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# Should biophysics study nonphysical quantities of biological systems? Take Max Delbrück for inspiration

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Biophysics is often loosely defined as the discipline that bridges physics and biology. However, Max Delbrück, often the first to be mentioned in conjunction with the proverbial origin of modern molecular biology in the work of physicists and trained in theoretical physics, considered "biophysics" an "ill-used" term.[1]

The picture of contemporary biophysics, readily obtained by a glance of any of the biophysics programs at academic institutions and of textbooks, is one of a narrower field. The typical domain of scientific investigation labeled "biophysics" nowadays mostly encompasses measurements of physical quantities pertaining to the material substrate of living systems, including the structure of macromolecules, mechanical properties of cells, or physical processes such as cell motility. These measurements can ultimately be reduced to elementary physical units of location, time, mass, and electrical potentials.

Biophysicists more often come from a background in applied physics and engineering sciences and are eagerly engaged in building instruments to manipulate biological systems and take such measurements. They seek to apply physics to biology and are less likely to seek fundamental principles that explain living matter and could expand physics—which is what had stimulated Delbrück to think about biology. Conversely, they are not particularly enticed to analyze "non-physical" quantities, such gene sequences, allele frequencies, gene expression patterns, and so on—quantities that emanate from genetics and now dominate quantitative biology. Biophysicists have largely yielded such investigations to the neighboring disciplines of bioinformatics and computational biology and now to "data scientists."

This penchant to seek *physical* measurables associated with the "hardware" of living organisms while de-emphasizing the "software," i.e., their information storage and processing, is very much aligned with a view articulated by Delbrück who in 1935 described genetics, which was and arguably still is the king discipline of biology, in the following way:

> "It is well-known that genetics is largely a logically strict science. It is quantitative but does not make use of the physical measurement system…. What differentiates genetics [from physics and chemistry] is that it faces a given organism as a natural entity for quantitative analysis, which makes it independent of the physical measurement system…."[2]

Fast-forward 80 years and we can see that modern biology, dominated by genomics, has amplified the concerns of Delbrück. Much of the quantitative aspect of modern biology in the wake of the genomic revolution requires quantitative analysis of "abstract" data that do not epitomize physical quantities resulting from biophysical measurements. They comprise DNA sequences, read counts, or peaks in mass spectra of peptides, giving rise to high-dimensional state variables of multi-omics measurements that are devoid of physicality. Their interpretation does not invoke known laws of physics but (currently) mostly utilizes machine-learning approaches to find patterns, attracting computational statisticians more than physicists.

Given the dominance of such *aphysical* big data in modern biology that is disjoint from the physical measurement system, should the ambitious biophysicist continue to build devices and conduct sophisticated measurements of material properties of living matter and explain their numbers within the known laws of physics? Or should classical biophysics be extended into the realm of multi-omics big data analysis and seek new principles to explain the patterns in the non-material genomic data?

Here again, considering Delbrück may offer a useful perspective. Delbrück started as a biophysicist in the modern meaning of the word, for what study could be more directly linked to the physical substrate of biological phenomena than establishing the material basis of mutations using ionizing radiation and visualizing bacteriophages using electron microscopy?[1] After this work on phages and notably after the discovery of the DNA double helix by his mentee James Watson, Delbrück lost interest in the characterization of the underlying biochemical details of living systems. He was more interested in finding phenomena unique to living organisms—ideally in the form of a paradox that would epitomize principles of biology that were not yet known to physics but would open up new thinking in physics, similar to the paradoxes in atomic physics made famous by Niels Bohr. In fact, as the geneticist Bernhard Strauss recounted,[1] Delbrück confided in a letter to Bohr in 1954 that this was his "ulterior motive in biology from the beginning."

Delbrück asked, and this may be his version of a minor paradox: How do a few quanta or a few molecules trigger macroscopic responses in organism?[1] This question is today at the heart of the genotype-to-phenotype mapping problem that exerts little appeal to the typical modern-day biophysicist. How does chemistry produce macroscopically distinct, qualitatively discontinuous traits (cell type, metabolic states)? At the meeting in Paris in 1948, Delbrück proposed a principle that, owing to non-linear interactions in an open system, could produce two distinct stable equilibrium states without a separate material basis for each of the states:

> "I would like to draw your attention to general properties of systems said to be in 'equilibrium of flux,' properties that one has to consider before postulating the existence of biological entities capable of genetic continuity…where such is observed."[3]

He presented the scheme below,[3] which systems biologists today readily recognize as the wiring diagram for a bistable switch, in which two entities (e.g., genes or, in this case, metabolites), $a_2$ and $b_2$, inhibit each other's formation in a non-linear fashion while being degraded in a linear fashion (Fig. 1). The principles of bi- or multi-stability arising from nonlinear interactions between molecules are at the heart of models behind the ordered macroscopic diversity of discrete entities (cell types, organs, species) in the biosphere.

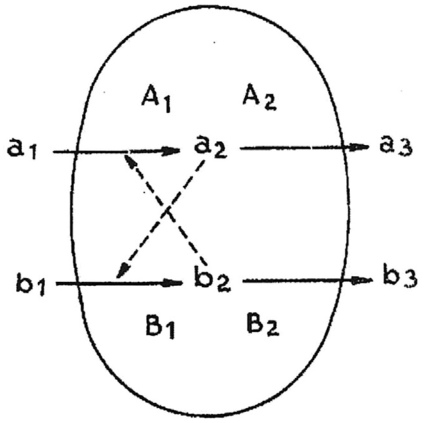

**FIG. 1.** Max Delbrück's depiction of a metabolic bistable switch, presented at a conference in 1948. From Delbrück, *Unités biologiques douées de continuité génétique Colloques Internationaux du Center National de la Recherche Scientifique*. Copyright 1949 CNRS. Reprinted with permission from CNRS.

Delbrück seamlessly moved between the two worlds of life sciences, that of physical materiality and that of abstract interactions and organization that nowadays is outside the realm of biophysical investigation because of its disconnect from the physical measurement system. As genetics is entering the era of multi-omics big data and, thus, even more so manifests Delbruck's notion of nonphysical genetics, it offers many opportunities for those biophysicists aspiring to uncover fundamental principles of living matter to follow Delbrück and embrace studies of the organism in the broader meaning of *physics*, not by being confined to studying the *physical*. Unlike the so-called data scientists, they possess the intellectual background for such endeavors. It is in this spirit that *Biophysical Reviews* has a big tent policy and publishes papers from a wide range of domains in quantitative biology.

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[3] Translated from French by the author from M. Delbrück, in *Unités Biologiques Douées de Continuité Génétique Colloques Internationaux du Centre National de la Recherche Scientifique* (CNRS, Paris, 1949), p. 33.