

70 Years – from DNA Double Helix *via* Approaching Systems Genomics to a Generalized Unified Evolution Theory

ABSTRACT

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70 years after the seminal description of the DNA double helix [1], recently also a consistent and likely final general description of the entire genome architecture and dynamics was put forward [2,3], which leads beyond to a generalized unified theory of evolution [4], similar – although on a much more fundamental level – to deciphering the genetic code following from its underlying material basis [5]. Thus, we not only understand now what is at the heart of “What is Life?” [6] and therefore presumably also “Mind and Matter” [6], but we also for the first time in the history of mankind approach a real grasp of “What Existence Is” – and this even in a cosmological sense, though even further advanced [7]. In respect to the long history of humans and evolution a really remarkable development once having started with various myth followed by religions already aeons ago.

The path to clarify existence has been long and in the true sense of the word stony, since already the earliest cave paintings of our ancestors, i.e. up to what we know now at least ~100.000 years ago, illustrate their occupation with matters of origin, being, and cosmological development in general. More elaborate descriptions in a mythical and religious respect reach first highs in the Buddhist and monotheistic trinities 2000–3000 years ago, later being found to be in many a resemblance of the scientific trinity of syntropy/structure/entropy which let to a first natural science based deep explanation of what life might be [6].

Besides many more noteworthy milestones, in respect to our understanding of life, the determination of tissues with their vesicle and bubble-like substructure by Robert Hooke or in the case of the cell nucleus by Anton van Leeuwenhoek in the 17th century, it took until 1830 when Robert Brown defined the cell nucleus as such an entity, and until 1839 when Theodor Schwann established the cell as the fundamental unit of all plant and animal tissues while interlinking with the assumed fundamental design principle of life as well as nature in general. In parallel, proposals on inheritance culminated e.g. in the proposal of Lamarck [8], and its replacement by theory of evolution of Darwin [9], although some essence of the first has already returned in what is known today as epigenetics [10]. Although, chemically the DNA was described already by Miescher in 1869 [11], its role as carrier of genetic information was envisioned by Avery only as late as 1944 [12], with Chargaff elucidating on the base composition following a “certain law” ~1948 [13].

Hence, with all the knowledge and technological development exploding, discovering the DNA double helix in 1953 by Watson and Crick [1] on the basis of Wilkins and Franklin [14,15], was inevitable. In retrospect, Watson and Crick considered their involvement as a great luck, and interestingly were knowing immediately not only the impact of their discovery even concerning human mankind [private communication/discussions by TAK with James D. Watson], but also approached how the genetic code must work [5], i.e. the functional essence of the DNA function in relation to life and evolution. The history of this and the

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https://doi.org/10.18388/pb.2021_544

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Acknowledgements: Deepest thanks go to James D. Watson and our personal communications/discussions, as well as to my son Leander A. Knoch for his outstanding contributions already at the age of 6 (!) and also to Olga Zimina for important long-lasting insights. Additionally, for deep thanks to many another people whom I was allowed to meet, work and discuss with – see for space reasons acknowledgments in [4].



Phot. 1. James D. Watson (seated in foreground) together with (from left to right) Olga Zimina, Leander A. Knoch, and Tobias A. Knoch, taken by Elizabeth Watson at the “Watson’s home”, Cold Spring Harbour Laboratory, 23rd October 2023.

revolution triggered by this has been described in detail by Watson and Crick themselves as by others in length [e.g. 16], but further milestones followed soon: Olins and Olins discovered (notably with a lot of challenges for their further scientific career [private communication to TAK]) the nucleosome – the first higher order bottom-up compaction state of DNA – in 1974 [17], whereas Cremer and Cremer described the two highest compaction states in interphase nuclei, i.e. the formation of chromosome territories and their positioning within the cell nucleus again both in a top-down approach in 1974 [18] and the latter ~2001 [19, present issue]. The cylindrical shape of compacted chromosomes during cell division, i.e. mitosis, was already discovered by Waldeyer in 1888 [history in 20]. For the possibly three compaction levels in-between, however, there has been a debate with all kinds of proposals and nevertheless seminal results since ~1870th (for a detailed recognition of major contributions see [21]) only until recently when we (Knoch and Wachsmuth) could undoubtedly discern between and describe the formation of a chromatin quasi-fibre, forming stable loops and again stable multi-loop aggregates/rosettes thereof [2] including its intrinsic physical dynamics [3]. The description of these middle three layers has been the hardest due to the huge orders of magnitude bridging scales of genomes being a polymer in an aqueous solution [21]. This finalization of genome higher-order architecture and dynamics also answered the reasons for its quantitative details in relation to its function, i.e. the stable storage, regulated access, and developing reproduction of genetic information consistently [2,3,21]. Beyond and interestingly yet again this lead to much more fundamental insights, since from this immediately a generalized universal theory of evolution [4] from the most fundamental properties of physics to the human cultural spheres follows, and is consistent with contributions on creativity and innovation [22] as well as the social/cultural (sub-)system theories of Luhmann [23] and Elias [24]. Although this has to be further investigated and quest for a consensus process in the field, i.e. a principia biologica, it is already clear that this approaches the essence of “What Existence Is” from the real explana-

tion of the directionality of time being the outcome of geno- and phenotype entanglement [4] and thus in a cosmological sense beyond previous contributions [7]. Thus, in sight of other parallel milestones on the fundamentals of evolution like elucidating the material basis of life coming into existence through self organized hyper-cycles [25,26], and of its hierarchic stability [27-29] being *in toto* far from equilibrium [30,31] are now understood on a much deeper level than the mere question of “What is Life?”.

As if it would not be enough, these in the very first moment academic achievements have beyond lead to an enormous amount of applied developments and applications in the biological and medical fields changing (daily) life tremendously: The development of the PCR by Mullis [32] using already the biological machinery itself for amplification of DNA has meanwhile reached every individual e.g. as diagnostic tool. The deciphering of the complete human genome by the human genome consortium [33] as well as the private initiative of Venter [34] in 2001 as well as meanwhile by thousands and thousands of species over all kingdoms of life has beyond its scientific impact on knowing part of the information coding for life, tremendous technical applications from hereditary (family) trees to (disease, i.e. cancer) diagnostics and treatment. Recently, the discovery of the Crisp/Cas9 system in 2012 [35], opens the door to gene manipulation and engineering in respect to the correction or enhancement of genetic codes even *in vivo* - an opportunity which fundamentally will change the abilities of mankind in general. Actually it is still an understatement that the entire biological, medical, and agricultural fields not only rely on the genomic field, but are furthermore driven by these advances. Applications in the more technical world are also gaining momentum, be it the usage of DNA as structural nanotechnology building blocks, as data storage, product security tagging, or even DNA based nano-electronics (see start and overviews of the underlying paradigms in e.g. [36-39]).

Hence, the latest developments in the genomic field, and especially the completion of the higher-order genome architecture and dynamics suggesting a generalized unified evolution theory will open huge opportunities whose impact cannot be underestimated in every field of life and existence: i) we will be able to really understand the holistic working of genomes *in toto*, which ii) will lead not only to better diagnostics and treatment of many a disease, but iii) will eventually also make us understand how intelligence and consciousness come about and how they can be influenced. We iv) will understand how the earth ecosystem works and evolves, and thus v) this will elucidate our human ecology dependence and contribution [40,41]. And beyond we will vi) not only understand extra-terrestrial as well as artificial intelligence and life, including their creation, development, and evolution, but vii) we will start grasping the fundamentals of life and existence in the entire universe. This is a huge opportunity for human mankind with tremendous technical applications as well as cultural and philosophical “enlightenment” as far as the *raison d’etre*.

Finally, looking retrospectively into the powerful disruptiveness of these fundamental achievements, reveals that

this stems from their scale-bridging systems-wide general importance as well as their groundbreaking trans-/inter-disciplinary yet again integrative systems determination methodologies, i.e. that solution and heuristics play out on the deep and at the same time broad holism. In other words only integrative systems approaches allow in the end to understand and manipulate the consequently holistic entangled interplay of geno- and phenotype creating e.g. in particular functional genomes [4]. Obviously genomics, the entire biomedical, and even in general complete systems sciences from the big-bang to (meta-)culture are going to be driven into the future by broad complex physical and mathematical methodologies and approaches. And hence, this will be ever more so also the case for any further investigation of genomes, life, evolution, and well basically all challenges we meanwhile face, including diagnostics and disease treatment, genome manipulation and engineering efforts, and ultimately also *de novo* created life forms. Thus, we are sure that this leaves ample space for many a great opportunities, and we are sure that the time ahead will lead to highly interesting insights following such a path.

In practical perspective, this has - as put forward already by me [42] - important consequences for all complex system wide challenges as e.g. the already mentioned health/disease/death, achieving extremely long or even "eternal" life of individuals, entire ecosystems, or even cultural systems as e.g. approached by the Sustainable Development Goals of the United Nations, and beyond anything which is concerned with artificial intelligence and life. Actually it demands [42] i) R&D *must* work inter-/trans-disciplinarily in an open innovative network! Here, *THE* keys are new virtual paper tools representing and seamlessly visualizing, integrating and manipulating the complexity of systems wholeness. Beyond, as foundation, ii) broad humanistic education (the baroque *Bildung* ideal) *must* be achieved with inter-/trans-disciplinary curricula of *ALL* sciences, arts, and professional crafts to efficiently exploit the opportunities of systems complexity. Learning for its own sake beyond mere training on the job *must* be the final mantra. Lastly, of ultimate importance, iii) society as a whole *must* epitomize an overall integrative thinking and operation, i.e. living a Human Ecology autopoietic systems perspective [41]. Hence, *ALL* this *must* be represented in a humanistic systems vision of terrestrial, interplanetary, and artificial intelligence/life, being for everybody *ad hoc* graspable in a playful "Glass Bead Game" [43] manner, both for the detailed daily practice as well as for a general "enlightened" understanding of existence.

70 years of the discovery of the DNA double helix, in conclusion, is one, if not *THE* symbol of a modern golden age of discoveries in (genome) biology and science in general with huge implications as visible here for even much greater insights into life and existence. The impressive knowledge we gained meanwhile is extremely powerful with ample opportunities if used wisely, i.e. in a systems manner, and thus avoiding the many a challenge misapplications can create as visible e.g. as what has lead to the climate challenge. Systems thinking, therefore is a must to be considered and has to be at the heart of our daily thinking and living. Hence, this will not only lead to a bright sustainable future,

but will also gain mankind unprecedented insights up to the *raison d'être*.

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