THE SIMPLY COMPLEX

# Is There a Newton of the Blade of Grass?

## The Complex Relation Between Mathematics, Physics, and Biology

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In 1790, Immanuel Kant makes the famous statement in his critique of judgment: "there will never be a Newton of the blade of grass, because human science will never be able to explain how a living being can originate from inanimate matter" [1].[1] The German naturalist Ernst Haeckel, about 70 years later, celebrates Charles Darwin to be such a "Newton of the grass blade" [2] Haeckel's enthusiasm about Darwin was not shared among his contemporaries and is not too widespread today, although the path-breaking role of Darwin's scholarly work is not the least doubted or questioned. The American philosopher, physicist, and molecular biologist, Evelyn Fox Keller, says that considering Darwin as the Newton of biology is simply wrong: [3] "Darwin himself has systematically avoided dwelling upon the question how life has originated from inanimate materials. Natural selection begins with a living cell." Kant's statement has a philosophical dimension and clearly addresses the popular origin-of-life [4] problem that will not be pursued further here. At the same time, Kant's issue has a historical and a technical scientific issue, which boils down to the problem of erecting modern biology on a solid basement of physics and chemistry supported by mathematics or in other words, bridging the gap between physics and chemistry on one side and biology on the other. Precisely, it is the relation between mathematics, physics, and biology that we shall try to illustrate in the light of historical developments and present-day life sciences.

Why are the relations between physics and mathematics and biology and mathematics as different as they could be? The alliance between mathematics and physics stands at the beginning of Western science and this "marriage" has proven to be extremely stable and fruitful. Two well-known quotations of past statements explain the situation perfectly: Galileo Galilei said (in abridged version): "The great book of Nature is written in (clearly-understood) mathematics," and Immanuel Kant expressed his esteem for mathematics in science in the phrase: "I maintain

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[1] *Original text in German: „ . . . es ist für Menschen ungereimt, . . . zu hoffen, dass noch etwa dereinst ein Newton aufstehen könne, der auch nur die Erzeugung eines Grashalms nach Naturgesetzen, die keine Absicht geordnet hat, begreiflich machen werde . . .".*

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only that in every special doctrine of nature only so much science proper can be found as there is mathematics in it" [5].[2] Mathematics provided and provides the tools for handling physical phenomena in quantitative terms and physics fertilized and fertilizes mathematics by initializing new disciplines. An impressive example stands at the beginning: the idea and the implementation of calculus. A large number of new and very fruitful developments in mathematics originated from problems in physics that waited to be formalized and formulated in new mathematical subdisciplines. A recent example of mutual fertilization of mathematics and physics is dynamical systems theory and, in particular, deterministic chaos. Initially, it was the question of stability of the solar system that has fascinated Henri Poincaré and lead to the discovery of irregular motion. In 1960, Edward Lorenz published his famous paper on deterministic nonperiodic flow [6] that had its roots in atmospheric science and led to development of the theory of deterministic chaos and strange attractors. Many other examples could be given, relativity theory and quantum mechanics being the best known ones from the first half of the 20th century. Only two further cases of cross-fertilization of mathematics and physics shall be mentioned here: (i) the theory of spin-glasses, renormalization, and the concept of universality classes and (ii) Brownian motion, the theory of diffusion, and the development of the mathematics of stochastic processes. Facit: Present-day mathematics would not be the same if there had not been the intensive and fruitful interaction with physics and vice versa.

Biology and its interaction with mathematics are completely different and the development of scientific thinking in biology took another route than in physics. In medieval times, mathematical models were popular also in the life sciences; Fibonacci's rabbit multiplication case may serve as an example [7]. Charles Darwin's evolutionary principle is a beautiful example of a fruitful abstraction from observational details he himself and others have recorded and reported. It reduces successfully the enormously complex phenomenon of evolution to three relevant features—multiplication, variation, and selection—but it is presented in the "Origin of Species" without a single mathematical expression [8], although a mathematical formulation of the selection principle is straightforward (see, e.g., reference [9]). Ernst Mayr's scholarly written book "The Growth of Biological Thought" likewise does not contain equations [10] and even D'Arcy Thompson's famous book "On Growth and Form" [11], which is often considered as the beginning of a mathematical biology has rather very little mathematics in it. Another interesting fact illuminating the cleft between mathematics and biology deals with the unification of genetics and evolutionary theory. The founding fathers of population genetics, Fisher [12], J.B.S. Haldane, and Sewall Write succeeded already in 1920 and 1930 to construct the mathematical model that united Darwin's selection and Gregor Mendel's genetics. It took more than 20 years before the experimental biologists conceived and finished the so-called synthetic theory[3] [13], that served precisely the same purpose of unification. Nothing could make the distinction between physics and biology clearer: whenever a new theory appears on the horizon of physical thinking all renowned experimental groups will hectically try to support or disproof the new concept. Admittedly and as we shall outline later, things appear to be much more complex in biology than in physics, and there is also good reason to be skeptic about theoretical biology of the past.

Why is theory in physics so successful? One reason certainly is the fact that theoretical physics is rooted in mathematics providing accurate answers to questions and experimental physics is amazingly successful in making high precision measurements meeting or contradicting the predictions of theorists. Determinism has dominated the early development of physics until the second half of the 19th century and when irregular motion on the atomistic level was included into physical thinking, the ensembles were always so large that statistics proper played very little role in observations on the macroscopic level. Observed regularities in biology are almost always of intrinsic statistical nature – Gregor Mendel's rules of inheritance may serve as an example—and then single experiments are not reproducible, as we are commonly dealing with small ensembles or few objects, which among themselves show appreciable variation. Mathematical description is tantamount to reduction: An observed regularity can be cast into a mathematical expression when only one particular aspect is or very few aspects are brought into focus and only a small number of other features considered to be important are introduced as parameters. Successful construction of mathematical models is enormously facilitated by the existence of a reference system of reduced complexity that is accessible to experiment or to observation. By such a reference system, we mean a model that can be applied to the real (complex) situation by introducing appropriate additional

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[2] *Original text in German: „ … Ich behaupte nur, dass in jeder besonderen Naturlehre nur so viel eigentliche Wissenschaft angetroffen werden könne, als darin Mathematik anzutreffen ist.‟*

[3] *Commonly the contribution by the botanist George Ledyard Stebbins on Variation and Evolution in Plants*[13] *is considered as the completion of the synthetic theory because it extended the unification of genetics and evolutionary theory to the plant kingdom.*

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effects. Newton's reference has been celestial mechanics and without belittling his genius I claim that the development of the theory of gravitation would have been delayed or even made impossible without the insight into the motions of stars and planets. Motions caused by the gravitational laws were observed free from complications by friction, winds, thermal columns, and other phenomena, which obscure free fall in the atmosphere of the Earth. To me, it seems to be anything but a simple abstraction to conclude from everyday observations that all bodies fall vertically and with the same acceleration (and velocity).

Biology is a fairly young discipline compared with physics. The beginning of physics is often dated by the works of Archimedes, who lived in Ancient Greece in the 3rd century BC. The word *biology* has not existed before the 19th century and is attributed to Jean Baptist Lamarck, Gottfried Reinhold Treviranus, und Lorenz Oken who coined this notion 1802 for *a science of life* [14]. Apart from the enormously large number of molecular players, the complexity of interactions, and high dimensionality of biological networks, it is the lack of a *celestial biology*, the difficulty to find a proper reference system, which encapsulates the essential features without the dispensable complications, what causes the different attitude of experimentalists toward theory and mathematics in biology and in physics. Two different examples of mathematical theories, which had to be built without the proper reference—because none was known then—and which had a very different fate, shall illustrate this point: (i) Mendelian genetics and (ii) embryonic morphogenesis.

Gregor Mendel recognized correctly the statistical nature of the inheritance of characteristics and postulated that genetic information is split into packages (atoms of inheritance in the *law of segregation*) and recombined at random from a pool (*law of independent assortment*). Hundred years later, molecular biology of DNA reproduction and cell division revealed that segregation and recombination occur during meiosis and deviations from the ideal Mendelian ratios can now be easily explained by incomplete segregation when the gene loci are too close to guarantee the occurrence of cross-over between them. Although Gregor Mendel had no idea of a proper reference for his theory, which was only later provided later by the molecular genetics of sexual reproduction, he did the right abstraction, guessed the proper reference, and drew essentially correct conclusions from his observations.

The second example is discussed extensively in Keller's monograph "Making Sense of Life" in the chapter "Untimely Birth of a Mathematical Biology" (p. 79ff. in Ref. 14): Turing in 1952 published a fascinating and pathbreaking paper on the chemical basis of morphogenesis in development [15] and initiated a highly fruitful branch of research on pattern formation in reaction-diffusion systems. Pattern formation in chemical reactions became a topic of primary interest in nonlinear dynamics and an impressive number of models and beautiful experiments were conceived, carried out, and analyzed [16]. Turing's model has been applied to build reaction-diffusion equations that were suited to describe morphogenesis and an impressive variety of biological patterns [17–19]. The biological applications to pattern formation—Turing's was originally aiming at—have not been successful on the long run, however. The computed reaction diffusion patterns created by the nonlinear dynamics of production and diffusion of *morphogens*[4] were found to be in poor quantitative agreement with observations and very sensitive to boundary conditions, in particular to the geometry of the morphogenetic field, and thus did not appear to be sufficiently stable for shaping organisms [20]. The major problem, however, arose from the proper molecular reference system: Molecular genetics experiments performed on the *Drosophila embryo* by Christiane Nüsslein-Volhard, Eric Wieschaus, and Ed Lewis—who received the Nobel Prize 1995 in physiology for their path-breaking investigations—revealed that pattern formation is not initiated in a homogenous medium but in a spatially organized structure, where messenger RNA transcribed from maternal genes is deposited and localized by means of microtubules at defined positions in the egg—*bicoid* at the anterior pole being the most relevant—and the patterns originate from cascades of gene activation, where the translated proteins activate or inhibit other genes [21, 22]. Recent work has shown that even simple gradients appear to be not sufficient as they were found to be supported by the action of further genes [23]. Thus, the proper (bio)chemical reference system for embryonic morphogenesis is not reaction-diffusion in homogeneous solution but a *morphogenetic* network of epigenetic (maternal) spatial organization and cascades of gene activities providing both (anterior–posterior) polarity and positional information for further gene activities. In an excellently written review, Maini et al. [24] describe the current situation: "…Therefore, although reaction-diffusion theory provides a very elegant mechanism for segmentation, nature appears to have chosen a much less elegant way of doing it." Turing's model does not provide a proper reference system for embryonic morphogenesis.

The present day situation in biology is different from the past in many respects. I choose three points that are relevant for a revision of Kant's statement: (i) New experimental techniques

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[4] *A morphogen is a signaling molecule that initiates development locally by means of its concentration. Different concentration levels produced, for example, by a concentration gradient initiate different patterns of gene activities, which in turn give rise to different pathways of cell differentiation and ultimately result in different cells and organs of the mature organism.*

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made the *chemistry of living* matter accessible to experimental analysis and produce an exponentially increasing amount of data, which, in principle, are highly relevant for any deeper understanding of life. (ii) The mechanism of evolution that is in the heart of biology has been reduced to cell-free molecular systems, which allow for completely bottom-up modeling of natural selection by chemical reaction systems under full control of conditions. (iii) Computer simulation in systems biology aims at a combination of holistic and reductionistic approaches in the sense that the properties of entire cells or organisms are described by models, which are rooted in molecular life sciences [25].

The *explosion* of biochemical data has been discussed on a plethora of individual articles and reviews. Here, we would like to emphasize three aspects only. (i) The necessity of large scale equipment for data harvesting at present and in the future, which is currently made available in the US, in the EU, in Japan and China and a few other counties, (ii) the requirement of world-wide huge databanks, which is commonly acknowledged and supported and, in addition, (iii) a new theoretical biology that allows for an efficient retrieval of information in suitable form. Data have to be filtered and put into a context before they can finally be stored in some data base, and this is impossible without a proper new theoretical biology as the experimental molecular biologist of the first hour, Sidney Brenner says: "... theoretical biology has a bad name because of its past ... I have decided to forget and forgive the past and call it (the new badly required discipline) theoretical biology [26]. ..." The comprehensive task for such a new theoretical biology is manifold. A new systematic language is required because the common notations based on laboratory protocol entries as used in current molecular biology are pre-Linnean. Standardization of multi-source and multi-disciplinary data bases is indispensable and a world-wide serviced and world-wide accessible data archive has to be established.

Evolution based on the Darwinian concept of multiplication, variation, and selection was considered as a privilege of cellular life for long time. A theory of evolution based on chemical kinetics of replication of molecules assured that selection can occur in cell-free media and in principle, there is no need for compartmentalization as long as one is interested only in selection [27,28]. This chemical approach to evolution – although not considered as evolution proper by many biologists – initiated a new branch of biotechnology that makes use of the evolutionary principle in the design of new molecules tailored for predefined purposes, mainly ribonucleic acids and proteins [29-31].

The change in scientific methodology between the 19th and the 21th century with the largest consequences was the establishment of a third source of scientific knowledge: The approach to problem solving, analysis and prediction based on computation and simulation became an equivalent partner of mathematics based theory and experiment. The spectacular increase in hardware capacities for computation and data storage, the enormous speedup of computation as well as the development of high-efficiency algorithms rendered numerical calculations into a powerful tool in the dialog between the researcher and nature. In particular, the investigation of large and strongly interacting networks that are not accessible to mathematical analysis became possible and computer simulations shed light on the forecasting of behavior of complex systems. It became clear, which features can be predicted and what the properties are that escape any serious forecast (at least for the time being). I mention only one example from physics: The theory of hurricane formation is almost perfect – the necessary surface temperature of the ocean is known to an uncertainty of less than a degree centigrade – but nobody can say when and where the next storm will originate. Enhancement of local fluctuations and deterministic chaos yielding turbulence in flowing air and streaming water obscure development of eddies and vortex formation.

In theoretical chemistry and biology computation and simulation became the most powerful tools in predicting system properties and behavior. In chemistry quantum mechanical calculations reached such a high degree of accuracy that computations of molecular properties are now often more reliable than experimental measurements. A new comprehensive theoretical biology understood as a merger of mathematical biology, bioinformatics, and theoretical systems biology, is still far away from the state of perfection theoretical chemistry has reached, but it is making fast progress and together with the spectacular achievements in experimental techniques it sets the stage for a new understanding of biology.

Coming back to the initial question: Yes, I do believe there is or there will be a Newton of the grass blade. As Evelyn Keller points out, Darwin did not fulfill Kant's criteria because he did not close the cleft between inanimate and living matter but modern molecular life science does. Choosing the molecular level as reference state for making models bridges this gap and has the advantage that the models are rooted on fairly safe grounds (cf., for example, the different cases, Mendelian genetics and Turing patterns discussed above). Biochemical kinetics and dynamics within the cell is modeled with increasing success in computational systems biology. It has, in addition, the advantage that many typical biological difficulties disappear. To give one example: In the molecular development of the drosophila embryo any sharp distinction between genetic and epigenetic effects becomes obsolete, since the embryonic pattern is a result of the concerted action of maternal and zygotic gene products and genes. Present-day computations are, in

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essence, based on the usage of calculus and differential equations, but simulations in the future may well use different techniques since living matter is highly structured and stochastic phenomena play an important role too. Casting dynamics into beautiful mathematical equations will be possible in a few exceptional cases only, but algorithm based analysis and model building through computer simulation have already become a highly estimated tool and will gain even more importance in the future.

Modern biology is a multilevel science and model building is required for each level making use of the known properties of the actors at the (next) lower level. Evidently, these levels ordered with increasing complexity are: molecules ⇒ cells ⇒ organs ⇒ organisms ⇒ populations. It is meaningless to describe a molecule in the language of elementary particles, and the same is true within the hierarchy of levels in biology. By the same token it is meaningless – although possible – to describe an entire organism in terms of the molecules from which it is built but whenever needed, for example in medicine and pharmacology, the – almost always complex – response to the action of a single molecular player has to be retrievable from the molecular level in order provide the desired understanding.

For short we did not discuss here environmental influence and interaction in ecosystems, which are indispensible, add another dimension of complexity to biological systems, and provide new challenges for finding the appropriate reference states.

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