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 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.
the progress of scientific knowledge, Max Planck pointed out that this pattern of confrontation has not been solved by exchange of good arguments[1]. In contrast to this new paradigm, it emerged that 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”[2]. 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[3]. 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[4]. 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 organisal plan, but only a description of these means[5]. Consequently it follows that biology is, in fact, physics with computation[6,7]. 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[8]. 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[9]. As inherent part of new revolution in life sciences, it emerges that genetic information in living cells is not the result of statistical errors 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[5-8]. Moreover, it is RNA, not DNA, which decides about gene expression, both from the temporal as well as spatial perspective[5-8]. 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[5-9].

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[5-9]. Non-coding RNAs, firstly denoted as junk, are playing central roles in genome organization and evolution[6,9]. In addition, the central dogma of molecular biology[10], 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[7,9,11]. 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[8,9]. As epigenetic variation precedes and facilitates genetic adaptation, the analog-based protein-conformation-mediated inheritance is representing the most radical violation[11] of the Central Dogma of molecular biology[10].

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[12].

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[13-15].

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[16].

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[17]. A new revolution in life sciences[5-9,11] 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[3].

REFERENCES
1 Brenner S. History of science. The revolution in the life sciences. Science 2012; 338: 1427-1428 [PMID: 23239722 DOI: 10.1126/science.1232919]
2 Kuhn TS. The Structure of Scientific Revolutions. Chicago: University of Chicago Press, 1967
3 Planck M. Scientific autobiography and other papers. New York: Philosophical Library New York, 1949: 33-34
4 Brenner S. Turing centenary: Life’s code script. Nature 2012; 482: 461 [PMID: 22358811 DOI: 10.1038/482461a]
5 Witzany G, Baluška F. Life’s code script does not code itself. The machine metaphor for living organisms is outdated. EMBO Rep 2012; 13: 1054-1056 [PMID: 23146891 DOI: 10.1038/embr.2012.166]
6 Villarreal LP. Viruses and the Evolution of Life. Washington: ASM Press, 2005
7 Mattick JS. Deconstructing the dogma: a new view of the evolution and genetic programming of complex organisms. Annu N Y Acad Sci 2009; 1178: 29-46 [PMID: 19845626 DOI: 10.1111/j.1749-6632.2009.04991.x]
8 Shapiro J. Evolution: A view from the 21st century. Washington: FT Press, 2011
9 Walsh AM, Kortchak RD, Gardner MC, Bertozzi T, Adelson DL. Widespread horizontal transfer of retrotransposons. Proc Natl Acad Sci USA 2013; 110: 1012-1016 [PMID: 23277587 DOI: 10.1073/pnas.1205856110]
10 Crick F. Central dogma of molecular biology. Nature 1970; 227: 561-563 [PMID: 4913914]
11 Koonin EV. Does the central dogma still stand? Biol Direct 2012; 7: 27 [PMID: 22913395 DOI: 10.1186/1745-6150-7-27]
12 Qureshi IA, Mehler MF. Emerging roles of non-coding RNAs in brain evolution, development, plasticity and disease. Nat Rev Neurosci 2012; 13: 528-541 [PMID: 22814587 DOI: 10.1038/nrn3234]
13 Jirtle RL. Epigenome: the program for human health and disease. Epigenomics 2009; 1: 13-16 [PMID: 22122631 DOI: 10.2217/epi.09.16]
14 Barlow DP. Genomic imprinting: a mammalian epigenetic discovery model. Annu Rev Genet 2011; 45: 379-403 [PMID: 21942369 DOI: 10.1146/annurev-genet-110410-132459]
15 Jeltsch A. Oxygen, epigenetic signaling, and the evolution of early life. Trends Biochem Sci 2013; 38: 172-176 [PMID: 23454078 DOI: 10.1016/j.tibs.2013.02.001]
16 Woese CR, Goldenfeld N. How the microbial world saved evolution from the scylla of molecular biology and the charybdis of the modern synthesis. Microbiol Mol Biol Rev 2009; 73: 14-21 [PMID: 19285350 DOI: 10.1128/MMBR.00002-09]
17 Noble D. A theory of biological relativity: no privileged level of causation. Interface Focus 2012; 2: 55-64 [PMID: 23386960 DOI: 10.1098/rsfs.2011.0067]

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