mainly for reasons of resources (e.g., grant money and publication space), the wonderful and all-encompassing institutes of physiology were replaced by institutes of physiological chemistry, biochemistry, molecular chemistry, molecular genetics, genomics, or systems biology despite all of them investigating "the functions and mechanisms in a living system".

Despite the success of Implementation Biology, the most influential breakthroughs in biology were descriptive, phenomenological and—above all—conceptual. Both Gregor Mendel[2] and Charles Darwin[3] gave us concepts that enabled the search for innumerable implementations. But how do we arrive at concepts? We use an older, much more rudimentary path of scientific progress (Fig. 1B), which is central to what I call "Conceptual Biology". Conceptual Biology starts with simply collecting stuff—ranging from biomaterial to data (Botanizing). This step involves sorting and categorizing and leads to the next step: playing around with physical or chemical conditions (Manipulations). Once the responses to these changes are observed and analysed, we arrive at the first cornerstone of this loop, the discovery of an observable fact (Phenomenon). Although hypotheses (openly or unconsciously) exist at all steps in both loops, the first concrete hypotheses can only be formulated when we become aware of an actual phenomenon, which we can then probe systematically in the laboratory (Behavioural and Physiological Description). This paves the way to Formal Descriptions that allow the phenomenon to be put into a contextual framework (Concept).

Here is an example that highlights the difference between the Conceptual and the Implementation approach: the former wants to answer the question what television is (i.e., reaching the masses by broadcasting not only auditory (radio) but also visual information) while the latter wants to know how a television works. The ultimate representation of the metaphorical "television" in biomedical science is the human body, which—unlike the constantly changing implementations of the concept television—has been (and is expected to be) implemented practically the same way for many centuries. Medical approaches need to know how this human implementation works in order to develop drugs that prevent malfunctions or help to recover from them. But none of these endeavours could even start their experimental path without having formed a concept of a phenomenon—they wouldn't have a Scientific Question to ask.

Notably, Conceptual Biology is being degraded in the modern territorial battle for resources. For example, grant applications are often disrespectfully being labelled as "botanizing expeditions", "purely phenomenological", or "merely descriptive", and formal contextual frameworks and concepts are thought to have become obsolete ("give me a gene and it tells me what it does"). The appreciation that concepts, like those laid out by Charles Darwin and Jacque Monod[4], are the very basis of our

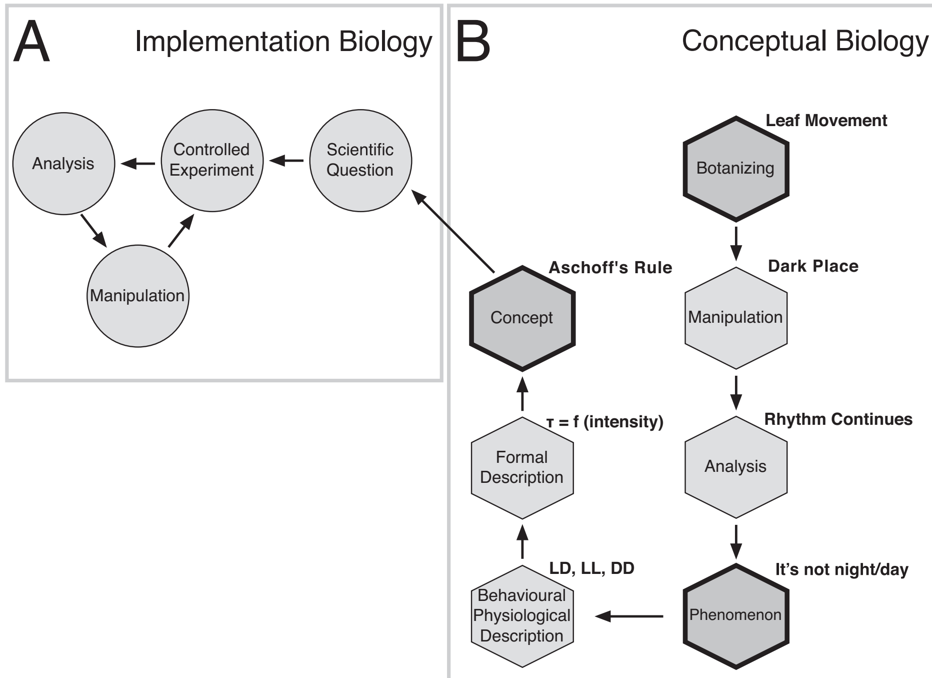

Fig. 1 | The Path from Collection to Insight. A represents the process of modern experimental biology that probes the mechanistic basis of a phenomenon (Implementation Biology). This process starts with a scientific question leading into a loop of Controlled Experiments, Analysis and Manipulations. While the Implementation-Biology loop is essential to, for example, develop drugs and other treatments against pathology, it needs prerequisites that allow the researcher to ask the appropriate scientific question (**B**). The Conceptual-Biology path starts with collecting, sorting and taxonomizing information (Botanizing), introducing first changes (Manipulation). The Analysis of the responses to these changes allows us to describe and thereby recognize a Phenomenon, which can be described in detail by further manipulations. The collected results pave the way to Formal Descriptions that allow the phenomenon to be put into a contextual framework (Concept). The cornerstones of this pathway are shown in darker symbols. The headings at each of these steps in **B** give examples in form of discoveries in biological rhythms research (see text for details).

biomedical world seems to be fading in recent years. Central to the concept of evolution are chance and necessity. I have asked many colleagues in the biomedical community, whether they thought that genes were selected for in evolution. Almost all of them replied that they did; this is wrong. Genes, especially if multiple genes "collaborate" in implementing a phenotype, are not selected for by evolution, but are merely the matrix for the random-mutation-side of evolution (chance). Evolution's selection works on the phenotype—on function and behaviour (necessity). The artificial mental boxes (represented by the explosion of institute names, see above) that territorial scientists have created are method- and not concept-driven; they are irrelevant for evolution because individuals simply need to propagate more genes into the next generation than their competitors, by whatever mechanisms.

At almost every conference, I wish my brilliant modern colleagues had more training in conceptual biology. I recently heard an excellent lecture about sleep genetics. The speaker very correctly pointed out that human EEG patterns were so characteristic that they could be used as a fingerprint for an individual and that only few genes were responsible for this. The speaker also very correctly pointed out, that—in contrast—such a reductionist genetic characterization of the behaviour of sleep was impossible. Although both statements are correct, the comparison is from a conceptualist's viewpoint flawed. The colloquial "apples" and "oranges" here are "Implementation" and "Concept". The EEG is merely a (partial) implementation of the concept "brain"; it is like the brain's complex sound (in humans, we call this voice, not speech!), and we know how characteristic the spectral composition of an individual's (content-independent) voice is.

A good metaphor for the word "sleep" is the word "phone". Many people (who clearly are not conceptualists) criticize modern public behaviour: "everyone is constantly on their phones". Truth is, hardly anyone is "on their phone". In the old days, commutes were filled with reading books or newspapers, solving puzzles, writing notes or letters, sorting photos, planning trips and many more activities. Nothing has changed—these activities are still filling up our commute times, but we now can do all of them on a single device we call "phone" that has vastly expanded our commute-activity possibilities, even allowing us to "go shopping" while sitting on a bus or train.

While the EEG is an implementation, the phenomenon "Sleep" is not only one function but a truckload of functions, that as such cannot be taken down the path shown in Fig. 1B. Therefore, it is no wonder, that its characteristics cannot be described by a couple of genes. We are only starting to botanize this truckload, by finding the sub-phenomena of sleep and formally describing and conceptualizing them.

One of the reasons why circadian biology was so successful is because our pioneers were masters of conceptual biology. The history of circadian biology allows us to flesh out the path of conceptual biology (bold text next to symbols in Fig. 1B). It started with French astronomer De Mairan, who procrastinated in 1729 from writing a book by developing an interest in why the mimosa plant on his windowsill moves its leaves over the course of a day (the initial, Botanizing step), he moved it into a dark space (Manipulation) and saw that the leaf movements continued (Analysis)[5]. He thereby discovered that the daily rhythms of plant movement were independent of night and day (Phenomenon), but he did not go as far as calling them "endogenous". This Phenomenon lay fallow for close to 200 years, when the pioneers of circadian biology (Erwin Bünning, Colin S. Pittendrigh and Jürgen Aschoff) began to explore this phenomenon in many different plant and animal species, systematically measuring daily rhythms under different light and dark regimes (LD), constant light (LL) and constant darkness (DD; Behavioural/Physiological Descriptions). One of the many lines of experimentation showed that the endogenous circadian period depended on conditions and on species: while many day-active animals shortened their circadian period with increasing LL intensity, many night-active animals lengthened their circadian period under these conditions (a Formal Description)[6]. This systematic relationship was later called Aschoff's rule (a Concept). The concept behind Aschoff's rule postulates that entrainment anchors daily behaviour to dawn in day-active organisms and to dusk in night-active organisms, i.e., to their respective activity onsets. What followed this Conceptual Biology was a highly successful Implementation Biology that culminated in a Nobel Prize in 2017 to Jeff Hall, Michael Rosbash, and Michael Young.

Over the past decades, we learned an enormous amount about the molecular underpinnings of circadian rhythmicity, and now our field is rapidly moving towards applying these insights in real life, again with a focus on the human body, its health, and pathology (circadian medicine). Nonetheless, we would greatly benefit from the Conceptual Biology branch in this expedition. I am concerned that—at this stage of circadian medicine—our Concepts may not be sufficiently mature to successfully enter the Implementation-Biology loop.

At the beginning of biological science, Botanizing consisted of collecting mushrooms, leaves, and insects in a tin and dumping them on a kitchen table to inspect and sort. Botanizing can just as well be measuring the different phase relationships among different organs within a body or collecting the phase-angle difference between Dim Light Melatonin Onset (DLMO) and sleep onset on an epidemiological scale. If we do these collections under different conditions of health and pathology, we already include the "Manipulation" step. Pathology is a real-life "manipulation" of the healthy steady state (e.g., 20th-century brain research accelerated its progress by studying the consequences of brain injury on brain function in soldiers). The analyses of these (manipulated) collections will surely reveal new "Phenomena" that we hadn't thought about. This will allow more systematic experiments in healthy controls and patients. Intensive-care units are excellent "laboratories" for this part of the discovery process: so far, their conditions are close to constant (a metaphorical LL), so, how systematically do the phenomena change when we boost rhythmicity (in the environment and/or endogenously) and can we come up with "Formal Descriptions" of these changes to reach the level of "Concepts", which we then can apply to foster recovery and improve prevention?

Another field that would greatly benefit from conceptual biology is sleep research, which jumped on the implementation train before having discovered basic phenomena beyond we need sleep and if we don't get it, our health worsens. As long we regard sleep as a single Phenomenon, we cannot even start with its Behavioural/Physiological Descriptions. Sleep research has to start fresh on the path of Conceptual Biology by botanizing the mentioned truckload of functions (they are the tin that has to be dumped on the metaphorical kitchen table), discover new Phenomena, describe them formally in contextual frameworks (we will not understand sleep if we only study sleep) and come up with new Concepts.

Most young colleagues are extremely versatile in the rich and rapidly developing pool of methods, but—as always—they need to find new niches to successfully fight for limited resources. The next generation of biomedical researchers should acquire the intellectual mindset required for Conceptual Biology before it is lost in time. The combination of Concept and Implementation is powerful; it will push the knowledge front (new understanding) instead of only polishing it (more knowledge). Science will never be a truly objective art, but scientists trained in formal thinking will be so much more aware of this limitation.

Data availability

No datasets were generated or analysed during the current study.

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Additional information

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