

## At the dawn of a new revolution in life sciences

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life science. In contrast to this we demonstrate, that biology and life is not only physics and digital information encoded in DNA sequences. In order to understand life in its whole complexity, the top-bottom processes such as occurs in epigenetics and non-coding RNA regulations leads to a new revolution in life sciences.

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### Abstract

In a recently published article Sydney Brenner argued that the most relevant scientific revolution in biology at his time was the breakthrough of the role of "information" in biology. The fundamental concept that integrates this new biological "information" with matter and energy is the universal Turing machine and von Neumann's self-reproducing machines. In this article we demonstrate that in contrast to Turing/von Neumann machines living cells can really reproduce themselves. Additionally current knowledge on the roles of non-coding RNAs indicates a radical violation of the central dogma of molecular biology and opens the way to a new revolution in life sciences.

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**Key words:** History of science; Paradigm shift; Information; Non-coding RNAs

**Core tip:** Sydney Brenner describes the radical revolution in life sciences during his lifetime: the occupation of biology by quantum mechanics, concerning the fundamental questions of matter and energy followed by the rise of genetics that showed that chromosomes were the carriers of genes. Biology is, in this respect, physics with computation, *i.e.*, the bottom-top approach in biology is sufficient to solve all our goals in

### COMMENTARY ON HOT TOPICS

In a history of science perspective, Sydney Brenner reminds us on the revolutions in the life sciences<sup>[1]</sup>. The remarkable aspect of sciences, as articulated by Kuhn<sup>[2]</sup>, is that the most relevant progress does not occur by small steps but, rather, by revolutionary changes. These so-called paradigm shifts do not reject the former mainstream paradigms but integrate them, as a small part of reality, into the most recent empirical data in a coherent manner.

Kuhn<sup>[2]</sup> described the scientific revolutions as periodic social patterns resulting from accumulation of anomalies not predicted, and explainable, *via* so-called normal science. The dominating mainstream paradigm is the leading background for spreading and teaching scientific knowledge in school and university curricula. Even if new empirical data does not fit into the realm, mainstream proponents insist in this explanatory model. This remains true even if more and more empirical data does not fit into this realm. Then, new concepts, new insights and revolutionary new ideas are published that could integrate this new available data also. Mainstream proponents become sometimes aggressive and reject new concepts not by stringent arguments but rather by dogmatic insistence. As Brenner<sup>[1]</sup> mentioned, half a century before Kuhn<sup>[2]</sup> developed his theoretical but empirically proved theory of

the progress of scientific knowledge, Max Planck pointed out that this pattern of confrontation has not been solved by exchange of good arguments<sup>[1]</sup>. In contrast to this new paradigms succeed because the proponents of the old one grow old and die, *i.e.*, it is a natural not a rational solution: “A new scientific truth does not triumph by convincing opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it”<sup>[3]</sup>. Then the revolutionary new paradigm becomes the mainstream paradigm and all the teaching curricula become adapted, until new empirical data not compatible with the ruling paradigm, start to repeat this process again.

Brenner describes the radical revolution in life sciences during his lifetime: the occupation of biology by quantum mechanics, concerning the fundamental questions of matter and energy followed by the rise of genetics that showed that chromosomes were the carriers of genes. Brenner calls it the big error of physicist Erwin Schrödinger, who speculated on the physical nature of the genetic material, in that he assumed that “chromosomes not only contained the plan for the development of the organism but also had the means to execute it.” The discovery of the double helix resulted in the acceptance of new paradigm that information is physically embodied in DNA sequences of four different bases<sup>[1]</sup>. In contrast to the time before 1953, the question of information became central. The components of DNA are simple chemicals, but the biological complexity that can be generated by the information of different sequences is revolutionary. The fundamental concept that integrates this new biological “information” with matter and energy is the universal Turing machine and von Neumann’s self-reproducing machines<sup>[4]</sup>. According to Brenner, it was the fundamental error of Erwin Schrödinger that he considered the chromosomes to combine both ‘the architect’s plan and builder’s craft in one’; as the chromosomes do not contain the means for the execution of organismal plan, but only a description of these means<sup>[4]</sup>. Consequently it follows that biology is, in fact, physics with computation<sup>[1,4]</sup>. In other words, the bottom-top approach in biology is sufficient to solve all our goals in life science, culminating in the generation of artificial intelligence in future.

But is this really true? The universal Turing machine and the self-reproducing machines of von Neumann still remain at the conceptual stage. However, no single self-reproducing machine had ever been observed within the last 80 years. There are good reasons for this, because it is, in principle, impossible that an artificial machine could reproduce itself<sup>[5]</sup>. In contrast to the artificial machines which cannot reproduce themselves, the living cells and organisms can reproduce itself and - additionally, generate an abundance of behavioral motifs for which no algorithm can be constructed, such as *de novo* generation of coherent nucleotide sequences<sup>[5]</sup>. As inherent part of new revolution in life sciences, it emerges that genetic information in living cells is not the result of statistical er-

rors in reproduction of DNA, or random assemblies of nucleotides which are subject to selection. As we know today, an abundance of RNA based agents are evolutionary genetic content operators<sup>[6-8]</sup>. Moreover, it is RNA, not DNA, which decides about gene expression, both from the temporal as well as spatial perspective<sup>[6-8]</sup>. Most recent empirical data show convincingly that infectious agents such as viruses, mobile genetic elements and an abundance of non coding RNAs serve as basic tools for generation of genetic novelties, variations and - most important - their regulations<sup>[6-9]</sup>.

Now we know that DNA, which is packaged into the epigenetically marked chromosomes, contains the genetic information as well as the abundance of non-coding sequences, proteins, and RNAs that regulate, also *via* control of chromatin assembly and higher-order structures, gene expression, replication, transcription, translation, repair and epigenetic markings<sup>[5-9]</sup>. Non-coding DNAs, firstly denoted as junk, are playing central roles in genome organization and evolution<sup>[7-9]</sup>. In addition, the central dogma of molecular biology<sup>[10]</sup>, according which there is only one way of the biological information transfer (from DNAs, *via* RNAs, to proteins), is refuted recently on basis protein-based analog heredity and non-random adaptive mutations<sup>[7-9,11]</sup>. Besides the digitally-coded heredity *via* coding DNA sequences, there are several layers of analog inheritance in which proteins, structural templates, and agent-based active organismal behavior feedback in a top-bottom manner back to the genome<sup>[5-8]</sup>. As epigenetic variation precedes and facilitates genetic adaptation, the analog-based protein-conformation-mediated inheritance is representing the most radical violation<sup>[11]</sup> of the Central Dogma of molecular biology<sup>[10]</sup>.

One example is the role of noncoding RNAs in neuronal plasticity, the prerequisite of learning and memory-based adaptation in contrast to genetically determined behavior: Non-coding RNAs can be regulated in a varying manner, coordinated or independently, autonomously or functionally interrelated. They can regulate individual genes as well as large genetic networks. They can precisely control spatiotemporal deployment of genes that are executing neuronal processes with extreme cell specificity. Various classes of non-coding RNAs target each other for post-transcriptional regulation *via* alternative splicing, polyadenylation, 5' capping, non-templated modifications and RNA editing. Especially RNA-editing can transmit environmental information to the epigenome and therefore enables neuronal plasticity with learning and memory<sup>[12]</sup>.

The second example is how epigenetic imprinting regulates gene expression. Several classes of macro non-coding RNAs are active in DNA methylation, generally active in clustered genes throughout the genome. Genetic imprinting serves as effective tool in gene silencing and is a crucial regulatory network to tissue specific expression in replication. The whole variety of spatiotemporal coherent expression patterns especially in complex organisms with its variety of tissues depends on these epigenetic regulations. According adaptational purposes such as extreme preda-

tor-pray stress situations, nutrition availability or dramatic change in environmental circumstances (temperature), epigenetic marking may change and therefore represents a top-bottom regulatory network<sup>[13-15]</sup>.

As predicted by Thomas Kuhn in his book, the adherents of the Central Dogma still cling firmly to previous paradigm, even accusing some proponents of the new view of life sciences being linked to the “intelligent design” creationist community. However, it is rather the dogmatic approach of these passing paradigm scientists, which inhibits dynamic advances of sciences, adding fuel to nonscientific worldviews such as that promoted by adherents of the “intelligent design”. In fact, dogmatic thinking is not compatible with the curiosity-driven sciences<sup>[16]</sup>.

In conclusion, contemporary biology is accomplishing current revolution in life sciences. It is getting obvious that biology and life is not only physics and digital information encoded in DNA sequences. In order to understand life in its whole complexity, the top-bottom processes and analog information are essential<sup>[17]</sup>. A new revolution in life sciences<sup>[5-9,11]</sup> will integrate current empirical data, not fitting into the present mainstream science, into a new conceptual realm which cannot be provided by the Turing/von Neumann machines<sup>[5]</sup>.

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