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Review

Robert Rosen's Relational Biology Theory and His Emphasis on Non-Algorithmic Approaches to Living Systems

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Abstract: This paper examines the use of algorithms and non-algorithmic models in mathematics and science, especially in biology, during the past century by summarizing the gradual development of a conceptual rationale for non-algorithmic models in biology. First, beginning a century ago, mathematicians found it impossible to constrain mathematics in an algorithmic straitjacket via öö's Incompleteness Theorems, so how would it be possible in biology? By the 1930s, biology was resolutely imitating classical physics, with biologists enforcing a reductionist agenda to expunge function, purpose, teleology, and vitalism from biology. Interestingly, physicists and mathematicians often understood better than biologists that mathematical representations of living systems required different approaches than those of dead matter. Nicolas Rashevsky, the Father of Mathematical Biology, and Robert Rosen, his student, pointed out that the complex systems of life cannot be reduced to machines or mechanisms as per the Newtonian paradigm. Robert Rosen concluded that living systems are not amenable to algorithmic models that are primarily syntactical. Life requires semantics for its description. Rashevsky and Rosen pioneered Relational Biology, initially using Graph Theory to model living systems. Later, Rosen created a metabolic–repair model (M, R)-system using Category Theory to encode the basic entailments of life itself. Although reductionism still dominates in current biology, several subsequent authors have built upon the Rashevsky–Rosen intellectual foundation and have explained, extended, and explored its ramifications. Algorithmic formulations have become increasingly inadequate for investigating and modeling living systems. Biology is shifting from a science of simple systems to complex ones. This transition will only be successful once mathematics fully depicts what it means to be alive. This paper is a call to mathematicians from biologists asking for help in doing this.

Keywords: non-algorithm; algorithm; Robert Rosen; living systems; relational biology; category theory; integral biomathics; (M, R)-systems

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1. Introduction

1.1. What Is Life? Is It Algorithmic?

In the universe, only a minuscule part of all matter is alive. This living matter is the purview of biology. The rest of matter, the ubiquitous dead part, has been the focus of physics, earth science, and much of chemistry. What makes only one small part of nature alive is a mystery, even though all matter, dead and alive, is composed of the same atoms found in a finite set of elements listed in a single periodic table. While an atom is an atom is an atom, atoms of different elements have unique combinations of elementary particles, but all are atoms of a finite set. Sub-atomic particles like electrons are viewed as essentially interchangeable. Vagabond atoms are constantly in motion, even in the human body, with 98% of the atoms being replaced yearly. Out of approximately 30 trillion human cells, Fischetti (2021) [1] reported that 330 billion cells, or 1%, are replaced daily, primarily blood and gut cells, and in 80–100 days, there is a 'new you'. There are continuous cycles of metabolism and repair. As Hofmeyr (2007, p. 217) [2] reported, "... an organism is a system of material components that are organized in such a way that the system can audit. . . and continuously fabricate itself, i.e., it can live longer than the lifetimes of all its components". It also appears that we do not own our atoms; they are just on loan from the Earth, a system closed to matter but open to energy. All of Earth's atoms were gifted from the universe. They endlessly pass through us and the rest of biodiversity. Although we can make an 'atomic parts list' of living systems for every level of the biological hierarchy, from cells to the biosphere, the largest ecosystem, life itself, is not on the list. It is not a part of an atom or an element. Both our atoms and our cells are ephemeral throughout our lives. Life is something else.

However, understanding how transient the physical 'stuff' of life is does not solve the mystery of why some matter is alive, but most is dead. Living systems are open to matter, energy, and information. They are self-organizing, are impredicative, are complex, are anticipatory, exhibit emergent behaviors, are dissipative, and defy entropy accumulation while alive. Robert Rosen (1991a, 2000) [3,4] claimed that life could be depicted by non-algorithmic models using Relational Biology/Category Theory and could never be defined as a computation, an algorithm, a simulation, or a recipe. Many biologists adopting the Rosennean approach believe that answering the most profound questions about life will require non-algorithmic approaches—we currently do not comprise the majority of biologists, but an increasing number.

To search for an operational non-algorithmic approach begins with a workable notion of an algorithm. For our purposes, perhaps an early and short definition of an algorithm is sufficient as a beginning. Stone (1971) [5] defined the term as "a set of rules that precisely defines the sequence of operations". Although algorithms have been used since ancient times, with the advent of modern computing, they have exploded in number, depth, and breadth. Algorithms have goals their creators and developers ascribed to them, and they turn inputs into desired outputs using a finite set of instructions in a finite time. Some algorithms are not related to computation with a computer, like a human making a chocolate pie by following a recipe or conducting other tasks such as calibrating a meter using stepwise instructions. This paper focuses on computational algorithms used on a computer or Turing machine.

Once constructed, the algorithm is mindless. Roger Penrose (2016, p. 531) [6], a prominent theoretical physicist, further refined being mindless as being unconscious: "I think that the kind of terminology that we tend to use, which distinguishes our conscious from our unconscious mental activity, is at least suggestive of a non-algorithmic/algorithmic distinction: consciousness needed [for] common sense, the judgment of truth, understanding, artistic appraisal, [non-algorithmic] and consciousness not needed [for] automatic, following rules mindlessly, programmed, algorithmic. Perhaps these distinctions are not always clear cut. . . but the judgments themselves, I would claim are the manifestations of the action of consciousness. . . [which] is quite different. It proceeds in a way that any algorithm cannot describe". Essentially, consciousness is an emergent property of our brain, a complex physical organ also composed of atoms and cells. This emergent property travels with us through life, embeds our essence, and is actively aware unless we are sleeping or in a coma. That consciousness itself can be reduced to a set of rules seems nonsensical.

In the 21st Century, we live in an algorithm-rich world. Modern life would be impossible without algorithms. Interestingly, many designed for purely machine world applications are given animal or other biological names such as the 'Hummingbird Algorithm', 'Skunk Search Algorithm', 'Chicken Swarm Optimization', and 'Frog Leaping Algorithm'. Algorithms have become an essential part of computer and mathematical development and programming in hardware, software, machine learning, AI, discrete mathematics, including Graph Theory, and combinatorics, and Network Theory, optimization problems, algorithmic Number Theory, logic, computational algebra and geometry, deep learning, neural networks, bioinformatics, social media, robotics, automata, cryptology, statistics, and data analyses among many other areas. Algorithms fall into many categories depending mainly on their task and degree of sophistication. They may be supervised, semi-supervised, or non-supervised (Sohail and Arif, 2020) [7].

In one sense, algorithms are like the syntax or rules of a language. In some languages, the verb follows the noun. Others do the reverse. In English, there are rules for using ‘ie’ or ‘ei’ in spelling or when to insert commas in a sentence. Distinct from syntax is semantics, or the meaning of a word, sentence, or text. It is the latter that biologists seek to understand when asking why some matter is alive. It is usually easy to distinguish a living system from a dead one but very difficult to explain what life is. Biologists often say that “A dead bug is a dull bug”. While good syntax can assist the reading of a text by being rule-consistent, it tells us nothing about what the text tells us. Likewise, Information Theory was never about meaning but rather the probability that a message would be sent (Shannon and Weaver, 1949) [8].

Mathematics uses algorithms in many areas, such as computational mathematics, but less frequently in Number Theory, Abstract Algebra, Topology, and Category Theory. Areas in discrete mathematics, such as Graph Theory and Network Theory, may use algorithmic methods for some goals but not others, so there are areas that can be considered hybrids in their use of algorithmic and non-algorithmic methods. Topology, Group Theory, Number Theory, Abstract Algebra, Graph Theory, and Category Theory all have non-algorithmic aspects and offer promising ways forward. Mathematicians, like biologists, have mathematical structures and theorem constructions that require semantic-like understanding and not syntax or computation rules per se. Penrose (2016, p. 533) [6] concluded that “algorithms never assert truth” but a conscious mind can discern it non-algorithmically. A current question is, ‘Can living systems be understood and even created artificially with a set of instructions?’ This conclusion is highly relevant as many laboratories seek to transform the mystery of life into a recipe or algorithm using a ‘parts list’. It is relatively easy to make a chimera from living organisms, but it is impossible to make life de novo with chemical elements. Clawson and Levin (2023) [9] summarized much of the recent work on engineering chimeras in the laboratory specifically and in synthetic biology generally.

1.2. Purpose and Rationale

In this paper, we delve into a highly curated subset of some of mathematical biology’s successes and failures to answer why algorithmic approaches have been inadequate for elucidating the fundamental nature of living systems. The theoretical and historical background of the search for non-algorithmic methods for the living is outlined. Computation, while useful for many purposes, has not yet been sufficient. As Hong (2013) [10] concluded, “attempts to build mathematical theories for biology in the past century were met with modest and sporadic successes, and only in simple systems”.

Comprehensive answers and final solutions cannot be given here, and it may take a long time to develop wholly non-algorithmic mathematical biology methodologies and approaches. Regardless of how long it takes, mathematical models will be needed to help biologists explain what it means to be alive. The task can likely be accomplished with an insightful biological–mathematical partnership. This paper’s rationale is to appeal to mathematicians who might be intrigued enough by the mystery of life to spend some time developing mathematical biology of the non-algorithmic variety.

2. Theoretical and Historical Background

In this paper, many investigators and their contributions are mentioned, with an emphasis on Robert Rosen. Table 1 depicts an imperfect timeline for the contributors and their ideas mentioned here. Whenever one undertakes to sketch the diverse roots and lines of theoretical development over decades that lead to the current thinking on a scientific subject, some aspects of history, both documented and undocumented, are omitted. Some contributions and ideas were never archived or published and will never be recoverable. Today, the new literature is also so vast that it is impossible ‘to read everything’. Thus, the timeline is included for the convenience of the reader. It may seem odd that there are so many physicists included in Table 1. There are two reasons for this. First, physicists were interested in biological systems and had insightful things to say about them. Second, Rosen was well versed in physics; he repeatedly used his knowledge of physical systems to delineate biological systems.

Table 1. Timeline of Early Major Scientists and Mathematicians and Their Contributions to Mathematical Biology and Rosen's Thinking as Discussed Below.

Date	Contributor	Contribution
1900	Max Planck (1858–1947)	Theoretical Physicist Created Planck Constant (1900), Founder of Quantum Theory.
1905	Albert Einstein (1879–1955)	Theoretical Physicist Published four papers while working as a patent clerk, including one on the photoelectric effect relevant to Quantum Theory (1905). Creator of general (1915) and special (1905) relativity.
1908	Godfrey. H. Hardy (1877–1947)	Mathematician Contributed to Number Theory and Mathematical Analysis. Formulated Hardy–Weinberg Principle independently (1908).
1908	Wilhelm Weinberg (1862–1937)	Medical Doctor Contributed to the theory of population genetics. Formulated Hardy–Weinberg Principle independently (1908).
1917	D'Arcy Thompson (1860–1948)	Biologist, Mathematician Wrote *On Growth and Form* (1917) and developed morphogenesis. Contributed to notions of the beauty of mathematics in nature and organismal forms.
1921	Niels Bohr (1885–1962)	Theoretical Physicist Contributed to early Quantum Theory. Created Bohr model of the atom. Founded Institute of Theoretical Physics at the University of Copenhagen—Copenhagen School of Quantum Theory (1921).
1925	Alfred J. Lotka (1880–1949)	Biophysicist Created Lotka–Volterra Equations in ecology independently (1925). Wrote *Elements of Physical Biology*.
1926	Vito Volterra (1860–1940)	Mathematician, Physicist Created Lotka–Volterra Equations in ecology independently (1926). Father of Functional Analysis.
1927	Werner Heisenberg (1901–1976)	Theoretical Physicist Major contributor to Quantum Theory. Published the 'Uncertainty Principle' (1927). Part of 'Copenhagen School'.
1928	David Hilbert (1862–1943)	Mathematician With Wilhelm Ackermann, posed the 'Entscheidungsproblem' or Decision Problem in 1928. Tried to formalize mathematics with a syntactical approach. Contributed to many mathematical areas.
1944	Erwin Schrödinger (1887–1961)	Physicist Created the Schrödinger equation used in Quantum Theory. Wrote on 'quantum entanglement'. Published *What is Life?* (1944).
1930	Ronald. A. Fisher (1880–1962)	Mathematician, Statistician, Geneticist Established much of modern statistical theory. Published *The Genetical Theory of Natural Selection* (1930). Made significant contributions to Modern Synthesis and population genetics.
1931	Sewell G. Wright (1889–1988)	Geneticist Published *Evolution in Mendelian Populations* (1931). Published on genetic drift (1948). Founder of population genetics with Haldane and Fisher, Modern Synthesis in Evolution, and inbreeding coefficient. Created 'Path Analysis'.
1931	Kurt Gödel (1906–1978)	Logician, Mathematician, Philosopher Answered Hilbert's (1928) challenge by publishing two Incompleteness Theorems proving the unsolvable nature of the 'Entscheidungsproblem'.

Table 1. *Cont.*

Date	Contributor	Contribution
1932	John B. S. Haldane (1892–1964)	Biologist, Mathematician. Published *The Causes of Evolution* (1932). One of the founders of Modern Synthesis and Neo-Darwinism in evolution.
1936	Alonzo Church (1903–1995)	Mathematician, Computer Scientist Contributed to mathematical logic and computer science theory. He was a mentor of Alan Turing. Published the Church Thesis using lambda calculus, later renamed the Church–Turing Thesis, illustrating how the Entsheidungsproblem was unsolvable.
1936	Alan Turing (1912–1954)	Computer Scientist, Mathematician, Theoretical Biologist Published 'On computable numbers, with an application to the Entscheidungsproblem'. Developed the concept of the Turing machine. Published 'Solvable and Unsolvable Problems' (1954).
1939	Nicolas Rashevsky (1899–1972)	Biophysicist Father of Mathematical Biology, founding the *Bulletin of Mathematical Biophysics* (1939). In 1973, it became the *Bulletin of Mathematical Biology*. Created Relational Biology. Created 'Principle of Biological Epimorphism'. Formed Committee on Mathematical Biology, U. of Chicago, and retired (1964).
1944	Erwin Schrödinger (1887–1961)	Physicist Created Schrödinger equation and many fundamental advances in Quantum Theory. Contributed to Unified Field Theory. Published *What is Life?* (1944).
1945	Samuel Eilenberg (1913–1998)	Mathematician Together with MacLane, developed Category Theory in 1945. He is credited with founding Homological Algebra.
1945	Saunders MacLane (1909–2005)	Mathematician. Together with Eilenberg, developed Category Theory in 1945. Published *Categories for the Working Mathematician* (1972).
1958	Robert Rosen (1934–1998)	Theoretical Biologist 1956—Rashevsy's graduate student at the University of Chicago. Published first application of Category Theory for metabolism–repair of cells (1958). Joined Committee on Mathematical Biology (1959–1964). Joined Center of Theoretical Biology, State University at Buffalo (1964). Joined Dalhousie University as a Killam Chair (1975–1994). Published: *Anticipatory Systems* (1985a) [11], *Life Itself* (Rosen 1991a) [4], *Essays on Life Itself* (2000), *Anticipatory Systems* (2012) 2nd Ed.
1966	Walter Elsasser (1904–1991)	Physicist Pioneering work in magnetism. Contributed to complex Systems Biology and Relational Biology. Published *Atom and Organism: A New Approach to Theoretical Biology* and 'biotonic law' (1966) and *Reflections on a Theory of Organisms* (1987).
1968	Ludwig von Bertalanffy	Biologist Published General Systems Theory.

2.1. Physics First, Chemistry Second, Biology Third

In studying nature, the development of the sciences has been uneven. Physics took an early lead, working with essentially closed systems of dead particles and forces acting upon them using the reductionist approach of the Newtonian paradigm. States could be discerned, and changes in states could be studied over time. Some elegant mathematical descriptions and laws of nature were discovered in the process. Eventually, physics became the leading science by the 18th Century, as the 'chief explainer' of nature from its smallest atomistic domain to the cosmos. Also, in this century, chemists began to formulate the periodic table that made spectacular advancements in chemistry possible, which was eventually understood as a set of categories of atomic structure, while also realizing that living systems had some peculiar chemical molecules based upon carbon.

Meanwhile, biologists were grappling with describing nature, categorizing its many wondrous forms, and developing taxonomic nomenclature and inherited relationships primarily by differentiating structural peculiarities of organisms, and undertaking numerous expeditions to describe exotic ecosystems and collect specimens, returning with mostly dead matter. Nature was no longer viewed as divinely created perfection since variation was everywhere, and all types of odd specimens, clearly imperfect, were prominently and proudly displayed in the curio cabinets of Victorian parlors. Darwin himself came out of such a background. His 'Theory of Evolution' described natural selection as working on biological variation and species' adaptations as being heritable long before there was a workable description of genetics and the role of DNA. Structure was similarly viewed as determining function in biology as in the other sciences.

Gare (2013) [12] traced much of the early history of science involving the Newtonian paradigm and its related ideas that preceded Rosen's views. Gerald Weinberg (2001) [13] concluded that physics initially appeared so successful because physicists were ingenious in formulating questions they could answer and ignoring the rest. This conclusion may not be fair given the past century of frenzied efforts and frazzled neurons in trying to explain quantum mechanics and reconcile it with relativity theory. Some Quantum Theory explanations, like the 'Many Worlds Interpretation', seem far more compatible with science fiction than science. Rosen (1991a, 2000) [3,4], who was also not enchanted with physics, believed that the physics of closed, dead systems produced no usable mathematics for open living systems.

2.2. Reductionism or the Highway for Biologists

By the 1930s, biology was safely subsumed under physics and chemistry since who could reject successes such as the laws of thermodynamics, gravitation, and mass action? To the extent possible, biology mimicked physics in its reductionist conceptions of nature and its methodologies even though, at that time, it was well understood that living systems were open to matter, energy, and information in ways in which inanimate systems were not. In particular, notions of purpose and function were dismissed as irrelevant and even dangerous, and the living became the minuscule, oddball, special case of physical nature. Reductionist thinking in biology was also encouraged by the discoveries of the gene and DNA, molecular and cellular biology successes, and the introduction of sophisticated laboratory technologies that widened the chasm between the living and the dead.

I offer a personal example to illustrate how inflexible biological thinking often was in the 20th Century. I took my oral examination to receive a bachelor's degree in biology at the unripe age of 19. It was convened and judged by the most senior faculty. All candidates were warned that mentioning purpose would constitute an automatic failure. (Later in this paper, Section 3.2.4 discusses final cause and how Robert Rosen defined it for living systems in relation to purpose and function.) It was the quick cut to eliminate the 'unfit', who had unwisely chosen teleology and vitalism over reason. Thus, biology by choice stayed in the shadow of physics for much of the early to mid-20th Century and beyond.

Science, however, is never finished. Carlos Rovelli (2020) [14], a noted theoretical physicist, detailed how our concept of reality has changed many times in science. He concluded that "reality is decidedly not how it is described by classical physics. This was an abrupt awakening from the pleasant sleep in which we had been cradled by the illusions of Newton's success. However, it was the reawakening that connects us back to the beating heart of scientific thinking, which is not made up of acquired certainties: it is thinking constantly in motion, the power of which is precisely the capacity to always question everything and begin over again, to be fearless in subverting the order of the world in the search for a more efficient one, only to then put a further question mark over everything, and to subvert it all over again" (Rovelli, 2020, pp. 72–73) [14]. In the latter part of the 20th Century, biology became more mathematical and eventually more independent of physics. Although reductionism still dominates in the current biological literature, there is more tolerance for differing viewpoints and a much greater range of publishing outlets for less orthodox ones.

2.3. Early Mathematical Biology

Simultaneously, a great deal of scientific technology and many mathematical and statistical tools developed in physics and chemistry were applied directly to studying life. These tools were exemplified in the early to mid-20th Century by Alfred J. Lotka and Vito Volterra, independently using Differential and Integral Calculus to study populations of organisms, especially pairs of predator–prey, competitors, and mutualists. Lotka's initial plan had been to mold a new sub-discipline of physical biology analogous to physical chemistry, focusing on energetic relationships. D'Arcy Thompson studied growth and morphogenesis (form) in organisms and demonstrated the mathematical beauty in nature. G. H. Hardy and W. Weinberg first published gene frequency calculations in 1908. J. B. S. Haldane, Sewell Wright, and R. A. Fisher developed mathematical and statistical methods to understand population genetics and evolutionary processes further. Essentially, organisms and their genes became simple homogenous inert particles in their early models like billiard balls on the green felt table of life despite the extensive chronicling of species variation and diversity of descriptive biology.

Regardless of so much emphasis on reductionism as the dominant scientific approach in biology, mathematical biology became undeniably necessary for understanding the living, but at first, mathematics was necessary for biology, like the way it was needed for physics, primarily for computation. With the almost universally accepted assumption that physics subsumed biology, few realized that life needed more custom-designed mathematics, at least for resolving some of the deeper issues. Thus, in the first half of the 20th Century, several prominent scientists bridged the biological–mathematical divide and began infusing conventional mathematical concepts and methods into biology. However, most did not question the supremacy of physics and its conceptual base. They primarily used mathematics developed for physical systems since they believed that living systems were not qualitatively different from dead ones. Consequently, life did not need any form of special mathematical treatment.

2.4. Physicists Puzzle About Life

Walter Elsasser, considered one of the first Ph.D.s in quantum mechanics at the University of Göttingen in 1927, became well known for his pioneering work on atomic structure, magnetism, meteorology, plate tectonics, and geophysics. He began to moonlight in theoretical biology and became fascinated by living organisms. He wrote four books on the subject. Early on, he was convinced that using mathematics to characterize life would be impossible, but perhaps logic would work. He explored the notion of how quantum mechanics might explain life. He also rejected reductionism, mechanics, and vitalism applicable to living systems. He advocated for a holistic theory for organisms to accommodate their 'organized complexity' and suggested a 'biotonic law' for organisms that could not be developed within physics (Elsasser, 1966) [15]. In his book, *Atom and Organism*, he surveyed the current state of mathematical biology and concluded, "We should be clear, however, about the fact that the pursuit of such [mathematical] analysis along purely mechanistic lines must have its intrinsic limitations and that modifications resulting from the semi-autonomous character of biological phenomenon will sooner or later have to come into play" (Elsasser, 1966) [15]. He also contrasted living with dead systems by showing how homogeneous all atomic particles were compared to the individuality and heterogeneity of living systems. He believed that physics and chemistry could explain many processes in organisms but never their existence. He was one of the founders of Systems Biology, presently a primarily algorithmic endeavor.

Meanwhile, the burning question for biology, "what is life?", was not seriously posed until Edwin Schrödinger, a renowned Nobel physicist, who pioneered quantum mechanics, and was not trained as a biologist, asked it in a 1944 book of the same title (Gumbrecht et al., 2011) [16]. Another physicist, Nicolas Rashevsky (1899–1972), became interested in applying mathematical thinking and methods of physics to biology. Rashevsky is considered the Father of Mathematical Biology, and he founded the *Bulletin of Mathematical Biophysics* in 1939 to better disseminate these ideas. In 1973, the name was changed to the *Bulletin of Mathematical Biology*, which is still being published. Rashevsky began by trying to model various physiological processes individually, such as digestion, respiration, nerve conduction, cell division, and circulation. Eventually, he joined the faculty of the University of Chicago and established the Committee on Mathematical Biology, where he would become Robert Rosen's Ph.D. supervisor. Shmailov (2016) [17] has detailed Rashevsky's academic career, research interests, and how his vision and research productivity were often thwarted by university politics and the relentless need to raise research funds. It is noteworthy that the three people at this time who dwelled upon the quintessential questions about life were physicists and not biologists. Part of the explanation of this strange fact was the prevailing, almost worshipful, if not envious, opinion of biologists regarding physics and their emphasis on the overall equivalence of living systems with machines—the 'Machine Metaphor' (Henning and Scarfe 2013) [18]. It appears that physicists knew better than biologists about how unreliable this equivalence was. To be alive was qualitatively different than to be dead.

A mathematical biologist like Rosen (1991a, 2000) [3,4] would always maintain that genuine systems have goals or purposes whether they are alive or constructed by humans, and that these goals can be understood without resorting to teleology, vitalism, or divine creation (Allen et al., 1998) [19]. Fundamentally, the goals of organisms and ecosystems are to survive and persist (Lane, 2018a) [20]. Even more contrary, Rosen (1991a, 2000) [3,4] believed that the simple systems of physics would someday be subsumed under biology, which deals with complex systems. To Rosen, physical science existed only as a branch of the Tree of Science, whereas biology was the tree trunk that supported the rest and that physics itself would be enhanced by a closer connection to biology. Friedrich von Schelling, with his notion of 'Speculative Physics', also believed that self-organization in living systems would require a special mathematics outside of what physics provided (Gare, 2013) [12].

Thus, biology was made 'computable' in the first part of the 20th Century with established conventional mathematics and step-by-step algorithmic directions. Proper scientists measured carefully and reported results numerically. To be as quantitative as possible meant better biology as a science. Dwelling too much on the alive part of the living was discouraged since it was not proper mechanics, and biological systems and their phenomena were considered messy and unpredictable. When has a respectable voltmeter or a pendulum ever given birth, and why have death and senescence only been attributed to batteries, stars, and universes in physics?

2.5. Nicolas Rashevsky, the Father of Mathematical Biology

As his work progressed, modeling diverse physiological systems, Rashevsky realized that he could model most biological processes and still not understand the whole organism or "what actually constitutes life". He considered that biology was in a pre-Newtonian stage of development, waiting for its biological Newton to identify its 'laws of nature' (Hoffman, 2015) [21]. Rashevsky concluded, "There is no successful mathematical theory which would treat the integrated activities of the organism as a whole. . .The fundamental manifestation of life . . . drops out from all our theories in mathematical biology" (Rashevsky, 1960, p. 306) [22]. Rashevsky (1954) [23] endorsed Relational Biology "to throw away the stuff and keep the organization" and he initiated a more qualitative approach to understand living systems. He proposed, "we must look for a principle which connects the different physical phenomena involved and expresses the biological unity of the organism and of the organic world as a whole" (Rashevsky, 1954, p. 321) [23]. In this paper, he argued that focusing on the qualitative and topological relationships within and among cells and organisms would be a more fruitful endeavor than determining quantitative values for process rates, 'the metrics', which became his 'Principle of Biological Epimorphism'. Rosen (1972) [24] would later describe his mentor's motivation as emphasizing the search for universal fundamental principles and laws in biology based upon functions at the organism level. Rashevsky thought that biology based upon structure would not be worthwhile since no study of structure had ever left an adequate basis for discerning biotic from abiotic systems: "Rashevsky (1954) [23] stressed the need for the development of general theoretical principles in biology, as in theoretical physics. . .He argued that these principles must necessarily be functional in character and arise ultimately from our belief that we can recognize an organism when we see it. That this intuition arises from functional and not structural properties follows, for example, from the fact that no enumeration of purely structural properties has led to a satisfactory definition of life, capable of including all systems we intuitively think of as alive and excluding all systems that we intuitively feel are not" (Rosen 1991a) [4].

Rashevsky then directed his total effort toward developing his newly named field, 'Relational Biology', using Topology, Set Theory, and Graph Theory. He reported, "There exist one, or very few, primordial organisms, characterized by their graphs; the graphs of all organisms are obtained from this primordial graph or graphs by a transformation, which contains one or more parameters. Different organisms correspond to different values of those parameters. . .In general biology, we do not have universal constants such as are found abundantly in physics. However, we do have certain invariant sets of relations between different properties common to all organisms" (Rashevsky, 1962, p. 1105) [25].

Success in physics certainly guided his thinking when he suggested, "Einstein's demonstration that a wide class of physical phenomenon was isomorphic to the geometric properties of a four-dimensional non-Euclidean hyperspace was an important milestone in the development of physics. If this were possible for biology, then by an appropriate dictionary we could translate the theorems that hold for the mathematical concept into laws of biology and thus discover such new laws" (Rashevsky, 1962, p. 1107) [25]. He continued to advocate for Relational Biology: "but, as we have seen, very many biological phenomena, and perhaps the most basic of them, are not quantitative but relational. But very definite statements can be made about them, and their importance is unquestionable. If we wish to describe mathematically this situation, we need a different mathematical apparatus from the one used hitherto in physics or in mathematical biology. Such an apparatus is provided by topology, which is the geometry of relations rather than of quantities. . .a move in the direction of geometrization of biology" (Rashevsky, 1960, p. 406) [22].

2.6. Algorithms for Biology and 'Life Itself' (?)

Rashevsky was a gifted scientist and a pioneer in mathematical biology and biophysics. However, his publications are clear that he felt his first 30 years in bringing mathematics to biology had missed the mark. It must have been difficult to change directions at a mid-late point in his career, especially given the malevolent university forces that were arrayed against him at the University of Chicago (Shmailov 2016) [17]. He found no way, however, to integrate so many individual biological processes mathematically. Whereas he had the strong vision and determination to give mathematical form to the relations among biological processes (functions), he was frustrated concerning selecting which tools to use as he sorted through the various mathematical tools available.

At one point, Rashevsky turned to a direct consideration of algorithms as he tried to find some congruence between processes in mathematics and processes in biology. In his view, algorithms had a "process-like character" like life itself (Rashevsky, 1962, p. 1108) [25]. Algorithms in the mid-century were enjoying an upsurge in popularity and interest given their usefulness in emerging computer technologies and associated needs for faster computational capacity. Rashevsky was enthusiastic about claims of the superior processing capabilities of algorithms by A. A. Markoff Jr., a gifted Russian mathematician. Rashevsky (1962, p. 1108) [25] suggested that "algorithms encapsulate a process of steps similar to how a cell might undergo a set of metabolic or gene regulatory steps". He also thought that “the result of an operation of an algorithm is a special case of a mapping. . .the theorem of composition of algorithms has its counterpart in the composition of mappings. An algorithm Ų maps the word P on the word Ų (P). Hence, our statement that an organism is a set of its components, is represented by a set of mappings, is identical with Rosen’s view, and all the results of Rosen’s can be properly translated into the language of the theory of algorithms” (Rashevsky, 1962, pp. 1112–1113) [25]. This conclusion was later firmly rejected by Rosen (1991a, 2000) [3,4], who believed that algorithms and computational models could never adequately describe living systems.

2.7. Physicists Puzzle About Relations and Reality

It is interesting that, once again, some relevant relational ideas for biology come from some renowned theoretical physicists. Albert Einstein created a paradigm shift in physics with his general and special relativity theories in the early 20th Century. Time and space were not the established invariant parameters of reality that most had thought. The world was not as it seemed many centuries before the everyday notions of ‘up and down’ had to be rethought. Quantum Theory was simultaneously developed by Niels Bohr, Max Planck, Werner Heisenberg, Edwin Schroeder, and Albert Einstein, among others, from 1895 to 1925. Carlos Rovelli (2020, pp. 76–77) [14], who conducts innovative research on quantum gravity, had this observation: “Individual objects are the way in which they interact. If there was an object that had no interactions, no effect on anything, emitted no light, attracted nothing and repelled nothing, was not touched, and had no smell. . . It would be as good as nonexistent. To speak of objects that never interact is to speak of something—even if it existed—that would not concern us. It is unclear what it would mean to say such objects ‘exist’. The world that we know that relates to us, that interests us, what we call ‘reality’, is the vast web of interacting entities, of which we are a part, that manifest themselves by interacting with each other. It is with this web that we are dealing. . . the discovery of quantum theory, I believe, is the discovery that the properties of any entity are nothing other than the way in which that entity influences others. It exists only through its interactions. Quantum theory is the theory of how things influence each other. And, this is the best description of nature that we have”.

Rovelli (2020, p.79) [14] credits Niels Bohr in the 1940s with the idea that “the properties of an object are the way in which it interacts upon other objects; reality is this web of interactions. Instead of seeing the physical world as a collection of objects with definite properties, quantum theory invites us to see the physical world as a net of relations”. Rovelli (2020, p. 150) [14], who also has an excellent command of the history and philosophy of science, reported that the notion “there is nothing that exists in itself independently from something else” can be attributed to a 2nd Century CE Buddhist philosopher, Nāgārjuna, and some other relational ideas as far back as Plato and Anaximander (Rovelli, 2020) [14]. A great deal of rethinking about relationships and reality has been occurring during the past century. What exactly does this web of interactions creating reality mean? This ‘rethinking’ sounds like Rosen’s concept of Relational Biology, and relational concepts are present in all sciences, mathematics, and arts, not just physics and biology. Ecosystem chimeras are also a web of interactions that may constitute the actual reality of evolution (Lane, 2018a) [20].

2.8. Mathematicians and Physicists Ponder over Computability and Algorithms

This section is a brief synopsis of the state of the question ‘when can algorithms be used in mathematics and when not’, needed to proceed to understand Rosen’s view on ‘what is life’ and his approach to algorithms, non-algorithmic modelling, and models of living systems in the last part of Section 2. Relevant philosophical parts of this subject are omitted; however, a good summary is in the online Stanford Encyclopedia of Philosophy under the title of the ‘Church-Turing Thesis’ (2023) [26].

For this paper, the mathematical story begins in 1928 when David Hilbert and Wilhelm Ackermann posed the ‘Entscheidungsproblem’ or Decision Problem, which challenged mathematicians to what Hilbert termed, ‘the main problem of mathematical logic”; that is, "there must be a systematic method for telling, of each mathematical statement, whether or not the statement is provable in the system. If the system is to banish ignorance totally from mathematics, then it must be decidable" (Copeland 2013a, pp. 45, 47) [27]. The question was whether a given expression is provable in a system of symbolic logic by the system itself. The 'Entscheidungsproblem' asked if there was an algorithm that could verify the truth of any mathematical statement. "Hilbert was led to deny that pure mathematics was about anything at all—even about itself. Indeed, he implicitly blamed the critics themselves entirely on unexpunged 'informal' semantic residues in mathematics, and he proposed replacing the entire enterprise with an inherently meaningless game of pattern generation, played with symbols on paper" (Rosen, 2000, p. 157) [3].

Kurt Gödel, a prominent mathematician, answered Hilbert's challenge by publishing two Incompleteness Theorems using mathematical logic in 1931. He proved that no consistent set of axioms or rules could produce all true mathematical statements in the whole of mathematics; he did this by assigning numbers to logical expressions (Piccinini, 2003) [28]. Gödel proved this was true even in arithmetic with his first theorem. Then, he went on to prove that the result was more general in that "a precise and unquestionably adequate definition of the general concept of a formal system can now be given, with the consequence that incompleteness can be proved rigorously for every consistent formal system containing a certain amount of finitary number theory…in his Incompleteness Theorems, Gödel has shown that no matter how hard mathematicians might try to construct the all-encompassing formal system envisaged by Hilbert, the product of their labors would, if consistent, inevitably be incomplete" (Copeland, 2013a, p. 48) [27].

Thus, there was no finite set of rules or algorithms that could ever be sufficient, and consequently, there were mathematics problems that could not be solved by a computer or Turing machine programmed with algorithms. Gödel caused a significant upheaval in mathematics because since Euclid's time and through the development of algebra, mathematics was essentially an algorithmic process (Avigad and Brattka, 2014) [29]. Penrose (2016, p. 145) [6] concluded, "Be that as it may, it seems to me that it is a clear consequence of the Gödel argument that the concept of mathematical truth cannot be encapsulated in any formalistic scheme".

The 1930s continued with a build-up to World War II and the early work on the pursuit of improved computation and cryptology, which were fundamental to the war effort and development of modern computers. By 1936, Alan Turing was a brilliant graduate student in mathematics, publishing his first paper, 'On computable numbers, with an application to the Entscheidungsproblem'. It essentially laid out what an 'effective computation' using a Turing machine is compared to human calculators. At the time, there were only human calculators. Simultaneously, Alonso Church, a prominent American logician, also entered the fray by suggesting that the best methods were recursion and definability, using lambda calculus to prove effective computability. His abstract method left even Gödel unsure of Church's results. Rosen (1991b) [30] explained, "Church's Thesis states that anything that can be obtained by following a set of rules can be obtained as the result of running a computer program on a universal Turing machine. The claim that it is possible to extend Church's Thesis to the world of nature and man, at large, constitutes the theoretical underpinnings for what is sometimes termed strong AI, i.e., the possibility to build a computer to think like a man". The thesis was also published in 1936 after an earlier set of papers that developed the conceptual base (Church, 1936) [31]. Turing's (1936) [32] paper and his subsequent work were eventually combined into the Church–Turing Thesis. Turing's conception was less abstract, more rooted in everyday experience, and more understandable than Church's abstract version of what was computable.

Both mathematicians, Church and Turing, concluded that the 'Entscheidungsproblem' is not solvable by using Functional Calculus. The ramifications of the Church–Turing Thesis have motivated a large and complicated literature and many 'side discussions' like the 'halting problem' that are not reviewed here. As Copeland (2013a, p. 47) [27] pointed out, "Unfortunately for the Hilbert program, however, it was soon to become clear that the most interesting mathematical systems are, if consistent, incomplete and undecidable". Hilbert wanted to formalize mathematics syntactically within itself and to expunge semantics, but in this endeavor, he was evermore disappointed.

Turing, the Father of Artificial Intelligence (AI), would later become well known for his work on formal algorithms for computers and the Turing machine. This virtual logic machine was the conceptual prototype of a physical computer. The Turing Test asked if a computer could solve problems so well that its responses would be indistinguishable from those of a human. The Turing Test did not prove machine intelligence; it was only a sufficient condition for that intelligence (Piccinini, 2003) [28]. Turing's last paper before his untimely death in 1954 was a transcript of a 1954 lecture entitled 'Solvable and Unsolvable Problems' (Copeland, 2013b) [33]. Between the 18 years of these two bookend papers of Turing's career was an amazing set of results and accomplishments that are perhaps more important today than in Turing's lifetime. He essentially lit the formal algorithmic match that illuminated the way to the Computer Age and Artificial Intelligence, but he was also aware of the limitations of algorithms.

Turing distinguished between mathematical problems that can be solved and those that cannot in his last 1954 paper (Copeland, 2013b) [33]. Because this was a talk for laypeople, he began by framing the computability question in a discussion about familiar puzzles and introducing the concept of the substitution puzzle. Turing realized that the 'Thesis' was not provable although it is generally accepted as true by many mathematicians. He believed that if one could define a puzzle, it was a theorem; if not, the 'Thesis' was a definition (Copeland, 2013b) [33]. In this paper, Turing concluded that no "systematic procedure" exists for determining whether a puzzle is solvable (Copeland, 2013b) [33]. Turing said in 1954, "No systematic method of proving mathematical theorems is sufficiently complete to settle every mathematical question, yes or no" (Copeland, 2013b, p. 582) [33].

Gödel (1964) [34] pointed out that "Due to Turing's work, a precise and unquestionably adequate definition of the general concept of formal system can now be given. . . Turing's work gives an analysis of the concept of 'mechanical procedure' alias algorithm or computation procedure or finite combinatorial procedure. . . A formal system can simply be defined to be any mechanical problem for producing formulas, called provable formulas" (quoted by Copeland, 2013b, p. 581) [33]. Over the intervening years between 1954 and today, the Church–Turing 'Thesis' has undergone numerous modifications and refinements and is more commonly referred to as a definition rather than a theorem. Types of algorithms and computing machines have greatly expanded, making the Church–Turing Thesis also broader than its original counterpart.

Although Turing worked toward an Artificial Intelligence that could someday be as creative as humans, he realized that while algorithms could capture much of human reason and perform many tasks better and faster than humans, there was a 'commonsense' side to human thought not included in algorithms. Even mathematicians satisfying themselves that a proof was valid needed to use intuition. Thus, there was a fundamental sense in which rules alone and endless iteration cannot pre-empt or erase the need for intuition in mathematics and biology. Turing (1954) concluded in his last paper that "The results which have been described in this article are mainly of a negative character, setting certain bounds to what we can hope to achieve purely by reasoning [algorithms] (Copeland, 2013b) [33]. These and other results of mathematical logic may be regarded as going towards demonstration, within mathematics itself, of the inadequacy of reason unsupported by common sense". Essentially, not all mathematical problems can be solved by a Turing machine, which is good at syntax and manipulating symbols but lacks the capability for semantics. Common sense for Turing included intuition.

3. Robert Rosen, Mathematical Biologist Extraordinaire

3.1. Rosen's Early Academic History and Development of Ideas

Robert Rosen entered the University of Chicago in 1956 as a Ph.D. student and was quickly drawn to Rashevsky's Relational Biology ideas and the Committee on Mathematical

Biology. Rosen became Rashevsky's graduate student and wrote his now classic first papers on using Graph Theory (1958a) [35] and then Category Theory (1958b) [36] to describe the essence of organisms. The latter was likely the first biological application of Category Theory. He remained with Rashevsky after receiving his doctoral degree in 1959 as a committee faculty member until his mentor retired in 1964. By the early 1960s, the student had surpassed the master. However, Rosen always remained respectful and appreciative of what he learned under Rashevsky's mentoring and the academic opportunities he enjoyed being part of the Committee of Mathematical Biology. Rosen then took a position at the Center for Theoretical Biology with Professor James F. Danielli as head at the University of Buffalo (SUNY) until 1975, when he became a Killam Chair and Research Professor in the Department of Physiology and Biophysics, Faculty of Medicine, at Dalhousie University in eastern Canada.

Even as a graduate student, Rosen was proficient in physics, including quantum mechanics, chemistry, biology, and mathematics. He was also well versed in the new areas of General Systems Theory, cybernetics, Information Theory, and control and optimization theory, and he later published papers on these subjects. Early on, Rosen was also influenced by Ludwig von Bertalanffy, Father of General Systems Theory (GST), who defined a system as follows: "a system is a set of interacting elements organized to achieve a particular goal" (Bertalanffy, 1926) [37]. Rosen interacted with Samuel Eilenberg, a topologist, and Saunders MacLane, an algebraist, who together founded Category Theory in 1945. As an undergraduate student, he took a Category Theory course with Eilenberg at Columbia and met with MacLane at the University of Chicago. Rosen was well versed in this methodology, as is demonstrated by the theorems he developed in his early papers (Rosen, 1958b, 1959, and 1962a, 1962b) [36,38–40]. To him, Category Theory was not 'abstract nonsense', a term, perhaps not of endearment, used by so many mathematicians at the time. Rosen had also read Edwin Schrödinger's (1944) [41] book, *What is Life?*, and had decided to spend his career on this most important and worthy question. It was his consuming passion until he died prematurely in 1998, at the age of 64, in his intellectual prime.

Rosen (1958a) [35] published his first (M, R) metabolism–repair model for a cell using Graph Theory and Set Theory. He quickly followed that paper with a new (M, R) system model using Category Theory (Rosen, 1958b) [36], which he considered a new method for Relational Biology. Rosen once explained, "I became intrigued by the historical roots of the theory [Category Theory], which had grown out of an attempt to make algebraic models of geometric objects in order to discriminate between them. It expressed in the mathematical realm the patterns of relations between objects and models, and between one model and another, which I was trying to find in the realm of the living" (Rosen, 2012, p. 428) [42]. Category Theory generalizes Russell's and Whitehead's earlier logical framework. In 1959, Rosen added much more biological and physical detail to his model.

Between 1958 and 1964, Rosen and Rashevsky often commented on each other's work in the *Bulletin of Mathematical Biology*. For example, Rashevsky (1962, p. 1107) [25] noted that "Robert Rosen in 1958 developed the idea further of using oriented graphs as the topological complex that corresponds to different organisms and generalized it in the following manner: every component or organ of an organism may be represented as the vertex of a graph. The oriented edges that converge on the vertex or that leave it represent then the inputs and outputs of the component or organ… itself is represented by a mapping and a single organism by a set of mappings. Rosen uses the theory of categories of Eilenberg and MacLane, which deals with sets of mappings, to derive an interesting biological conclusion… Life, while essentially closely related to complex structures, is basically a process; therefore, if we seek a mathematical conceptual framework to which life is isomorphic, it is natural to seek such a framework through mathematical processes that involve sequences of certain mathematical manipulations". "Rosen has shown that the notion of a self-replicating system leads to a logical paradox. The self-replication is a particular type of mapping in which, however, the range is not defined until the mapping is performed" (Rashevsky, 1962, p. 1113) [25]. Ehresmann and Vanbremeersch (2006, p. 138) [43] later described Category Theory as "between mathematics and metamathematics. . .thus capturing the thinking process of the "working mathematician. . . as for example when the mathematician develops models to fit the reality that one observes and therefore gains predictive power through such models".

Many authors have been disappointed that Rosen did not address their topics of interest more fully since when they read his published work, they did not find the guidance they sought. This criticism is understandable but not a fair critique. Rosen was on a lifelong mission to answer the question 'what is life'? His ancillary mission was to bury reductionism and the use of the Machine Metaphor in biology in as deep a hole as possible for time and all eternity. He wanted to be as clear and concise as possible on his central question and expended the most effort at the cellular level. He believed that the best route to his answer was a minimal, category-theoretic model at as low a level in the biological hierarchy as possible. Until his death, he did not significantly modify the first model in his early papers (Rosen, 1958a, 1958b, 1962a) [35,36,38]. Since the cellular level is the smallest unit of life, he did not believe that involving higher levels would help his case. He sometimes discussed organisms but left it vague if they were single or multicellular, and he said little about populations, species interactions, communities, and ecosystems.

Rosen also placed little emphasis on evolution. He once told me that studying how species change over time did not answer his question. He wrote, "To me, it is easy to conceive of life, and hence biology, without evolution. But not of evolution without life. Thus, evolution is a corollary of the living." (Rosen, 2000, p. 255) [3]. In contrast, many evolutionary biologists believe that the study of evolution involves everything necessary to know about life. Rosen had even less tolerance for fitness arguments based on genotypes and population genetics. He was sometimes amused by the amount of attention genes received. Rosen was not a fan of measurement, nor did he rely on field/observation or laboratory/experimental data for his models. He believed that once an investigator assembled meters and made measurements, so many assumptions, errors, and confusion made the endeavor pointless, again and always in the context of his mission. In addition, observers intruded as they measured systems. He did not propose empirical studies to prove or disprove his theories. During his career, many people wanted to test hypotheses for him. He did not encourage them, and he did not participate in such endeavors. His reality was in models, mathematics, and pure non-algorithmic thought. He also did not explore graphs or networks to any significant degree, although his first (M, R) system model was a graph (1958a), but in the same year, 1958, he moved quickly to a Category Theory model (1958b). Rosen occasionally published on graph theory in the context of Relational Biology (Rosen 1963a,b; 1961) [44–46].

While Relational Biology, which he championed, has predominantly used graphs and networks, he believed that Category Theory was the preferred mathematical vehicle to answer his question. Once he had used Category Theory successfully, he was not motivated to apply the methodology to other aspects of living systems or to study related questions. Rosen was simply a man on a critical mission with an unwavering focus on his goal (Rosen, 1991a, 2000) [3,4]. He considered it his mission to explain the minimum requirements for life. That said, few scientists have a legacy like his that is so brilliant, comprehensive, consistent, and systematic. This is what I remember he told me, although there are some days I wish, like others, I could have motivated him to think about my interest: ecosystems. I am indebted to him, however, for his suggestion that ecosystems are chimeras, which presents some clear possibilities for characterizing life at the ecological level using Relational Biology and Graph Theory, and perhaps eventually, Category Theory.

If Rosen had lived longer, undoubtedly, we would now be in a different place in understanding and modeling living systems and developing non-algorithmic mathematical tools to improve this understanding, specifically under the overarching superstructure of Relational Biology. He left a few hundred published papers and several books since he always maintained it was his 'duty to report' his findings to whoever found them helpful. Many have. There have been several polymaths and geniuses in the 20th Century; Rosen was broad and deep in many subjects, including science (biology, physics, chemistry, and mathematics) and the arts (Lane, 2018a, b, c) [20,47,48]. He was as deep as he was broad across many disciplines. Over the past 20+ years, we have been colleagues and friends at Dalhousie University. Rosen was simply the most creative and intelligent person I have known. I took great delight in nudging him with questions and watching him spout ideas that came as effortlessly as he could talk; it was a game we played. He also lectured in my ecosystem class and delighted the students.

Rosen's question was 'what is life?' and he went a long way in answering that question at the cellular level without using algorithms. His approach was to describe the minimum functional relationships for life using an abstract model via Category Theory that did not provide any discrete cellular locations or structures. It is not, however, an easy stepping stone to further investigation. By his admission, he did not provide a complete answer. I have good reason to believe that he chose not to give a fuller answer as he told me he had only left clues for a world not ready to be entrusted with life's essence. This was one subject so serious that it could not be a game between us. I did not want to be entrusted with this information, just like I do not want to know how to build an atomic bomb. Scientific curiosity has a few limits. I do not know with certainty if he could have left both a 'necessary and sufficient' answer. Later, Rosen (2000) [3] said that an M-R system is not necessarily sufficient to realize life. Cazalis (2011) [49] pointed out that this was similar to autopoiesis because life cannot be fully defined by using only the term 'autonomous'.

3.2. Rosen's 'Selected' Conceptual Legacy

Rosen wrote about many subjects, and it is impossible to outline them here. Instead, I briefly summarize what he said about algorithms and the areas of his theory that are directly relevant to whether one is using an algorithmic approach. Rosen believed in dualities and often used them for comparison. Here, five of them are considered: (1) algorithmic versus non-algorithmic, including syntax versus semantics; (2) model versus simulation; (3) complex versus simple; (4) efficient cause versus material cause; and (5) relational versus metric, including qualitative versus quantitative. (Note: Rosen's own words are used as much as possible in this section not to distort his meaning.)

3.2.1. Algorithmic Versus Non-Algorithmic Including Syntax Versus Semantics

Starting in 1962, Rosen, as a new Ph.D., went on a crusade to defeat the Church Thesis (Rosen, 1962b) [39]. He repeatedly discredited Church's ideas in papers, talks, and up to his last books (Rosen, 1991a; 2000) [3,4]. In 1962, Rosen wrote: "Church's Thesis remains a conjecture in Mathematical Logic because the notion of effective calculability is an informal and qualitative one, and it is not possible to prove formally that quantitative concepts, such as recursiveness, or Turing-computability, are broad enough to include all the aspects which could appropriately be included in the intuitive term "effectively calculable"" (Rosen, 1962b, pp. 378–379) [39]. To Rosen, Church's views were detrimental to the scientific enterprise and his answer to 'what is life'? Church epitomized everything wrong in mathematics, physics, and biology. In his last book, *Essays on Life Itself*, Rosen (2000, p. 124) [3] concluded, "... if we can thus discriminate between artificial and real mathematics, we thereby discriminate between an artificial and a real mathematician". It seems clear to Rosen who an 'artificial mathematician' might be. Turing fared much better since Rosen did not attach Turing's name to the thesis, which has been the convention for almost a century (Church–Turing Thesis). Turing admitted that common sense (intuition) was not computable.

Rosen (1991a, p. 190) explained: "Algorithms... are, in a sense, the most general, purely syntactic inferential structures... formalization is nothing but an alphabet... Formalization in practice means the replacement of external referents with equivalent internal syntactic entailments. Thus, any limits of formalization, i.e., any entailment process that cannot be captured by algorithms, pertain precisely to external referents, and hence, to what is inherently semantic". Writing years later, he said, "The repetition of rote operations is the essence of algorithm. The effect of commensurability was to assert an all-sufficiency of the algorithm. In such an algorithmic universe, as we have seen, we could always equate quality with quantity, and construction with computation, and effectiveness with computability. Once inside such a universe, however, we cannot get out again because all the original external references have presumably been pulled inside with us. The Thesis, in effect, assures that we will never need to get outside again, that all referents have indeed been internalized in a purely syntactic form, but commensurability was false" (Rosen, 2000, pp. 77–78) [3].

He also explained the historical context of algorithms. "It is my contention that mathematics took a disastrous wrong turn sometime in the 6th century B.C. This wrong turn can be expressed as an ongoing attempt, since then, to identify effectiveness with computability. That identification is nowadays associated with the name of Church and is embodied in the Church thesis. But Church was only among the latest in a long line going back ato the original culprit. And that was no less than Pythagoras himself" (Rosen, 2000, p. 65) [3]. "The germ of such a strategy [also] goes back to the Characteristica Universalis of Gottfried Wilhelm von Leibnitz, among others. . ..One of the profound consequences of Characteristica Universalis is its claim that, in principle, we could dispense entirely with this world and subsume its laws into syntax only. The most modern expression of this belief is Church's Thesis, which projects back from language into an exceptionally strong restriction on the nature of the external world. . .One area in which this strategy has been most relentlessly pursued is a branch of language called mathematics" (Rosen, 2000, pp. 156–7) [3]. "The successive attempts to maintain the nice consequences of commensurability, in the face of the falsity of commensurability itself, have led to ever-escalating troubles in the very foundations of mathematics, troubles that are nowhere near their end at the present time" (Rosen, 2000, pp. 77–78) [3]. "The impact of that wrong turn, made so long ago, has spread far beyond mathematics. It has entangled itself in our most basic notions of what science is" (Rosen, 2000, p. 65) [3].

Rosen (1962b) [39] wrote, "Church's Thesis remains a conjecture in mathematical logic because the notion of effective calculability is an informal and qualitative one, and it is not possible to prove formally that a qualitative concept, such as recursiveness, or Turing-computability, is broad enough to include all the aspects which could appropriately be included in the intuitive term 'effectively calculable'". Louie (2020, p. 11) [50] later explained, "Church's Thesis is most likely true in the formal realm. One may, indeed, define a formal process to be effective if and only if it is computable (i.e., only if it has a Turing-machine model). Then Church's Thesis becomes tautologically true. . . when Church's Thesis is true, however, whatever is not computable is thereby merely relegated to the category of ineffective". The jury is out on the Church–Turing Thesis concerning quantum computing.

Gödel did fare best of all. In distinguishing between what he termed a formalization of Number Theory based only on syntax producing an 'artificial arithmetic' and 'real Number Theory', emanating from human thought, Rosen (2000, p. 157) [3] pointed out that "Within a short time, however, Gödel proved his celebrated Incompleteness Theorem, which in effect showed that syntactic rules captured only an infinitesimal part of "real" mathematics—in effect, that Church's Thesis was false, even in this realm or stated another way, the mathematical systems that are formalizable, in the Hilbertian sense, are infinitely rare (non-generic) among mathematical systems in general. So, in this realm, there is no way to reduce semantic aspects to syntactic ones in general; the result is only a mutilation, with the creation of artifacts" (Rosen, 2000, pp. 156–7) [3]. "In fact, Gödel (1931) [51] showed that any attempt to formalize Number Theory, to replace its semantics by syntax, must lose almost every truth of number theory" (Rosen, 2000, p. 267) [3]. Thus, to Rosen, living organisms are not machines or mechanisms and are not computable by algorithms. The complexity of life precluded its computation, which was possible for simple syntactical systems.

Rosen (1991a, pp. 8–9) [4] concluded, "Gödel's Theorem thus shows that formalizations are part of mathematics, but not all of mathematics, like language itself, cannot be freed of all referents and remain mathematics. Any attempt to do this (i.e., any attempt to capture every percept through a formalization of any finite set of percepts) must already fail in the Theory of Numbers… in a precise sense, Gödel's Theorem asserts that a formalization, in which all entailment is syntactic entailment, is too impoverished in entailment to be congruent to Number Theory, no matter how hard we tried to establish such a congruence". Rosen (1991b) [30] concluded "If Church's Thesis is true, then every material system is a mechanism; everything is physics; the reductionists are right, and science, in effect, becomes identified with a search for syntax. If, on the other hand, Church's Thesis is false, then there are material systems that are complex; physics as we know it then becomes only the science of the simple; the reductionists are wrong; science itself acquires an ineluctable semantic aspect". Obviously, for Rosen, a great deal rested on the falsity of Church's Thesis. "If anticipatory systems exist, then Church's Thesis is false". Rosen later published a book, *Anticipatory Systems*, in 1985a (updated in 2012 by Judith Rosen) showing how anticipation works within organisms. The Church–Turing Thesis is an assertion based on empirical evidence, so whether it is true depends on the interpretation.

Penrose (2016) [6] concluded, "One thing should be made clear. Computability is a genuine 'absolute' mathematical concept. It is an abstract idea, which lies quite beyond any particular realization in terms of the Turing machines… [although] solvable computations are termed, 'Turing complete'". Turing made major contributions to the whole area of computation throughout his career, and his central theme was "the extent and the limitations of mechanistic explanations" (Copeland, 2013a, p. 3). It is easy to see why Rosen quoted this work on computational mathematics so frequently; it provided significant support to his conclusion that mathematics itself is not wholly algorithmic, there is no method of proof or set of finite proofs to generate all mathematical truth, and more importantly to Rosen, life is not algorithmic.

3.2.2. Model Versus Simulation

Rosen had a precise definition of modeling. "A modeling relation is the functorial relationship between a natural and a formal system. Modeling is therefore the art of bringing the causal entailment structure of the natural system and the inferential entailment system of the formal system into congruence with each other" (Rosen, 1991a) [4]. A model can be diagrammed as a natural system (N), encoded into a formal system (F), and then decoded back into the natural system. Encoding occurs with measurement, which Rosen believed was an act of abstraction: "An act of replacing the thing measured (e.g., the natural system N) by a limited set of numbers. Indeed, there can be no greater act of abstraction than the collapsing of a phenomenon in N down to a single number, the result of a single measurement" (Rosen, 1991a, p. 60) [4]. The natural system has causal entailments on itself, and the formal system has inferences within itself. (Note: See Judith Rosen's paper in this Special Issue for Rosen's diagram of a model.) "Natural law consists essentially of the belief that the two great realms [natural and formal] of entailment or necessity can be brought into some kind of congruence… if commutativity holds, we can then say that our formalism is a model of the phenomena occurring in the external world, or equivalently that the events themselves constitute a realization of the formalism" (Rosen, 1991a, pp. 16–17) [4]. Rosen believed that some models include semantics and are non-algorithmic.

Lennox (2022, pp. 87–88) [52] explained, "Although the terms have slightly different meanings, the term simulation is nearly synonymous with the terms computable or algorithmically". In contrast, Rosen (1991a) [4] considered that Turing machines are simulators that process purely syntactic objects. "Any mathematical system, whether it can be an explicit model of something in the material world or not, may possess the property of being formalizable. There are many ways of describing the property, but they all amount to being able to describe the entire system as software to a mathematical machine (a Turing machine) in such a way that the machine can simulate the system. Everything about a formalizable system can be expressed as pure syntax; every inferential process in such a system can be considered rote symbol manipulation or word processing" (Rosen, 2000, p. 324) [3].

"Church's Thesis, which originally identified the informal notion of effectiveness with the formal one of computability, accordingly cuts very little ice in mathematics, which generically concerns itself with much larger universes then computability or algorithms or programs allow. Stated another way, abstractions from mathematics that satisfy the procrustean strictures of Church's Thesis are neither necessary nor sufficient for real mathematics; they are at best feeble mimics of real mathematics" (Rosen, 2000, p. 324) [3]. "Mimesis does not extend that far; the geometric construction of $\sqrt{2}$ from the Pythagorean theorem has nothing to do with the arithmetic algorithm that computes it, or measures it, or "constructs" it. In short, mimesis is not science it only mimics science. . . This is precisely why, as I have said in 'Life Itself', formalizable systems are so incredibly feeble in entailment. They attempt to do mathematics in large realms with only those procedures [operations] appropriate to small ones" (Rosen, 2000, pp. 78–79) [3]. "Mimesis is based on the idea that if two systems act enough like, they can be identified. We have explored this idea mainly through the Turing Test, asserting that a properly programmed machine, operating via syntax alone, behaves enough like a thinking human being is thinking. By extension then, the argument is that every subjective property of mind or sentience is in fact present in a sufficiently programmed syntactical device. As far as actually understanding life and mind is concerned, I claim that mimesis is more akin to some sympathetic magic, and as such it has primarily a recreational value. . . in other words, fields such as artificial intelligence deal no more with intelligence than say, symbol manipulation, deals with literature or poetry" (Rosen, 2000, p. 124) [3].

Roland Cazalis (2011, pp. 813–814) [49] explained, "he [Rosen] establishes a distinction between models and simulations stating that while models preserved the relationships in the system, simulation adds causal factors from outside to the model to make it a machine. On the other hand, it is possible to simulate the sub-categories of a system. As a result, a computational simulation of an organism cannot serve as an adequate metaphor for life. Whether model or simulation, Rosen's proposition is still relevant as it precisely aims at the uniqueness that symbolizes the identity arrow. This uniqueness, having a transcendental dimension is always a hapax; this is also the reason it is universal. That way, it is algorithmically incompressible. The shortest algorithm of relationships is the relationship itself. It is impossible to break down the identity relationship in order to create an algorithm without losing the object as a self. It is impossible to talk about the unique character of organisms without redundancy. Thus, an organism is a living system defined by both a functional and ontic aspect that is the two inseparably linked faces of the same thing. Life itself, however, is described as quale".

Gatherer and Galpin (2013, p. 2) [53] pointed out that "relational biologists do not deny that complex systems can be simulated but maintained that they can never truly be computed as functions. . . the full computational analysis of complex biological systems is therefore postulated to be beyond our current computing abilities. . . A simulation, by contrast, represents the world in a much more approximate way than a model without the requirement for congruence of internal console relations. A simulation may be an excellent predictive tool for the natural world. However, when it goes wrong, one may have no idea why since its entailment structure is primarily the work of creative approximation. Relational biologists maintain that much of conventional systems biology is merely about developing approximation simulations".

3.2.3. Complex Versus Simple

Over his career, Rosen used three different definitions of complexity (Laurent, 2019) [54] as follows:

(a) Complexity: Observing multiple interactions.

"This approach to complexity is novel in several ways. For one thing, it requires that complexity is not an intrinsic property of a system nor a system description. Rather, it arises from the number of ways [non-equivalent] in which we are able to interact with the system" (Rosen, 1985a, p. 322) [11]. "Hence, another characteristic feature of complex systems; they appear to possess a multitude of partial dynamical descriptions, which cannot be combined into a single description (Rosen, 1985a, p. 424) [11]". "Each of these [descriptions in turn gives rise to a particular kind of representation, encoding or description of the system... encoding so it cannot be transformed or reduced one another. Stated yet another way: since each encoding describes the subsystem of the given system, a system is complex to the extent that we can discern many distinct subsystems of it here".

(b) Complexity: possession of non-simulable model.

"If, and only if, a system is simple, which means that all of its models are computable or simulable, then this set of all models becomes the reductionist paradise—otherwise, not" (Rosen, 2000 p. 280).

"A system is simple if all its models are simulable. A system that is not simple, and that accordingly must have a non-simulable model, is complex" (Rosen, 2000 p. 292).

(c) Complexity: possession of impredicative loops.

"Impredicativity [is] the hallmark of complex systems, and precisely the sort of thing which syntax alone cannot handle" (Rosen, 2000, p. 271). "I would rather, then, call a system complex if it has inherent impredicative loops in it" (Rosen, 2000, pp. 42–44). Palmer, Williams, and Gatherer (2016) [55] noted that impredicativity occurs when a set is a member of itself and can be found when analyzing a self-referential system. [Note: Impredicativity relates to non-simulable, non-algorithmic, and semantic. Predicative systems are computable with algorithms, are syntactical, and are simulable.] According to Rosen (1977, 1987) [56,57], there are only two kinds of systems: complex and simple. He explained this dichotomy: "A complex system is one in which there must exist closed loops of entailment... Such loops cannot exist in a machine or simple system... In mathematics, loops of this kind are manifested by impredicativities or self-references—indeed, by the inability to internalize every referent. In science, where entailment means causality, closed causal loops...allows us to talk rigorously about categories of final causation... this kind of finality, in turn, is what allows us to talk about function and anticipation, in terms of what an effect entails in a complex system, rather than exclusively in terms of what entails the effect".

Rosen (1985a, p. 424) [11] explained "the category of simple systems is, however, still the only thing we know how to work with. But to study complex systems by means of approximating simple systems puts us in the position of early cartographers, who were attempting to map a sphere while only armed with pieces of planes. Locally, and temporarily, they could do very well but globally, the effects of the topology of the sphere became progressively important. So it is with complexity that, over short times and only a few information levels, we can always make do with a simple (i.e., dynamical) picture. Otherwise, we cannot; we must continually replace our approximating dynamics by others as the old ones fail".

Thus, to Rosen, living systems are complex, and non-living ones are simple. Simple systems can be complicated because they may possess a large number of parts and interactions, but these large numbers can never transform a simple system into a complex one. There is also no concept of quantities of complexity, as one system is more complex than another. Rosen believed that there was a barrier that could not be crossed in attempting to go from simple to complex, and even going from complex to simple, as in everyday reductionism, is not easy. Although reductionism is repeated thousands of times a day in laboratories worldwide, few have boasted that after disassembling an organism's parts, they could reassemble the whole. However, a part can be added to a living whole, as evidenced by the many successes in making laboratory chimeras (Nanos and Levin, 2022) [58].

3.2.4. Efficient Cause Versus Material Cause

Science is an undertaking to answer 'why' and, in doing so, to identify causal relationships. To Rosen, this is "the study of entailment relations between phenomena... Aristotle correctly identified science with the study of the 'why' of things and scientific explanation with the elucidation of causal sequences. . . [more precisely] Aristotle . . .associated the notion of entailment between phenomena with the question 'why' and answered it with a 'because'. Indeed, the pair consisting of the question 'why A?' and the answer 'because B' precisely asserts an entailment of A by B, and explanation of B in terms of A" (Rosen, 1991a, p. 57) [4]. In formal systems, entailment is synonymous with inferential rules.

Rosen (1991a, 2000) [3,4] pointed out that Aristotle distinguished four categories of causes to explain phenomena: (1) material, (2) formal, (3) efficient, and (4) final causes. The material cause has to do with the physical composition of a system, whereas the formal cause is the form, arrangement, or structure of a thing. The efficient cause is how the system was put together. The final cause is why the system exists in terms of its purpose. Thomas Aquinas thought that the final cause was the queen of causes. Thus, these causes can be translated into (1) wood (material cause) plus (2) a blueprint (formal cause), which can be used by (3) a carpenter (efficient cause) to build a chair, (4) with the purpose for humans to sit upon (final cause). We can measure the material cause by breaking down a living system into its chemical elements with the convenient periodic chart. It is the other causes that are more difficult. For example, "The idea of function is resisted in orthodox biology because it seems to carry with it a notion of design, and it seems necessary to expunge this at any cost. This is because design seems to presuppose a category of final causation, which in turn is confused with teleology" (Rosen, 2000, p. 273) [3].

In particular, Rosen concluded that living systems are 'closed to efficient causation' or CLEF. They are self-organizing and autopoietic systems that make themselves. It has been challenging to find mathematics for the efficient cause; it involves impredicative loops that Rosen sought to encode in his category-theoretic model of the metabolism and repair of a cell (M, R) system. Whereas cells and ecosystems are open to matter, energy, and information, they continuously create and renew themselves with raw materials. There is no carpenter. There is also no separate blueprint; we can only a posteriori observe the arrangements and structures of living systems after they are formed. The information they receive from the environment is neither a blueprint, a constructor, nor a telic reason 'why'.

In explaining these types of 'whys', we lack mathematics. Another problem is that these causes cannot be substituted for each other, and yet we use the same mathematics for all of them indiscriminately. "The whole thrust of the old Aristotelian analysis of causation is to make it manifest that no one mode of causal entailment suffices to understand anything. At root, this is because the causal categories do not entail each other. . . For instance, we may know how to build a watch without knowing anything about how a watch actually works. Conversely, we may know how a watch works, without any idea of how to build one" (Rosen, 1991a, p. 132) [4].

3.2.5. Relational Versus Metric Including Qualitative Versus Quantitative

At the beginning of Rosen's now classic book, *Life Itself*, he begins with the distinction of the 'truth' of biology and the 'truth' of mathematics, between the relational or qualitative and the metric or quantitative, respectively. He wrote: ". . .they say that all science must start from experience. Mine was that relational models and mechanical [metric] models, drawn from physical analysis through reductionism, were not going together. That was a fact. My conclusion from that fact was that I was simply being stupid, or else there were some deep and essential things embodied in that fact. I was never able to rule out the first possibility, but the possibility of the second is what has led circuitously, in the course of time, to what is chronicled herein. In short, this is where I have been left merely by following the problem. It is the problem that imbues the path itself with whatever intrinsic logic is discernible in retrospect" (Rosen, 1991a) [4].

Likewise, the student frequently commented on the mentor's publications. Rosen (1962a, p. 1) [38] interpreted what Rashevsky defined as Relational Biology as "an approach to biological systems in which, roughly speaking, one seeks to understand the properties of these systems in terms of a decomposition into functional components, rather than into structural components as is commonly done in (metric) biology". Rosen (1968) [59] further explained Relational Biology as follows:

"Explicitly, Relational Biology involves:

a. the specification, in purely mathematical terms, of important kinds of functional activities characteristic of biological systems.
b. the formal study of the properties common to all realizations of these functional activities; and finally,
c. the specification (using criteria of optimal design) of individual physical realizations whose structural properties may then be studied in detail and compared with the experimental information which still comprises the overwhelming bulk of our biological knowledge".

In 1969, Rosen prepared a book-length manuscript entitled 'Relational Biology' that he never published. One day, he handed me a folder containing several book chapters, saying I might find it helpful. I do not know if the three missing chapters were written, but they probably were. These were the days of using an IBM Selectric typewriter with white correcting tape and making mimeographed copies. At this point, the paper is yellow, and the print faded. Here are two excerpts from this manuscript (Rosen, 1969; unpublished, pp. 11–12) [60]:

(1) "Relational Biology may be viewed on one hand as a systematic attempt to develop a theory of functional organization in biological systems. As such, it deals with large classes of physically diverse systems that are defined by the sharing of some element of functional similarity. In its way, Relational Biology is as mechanistic a theory as any reductionist theory, but it aims to organize biology around functional rather than structural properties".

(2) "Technically, the distinction between conventional metric biology and Relational Biology may be expressed as follows: metric biology approaches a biological system by abstracting out the biological organization, leaving behind a purely physico-chemical system to be studied and analyzed by purely physico-chemical techniques. Relational Biology, on the other hand, proceeds by abstracting out the physics and chemistry of biological systems, leaving behind a purely functional organization that can be studied and characterized by means of appropriate system-theoretic techniques".

Thus, Relational Biology studies large classes of systems with enough physical diversity to identify the similarities in their functional organization. Laurent (2019, p. 155) [54] explained that "the nature of a system's part which is responsible for the behavior change is relational and not material: by manipulating a part of the living system, we have perturbed the relation between this part and the whole system. . . Such a functional approach is characteristically independent of the specific physiochemical details of the structures composing the living system. . . Indeed, since pure relational organization comes first in the description of living systems, we need to build formalisms in order to be able to express it. Although infinitely more respectful of what life is, this approach has always been the ugly duckling of modern biology".

Relational Biology is a qualitative undertaking. Of qualitative versus quantitative, Rosen said that "I discuss the duality between qualitative and quantitative. As we will see, in the sciences, this dichotomy rests on (generally unrecognizable) presuppositions about the nature of material reality and on how we obtain knowledge about it. . . these presuppositions themselves have formal, mathematical counterparts, which allow us to reflect this scientific dualism into an exactly parallel one that exists within mathematics itself. This mathematical form of the dualism is centered around the notion of formalization; it can be expressed as the duality between syntactic and semantics; between what is true by virtue of form alone, independent of any external reference, and what is not" (Rosen, 1991a, p. 2) [4].

Rosen disparaged Rutherford's notion that the "qualitative is nothing but poor quantitative. . .For Rutherford, science does not begin until the quantification is made, until crude and inexact talk about quality is replaced by precise, exact, and completely equivalent talk about numbers" (Rosen, 1991a, p. xix) [4]. Levins (1966) [61] suggested that in building models, the primary goals were reality, generality, and precision. However, all three could not be optimized simultaneously. Rosen pursued the first two, but Rutherford and others, especially in physics, championed precision. Precision was essential in their search for invariants that motivated the laws of nature. How could one have a law of nature with a 5% error term? "Rutherford's position, as articulated above, can be rephrased as asserting that every material system is a simple system. Indeed, I have shown elsewhere that this position is just another form of Church's Thesis, a direct assertion of the simulability (i.e., the purely syntactic character) of mathematical models of reality (i.e., of systems of causal entailments). To a mathematical Rutherford, then, Number Theory would look most relevant to its formalizations precisely because there are more qualities, and hence more entailments, in Number Theory than could be accommodated in terms of "hard" (i.e., syntactic) entailments" (Rosen, 2000, p. 9) [3]. "Rutherford's view that every perceptual quality can and must be expressed in numerical terms is associated with the viewpoint commonly called reductionism. In practice, reduction as some actually assert is much, much more than this; in its most extreme form, it actually identifies a specific family of elementary numerical qualities and the procedures for measuring them, at least in principle and anchors them in physics. . . according to this view there is no other science than physics, everything else we call science is ultimately a special case of physics" (Rosen, 1991a, p. 3) [4].

"At present, the fact is that there is still no single inferential chain that leads from anything important in physics to anything important in biology. This is a fact, a datum, a piece of information. How are we to understand it? There are various possibilities. [First,] Kant, long ago, argued that organisms could only be properly understood in terms of Final Causes for intentionality; hence from the outset he suggested that organisms fall completely outside the canons of Newtonian science, which work for everything else. Indeed, the essential telic nature of organisms precluded even the possibility that a Newton of the grass blade would come along and do for biology what Newton had done for physics. [Second,] Another possibility is the one. . . we have simply not yet characterized all those special conditions necessary to bring biology fully within the scope of universal physical principles. Still, a third possibility has grown up within biology itself as a consequence of evolutionary ideas; it is that much of biology is the result of accidents that are, in principle, unpredictable and hence governed by no laws at all. In this view, biology is as much a branch of history as of science. At present, this last view sits in a kind of doublethink relation with reductionism; the two are quite inconsistent but do allow modern biologists to enjoy the benefits of vitalism and mechanism together. Still a fourth view was expressed by Einstein, who said in a letter to Leo Szilard: "one can best appreciate, from a study of living things, how primitive physics still is" (Rosen, 2012, p. 421) [42]. To Rosen, the Newtonian paradigm was successful because it represents the science of simple systems (Rosen, 1985b) [62]. Whenever this approach is applied to complex systems, they become simple ones.

3.3. Post-Rosen Modeling of Living Systems in a Rosennean Context

Since his death, Rosen's work has become much better known to biologists of all subdisciplines, facilitated by the tireless efforts of his daughter, Judith Rosen, custodian of his intellectual legacy. This interest has motivated many additional lines of inquiry, including a recent doctoral thesis on Rosen's vision of Relational Biology (Lennox, 2022) [52]. A. H. Louie (2009, 2013, 2017) [63–65] and John Kineman (2012) [66] have also published widely, building upon Rosen's ideas, sometimes explaining and defending them and sometimes extending them. Their publications have also helped reach a larger audience. There have also been three Special Issues in journals focused upon Rosen's ideas [*Computers and Chemistry* 25, 313–428 (July 2001); *Chemistry and Biodiversity* 4 (10), 2269–2491 (October 2007);

and *Ecological Complexity* 35, 1–114 (September 2018)], and of course, many individual papers and books by other authors.

This section includes some examples of biological modeling approaches and suggestions published after Rosen's death in 1998, mostly referencing his work, with some dealing directly or indirectly with the algorithm/non-algorithm issue. A few examples are not strictly in the Rosennean tradition, although they usually reference his work, and both types often criticize Rosen's (M, R) system model. Andrée C. Ehresmann and Jean-Paul Vanbremeersch, a mathematician and a physician, have published extensively on Memory Evolutive Systems (MESs), including a major book (2007) [67] that extends Rosen's Category Theory to more biological systems in more detail and with more focus on hierarchies than his original cell model including neural and social systems. They also extend concepts of Relational Biology, phenological philosophy, and complex systems while involving multi-level, multi-agent, and multi-temporality in their models. The authors wrote: "Category Theory is now recognized as a powerful language to develop a universal semantics of mathematical structures" (Ehresmann and Vanbremeersch, 2007, p. 26) [67]. They defined "an evolutive system (ES) as a family of categories indexed by time, with partial functions, called transitions between them" (Ehresmann and Vanbremeersch, 2006, p. 139) [43]. With their advancements, there is more hope for semantics than just syntax in mathematical modeling.

Their modeling focuses on how groups of mathematical objects or categories interact with each other through morphisms. The categories in their model evolve with time, and there is an underlying hierarchical structure. A system of co-regulators with feedback and varying time scales achieves control. Most of their models are at the organism level. Brown (2009) reviewed their book and concluded that "The theory of Memory Evolutive Systems presents a mathematical model for natural open self-organizing systems... The dynamics are moderated by the cooperative and competitive interactions between the global system in a net of Internal Centers of Regulation (CR) with a differential access to a central hierarchical memory". The MES approach is the most developed one, using Category Theory to conceptualize biological systems. Nevertheless, Cottam and Ranson (2017) [68] criticize the MES approach for its lack of a 'one to many mapping' and the failure to include any formalization of the colimits.

Ehresmann and Vanbremeersch (2007, p. 33) [67] commented on Rosen's various papers using Category Theory on the cell, organism, morphogenesis, and natural systems; "in these works, the role of categories is most often purely descriptive, and the deep results of Category Theory are not exploited. On the contrary, in our model where we use categories to represent the successive configurations of a system, we make use of fundamental constructions, to give an internal analysis of the structure and dynamics of the system".

Hofmeyr (2021) [69] identified three types of efficient causes at the cellular level that he diagrammed with Relational Biology mappings because he said that it has been impossible with Rosen's (M, R) system to determine biologically reasonable biochemical processes. Hofmeyr explained, "What is, however, abundantly clear from his writings is that Rosen constructed the replication map purely on the basis of mathematical convenience, and not because he had some physical realization in mind... Since its inception, the replicative (M, R)-system has remained the starting point of all elaborations of Rosen's pioneering work. In unkind moments I have come to think of it as akin to a black hole from whence, once sucked in, there is no escape" (Hofmeyr, 2021, p. 11) [69]. Vega (2023, 2024) [70,71] continued Hofmeyr's work and produced both an elaborated and semiotic system, suggesting that the material system must be retrieved from its formal counterpart. Cornish-Bowden and Cardenas (2020) [72] listed the deficiencies in Rosen's (M, R) system model of the cell, which Vega (2023) [71] attempted to remedy. "It has been shown that closure to efficient causation is what establishes the difference between the (M, R)-system without replication... and with replication...; which defines the difference between an inanimate system and an organism. It has been argued that biochemistry is not enough to build a model of a cell;

that it is necessary to add a function, the replication function, which defines and is defined by closure to efficient causation. . . this relationship does not correspond to the application of commonly accepted laws of science, but to the fulfillment of additional rules imposed by closure" (Vega, 2023, p. 13) [71]. Thus, both Hofmeyr (2017) [73] and Vega attempt to demonstrate how metabolism, repair, and replacement would work in a cell. Gatherer and Galpin (2013) [53] used process algebra (Bio-PEPA) to try to represent Rosen's (M-R) system in an attempt to demonstrate algorithmic computability because this is a common approach to living systems in Systems Biology, which "represent biological network systems as software objects for simulation on computers. These network structures may vary in their degree of complexity, but the difference between simple and complex networks is treated as one of degree rather than of kind. . . for relational biologists, complex systems are therefore qualitatively different to simple ones" (Gatherer and Galpin, 2013, pp. 1–2) [53]. They could not carry out this but suggested that it might eventually be possible to integrate Relational Biology and Systems Biology.

Siekmann, an applied mathematician, also agreed with their conclusion. "From the introduction [of Category Theory] by Rosen (1959) [40], it becomes clear that Rosen regards Category Theory as an incremental extension of Graph Theory that enables him to describe relations between black boxes more flexibly. Unfortunately, this prevents him from taking much advantage of the main strength of Category Theory, namely, relating the structure of mathematical objects appearing in different disciplines of mathematics. The negative impact of this use of Category Theory on an audience of applied mathematicians must not be underestimated. A strong motivation in mathematics itself, as well as in the community of applied mathematicians, is to use mathematical notions as efficiently as possible. By failing to take full advantage of the ability of Category Theory to relate mathematical structures, Rosen does not only miss the chance to capture properties of a biological system that might be encoded in such structures. Even worse, an audience from a mathematical background might be detoured from Rosen's ideas not because of the ideas themselves but due to the perceived shortcomings in their mathematical presentation" (Siekmann, 2018, p. 35) [74].

Mossio, Longo, and Stewart (2009) [75] complained, "Rosen's original formulation in terms of Category Theory, although intuitively understandable, was not easily biologically interpretable, nor operationally generative". Varenne (2013) [76] also identified shortcomings in Rosen's use of Category Theory and (MR) systems. Cornish-Bowden (2015) [77] contrasted Rosen's and Gánti's concepts on the theory of life. He said, "Rosen's theory of life [using (M-R) systems] needs much more explanation than Gánti's because he [Rosen] never considered it necessary to present it in a way that ordinary biologists would find intelligible".

Plamen Simeonov, Leslie Smith, and Andrée Ehresmann co-edited a book entitled *Integral Biomathics* (2012) [78] with 31 contributions, which followed year-long funded discussions by many dozens of collaborators on the 'biological foundations of mathematics and computation', and two Special Issues in 'Progress in Biophysics and Molecular Biology' (Simeonov et al., 2013a, 2015a,b) [79–81]. So many methods are included within these three references that it is impossible to summarize them here; over 100 investigators have been involved. Simeonov and Ehresmann (2017) [82] explained, "Integral Biomathics was proposed as a unifying framework for both top-down and bottom-up research methodology. . . Integral Biomathics considers itself a continuation and extension of the research line traced by Rashevsky, Waddington-Goodwin, Maturana, Varela, Rosen, Louie, and others (Simeonov, Wepiwé, Salte, and Kaufmann)". (Associated references for these authors are available in the original paper.)

Simeonov et al. (2013b) [83] wrote an excellent summary of the state of mathematical biology in 2013. They observed that "many biological phenomena do not have adequate mathematical representations because living systems are deploying logic and semiotics beyond our conception of mathematics into the domain of computation, which is on its part much richer than the standard Turing machine paradigm" (Simeonov et al. (2013b, pp. 216–217) [83]. They identified four main challenges facing Biomathics including (1) "a theory of self-emergent objects that carry out functions of interactive variances of the constituents of living systems;... (2) a theory of complementary assembly: biological systems build themselves based upon the principle of molecular complementarity to produce robust aggregate/molecules;... (3) a qualia jump theory [involving transitions from scalar to vector properties];...and (4) a hidden morphology theory: the linkage between form and function...". In addition, they conceptualized these points at the lower levels of the biological hierarchy while disregarding many aspects of the ecological level. Thus, an ecologist might see the 'challenges' somewhat differently.

The methods they recommended included both algorithmic and non-algorithm ones and hybrid modeling using different types of specific models to explore a particular biological phenomenon. They used the term more broadly, meaning that a system or problem would be studied with more than one type of mathematics, versus the definition used in this paper that hybrid modeling specifies the use of both algorithmic and non-algorithmic methods in studying a system or problem. Hong (2013) [10] explained that many mathematical methods are needed to describe biological systems to integrate their processes and functions simultaneously, indicating the inadequacy of mathematics, not biology. Simeonov et al. (2013b) [83] concluded that many of life's primary features, like emergence, robustness, complementarity, and contextuality, have been ignored when describing living systems with reductionist approaches. Rosen's list (1991a, 2000) [3,4] for living systems would be somewhat different: model (not simulation), self-organizing, impredicative, closed to efficient causation (CLEF), complex, anticipatory, and open.

Their question for Integral Biomathics, "Can biology create a profoundly new mathematics and computation?" (Simeonov, et al., 2013a, p. 1) [81], was different but related to Rosen's 'what is life', but more like the present Special Issue asking, 'What non-algorithmic approaches might be appropriate for biological systems?' Simeonov, Ehresmann, and Vanbremeersch have combined efforts and concepts to create WILMESs: Wandering Logic Intelligence–Memory Evolutive Systems. WLI is a "computational logic for self-organizing networks", like those developed in a Loop Analysis (see below), but it is essentially algorithmic. Ehresmann and Simeonov (2012, p. 105) [78] explained Wandering Logic Intelligence (WLI) as follows: "the approach represents the next step of network visualization and evolution of application- and user-aware networks as adaptive systems consolidating both network element and infrastructure flexibility". "WILMES are complementary formalisms with capabilities at different conceptual levels... Informally, we can regard WLI as the physics or the computing implementation of the mathematics in MES... MES intermingle two mathematical domains, namely Category Theory and Hybrid Dynamical Systems, which must be rendered coherent".

Referencing algorithms, Simeonov et al. (2013b) [83] mentioned in terms of building Biomathematics for the future that he realized WLI did not satisfy Rosen's requirements: "it turns out computation that is now performed is unnatural in biology. Computations conceived in the first type and order logic are generally not decidable. This fact implies that there is no guarantee that such an algorithm can lead to an effective procedure to decide upon membership in a legitimate domain of discourse, or on allowed set of formulas using Boolean true or false values". There have been few literature references to Integral Biomathics in the past ten years. However, there have been several other suggestions for alternative types of mathematics for living systems by other authors in the three publications listed at the beginning of this section under Integral Biomathics as well as in individual papers from authors not in the Integral Biomathics project:

1. Rubin et al. (2021) [84] used Chemical Organization (COT) and the Zero Deficiency Theorem (ZDT) to tackle Rosen's notions of an (MR) system and Maturana and Varela's concept of autopoiesis at the largest level of biological organization, the biosphere, regarding the Gaia hypothesis of Lovelock and Margulis (1974) [85]. Because ZDT centers upon the self-production of the components of the reactive systems involved, it comes close to the notions of CLEF and metabolic closure. COT is a

methodology that focuses on how structures and their patterns persist in pathways of chemical reaction networks. It uses a variety of mathematical methods, including Category Theory. The two methods, COT and ZDT, appear to include the potential for both algorithmic and non-algorithmic methods, constituting a hybrid methodology as defined in this paper. Since Professor Rubin is organizing this Special Issue, his paper explains his approach more fully. It has considerable potential, not only for its inclusion of a network-pathway analysis and CLEF-closure principles but also for its application to the largest level of biological organization—the planetary ecosystem (Rubin and Crucifix, 2022) [86].

2. Hofman (2013) [87] recommended using Algebraic Geometry, which combines Topology and geometry, as developed by Felix et al. (2008) [88].
3. Hong (2013) [87] suggested that "... by treating problem-solving as a process of pattern recognition, the known dichotomy of visual thinking versus verbal thinking can be recast in terms of analog pattern recognition (non-algorithmic process) and digital pattern recognition (algorithmic process), respectively".
4. Baianu and Poli (2011) [89] traced the types of mathematics used in systems theory and Rosen's (M, R) systems and suggested that Algebraic Topology, Groupoids, Algebra Geometry, Many-Valued Logic, Category Theory, LM-Logic Algebra, and Non-Albelian Topology might be helpful in characterizing living systems. These authors commented that "the simplest mathematical models exhibiting such biological capabilities are arguably Robert Rosen (M, R)-systems... their categorical construction using natural transformations utilizing the fundamental Yoneda Lemma elicited their implicit algebraic structures". Baianu's results have been explored in several papers published after 1998 when Rosen died before he died in 2013.
5. Lane (2024, 2025) [90,91] proposed using a Loop Analysis, a Relational Biology tool, as a hybrid non-algorithmic methodology with marine field and laboratory data at the ecosystem level given the existential risks from environmental problems such as climate change.
6. Siekmann (2018) [74] offered several alternative methodologies for living systems, including (1) John Baez's work on open reactive networks using Applied Category Theory in which they formalize Petri Nets of chemical reactions and compare different types of networks (Baez and Pollard, 2017) [92]. Baez has also pioneered several applications of Category Theory using Algebraic Julia in epidemiology, among others. (2) Barabási (2016) [93] has published extensively on Network Theory and Graph Theory, which are close to Relational Biology and could be helpful, especially when understanding that the nodes are more than black boxes; (3) Borutzky (2010) [94] uses Bond Graphs to model energy flows to biochemical and physiological systems and living systems that are open to matter and energy.

Rosen is not alone in his opinion that too much emphasis has been placed on mathematics for abiotic systems. Root-Bernstein (2012, p. 14) [95] explained, "To summarize, my contention is that the reason biology has failed to develop a viable set of mathematical methods appropriate to solving its problems is that we have relied too long on mathematics developed to model physical problems that are intrinsically different. The assumption has been that biology can be reduced to chemistry and eventually to physics [Unity of Science Concept] and therefore that physics-derived mathematics should be sufficient. But hierarchy theory suggests that reductionism can never explain how novel properties and processes emerge". Perhaps Rosen should have the last word here. In his 1996, pp. 211–212 [96], paper entitled 'The Limits of Scientific Knowledge', he explained, "I cannot claim that these (M, R)-systems fully answer the question 'what is life?' but I do claim that the answer must at least comprehend them. The (M, R)-systems manifest inherent semantic properties, expressed in closed causal loops within them. Such closed loops, in inferential contexts, are called impredicativities... At any rate, my little (M, R)-systems are inherently unformalizable as mathematical systems. That means not only do they have non-computable models, but any model of them that is computable is not itself an (M, R)-system and hence misses all of its biology”.

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