"Engineering" life, mechanistic biology, and basic biological principles.

Research and reflections by Jacques Loeb

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Abstract

This paper elucidates the scientific and philosophical origin and further development of the concept of 'engineering' life by focusing on the experimental biologist Jacques Loeb (1859-1924). I show, first, that Loeb's 'engineering' approach was strongly influenced by the philosophy of Ernst Mach; understanding life meant controlling life phenomena through physical or chemical means. I then analyse Loeb's transition from the positivist-'engineering' approach to a causal mechanistic one, based on a physicochemical concept of life. The ideas that biological specificity is based on protein diversity and that the synthesis of life must begin with the synthesis of the genetic material were central. Third, I argue that experimental control and prediction have recently been fruitfully combined with causal-mechanistic research in experimental systems biology, such as research on gene regulatory networks, and synthetic biology.

Keywords: Positivism, causal-mechanistic science, Ernst Mach, reductionism, genetics, synthetic biology

Introduction

The "engineering" life concept, i.e. the idea of controlling, manipulating, and synthesizing life in the laboratory, is widely applied in many areas of biology, perhaps most successfully in synthetic biology, where it serves numerous practical purposes and also contributes to research on the origin of life or cellular organization (see section 3). An early version of the idea of "engineering" or "controlling" life originated as a purely empirical concept in the late 19th century, when researchers began using experimental perturbations of organisms to control and predict their responses but did not examine underlying mechanisms or causes. The German American physiologist and experimental biologist Jacques Loeb (1859-1924) most vigorously promoted biology as an experimental science with the ideal of experimentally controlling animals' life functions, research that Loeb's biographer Philip Pauly called Loeb's "engineering" approach (Pauly 1987). This term is, however, problematic, since Loeb's research, unlike much of today's biological "engineering," did not have practical aims. Instead, it was aimed at devising experimental techniques for controlling and manipulating organisms as an epistemological tool for demonstrating that every life phenomenon is, at least in principle, explicable without invoking an immaterial or vitalistic 'life force', when it is controlled through external chemical and physical means. Other scholars use the term "technical biology" (Fangerau 2009) but they overlook the fact that this term was used by Loeb himself for applied biology that he contrasted with "theoretical biology." (Loeb 1904)

Due mainly to new developments in biochemistry and genetics around 1900 which pointed to the crucial role of macromolecules in biology, Loeb abandoned the empiricist-phenomenological approach and the aim of "controlling" life by purely empirical means, increasingly focusing instead on the search for mechanisms and causes.[1] The "corpuscularian" or mechanical philosophy originated in the ancient Greek atomists' conception of nature as a complex world without purpose, design or divine intervention. The mechanistic concept that existed as a metaphor since it was promoted by Descartes in his famous

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[1] Some authors depict Loeb's "engineering" biology, but do not distinguish between engineering and mechanistic, mistakenly characterizing Loeb's positivistic engineering as mechanistic (e.g. Campos 2009; Fangerau 2009). In contrast, John A. Fuerst (1982) characterizes Loeb as a mechanistic reductionist

1637 dictum of *bête machine* (animal machine), became a research strategy in biology in the late 19th century, when scientists began to search for mechanisms and causes at the level of cells and, later, molecules. Purpose or immaterial vital forces were excluded from explanations. The mechanistic approach was rejected by vitalists and nature philosophers, morphologists, monists such as Haeckel, and positivists/empiricists such as Mach.[2]

Though Loeb himself discontinued research on "engineering" life, his subsequent mechanistic research implicitly and explicitly laid the basis for modern biological engineering approaches by demanding any that successful manipulation or artificial synthesis of life has to begin with the manipulation or synthesis of the genetic material. Modern engineering biology thus does not originate in the 19th century phenomenological "engineering," but is rooted in causal-mechanistic approach combined with the old vision of creating new forms of life.

I begin with a historical review of the scientific, philosophical, and social origins of the empirical "engineering" or "controlling" life concept. After analyzing Loeb's transition to mechanicism, I comment on his theoretical demands for a successful approach to manipulating and synthesizing organisms in the laboratory. For Loeb, the principles of biological specificity residing in protein diversity, and genetic causality based on the "nuclein" in chromosomes were crucial. These principles and the causal-mechanistic approach in biology to which Loeb significantly contributed at an early stage, are bases of today's biological "engineering" in synthetic biology that I will briefly review in the last part. I will show that gene network engineering here is playing a major role, an approach that is based on the concept of gene regulatory networks that was created by

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[2] A detailed analysis of the historical development and current dispute of the conflict between mechanistic and vitalistic conceptions of life since the seventeenth century is provided by Dan Nicholson (Nicholson 2010).

developmental systems biologist Eric Davidson. Like Loeb an ardent proponent of mechanistic biology, Davidson envisioned creating new animal body plans by manipulating gene networks.

1. The origins and development of Loeb's conception of "controlling" and "engineering" life

Jacques Loeb developed his vision for experimentally controlling life processes at the end of the 19th century in Germany, a vision that reflected his upbringing, philosophical predilections, and the scientific-philosophical discussions at the time. The mid-19th century saw many contradictory scientific/philosophical currents to which Loeb was exposed in the early part of his career. Representatives of the *Romantische Naturphilosophie* (romantic nature philosophy) with its vitalistic notions of *Lebenskraft*, or *'vital force',* denied that the fundamental life processes could be scientifically elucidated. Opposing their prevailing influence, a group of physiologist-physicists, among them Hermann von Helmholtz and Emil du Bois-Reymond, promoted a research program that aimed at accounting for all bodily processes in physicochemical terms. By introducing mathematical and physical methods into physiology, they determined the development of experimental physiology for the next fifty years (Kichigina 2009). In contrast, the medical materialists who likewise protested against the romantic idealism of German scientists, promoted an extreme empiricist materialism in biomedical research. Zoologist Ernst Haeckel became the most famous proponent of a materialistic Monism - the postulation of a materialistic unity of the world - that he based on the theory of evolution.

Following his parents, Francophile Jews who adhered to the values of the Enlightenment, Loeb early on held liberal and materialistic views, rejecting vitalism and religious influences on science. Vitalism was especially widespread until the middle of the 19th century, when the fields of biology and medicine slowly emerged as separate disciplines in their own right, with biology focusing on natural history and the concept of organic forces (Zammito 2018).

Loeb studied medicine and his early research was in experimental brain physiology. Under the influence of Helmholtz and du Bois-Reymond, mainstream physiology in Germany had shifted from a teleological-materialistic to a physical-mechanistic approach. Thus, areas such as biochemistry, development and behavior were marginalized in favor of physicalist fields in electrophysiology and sensory physiology. Loeb's education and early work were outside mainstream physiology. His psychophysiological research on dogs' brains focused on the whole organism; it was materialistic and function-oriented, but not mechanistic. Loeb became, however, increasingly dissatisfied with this work, and, after a few years, encouraged by his contacts with zoologists, began to move away from medical physiology to tackle broader biological questions.

In this phase, his contact with botanist Julius Sachs proved most influential. An outsider in the profession, Sachs studied plant tropisms as a contribution to a general physiology that entailed plants and animals, a theoretical aim that included the practical goal of developing general techniques for the manipulation and control of organisms (Pauly 1987, p. 36). Loeb applied Sachs's concept of tropism in plants to animals (e.g. caterpillars), thus experimentally controlling animal behavior from without. His aim was to refute claims of the existence of mysterious instincts for self-preservation (Loeb 1888). By manipulating Tubularians (a genus of hydroids) e.g. to generate two mouths, he aimed at generating a “technology of living substance” (Loeb 1891, p. 80). Loeb's work on animal tropisms led him to embark, for a short period of time, on envisioning a program of theory reduction in which behaviors such as heliotropism or other tropisms were explained in terms of chemistry, i.e. the molecular or atomic structure of the protoplasm (Pauly 1987, p. 38). However, during the following years he focused on animal control through changing the external physical conditions and excluded questions of possible mechanisms. Loeb's studies on the heliotropism, geotropism and other forms of tropisms in small animals, such as caterpillars and crabs, excluded his former holistic considerations on function and adaptiveness of reactions. Epistemologically, a successful animal control became equivalent to scientific explanation.

Based on these studies, Loeb developed between 1889 and 1891 a program for an "engineering" biology (Pauly 1987, p. 29) or, rather, for experiments to control life phenomena. He achieved what was then regarded his most spectacular result in this program after his emigration to the US in 1891. After having included embryological development of invertebrates to this program, he succeeded to develop a technique for inducing artificial parthenogenesis in sea urchins by inorganic salt solutions, in his words, “the substitution of well-known physicochemical agencies for the mysterious action of the spermatozoon” (Loeb 1899). This work and the anti-vitalistic view that it promoted brought him much acclaim from American and also some German scientists.

The "engineering" life program was, to a large extent, a result of the advice he received from the Austrian physicist and philosopher Ernst Mach, with whom he began to correspond in 1887, on questions of epistemology. While he never met Mach in person, the correspondence that lasted until ca. 1910, strongly influenced Loeb for many years.

Mach's empiricist-positivist philosophy that he developed as a reaction to the prevalent idealistic philosophy promoted the view that all knowledge regarding matters of fact is based on the “positive” data of experience.[3] Mach was a strong opponent of Helmholtz's and du Bois-Reymond's physicalist views, rejecting, among other things, their views of perception and behavior as physical, not biological functions (Pauly 1987, p. 43). Emphasizing action and experiments in science, Mach considered science as derived from and subordinate to technology, a reversal of mainstream ideology in German academia where technology was considered inferior to science. As a strict empiricist, Mach held anti-mechanistic views and considered the notion of causality superfluous. He rejected the atomistic view that natural phenomena can be reduced to matter in motion, as was assumed in the kinetic theory of gases, and he rejected the notion of atoms altogether. Considering "the simplest and most economical abstract expression of facts" to be the goal of science (Mach 1898), he conceived of science not as description of nature but as 'economy of thought', in which efficiency and prediction prevailed and analysis was subordinated to action. The search for the 'nature of things' - a deeper reality behind the phenomena - was deemed metaphysical and thus unscientific.

For some years, Loeb followed Mach in adopting an empirical, anti-mechanistic stand, an attitude that was reinforced and expanded by technology when Mach introduced him to the writings of the Austrian-Jewish engineer and social reformer Josef Popper-Lynkeus. Popper (an uncle of Karl Popper) believed in the cultural importance of technology. He held that technological activity was the expression of a technological and aesthetic drive and that scientific and technical advancements would contribute to a human society.

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[3] Mach accepted, however, that as a result of evolution, there were *a priori* truths without experience, which were *a posteriori* to that of biological ancestors.

Loeb's appreciation of Mach and Popper-Lynkeus might also have a social basis. Like most German-Jewish scientists of his generation, Loeb came from the commercial class, not the educated middle-class. Due to a shortage of money, he at first was unable to attend school through the Abitur level, the prerequisite for studying at universities (he completed it a few years later), but rather finished school after the 10th grade with a degree that allowed him to embark on technical professions. However, Loeb never engaged in political activities aimed at raising the academic reputation of technology. His main concern in his "experimentally controlling life" or "engineering" biology as well as his subsequent mechanistic research was to set and keep high scientific standards, fight vitalism and irrationalism, and denounce what he considered bad science. Loeb developed his "engineering" approach during the fast industrialization that took place in Germany after 1870. This industrialization affected biology in various ways. Of particular importance were the staining tools for cytology and histology provided by chemical industry. However, unlike how the term “engineering” is mostly understood today in general and specifically in biology, Loeb's "engineering" did not have practical aims. Rather, to be a Popperian (Popper-Lynkeus) "engineer" (*Techniker*) of organisms for him meant *doing*, i.e. the establishment of scientific facts through experiments and predictive manipulation of organisms. He held that "in chemistry, as in biology, the control (*Beherrschung*) of phenomena in nature and their complete imitation is the only certain way of generating knowledge" (Loeb 1907, translation by the author). Putting predictive manipulation of entities at the center of scientific practice implied knowledge of their existence and was thus a means for reaching scientific truth.[4] Loeb's engineering was explicitly directed against metaphysical explanations (e.g. vitalism) and speculation on causes; it was **not** industrial engineering or applied science.

To Loeb, solutions to problems in society should be derived primarily from science and technology. In a 1904 review article in *Science* on recent developments in biology, Loeb highly commended "technical biology", science that leads to practical applications, highlighting, in particular, the significance of Liebig's work on fertilization for agriculture and Pasteur's work on micro-organisms for the industry of fermentation. He did not consider his own attempts to control or "engineer" organisms "technical biology." Loeb also emphasized the role of technology for stimulating basic research: "It is natural that the rapid development of technical biology has reacted beneficially upon the development of theoretical biology. Just as physics and chemistry are receiving steadily new impulses from technology, the same is true for biology." (Loeb 1904) For example, in immunity, the question of how antitoxins rendered toxins harmless opened up a new field of research in "theoretical," i.e. non-applied biology (Loeb 1904). Interestingly, he concluded the article with an appeal for the necessity of more support for basic "*general or experimental* biology" as that part of biology where "the chances for the great discoveries seem to lie" (Loeb 1904).

2. Mechanistic research - the search for causes and physico-chemical explanations of life

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[4] A similar reasoning can be found also in the writings of philosopher Ian Hacking who supported his view of scientific realism of entities (not necessarily of theories) by the argument that knowledge about the existence of entities can be robust when they can be successfully manipulated (Hacking 1983, p. 262).

New scientific developments around 1900 led to a change in Loeb's views on science. Among them were Buchner's 1897 demonstration of alcoholic fermentation in cell-free yeast extracts as a result of the catalytic action of a chemical ferment or enzyme, Wilson's 1896 hypothesis that *nuclein* (today DNA and attached proteins) that had been discovered in 1859 might be the hereditary substance (Deichmann 2015), and the rediscovery of Mendel's rules in 1900. Of particular importance was the multiple confirmation of the number of molecules in a known unit of any substance between 1908 and 1911 that had removed the doubts of the existence of molecules, on which Wilhelm Ostwald's and Mach's rejection of causal analysis in science was based.[5]

Distancing himself from Mach and empiricist/positivist philosophy in general, Loeb became increasingly critical of the insufficiency of the positivist/engineering approach and convinced of the necessity to include the exploration of mechanisms, in particular chemical mechanisms, to reach explanation of life phenomena. While before he manipulated organisms' phenotypes from without, he now reflected on the molecules underlying biological phenotypes and processes and on synthesizing life in the laboratory based on a prior manipulation of the genetic material. He explicitly rejected Mach's and Ostwald's "demand for a science free from hypotheses" (Loeb 1915). This transition from positivist "engineering" towards causal-mechanistic research will be highlighted through short sketches on Loeb's approaches towards Darwinian theory, genetics, and synthetic biology.

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[5] Loeb related here to the confirmation of Avogadro's number (the number of molecules or atoms in a known unit (mole) of a substance) by different scientists using different methods in entirely different fields of physics (Loeb 1915). A detailed analysis of the multiple determination of Avogadro's number is in Coko, forthcoming.

Mechanistic science and Darwinian theory

While appreciating Darwin for his materialistic stance, Loeb was skeptical regarding the scientific nature of Darwinian practices because they lacked experimental tests. He demanded that theories of evolution be given an experimental basis once Darwin's outdated concepts of heredity and variation were replaced by concepts of experimental biology such as mutation and Mendelian genetics (Loeb [1909], 1964, p. 209). He disagreed with the widespread approach of Darwin scholars who separated areas such as development, behavior, and evolution as 'biological' from the 'physiological' parts of life sciences. He rejected a methodological division of the phenomena of life into 'biological' ('ontological') and 'physiological,' because "the great diversity of natural phenomena are determined through the altered combinations of these [chemical] elements, and our understanding of the individual phenomena depends solely on the demonstration of the elements and their ordering in a given combination," i.e. causes at the level of chemistry, not phenomena, as with Mach.[6]

Before 1900, when influenced by positivistic ideals, Loeb sought to avoid problems of evolution and causes of biological organization as metaphysical (Pauly 1987, p. 5). Mechanistic biology now provided the means for evolutionary

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[6] Unpublished ms ca. 1896, cited in (Pauly 1987), p. 83. As is well known, some decades later, two of the main architects of the Modern Synthesis of Evolutionary Theory, Ernst Mayr and Theodosius Dobzhansky, proposed another distinction between an ahistorical physiological characterization of biology and a historical one by distinguishing between proximate and ultimate causes or Cartesian, i.e. mechanistic, and Darwinian, i.e. historical, features of biology (see e.g. Deichmann 2010). We can assume that Loeb who died in 1924, would not have considered their distinctions methodologically fruitful.

theory to become scientific. Loeb demanded that physico-chemical explanations be found for variations, regarding de Vries's mutations as starting point, and he held that any theory of evolution cannot be considered as proved unless "it permits us to transform at desire one species into another" (Loeb 2016, p. 6). Recently, Eric Davidson and Douglas Erwin, have envisioned theoretical and experimental approaches that fulfill Loeb's vision on the basis of manipulating gene regulatory networks (see section 3).

Mechanistic science and genetics

Loeb's research on biochemical genetics clearly shows his transition from controlling and manipulating organisms to searching for explanations on the level of molecules. After Eduard Buchner separated the enzymes responsible for alcoholic fermentation from yeast cells in 1897, thus showing that enzymatic action was not dependent on living cells; many biochemists expected that the basic functions of the cell and life might find their explanations in the properties of enzymes. Loeb envisaged that “the specific character of each cell may possibly one day be characterized by the specific ferments it contains and produces.” (Loeb 1915, p. 773). Convinced of the genetic causality of cellular and organismal specificity, he experimentally developed the idea that genes are the "determiners for a certain mass of enzymes" (Loeb and Chamberlain 1915) in a series of papers between 1907 and 1915. At a time when classical genetics was based on an abstract notion of genes, Loeb was thus one of the few biologists at the time who considered the examination of the material basis of genes and gene action important.

In contrast to his earlier work on development, which culminated in his experiments on artificial parthenogenesis, Loeb was now convinced that questions of fertilization, development and heredity had to be approached on the molecular level. As with only a few other scientists of his time, among them Edmund Wilson, Loeb assumed that the *nuclein* in the cell nucleus (later shown to be DNA and attached proteins) played a crucial role in life and reproduction, pointing to its species specificity and its capacity to replicate identically (Loeb [1909] 1964).[7]

In Loeb's opinion, the chemical differences between the nuclei of different organisms were the cause of the differences of form between organisms (Loeb 1909, p. 232). This emphasis on chemical specificity as basis for morphological and genetic specificity strongly contrasted with the purely morphological approach of most cell biologists at the time. The notion that the nucleic acid of the nucleus, which after the 1929 discovery of the sugar deoxyribose was called 'nucleic acid of the deoxyribose type,' later DNA, might be able to carry specificity, was also increasingly rejected by a growing number of chemists and biochemists who assumed that DNA consisted of small uniform molecules of four nucleotides (tetranucleotides).[8]

It should be added that Loeb, whose approach is often depicted as 'reductionist,'[9] was well aware of the importance of organization and regulation. He asked, what makes a harmonious whole organism out of the assortment of Mendelian

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[7] Loeb's assumption was based, among other things, on Theodor Boveri’s demonstration of chromosomes as the carrier of hereditary properties. Hans Driesch’s and Julius Sachs’s finding of a characteristic temperature coefficient of embryonal development justified, to Loeb's mind, a chemical conception of development, the basic chemical reactions being syntheses of *nucleins* (Loeb 1909, p. 225).

[8] See e.g. (Deichmann 2004). Only in 1950 did Erwin Chargaff demonstrate the species specificity of DNA.

[9] For example (Fangerau 2009; Fuerst 1982), and, concerning Loeb's later work, (Pauly 1987).

elements in the chromosomes, and wrote a book on the topic of how the organism as a whole can be understood from a physicochemical viewpoint, rejecting existing vitalistic notions to this effect (Loeb 2016).

Mechanistic science, essential principles of life and the synthesis of new forms of life

As indicated in the last section, Loeb's transition to mechanistic science was accompanied by a reflection on essential principles of life. These principles, to which he repeatedly referred in the later phase of his life, were biological specificity - the specificity of individuals, species, and higher taxonomic taxa - based on the specificity of proteins and "nuclein" (DNA), as well as DNA as causal agent of central life processes. Convinced of the fundamental importance of these principles, he criticized the views of the unity of nature by monists[10] and the claims of having created synthetic life through imitating life forms by osmotic growth processes. In the controversy over whether the essence of life is based on its physical properties such as shape and growth or on the specificity of certain cell structures and molecules, Loeb took the latter position.

This stance proved particular relevant in regard to various claims of physical chemists to have artificially produced new life forms through unspecific osmotic

[10] Loeb rejected attempts to blur differences between animate and inanimate nature, as proposed by Ernst Haeckel who attributed a life-like nature even to inorganic crystals by emphasizing that the essential difference was rooted in the fact that "the living cell synthesizes its own complicated specific material from indifferent or non-specific simple compounds of the surrounding medium, while the crystal simply adds the molecules found in its supersaturated solution" (Loeb 2016, p. 23).

growth processes.[11] Loeb was not opposed to the idea of synthesizing life in the laboratory in principle, but he rejected the claims that imitating cellular structures and living organisms using colloidal precipitates (the spontaneous formation of particle clusters or aggregates in a suspension) had anything to do with synthesizing life. While he considered these activities important for studying the origin of structures in the living, he held that they were not "an imitation of the living, since they are lacking the characteristic synthetic chemical processes" (Loeb 1916, p. 39). For him, species specificity as a basic characteristic of life was based on the specificity of the "nucleins" and the synthesis of self-replicating nucleins was the minimal condition for artificially creating life: "Whoever claims to have succeeded to making living matter from inanimate will have to prove that he has succeeded in producing nuclear material which acts as a ferment for its own synthesis and thus reproduces itself. Nobody has thus far succeeded in this, although nothing warrants us in taking it for granted that this task is beyond the power of science." Loeb [1909] 1964, p. 210)

Loeb's reflections were purely theoretical; his own research at the time was devoted to questions of the molecular basis and physicochemical mechanisms of cellular processes. But his causal-mechanistic stand and the biological principles that he espoused in these debates anticipated prevalent approaches of modern engineering in synthetic biology. Thus in 2010, ca. 100 years after Loeb's prediction, a new bacterial cell was produced by transferring a completely chemically synthesized and fully functioning DNA into a bacterial host cell by Craig Venter and his team (Glass 2012). It is interesting that the German organic

[11] An example is French physicist Stéphane Leduc, who produced "creatures" closely resembling fungi, lower plants and animals (e.g., sea-urchins) by combining several inorganic chemicals, such as calcium nitrate in a solution of sodium silicate (for details of the controversy see (Deichmann 2012)).

chemist and Nobel laureate Emil Fischer, while working on the purine bases of DNA, envisaged genetic engineering with synthetic DNA as early as 1914.[12] I cannot establish a link to Loeb's statements, but it is known that Fischer appreciated Loeb and was one of the few German scientists who attempted to get Loeb back to Germany.

In conclusion: Loeb’s emphasis on exact quantitative experimentation, his early vision of "controlling" and "engineering life", and in particular his subsequent mechanistic scientific perspective and worldview had a major impact on the development of the life sciences. He strongly influenced the work of leading scientists in the early 20th century, such as biochemist Otto Warburg, geneticists Thomas Hunt Morgan and Hermann Muller, and behavioral scientist Herbert S. Jennings. He became, according to Natan Reingold, "one of the widely recognized titans of science" (Reingold 1962).

In his pioneering mechanistic research and reflections on genetics, development, and evolution, Loeb envisioned that life would one day be fully explainable on the level of molecules and new forms of life created by synthesizing the genetic material in the laboratory. Science had not yet advanced enough for controlling and engineering organisms to be conducted in a mechanistic way at Loeb's time. But engineering in modern synthetic biology now seems to be able to fulfill this vision.

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[12] "With the synthetic approaches to this group [of nucleotides] we are now capable of obtaining numerous compounds that resemble, more or less, natural nucleic acids. [...] I am bold enough to hope that, given the right conditions, [...] artificial nucleic acids may be assimilated without degradation of the molecule. Such incorporation should lead to profound changes of the organism, resembling perhaps permanent changes or mutations as they have been observed in nature." (Deichmann 2004, p. 1)

Mechanistic science and humanism

For Loeb, promoting biology as a mechanistic science was also a tool to serve humanity. The First World War severely affected his positive and optimistic stance. Deeply depressed by rising nationalism, racism, and anti-Semitism in Europe, especially Germany, and also the US, he dedicated his book *The Organism as a Whole* (1916) to the prominent French philosophers of the Enlightenment, d'Alembert, Diderot, Holbach, and Voltaire, "who first dared to follow the consequences of a mechanistic science ... and who thereby laid the foundation of that spirit of tolerance, justice, and gentleness, which was the hope of our civilization until it was buried under the wave of homicidal emotion, which was swept through the world." (Loeb 1916, p. viii)

For Loeb, romanticism, if defined as an "appeal to the emotions in combination with a neglect for severe standards of truth" was in no small degree responsible for "unnecessary hatred and unnecessary opposition to intellectual progress" (Loeb 1915, p. 785). In his opinion, scientific reasoning as rational reasoning - epitomized by mechanistic science - was the only effective weapon against irrational political currents, e.g. the Chauvinist and anti-Semitic propaganda of philosopher Eugen Dühring and historian Heinrich von Treitschke, as he expressed in 1915: "The question whether humanity wishes to be guided by mechanistic science or by metaphysical romance is, therefore, not only of merely academic importance. What progress humanity has made, not only in physical welfare but also in the conquest of superstition and hatred, and in the formation of a correct view of life, it owes directly or indirectly to mechanistic science." (Loeb 1915)

During his last years, his work focused on the physical chemistry of proteins. This shift reflected on the one hand his increasing conviction of the importance of physical chemistry for understanding biological phenomena, on the other, the fact that in this field a new kind of irrational beliefs had become widespread in the face of exaggerated claims by biocolloidists. This group of biologists and biochemists believed that biological systems could not be described in mechanistic terms because the central life processes were governed by the laws of a special biological colloidal science (Deichmann 2007). Loeb rejected these claims not only for scientific but also political reasons. The fact that biologist Wolfgang Ostwald, a leading representative of colloidal biology in Germany combined an anti-mechanistic stand, in which explanations on the level of molecules following chemical laws were denied, with fierce nationalism and militarism, proved, according to Loeb, the danger inherent in what he called a “metaphysical romance in science.” (Loeb 2015)

Loeb’s aversion to the vague, speculative and inherently vitalistic concepts of biocolloidists and his concern about their increasing acceptance by American scientists such as Wilder Bancroft stimulated him to refute these claims by experiment. His long series of publications on proteins and membrane equilibria, culminated in his 1922 book, *Proteins and the theory of colloidal behavior*, where he showed that colloidal biochemistry was obsolete at least as far as proteins were concerned (Loeb 1922). An article that he published a year later in German (Loeb 1923) was heavily criticized by Wolfgang Ostwald who rejected Loeb’s “purely chemical theory” for the behavior of proteins as a mere “fallacy” (Deichmann 2007). But Loeb’s view became increasingly accepted. For Loeb, taking a moral stand included not only the fight against racism and militarism, but also actions against bad science.

3. Loeb's ideals of controlling ("engineering") life and mechanistic explanations in present-day research

Mechanistic science in development and evolution: Eric Davidson's research on gene regulatory networks.

Around 100 years after Loeb, American molecular embryologist and systems biologist Eric Davidson propagated the modern mechanistic view in biology with a passion similar to Loeb's, though not inspired by him. He considered the modern causal-mechanistic view as the current criterion in experimental molecular biology for successful scientific analysis, "one that succeeds in explaining with good causal evidence how something works and why" (Davidson 2016). Like with Loeb, experimental perturbation was crucial. Without perturbation, mechanisms and causes cannot be revealed.

Davidson's work led to the proposition of a "rooted" mechanistic explanation for the early development of the sea urchin that included molecular mechanisms and a causal analysis of the underlying process, namely the "regulatory control of the genes which encode transcription factors in space and time" (Davidson 2016). As one of the first scientists to pursue a systems approach in molecular embryology, he created the concept of developmental gene regulatory networks in the early 2000s, achieving an almost complete model of such a network for the development of a particular phenotype (Rothenberg 2016). The existence of hierarchical gene regulatory networks was widely confirmed in the following decades, and the concept's fruitfulness widely acknowledged.

Despite fundamental differences in their research and scientific achievements, Davidson's scientific worldview has distinct similarities with Loeb's mechanistic worldview. Both strongly promoted the view that simulating biological processes without experimentally elucidating their mechanisms and causes was not fruitful. Based on experiments that proposed linkages based on perturbations, not on correlations, Davidson's regulatory network models thus fundamentally contrasted with purely computational simulations or mathematical representations of developmental processes in silico (Davidson 2016). Similarly, Loeb's demand that an artificial synthesis of new forms of life be based on the experimental synthesis of the molecules of genes contrasted with claims that artificial life was created by simulating it through osmotic processes in inorganic salt solutions.

For Davidson, as for Loeb, the mechanistic philosophy was an important criterion for assessing evolutionary theories, though, of course, based on a long scientific development since Loeb's time. Like Loeb, Davidson considered the neo-Darwinian theory of evolutionary change by small mutations and natural selection incomplete, because the accumulation of small mutations cannot explain systems changes such as the generation of new body plans that underlie the evolution of new species and higher taxa.

Based on his work on gene regulatory networks, Davidson had begun to experimentally tackle questions of evolutionary change and evolutionary stability over long periods of time. Together with palaeobiologist Douglas Erwin, he suggested new evolutionary mechanisms that were based on changes in regulatory patterning and developed hypotheses about how to re-engineer the split between two species of sea-urchins about 260 million years ago. This "synthetic experimental evolution," as Davidson termed it, fulfills most clearly Loeb's vision of experimentally creating new species by chemically manipulating the genetic material (Davidson 2006; Davidson and Erwin 2006; Erwin 2017). Many decades after Loeb, conceptual and methodological advance meanwhile had provided experimental tools for this goal, as Davidson's emphasis on experimental perturbation such as "changing a sequence experimentally" or the "insertion of synthetic expression constructs" indicates. This research was part of his mechanistic scientific perspective based on the search for causes and mechanisms.

In conclusion, while Loeb influenced future generations of biologists more through his ethos of open-ended experimentation in biology and his anti-vitalistic mechanistic scientific worldview than through particular discoveries, Davidson became influential through his seminal causal-mechanistic research on gene regulatory networks. His causal-mechanistic gene regulatory network concept deeply impacted modern synthetic biology, where "engineering" methods based on gene regulatory networks are most widely applied. Today, "engineering" serves many goals, particularly, but not only, practical ones.

Engineering and mechanistic science in synthetic biology

Gene regulatory networks and the genetic circuits they entail are of central importance to synthetic biology today. Regulating major biological functions such as development and tissue homoeostasis, they have given rise to new possibilities of engineering practices. To find "minimal, easy-to-engineer networks capable of specific functions" therefore is of crucial importance for engineering circuits in synthetic biology (Perez-Carrasco et al. 2018). Such circuits have already been used for screening drugs and detecting diseases. Gene network engineering is today a key technology in synthetic biology and is also the basis for applications of paramount importance in the future.[13] Other important parts of synthetic biology are synthetic genomics, protein engineering,

[13] Mark Isalan in a letter to the author, 2 August 2019. See e.g. (Nielsen et al. 2016).

protocells, unnatural genetic codes and amino acids. Ultimately, though, it is DNA that is engineered, but using very different approaches.

Building biological systems in the lab is also a means of understanding them. Interestingly, this idea, popularized by Richard Feynman ("what I do not create I do not understand"), was a widespread practice of the early organic chemists to determine the correctness of their predicted molecular structures. According to synthetic biologist Chris Barnes, "ideas from engineering are very important to science generally," where they allow, e.g. for looking at "tradeoffs between robustness and evolvability, size and energy etc."[14] For him, as for some other synthetic biologists, the application is not the goal, but "synthetic biology is just a tool, a bit like systems biology, which scientists will use to interrogate their biological system of choice. But it is true that synthetic biology is driven most of the time by biotechnology."[15]

These examples suggest that successful engineering in synthetic biology today, unlike in the late 19th century, is based on molecular mechanisms and mostly consists of manipulating or synthesizing genetic circuits. Synthetic biology can be used to test the value of mechanistic models. Loeb's vision that synthesizing life must begin with synthesizing the genetic material (*nuclein*) has come true, and his belief that biological specificity is based on genetic specificity is the basis of synthetic biology today.

Summary

Jacques Loeb's "engineering life" concept was an epistemological tool used to highlight the importance of experimentation in those fields of research formerly

[14] Chris Barnes, in conversation with the author, 9 August 2019.

[15] Barnes, conversation.

considered unapproachable by science and explained by vitalistic speculations. Loeb's program for an "engineering" biology that he developed early in his career was strongly influenced by Ernst Mach's empiricist-positivist epistemology. The elucidation of mechanisms or causes other than outside physical or chemical agents was anathema. Predictive manipulation was a method for gaining knowledge about organisms' functions i.e. a means of finding scientific truth, not of pursuing applied goals.

When the increase of scientific knowledge in biochemistry and genetics enabled studies of mechanisms and causes of biological phenomena, Loeb abandoned the purely empiricist view and the ideal of "engineering" life based on it. Instead he began to propagate a mechanistic, physicochemical concept of life, a change which was accompanied by a reflection on basic principles of life. Central among them were the idea of biological specificity based on protein diversity and the notion that any attempt to synthesize life must begin with synthesizing the genetic material. Such an approach was unthinkable in a positivistic epistemology. These principles became the philosophical-scientific basis of molecular biology and synthetic biology and the engineering approaches in both. Conceptually and epistemologically, modern engineering in biology is therefore not a continuation of 19th century "engineering" life attempts, but is based on the causal-mechanistic approach that Loeb and others developed at the beginning of the 20th century.

Loeb's change of scientific outlook was reinforced by his suffering from the knowledge of the atrocities of the First World War, to him largely a result of irrational currents in German and other European politics and societies, which caused his general optimism to fade away. To him, mechanistic science became a bulwark against irrationalism in science and society as a whole, such as racism, anti-Semitism and Chauvinism. Today, engineering approaches based on causal-mechanistic science achieve reliable knowledge through methods of causal-mechanistic experimental control of life phenomena. Mechanistic engineering thus stands in opposition to tendencies that deny the existence of objective scientific truth and 'post-truth' attitudes in general.

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