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Issue: *DNA Habitats and Their RNA Inhabitants***Preface to *DNA Habitats and Their RNA Inhabitants***

When I turned my focus from debates on the philosophy of science to the philosophy of biology and life sciences in the mid-1980s, one of the most interesting things that struck me was that the results of these debates failed to penetrate any biological discipline. Yet biological disciplines have methods, methodological discussions, and a scientific history with developmental stages. Like all other scientific disciplines, they embrace basic research, definitions, and a historical process in the search for appropriate methods, scientific foundations, and justification.

After 2000 years of metaphysics, in the early twentieth century a group of empiricists wanted to establish “exact science” and clearly delimitate scientific research and knowledge from metaphysics. Metaphysics assembles all those world views and paradigms of the past with which we are familiar from the history of philosophy. All of them propose a central paradigm as a basis for their system of thought, such as “all is one” or the contradictory one “all is many.” Essential to all of them is the basic proposition that their sentences about everything are depictions of the reality; that is, there is a stringent coherence between the sentence and the being. We know them as, for example, materialism, idealism, subjectivism, and objectivism applied to logic, knowledge theory, ontology, psychology, anthropology, natural philosophy, and other special disciplines. To identify metaphysics we simply have to look at their self-definition: they usually end in “-ism,” which indicates their claim to have access to the ultimate truth in terms of explaining reality that competing disciplines do not have.

The vision of an exact science was a titanic endeavor to gain insight into the basics of material reality: the only thing we can be sure of is what our senses tell us; what our experiments show us; and empirical knowledge proved by reproducible experiments, measurements, and computations. In the future, exact science will insist on empirical foundations and results that represent material reality and not belief states or confusing theoretical constructions that cannot be proved empirically.

Because both metaphysics as well as exact science depend on linguistic sentences to outline their ideas, the crucial question now is how to construct sentences that are scientific and not metaphysical. It is inevitable that we must use the sentences of a language to express observations and construct theoretical models. The interesting thing at this stage of discussion is that the basic delimitation between metaphysics and exact science from now on will need to focus on a language problem. Rather unexpectedly, the focus on basic research moved from things, beings, and senses to the essential requirement for its description, thoughts, and interpretation.

Within the predominant paradigm, language was thought to be a feature of material reality or, more exactly, material reality was built out of atoms and molecules—even language using biotic entities. Therefore, all beings are strictly subject to natural laws; physics is the leading science, and mathematical equations are the only appropriate tool for depicting physical reality. A breakthrough in science and scientific methodology seemed close, and philosophers were keen to solve the historical problem of metaphysical thinking. A scientific revolution in terms of the birth of a better world and true insights into nature seemed to be at hand.

Unexpected problems with the basic foundation of this concept arose, however. Kurt Gödel formulated his incompleteness theorem; Wittgenstein rejected his early works in favor of a pragmatic view on language. Additionally, the ultimate criteria for scientific sentences, their “verification” and later on their “falsification,” were adulterated. There will always be scientific sentences that cannot be verified or falsified in principle. Additionally, the problem with terms of disposition (*gaseous* and *soluble*) were unsolvable in the attempt to build coherence between the language of theory and the language of observation. The end of the story is part of the history of science:

- the concept of a coherent axiomatic system with error-free logical sentences is impossible, in principle; the concept of an exact scientific language was a pipe dream;
- natural languages do not speak themselves; there are always real-life individuals in populations that generate and use such languages to coordinate and organize the real-life world; and the usage of natural languages is, therefore, a kind of social interaction;
- living agents that use natural languages are principally able to generate new sign sequences that cannot be predicted or deduced from former ones and for which no algorithm is available; and
- the meaning of the signs and sign sequences in natural languages depends on the real-life context (pragmatics) within which signs are used and not on its syntax.

This means that mathematical theories of language are not an appropriate tool for explaining the essential features of natural languages, such as *de novo* generation of sentences (sign sequences). Mathematical theories of language cannot identify the context dependence of meaning that helps to transport different and even contradictory meanings with identical sign sequence. Additionally, they are not very helpful in describing the social character of real-life organisms, because, for the inherent feature of generating new sequences, new behavior, and new interactional motifs, no algorithm is available in principle.

One key assumption of the philosophy of science and exact science debates, that scientific progress is made up of a number of small steps, has been refuted by Thomas S. Kuhn. In his *Structure of Scientific Revolutions*, he empirically found that new world views occur in a contradictory way: the history of science presents a motif of three phases in the process of scientific revolutions.

The starting phase is that in which it competes with a predominant paradigm of explanation. In the second phase, the upcoming and competing dynamics are reduced, because their explanatory power is evidently better than that of the previous one. Although the previous one in most cases is not completely refuted, it is acknowledged to represent only a small part of the explanandum, and the emerging new paradigm can explain many more empirical data in a more coherent way. Additionally, in this second phase the new paradigm loses its revolutionary status and becomes a mainstream paradigm underlying a variety of similar concepts in various disciplines and core assumptions in most curricula. As with all theories we know there remains a third phase in which there are data that do not fit into the realm of this explanatory model increase. After a time of ignorance and defense against competing new explanatory models, the successful model is replaced by a revolutionary new concept. Interestingly, the success story of the new paradigm does not depend on the changed convictions of the proponents of the old one. In most cases it is rather resistant and develops strategies to defend its beliefs dogmatically. A new paradigm succeeds because young scientists adopt it in practice, as it is able to integrate more of the available empirical data.

We can also look at molecular biology from this perspective and identify some core assumptions from the early 1960s when the genetic code and its relation to the amino acid code were deciphered. The explanatory power of core assumptions, such as (1) the central dogma of molecular biology, (2) the one gene–one protein model, (3) the “non-coding DNA is junk” hypothesis, and (4) the exclusive reason for genetic variation is replication error (mutation), predominated for more than half a century.

Since the early 1960s a limited number of authors have presented empirical data that did not fit into these assumptions of the mainstream paradigm. After the deciphering of the genetic code of humans in the Human Genome Project, it was clear that the one gene–one protein assumption was not correct. The rise of epigenetics demonstrated a variety of possible functions encoded in identical genetic sequence structures

depending on context-specific circumstances. Additionally, a variety of mobile genetic elements were considered to play key roles in genome structure and expression. Also the role of viruses, especially persistent retroviruses, in the evolution of organisms has come increasingly into focus. Some parts (“defectives”) of persistent viruses became exapted and gained new roles in gene regulation of the host. The acknowledgment of the increasing empirical data on non-coding RNAs and their relationship to the persistent virosphere and epigenetic markings falsified the four pillars of traditional molecular biology.

Although these core assumptions do not fit the old molecular biological paradigm, the explanatory model used remains the same today. Some conceptual adaptations and new disciplines try to integrate new data into the realm of quantitative analyses and interpretation in biochemistry, such as systems biology, biolinguistics, bioinformatics, mathematical biology, and synthetic biology. All of them inherently investigate the genetic code in the light of an underlying mathematical theory of language: *Information* is essentially a physicochemical property that can be investigated by quantitative analysis sufficient to identify the meanings in the sequence structure. Genome comparisons as well as phylogenetic analyses have therefore been successful.

In this half century not only was there a tremendous expansion of research, but there was also parallel development of commercial applications for fighting diseases. In the early twenty-first century, the annual investment in drug research and development in the United States was \$400 billion. But, as indicated by official reports, in contrast to investment in research and development of appropriate techniques in the material sciences (increased to 45%), applicable output in life sciences remained at approximately 15%. Therefore, in addition to the theoretical deficits in justification of scientific sentences in biology, we also have to evaluate whether the dominant paradigm of the last 60 years was the appropriate tool in the development of new drugs.

To initiate a discourse between the philosophy of science and the biological disciplines about the outlined historical facts and to install the results of this discourse into biology, I decided to organize symposia in a series of meetings. In 2008, I organized a symposium entitled “Natural Genetic Engineering and Natural Genome Editing” (www.naturalgenome.at) with a number of excellent researchers in these fields.

In 2013, James Shapiro persuaded me to organize a follow-up conference, and I decided to organize a meeting based on the increasing empirical data in RNA biology, virology, mobile genetic elements, and epigenetics. The meeting was held on July 3–5, 2014 in Salzburg, Austria and provided a relaxed atmosphere for discussing a fundamental new understanding of genetic novelty; code-generating, genome-formatting factors; the multiuse nature for RNA agents; and behavioral motifs of RNA consortia. Consistent with the line of thought outlined above, it was made clear that interest in DNA molecular biology has now been replaced by interest in the more important roles that RNAs play in DNA change, storage, repair, and regulation. The DNA genetic storage medium remains a rather limited ecosphere habitat with an abundance of multicompetent RNA agents that are clearly at the core of all relevant cellular processes. The conference entitled “DNA Habitats and Its RNA Inhabitants” (www.RNA-agents.at) included 33 talks and 22 poster presentations of very high quality.

I would like to thank Luis P. Villarreal and the Center for Virus Research (Irvine, CA, USA) for cooperation in organizing this symposium. Elisabeth Resmann from Kulturelle Sonderprojekte Land Salzburg and Kulturstadt Salzburg sponsored the meeting. Tecan Austria and Greiner Bio-One supported the meeting. The RNA Society enabled several postdoc participants to attend. Special thanks are owed to the organization staff—Hiltrud Oman, Tabea Baumann, Renate Seidl, and Andreas Oman—who gave excellent support to everyone and without whom it would not have been possible to organize this symposium.

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