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Early 20th-century research at the interfaces of genetics, development, and evolution: Reflections on progress and dead ends

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ABSTRACT

Three early 20th-century attempts at unifying separate areas of biology, in particular development, genetics, physiology, and evolution, are compared in regard to their success and fruitfulness for further research: Jacques Loeb's reductionist project of unifying approaches by physico-chemical explanations; Richard Goldschmidt's anti-reductionist attempts to unify by integration; and Sewall Wright's combination of reductionist research and vision of hierarchical genetic systems. Loeb's program, demanding that all aspects of biology, including evolution, be studied by the methods of the experimental sciences, proved highly successful and indispensible for higher level investigations, even though evolutionary change and properties of biological systems up to now cannot be fully explained on the molecular level alone. Goldschmidt has been appraised as pioneer of physiological and developmental genetics and of a new evolutionary synthesis which transcended neo-Darwinism. However, this study concludes that his anti-reductionist attempts to integrate genetics, development and evolution have to be regarded as failures or dead ends. His grand speculations were based on the one hand on concepts and experimental systems that were too vague in order to stimulate further research, and on the other on experiments which in their core parts turned out not to be reproducible. In contrast, Sewall Wright, apart from being one of the architects of the neo-Darwinian synthesis of the 1930s, opened up new paths of testable quantitative developmental genetic investigations. He placed his research within a framework of logical reasoning, which resulted in the farsighted speculation that examinations of biological systems should be related to the regulation of hierarchical genetic subsystems, possibly providing a mechanism for development and evolution. I argue that his suggestion of basing the study of systems on clearly defined properties of the components has proved superior to Goldschmidt's approach of studying systems as a whole, and that attempts to integrate different fields at a too early stage may prove futile or worse.

Beginning in the late 19th century, after the establishment of the unifying concept of the cell, modern experimental biology owed its early successes mainly to analytical approaches that fragmented biology into many different sub-disciplines. Experimental embryology (*Entwicklungsmechanik*) was founded by Wilhelm Roux as a direct response to the merely descriptive evolutionary morphology of Ernst Haeckel, in which development and evolution were considered as a unity. By methodically (not conceptually, see Griesemer, 2007) separating questions of the transmission of traits from those of development and evolution, Mendel laid the basis for modern genetics. (In contrast, Darwin's attempt at about the same time of a great synthesis of development, genetics, and evolution quickly turned out to be a dead end (Deichmann, 2010)). Some decades later, biology was to owe its progress also to successful syntheses between formerly disconnected fields: (1) The chromosome theory of heredity integrated cytology and genetics, first vaguely proposed by Theodor Boveri and, independently, Walter Sutton, in 1903, then developed in an extremely successful way by Thomas H. Morgan and his school from 1910; and (2) The "Modern Synthesis" that integrated Mendelian genetics, population genetics and Darwinian evolution. Major protagonists in the 1930s and 1940s were Ronald A. Fisher, J.B.S. Haldane, and Sewall Wright.

I here review three other early attempts at unifying separate areas of biology, in particular development, genetics, physiology, and evolution: Jacques Loeb's *reductionist* project for unifying through physico-chemical explanations in the late 19th and early 20th century; Richard Goldschmidt's *anti-reductionist* attempts to unify by integration in the first half of the 20th century; and Sewall Wright's combination of *reductionist* research and *vision of hierarchical genetic systems*, also in the first half of the 20th century. I compare the fruitfulness of these projects and analyze to what extent their successes and failures can be related to the approaches applied.

Jacques Loeb's reductionist project of unifying by physico-chemical explanations

Jacques Loeb, born in Mayen near Cologne in 1859, was a physiologist, later experimental biologist. He immigrated to the United

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States in 1891, because he considered it unlikely that he would receive a position, since he was Jewish and outspokenly liberal. Holding positions at, successively, Bryn Mawr College, University of California, Berkeley, and, from 1910 until his death in 1924, at the Rockefeller Institute for Medical Research, he was increasingly regarded as "America's emblem of pure wissenschaft" (Kay, 1993), as someone who by the turn of the century "had come to symbolize the appeal and temptation of open-ended experimentation among biologists in America" (Pauly, 1987).

Loeb's strong conviction that the basic life phenomena can be explained in principle by physical and chemical laws, was accompanied by a preoccupation with finding physical and chemical explanations for basic life phenomena. This also made him a pioneer in studies relating genetics, biochemistry, in particular enzymology, and development (a detailed overview on this convergence is in Ravin (1977), see S.I. note 1). After Eduard Buchner in 1897 separated enzymes responsible for alcoholic fermentation from yeast cells and thereby showed that enzymatic action was not dependent on living cells, enzymes became a major focus of biochemical research. Biochemists expected that the basic functions of the cell and life might find their explanation in the properties of these enzymes. Loeb (1912) envisaged that "the specific character of each cell may possibly one day be characterized by the specific ferments it contains and produces".

In a series of papers between 1907 and 1915 Loeb, through experiment, developed the idea that genes were the determiners for enzymes in development (Loeb and Chamberlain, 1915). Though highly appreciative of the work of Mendel and Morgan and of the fertility of the concept of genes as abstract units, he was one of the few biologists to consider worthwhile to also examine the material basis of genes and gene action, demanding that geneticists should determine "the chemical substances in the chromosomes […] and the mechanism by which these substances give rise to the hereditary character" (Loeb, 1912). He rejected the notion held, e.g. by Richard Goldschmidt, that genes were in fact enzymes, based on quantitative grounds: "The hereditary factor in this case must consist of material which determines the formation of a given mass of these enzymes, since the factors in the chromosomes are too small to carry the whole mass of the enzymes existing in the embryo or adult." (Ibid.) This reasoning was appreciated by Thomas H. Morgan, who was in general disinclined to speculate on the chemical nature of the gene and its action and in particular rejected assertions of genes being enzymes, because they disregarded the crucially important distinction of genotype and phenotype, proposed by Wilhelm Johannsen (1909). Morgan considered Loeb's and Chamberlain's standpoint concerning genes and enzymes "the most correct one" (Morgan, 1919).

Loeb introduced the concept of "autocatalysis" as basis for "the mechanism for the continuity of the hereditary substances", which, he thought, was identical with the "secret of life" (Loeb, 1909a). The concept of autocatalysis was taken up by several authors e.g. Hermann Muller (1922), who later analyzed this concept's role in stimulating research into material properties of the gene, but also drew attention to its conceptual shortcomings (Muller, 1967). An example of a flawed usage of this concept is phage research. In analogy to the autocatalytic activation of some enzymes such as trypsin, some biochemists applied this concept also to phage replication. But Max Delbrück and Emory Ellis showed in 1939 that phage replication did not show any signs of sigmoid curves, thus could not be autocatalytic (Morange, 1998), a conclusion that was the basis for genetic phage research. Loeb based his assumption of self-replication of the hereditary material on Theodor Boveri's discovery that the nucleus was the carrier of the hereditary properties, Boveri's demonstration that the nuclei of all cells of an embryo have the same size, and Hans Driesch's and Julius Sachs's analyses of the relation between the sizes of protoplasm and nuclei during development.

After Miescher's discovery of DNA as a new macromolecule in the nucleus (1871) and some biologists' assumptions of DNA being chromatin, Loeb anticipated with a clarity that was exceptional at his time, the crucial role of DNA for life and reproduction, its species specificity, and its capacity to replicate identically (for example Loeb, 1909a). In Loeb's opinion, the solution to the question of what life is, and how it can be made from non-living material, had to come from the chemistry of proteins and DNA.

Loeb's attempts to relate central features of life, such as heredity, to the chemistry of macromolecules strongly contrasted with the morphological approach employed by the vast majority of cell biologists. Moreover, the notion that DNA might be able to account for biological specificity (in today's terms: to carry biological information) was rejected by a growing number of chemists and biochemists who assumed that DNA consisted of small uniform tetranucleotide molecules; only in 1950 was the species specificity of DNA demonstrated (by Erwin Chargaff, see e.g. Deichmann, 2004). A remarkable exception of a chemist who as early as 1914 envisaged genetic engineering with synthetic DNA was Nobel laureate Emil Fischer, while working on the purine bases of DNA (see S.I. note 2). However, neither Fischer nor anybody else pursued this idea seriously or devised experiments to this end. The interest of scientists in the material basis of inheritance and in the biological functions of DNA, which emerged in the late 19th century, to a large extent disappeared during the first decades of the 20th century, when genetics was established as a scientific discipline (Deichmann, 2004). When, in the 1930s, a new interest in the chemical basis of heredity emerged, it was related to proteins, which were considered as sole carriers of biological specificity, a notion called "protein paradigm" (Kay, 1993) or "protein dogma" of the gene (Olby, 1994).

Loeb's passionate promotion of biology as an experimental mechanistic science made him dissatisfied with the merely descriptive and speculative approaches of evolutionary biology: "In science we [can] only take things for proven when they are based on quantitative experiments and from this point of view ours [is] not the era of Darwin but the era of Pasteur" (Loeb to E. G. Conklin, 9 January 1924, Library of Congress, Manuscript Dept, Loeb Papers, file Conklin) was his response to a group of Darwin scholars whose arguments he considered unscientific. Loeb criticized evolutionary biology for the incompleteness of the theory of natural selection, i.e. the lack of mechanistic explanations for variation and species transformation, and the lack of experimental evidence for this transformation. According to Loeb, "any theory of life phenomena must be based on our knowledge of the physicochemical constitution of living matter, and neither Darwin nor Lamarck was concerned with this. Moreover, we cannot consider any theory of evolution as proved unless it permits us to transform at desire one species into another, and this has not yet been accomplished." (Loeb, 1916).

Loeb rejected the methodological division of the phenomena of life into 'biological' ('ontological') strands, e.g. behavior, development, and evolution, and 'physiological', as was prevalent at his time, as counterproductive; his models for biology were Liebig, Pasteur, and Emil Fischer (Pauly, 1987). A similar division was reintroduced some decades later by Ernst Mayr (1962) and Theodosius Dobzhansky (1964, 1969), who distinguished between proximate and ultimate causes, and Cartesian (mechanistic) and Darwinian (historical) aspects of biology respectively. This division became methodically increasingly irrelevant as mechanistic and molecular approaches also became widespread in evolutionary biology.

For Loeb one possibility to give the study of evolution an experimental basis had to come from genetics. He called on geneticists to experimentally generate mutations (1912): "The discovery of de Vries that new species may arise by mutation and the wide if not universal applicability of Mendel's law to phenomena of heredity, as shown especially by Bateson and his pupils, must, for the time being, if not permanently, serve as a basis for theories of evolution. These discoveries place before the experimental biologist the definite task of producing mutations by physico-chemical means." Some years later, in 1927, Hermann Muller indeed successfully carried out artificial mutagenesis by X-rays, in which mutations were generated in a controlled way.

Another aspect of evolutionary theory which Loeb wanted to bring under experimental control was the question of the origin of life, which he related to that of synthesizing artificial life. For Loeb the generally accepted view that spontaneous generation of life, even of simple bacterial cells, does not occur in nature (Pasteur, 1861), did not contradict the assumption that under special conditions this had been possible in nature, and could be achieved in the laboratory (for details of Loeb's views, see Deichmann, 2010). Based on his conviction that life was characterized by a capacity to synthesize “complicated specific material from indifferent or non-specific simple compounds of the surrounding medium”, Loeb was critical of inanimate models for life processes. He disagreed for example with equating life with crystals, the growth of which was simply adding the same molecules as found in its supersaturated solution (Loeb, 1916). He also rejected the claims of some physical scientists of having artificially produced new life through osmotic growths resembling fungi and lower plants and animals, such as sea urchins. According to him these growth processes and forms were not “an imitation of the living since they are lacking the characteristic synthetic chemical processes” (Loeb, 1916). He held that whoever claimed to have succeeded in making living matter from the inanimate would have to prove that he succeeded in producing nuclear material able to reproduce identically (Loeb, 1909b, cited in Loeb, 1912). Thus for Loeb, the characteristics of life were inseparably connected to properties of macromolecules, i.e. proteins and DNA.

To conclude, Loeb's mechanistic and reductionist biological research program strongly and directly influenced the work of leading figures in experimental biology during the early 20th century, such as biochemist Otto Warburg, geneticists Thomas Hunt Morgan and Hermann Muller, and behavioral scientist Herbert S. Jennings. The molecular biological approach, which resulted from this program, proved highly successful. It was necessary for explaining evolutionary change, but, taken alone, thus far was insufficient to explain mechanisms for major such changes. It was the rapidly progressing systems approaches based on hierarchical gene networks that seemed to bring about a revolution in regard to the scope of explanation (see e.g. Erwin and Davidson, 2009; Laubichler, 2009). Loeb's demands that evolutionary theories be given an experimental basis and that species generation and transformation be shown in the laboratory have been transformed into actuality in recent decades, e.g. in synthetic experimental evolution (ibid.).

Richard Goldschmidt's anti-reductionist attempts to unify by integration

The zoologist Richard Goldschmidt, born 1878 in Frankfurt, started his career in Germany twenty years after Loeb, at a time when genetic research was already established in various centers. Studying and working with the most renowned German zoologists at the time, in particular Richard Hertwig, he began his scientific work with the morphology and histology of nematodes (1900–1909). This was followed by works on sex determination and genetics (1909–1934) and organic evolution (from 1930). In 1914 he became head of the department for animal genetics at the newly founded Kaiser Wilhelm Institute (KWI) for Biology in Berlin, of which he became Second Director in 1919. Since he was Jewish, Goldschmidt was expelled from his position in 1935; he emigrated to the United States, where he became a professor at the University of California, Berkeley. Unlike Loeb and Sewall Wright, he has received wide attention from historians and historically oriented scientists (see below).

Goldschmidt became best known for his work, starting in 1909, on sex determination and genetics of different geographical races of *Lymantria dispar*, the gypsy moth, of which he bred hundreds of thousands of individuals. Observing ambiguous sexual forms during different times of development, he coined, in 1915, the term intersexuality for the switch-over at a certain time during the development from one sex to the other in regard to secondary sexual properties (*turning point theory*) (Fig. 1). According to this theory, the time until the turning point was genetically determined and a measure of the degree of intersexuality (a quantitative correlation which he called *time law*). Goldschmidt claimed to have received the highest percentages of intersexes when he crossed Japanese and German races. He explained this phenomenon with large quantitative differences in the sex determining genes between these races and formulated mathematical equations, from which the turning point during the development of intersexes could, allegedly, be determined (Fig. 2).

Goldschmidt interpreted the existence of a time law and the quantitative characteristics of the controlling gene balance by an enzymatic action of genes in development. Based on this view, he proposed the theory of genic action by intertwined and balanced velocities of the reactions of sex determining processes, controlled by the quantities of the genes (enzymes), which he called the *Physiological Theory of Heredity* (Goldschmidt, 1927, 1934). This theory implied a disintegration of the chromosome during the interphase, asserted that mutations were quantitative (not qualitative) changes in the amount of a gene (enzyme), and claimed that alleles of genes differed in quantity not in quality. Different quantities of genes catalyzed, in development, different reaction rates.

The *Physiological Theory* rejected central elements of the chromosome theory of heredity, in particular what Goldschmidt called the factorial “hypothesis”, and the notion of crossover and its implications for gene mapping. He tried to explain the regularities of crossover by a colloidal gene-concept, claiming that the task of chromatin was adsorption of hereditary enzymes and that the variables and constants of crossover reflected the variables and constants of the laws of adsorption (Goldschmidt, 1917; see comment of Sturtevant, 1917).

Goldschmidt's gene concept changed again in the 1930s, when it became closely linked to his concept of evolution, which likewise underwent dramatic changes. An early advocate of neo-Darwinism, he became a fierce critic later on, regarding neo-Darwinian mechanisms, that is, the accumulation of small mutations, as irrelevant for evolutionary changes. Following Hugo de Vries and William Bateson who advocated a saltationist interpretation of evolution, in the words of de Vries (in 1906): “The theory of mutation assumes that new species and varieties are produced from existing forms by certain leaps” (Mayr, 1997), Goldschmidt postulated “bridgeless gaps” between species and

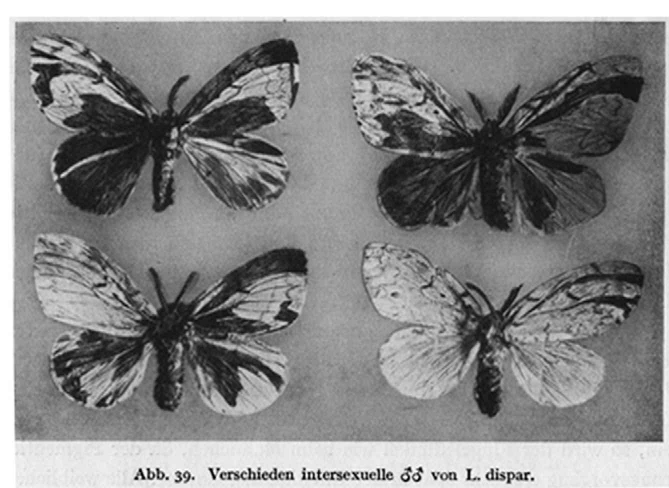

Fig. 1. Intersexual males from L. dispar, (Goldschmidt, 1927), upper left: almost female, lower right: male.

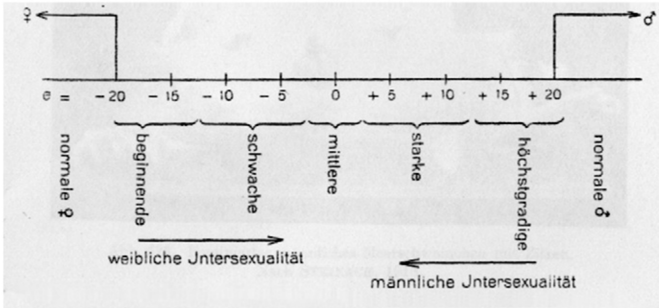

Fig. 2. Types of intersexuality as a representation of the difference between female and male valences F minus M (Goldschmidt, 1920).

proposed that they can only be accounted for by large sudden evolutionary jumps (saltations). For these he proposed two genetic mechanisms: Developmental macromutations which were supposed to lead to "hopeful monsters"; and "systemic mutations", a re-patterning of chromosomes, i.e. a re-organization of the chemical system of the chromosomes (Goldschmidt, 1940, see also Dietrich, 2000, 2003).

In his concept of "systemic mutations" Goldschmidt now questioned the classical gene concept altogether and replaced his former genetic theories with a model in which the concept of particulate genes was abandoned. Chromosomes were supposed to act as a whole, and all mutations were chromosomal rearrangements (Goldschmidt, 1940, 1951). He related his holistic genetic speculations to what he called the reaction system of an organism: "The idea of the reaction system […] is opposed to the idea of integrated genic action. It means that the germ plasm as a whole; i.e., predominantly the chromosome complex, controls the general feature of development which leads to a definite type, the species in question. This idea dispenses completely with the individual gene and its individual action, […]." As a result, "the germ plasm as a whole controls a definite reaction system, which, then is not a mosaic of separate effects but a single developmental system controlled as a whole by one agency" (Goldschmidt, 1940). Genes and gene mutations were not needed "at all" to understand evolution, they were replaced by the "serial pattern of the chromosome and its parts" (ibid). He held that "an unlimited number of patterns is available without a single qualitative chemical change in the chromosomal material and that the systemic pattern mutation – as opposed to a gene mutation – appears to be the major genetic process leading to macroevolution, i.e. evolution beyond the blind alleys of microevolution" (ibid). Consequently he dismissed Bridges' seminal idea that new genes were formed by duplication and subsequent mutations as "not [to] be taken seriously" and considered the fact that inversions and other chromosomal rearrangements occurred without noticeable effects – a clear contradiction to his theory – "as an accident, without any significance" (ibid).

From the 1940s Goldschmidt studied homoeotic mutations in Drosophila in order to support his view of large evolutionary jumps. Homoeotic (later homeotic) mutations cause an organ to differentiate abnormally and usually have large phenotypical effects such as legs growing in place of antennae or an extra set of wings; they were first described by William Bateson in plants (in 1894). Goldschmidt used mutations, in which wings were transformed into leg-like structures (podoptera mutations see below). He argued that if it is possible to "mutate [complex organs like wings] in one step into another more primitive organ [like a leg]", then it is very likely "that the opposite also happens, namely mutation of leg into wing" and it has to be accepted as a fact that "insect wings originated as a 'saltation' and not through slow evolution" (Goldschmidt, 1945, cited in Lipshitz, 1996). The questionable logic of this reasoning was criticized by Howard Lipshitz (Lipshitz, 1996). Goldschmidt had a broad knowledge of genetics but he used, disregarding logical contradictions, his knowledge of novel developments mainly to provide evidence for his own claims. By interpreting homoeotic mutants in a purely speculative way in terms of the (fictitious) rearrangement of chromosomal sections, he did not contribute to an understanding of these mutations.

Goldschmidt's "synthesis" — historical assessments

Goldschmidt was a controversial scientist. Because of this and because his work is still credited with having pioneered a new evolutionary synthesis, I insert here a section on the reception of this work and a reflection on successful syntheses and dead ends.

Appreciation

Goldschmidt has been appreciated by historians as well as biologists as the first scientist to integrate heredity, development, evolution and biochemistry. According to his student Curt Stern, Goldschmidt, by emphasizing the role of genes in physiology and development, developed a new theme for future research (Stern, 1967), a remarkable assessment given the fact that Stern not only never worked along Goldschmidt's lines but even (in 1931) published, in opposition to Goldschmidt's *Physiological Theory*, definitive cytological confirmation for crossing over. Geneticist Ernst Caspari emphasized Goldschmidt's motivational influence: Goldschmidt's "quantitative theory of genetics" was attractive to students "because it united concepts from genetics, embryology and biochemistry and in this way offered a more comprehensive view of life processes than the competing theory based on interactions at the gene level only" (Caspari, 1980). According to developmental biologist Klaus Sander, Goldschmidt was one of the few biologists to spend time and thought on the role of genes in development, anticipating that "gene activation" would assist in generating a stratified pattern of organ-forming substances in the insect oocyte (Sander, 1986). According to the evolutionary developmental biologists Scott F. Gilbert, John M. Opitz and Rudolf A. Raff, Goldschmidt's (and C.H. Waddington's) research was the key for understanding the relationship between genetics, development and evolution (Gilbert et al., 1996). Stephen J. Gould, who through his and Eldredge's model of punctuated equilibria, that is discontinuous tempos of change in the process of speciation, became a dissenter from neo-Darwinian gradualism, praised Goldschmidt for his stand against neo-Darwinism (but was vehemently opposed to his concept of systemic mutations): "As a Darwinian, I wish to defend Goldschmidt's postulate that macroevolution is not simply microevolution extrapolated, and that major structural transitions can occur rapidly without a smooth series of intermediate stages" (Gould and Eldredge, 1977).

Historian Michael Dietrich, who for decades has analyzed Goldschmidt's work, strongly promotes the view that Goldschmidt pioneered the integration of development, evolution, and genetics (e.g. Dietrich, 2000), a view that was expounded in wikipedia (July 2010). In a more recent publication, he holds, more cautiously, that Goldschmidt's dissent from orthodox views in genetics and evolution, even though it met with strong criticism, created an opportunity for innovation, the proposal of alternatives to the accepted foundations of genetics and neo-Darwinian evolution (Dietrich, 2008). Similarly, following Gilbert et al.'s assessment, historian Marsha Richmond holds that "Goldschmidt's program of physiological genetics stimulated a number of developmentally minded geneticists and developmental biologists in the 1930s and 1940s", in particular physiological geneticists in Britain, such as Conrad Waddington and Joseph Needham, and his "approach to problems of heredity, development, and evolution […] continues to resonate today" (Richmond, 2007).

There is, however, no evidence that the scientists who initiated developmental genetics in the 1980s did so with reference to Goldschmidt. Edward B. Lewis, one of the founders of this field, never cited Goldschmidt, not even in his historical treatise (Lewis, 1994). Ernst Caspari, an early pioneer of the field, was the first to examine the mechanism of genic action by the method of tissue transplantation and the first to show that genes act via the production of a specific substance (which for a while was called gene-hormone), (Caspari, 1933; Kühn et al., 1935). Even Caspari, in his treatise on the history of research in genic control of development (Caspari, 1960), did not mention Goldschmidt as one of the pioneers of this field despite his high praise for Goldschmidt in his biographical essay (Caspari, 1980).

Criticism

Goldschmidt was criticized because of methodological flaws in his work, in particular the (hidden) speculative nature of his theories and vagueness of core concepts, and the lack of reliability of his experiments.

The speculative nature of theories and vagueness of core concepts. Goldschmidt himself emphasized – in words – the importance of empirical research. He explicitly rejected as pure hypotheses and speculations central contents of the chromosome theory of inheritance as suggested by Morgan and his school: "A theory of inheritance has to be grounded above all in facts, the facts of experimental genetics and developmental biology" (Goldschmidt, 1927, author's translation). He recommended to his critics the view of Darwin whom he quotes as follows: "I have steadily endeavoured to keep my mind free so as to give up any hypothesis, however much beloved (and I cannot resist forming one on any subject) as soon as facts are shown to be opposed to it." (Goldschmidt, 1951).

That his actual research practices were, however, quite different, was perceived and criticized early on. In Germany, the speculative nature of his genetic theories was received with a mixture of appreciation and criticism. An example is renowned zoologist Alfred Kühn who appreciated Goldschmidt's "courageous attempt to form a broad embryological synthesis between gene and phenotypical properties", which he placed in the tradition of great German speculative biological theories ("very impressive in its intellectual consistency, altogether not compelling"). "However", Kühn warned, "it would be dangerous, if [Goldschmidt's] construction of genius were regarded as already reliable knowledge and were dogmatized" (Kühn, 1928, author's translation). In contrast to the United States, comprehensive speculative biological theories were still generally accepted in Germany in the first half of the 20th century. Further examples are Hans Driesch's *Analytical Theory of Organic Development* (1894) and Fritz von Wettstein's *Plasmon Theory* (v. Wettstein, 1927, 1930).

In the United States Goldschmidt's work was severely criticized early on. The criticism focused on methodical flaws and the hidden speculative nature of his supposedly empirical work. Alfred Sturtevant from the Morgan school made it clear that the allegedly quantitative basis of Goldschmidt's concept of intersexuality lacked any empirical evidence: "The interpretation is in appearance a quantitative one, and is often so described, but there are no quantitative data. The numerical values [of the strengths of the male and female tendencies] are arbitrarily assigned hypothetical ones; a value of 80 assigned to a single M does not refer to any measured or defined units. The papers contain numerous curves, representing specific hypotheses about the course of development, but these are also arbitrary and not based on any measurements. The papers contain accounts of a large number of crosses, descriptions, and photographs of many intersexes. One cannot fail to be impressed by the extent of the work — but I confess that I should be more impressed if there had been use of more powerful genetic and cytological techniques, and more attempt to get objective quantitative data." (Sturtevant, 1965).

Similarly, but without mentioning Goldschmidt's name, Hermann Muller, likewise a student of Morgan's, held that, "The real trouble comes when speculation masquerades as empirical fact. For those who cry out most loudly against 'theories' and 'hypotheses' — whether these latter be the chromosome theory, the factorial 'hypothesis', the theory of crossing over, or any other — are often the very ones most guilty of stating their results in terms that make illegitimate implicit assumptions, which they themselves are scarcely aware of simply because they are opposed to dragging 'speculation' into the open. Thus they may be finally led into the worst blunders of all." (Muller, 1922, see also Schultz, 1935).

Asked about possible reasons for Goldschmidt's "cold reception" in the United States, geneticist James Angus Jenkins considered "the vagueness of ideas" to have been in the main responsible. Jenkins himself found Goldschmidt's ideas "not so revolutionary but vague and to use a very trite expression, he appeared to throw the baby out with the bath" (Jenkins to C. Stern, n.d., ca. 1958, Goldschmidt papers, Bancroft library, UC Berkeley).

Sewall Wright, geneticist and one of the main architects of the neo-Darwinian synthesis of evolutionary biology in the 1930s, shared with Goldschmidt the conviction of the necessity of physiological genetic research (Provine, 1986). But he rejected Goldschmidt's claim of chromosomal rearrangements as mechanisms for saltatory evolution, because Goldschmidt did not provide any concrete data and because it contradicted already confirmed theories: "No data are given that support the conception of a spatial pattern of the germ plasm, correlated with the reaction system of the organism." (Wright, 1941a) According to Wright, Goldschmidt's attempt to base his notion on the position effects of genes contradicted the known facts of "the independence of the chromosome and the apparent absence of any correlation between location of genes and at least the more conspicuous effects of their mutations." (Ibid.) In other words, position effects accounted only for occasional second order effects.

Howard D. Lipshitz pointed to a crucial methodological vagueness in Goldschmidt's work on homoeotic mutants, through which he (Goldschmidt) attempted to support his concept of saltatory evolution. Goldschmidt decided to study homoeotic transformations of the *podoptera* type in Drosophila, which had a very low penetrance (frequency with which a heritable trait is manifested by individuals carrying the principal gene or genes) and were multigenic in contrast to those of the *bithorax* type, which had a close to 100% penetrance. The bithorax mutant in Drosophila was discovered by Bridges and in the 1940s used by Edward Lewis to link genetic analysis and development. According to Lipshitz, Goldschmidt's "focus on multigenic mutant characters with low penetrance meant that analytical studies were close to impossible" (Lipshitz, 1996). By contrast, Lewis' success in using the *bithorax* mutation as a basis for linking genetics, development and evolution was a result of its being experimentally tractable (unlike *podoptera*) and of Lewis (in contrast to Goldschmidt's) reductionist approach: major advances in scientific understanding, Lipshitz argued, "do not come from compendia of poorly understood phenomena or from erudite-sounding speculations; they come from mechanistic hypotheses and their empirical tests" (ibid.).

Scott Gilbert, John Opitz, and Rudolf Raff hold a different opinion. They consider it of the greatest importance that Goldschmidt used homoeotic mutants in order to criticize the neo-Darwinian claim of gradual evolution. According to them, Goldschmidt's methodological vagueness served his aims better than clear-cut research e.g. in bithorax mutants. They assume that Goldschmidt in trying to formulate a *physiological genetics* preferred a gene locus with graded phenotypes and that this aim also explained his usage of Lymantria with its unclear sexual types and ecotypes rather than cleaner, more easily interpreted systems (Gilbert et al., 1996). These authors describe what they think were Goldschmidt's motivations but they avoid the question as to whether he was able to provide clear and reproducible evidence with his approach. As the next section shows, this was not the case with his *Lymantria* work.

Lack of reliability of Goldschmidt's research. The reliability of Goldschmidt's experimental genetic work was drawn into question early on, though the difficult availability of the *Lymantria* races used by Goldschmidt made a control of the experiments problematical. Among the biologists who, using different species, were unable to confirm central elements of Goldschmidt's *Physiological Theory*, such as his quantitative explanation of sex determination and the “time law”, were Friedrich Baltzer and Goldschmidt's student Jacob Seiler. With the aim of confirming Goldschmidt's *Physiological Theory*, Seiler analyzed the phenomenon of intersexuality in the moth *Solenobia* for 25 years. Yet he came to the conclusion: “as far as our object is concerned, the time law does not apply!” (Seiler, 1949) Seiler's conclusion was soon generally accepted, except by Goldschmidt (Goldschmidt, 1949).

Seiler related Goldschmidt's inability to accept criticism to his scientific practice in general: “In the argument with me Goldschmidt, as he did so often proceeded from the idea and perceived in the specimen what he wanted to see and overlooked what he did not want to see. One may think of the anecdote: ‘Herr Geheimrat, the facts are not in accordance with your theory!’ ‘The worse for the facts’” (Seiler to C. Stern, 19 October 1963, Goldschmidt papers, Bancroft library, call no. 72/241). Seiler's results were soon generally accepted also by previous supporters of Goldschmidt's *Physiological Theory* in Germany, e.g. by Max Hartmann, Goldschmidt's colleague at the KWI for Biology in Berlin who in the 1950s distanced himself from Goldschmidt (Hartmann, 1956). Cytogeneticist Hans Bauer at the same institute spoke of “Goldschmidt's fehlgeleiteter Lymantria-Entwicklungs-Physiologie” (Bauer to Hartmann, 8 July 1955, Archive of the MPG, III. Abt. Nr. 26B), and Hans Friedrich-Freksa, director of the MPI for Virus Research, accepted that Seiler had demonstrated that Goldschmidt's “geistvolle Drehpunktstheorie […] does not hold true” (Friedrich-Freksa, 1961).

Only decades later did several groups of scientists repeat the crossings with the *Lymantria* races used by Goldschmidt. They demonstrated that Goldschmidt's results could not be reproduced and that his generalizations were untenable. In 1973 Seiler's results were confirmed for Lymantria (Mosbacher, 1973). The most extensive studies were carried out by Cyril Clarke and E. B. Ford in Cambridge (Clarke and Ford, 1980, 1982, 1983). Repeating those of Goldschmidt's racial crosses that he regarded as of a particularly fundamental kind, they found that their results “in the main differ markedly from [Goldschmidt's findings]” (Clarke and Ford, 1980). In particular they found a gross deficiency of intersexes in all crosses where intersexes were expected to occur on Goldschmidt's hypothesis (ibid). Clarke and Ford confirmed the great excess of males in a crucial cross but showed that they were not, as Goldschmidt had claimed, transformed females, but chromosomally males, and in other cases found sex ratios which differed from Goldschmidt's (Clarke and Ford, 1983). They interpreted the excess of males as a result of selection — female embryos or larvae, which in *Lymantria* are heterozygous, died due to genic imbalance between the races (Haldane's rule) — and not of the transformation of sexes. Haldane's rule of 1922 was known to Goldschmidt, but he did not use it in his interpretations or cite it, a fact that was criticized also by Julian Huxley (1923).

These studies support the conclusion that Goldschmidt's experimentation was questionable, and that, despite his claim to the opposite, his major genetic theories had no experimental basis. The discovery of intersexes and the subsequent development of the *Physiological Theory* of heredity would have been Goldschmidt's most original contributions, since all his other theories were speculative generalizations of discoveries and theories by others such as the relationship between genes and enzymes (see Jacques Loeb's reductionist project of unifying by physico-chemical explanations), the position effect (discovered by Sturtevant in 1925), and homoeotic mutants (found by Bateson in 1894 and rediscovered in their importance for evolution by Bridges in 1915). Thus with experiments not reproducible and generalizations untenable, Goldschmidt's potentially most original work did not stand the test of scrutiny and finally disappeared.

Putting forward theories that were mutually exclusive. In essential questions Goldschmidt not only changed his views but even discarded his previous views altogether. He began his evolutionary studies as a convinced neo-Darwinist. Then he changed his mind and rejected the neo-Darwinian concept of small changes completely. “I can see no justification for your too exclusive alternatives: either neo-Darwinism or no neo-Darwinism”, was the comment of geneticist Ernest Brown Babcock in 1941 (E.B. Babcock 23 April 1941 to Goldschmidt, Goldschmidt papers, Bancroft library, UC Berkeley).

Goldschmidt rejected the Mendelian concept of genes as put forward by Morgan and his school by proposing a physiological concept of genes, based on the idea that they were enzymes. Later he changed this view by discarding the concept of discrete genes altogether, putting forward his concept of chromosomes as a whole. However, contrary to this notion, he used the gene concept again when he based his claim of saltatory evolution on homoeotic genes. In none of these cases did he critically re-evaluate the evidence on which he had based his previous views.

My assessment of Goldschmidt's work on genetics, development and evolution

(i) Contrary to the opinion of some of Goldschmidt's colleagues and of historians, Goldschmidt, as shown above, did not integrate genetics, development and evolution in any meaningful way. Curt Stern (1969) suggested that if “Darwin had his protecting bulldog, Huxley, and his prophet, Haeckel, Goldschmidt was his own bulldog and prophet.” This may explain in part why he was considered a prominent figure in physiological genetics, but it unjustly pushed into the background those many researchers who at an early stage, unlike Goldschmidt, contributed to a real understanding of the biochemical developmental action of genes, a long process, culminating in the one gene-one enzyme hypothesis. Among these researchers were Garrod, 1902; Cuénot, 1903; Bateson, 1909; Loeb and Chamberlain, 1915; Wright, 1916; Caspari, 1933; Butenandt et al., 1940; Kühn, 1941; Beadle and Ephrussi, 1936 and 1937; Beadle and Tatum, 1941; Horowitz and Leupold, 1951; see also the overviews in Ravin, 1977; Burian et al., 1991; Kohler, 1991; Rheinberger, 2000.

(ii) The most fundamental criticism of his work relates to the purely speculative nature of his allegedly quantitative experimental work on the one hand, and the non-reproducibility of core experiments on the other.

(iii) His anti-reductionist approach to developmental genetics – the germ plasm as a whole controls “a definite reaction system, which then is not a mosaic of separate effects but a single developmental system controlled as a whole by one agency” – was too vague in order to serve as a basis for further research. Progress in developmental genetics as well as in systems biology was not achieved by giving up the notion of underlying discrete genetic elements, even though recent developments have rendered the concept of the gene (or rather genes) very complex. An example is Eric Davidson, discoverer of developmental gene-regulatory networks and their crucial role in evolutionary mechanisms, who considers it important that “now there are literally scores of genes for which detailed experimental analyses have demonstrated sharply modular cis-regulatory elements, such that given, nonoverlapping regions of the genomic DNA each control a specific subcomponent of the overall expression pattern” (Davidson, 2006). Even though scientists like Gould related to Goldschmidt because of their common criticism of neo-Darwinian gradualism as the only evolutionary mechanism, there is no evidence that Goldschmidt stimulated the work of present-day evolutionary developmental biologists to this effect.

(iv) Speculative theories, which claim to be experimentally proved, can be harmful. Certainly, Goldschmidt was influential, if only in the motivational sense, but such influences do not necessarily turn out to be beneficial. The case of Jacob Seiler who unsuccessfully spent many years of his active research life attempting to confirm Goldschmidt, is a case in point. According to Marsha Richmond (2007) British biologists were strongly influenced by Goldschmidt. Thus Conrad Waddington in his 1939 textbook on genetics frequently and approvingly cited Goldschmidt's questionable *Lymantria* work on sex factors and genes as enzymes (ibid.), which shows that influences can be detrimental. Later on Waddington became critical of Goldschmidt's work and J. B. S. Haldane seemed to have been quite unaffected by Goldschmidt's revolutionary claim that the classical gene no longer existed: "I am not so alarmed as I should be by your letter in Nature. After all the gene is not an indivisible atom, but a region of the chromosome generally behaving as a unit. We have to treat genes as indivisible for some purposes, but I don't take this indivisibility too seriously. However perhaps this is because I am a dialectical materialist." (Haldane, Nov. 24 n.d., between 1938 and 1940, to Goldschmidt, Goldschmidt papers, Bancroft library, UC Berkeley).

(v) Goldschmidt tried late in his life to present himself as the originator of a dynamic philosophy of genetics: "Two philosophies of genetics … One is the statistical, or static, point of view, the other the physiological, or dynamic point of view" (Goldschmidt, 1954). This appears as an attempt to downplay the criticism he received, in particular from the Morgan school. Goldschmidt's view has been taken up again recently by historians of science: "ultimately, the conflict between Goldschmidt and the Morgan school can be regarded as a kind of struggle for authority between two competing theories, methods, and programs for genetics. … [Morgan's] transmission genetics [and Goldschmidt's] vision of a physiological or developmental genetics." (Richmond and Dietrich, 2002) In contrast, I conclude that it was not Goldschmidt's philosophy, but his fundamental methodological flaws, which made his work unacceptable to the Morgan school and other geneticists.

(vi) I assume that the positive assessments of Stern and Caspari, whose own research practices differed markedly from those of Goldschmidt, were also motivated by a feeling of solidarity, all three of them being refugees from Nazi Germany. Curt Stern depicted Goldschmidt as influenced by Goethe and displaying an attitude of genius, which in early 20th century was not unusual among scientists: "Goldschmidt's influence on the biology of the twentieth century rested on observation and experiment as well as on the theory-building sweep of his imagination. … He had early trained himself to be a revolutionary of science. … He molded his life after Goethe. … He knew his worth. … [He] formed his existence into a piece of art" (Stern, 1958; see comments in Charpa and Deichmann, 2007). This attitude of self-aggrandizement here led scientifically into a dead end because it was accompanied by the violation of basic scientific standards and a complete lack of self-criticism.

Sewall Wright's combination of *reductionist* research and vision of hierarchical genetic systems

Finally, I briefly contrast Goldschmidt's attempts to integrate development, genetics, physiology, and evolution to those of Sewall Wright, who, born in 1889 in Melrose, USA, was 10 years younger than Goldschmidt. Wright studied zoology and mathematics before he became a genetics student of William Castle at the Bussey Institution at Harvard University, where he received his Ph.D. in 1915. After working at the Animal Husbandry Division of the United States Department of Agriculture, he became professor of zoology at the University of Chicago in 1926, and from 1955 until 1960 was professor, afterwards emeritus professor, of genetics at the University of Wisconsin in Madison. Wright is best known for his work on animal breeding, mathematical population genetics, and evolutionary theory: he became one of the three major architects of the neo-Darwinian Synthesis between Mendelian genetics and Darwinism (the two others were Ronald A. Fisher and J.B.S. Haldane). His "shifting balance theory" of evolution, according to which evolutionary change is best achieved by a large population which is comprised of many small, partially isolated local groups, has been very popular and influential among biologists (Crow, 1994). Here I do not comment on his evolutionary theory (for details see e.g. Provine, 1971, 2001, 1986).

Wright was, unlike Fisher and Haldane, also a pioneer in physiological and developmental genetics, in particular of small mammals. He worked on pigment genetics mainly of guinea pigs from his time as a graduate student until his retirement from the University of Chicago in 1955 (see e.g. Wright's extensive review (Wright, 1941b)). His approach was methodically broad. In his papers on color inheritance he used the latest knowledge of pigment chemistry and enzyme kinetics in order to interpret color interactions (Crow, 1994). From the beginning of his genetic work he was more concerned with interaction effects of genes than were Fisher and Haldane (Provine, [1971], 2001). He examined how multiple genes interacted to produce specific phenotypes and, referring to works of Morgan and Bridges on the interaction of genes affecting eye color in Drosophila, showed that the combined effect of the alleles at two different loci could be either equal to the sum of the alleles' individual effects (additive model) or non-additive (stronger or weaker); (a review of these papers is in Wright, 1941b). Examining the genetics of coat color in guinea pigs, he found four factors, which were closely linked and had a quantitative effect on the production of dark pigment. He interpreted them as "variations of the same thing", as variations in a "factor which determines the power of tyrosinase" (Wright, 1916, cited in Ravin, 1977), a statement which implies the notion that genes and also multiple alleles act by determining specific enzymes. Unlike Goldschmidt, Wright differentiated between the power to determine an enzyme from the enzyme itself. Using a complex model with interacting genes, Wright was able to predict quantitatively the pigment measures of genotypes involving alleles at six loci, a major achievement in physiological genetics (Crow, 1987).

His major analyses of the physiology of the gene, i.e. genic action, in development were published in 1941, the same year as George Beadle's and Edward Tatum's study on biochemical mutants in *Neurospora*. This latter work, which some time later gave rise to the one gene-one enzyme theory (Horowitz and Leupold, 1951), initiated what was later called molecular genetics in microorganisms. Biochemical genetics in *Neurospora*, and shortly after bacteria, with their large number of mutations and traceable biochemical pathways, was more efficient than Wright's. Therefore, though Wright continued his guinea pig studies for another fifteen years, and though they were conducted at high standards, "masterful studies in extracting maximum information from difficult material" (Crow, 1994), these studies received little attention.

Wright's experimental developmental genetics, in particular his emphasis on gene interactions, influenced strongly his work on evolutionary theory, as was observed by Richard Lewontin (1980): "Wright — unlike Fisher, based his evolutionary synthesis on the importance of gene interactions. Wright always identified himself primarily as a developmental geneticist. He said to me once that the mathematical work was really a diversion from his first love, which was guinea pigs. Wright's papers provide immensely complicated diagrams of the interactions of all the coat color genes in guinea pigs. He introduced his new four-volume work on evolution (1968–1978) with this kind of developmental genetic manipulation."

Wright held that evolutionary creativity often depended on putting together favorable combinations of genes that were individually deleterious. As he pointed out in his shifting balance theory, small local populations provide the best chance for the evolution of a harmonious gene combination. This conception was received well by many biologists but rejected by others, in particular by Fisher (Crow, 1994).

Generally Wright was more than most of his contemporary geneticists open not only to mathematical modeling and the notion of gene interactions, but also to chemical explanations, for example of these interactions. He strongly rejected Ernst Mayr's view that all population geneticists used "beanbag genetics", which disregarded gene interactions and natural populations (Wright, 1960). According to Wright, abstract mathematical theory, which alone cannot analyze and predict events in natural populations, should be reciprocally related to the concrete facts of experimentation. The role of theory, he held, was that of an intermediary between "the bodies of factual knowledge discovered at two levels, that of the individual and that of the population" (ibid.).

Wright confined his evolutionary work to populations; he deliberately left aside questions of the generation of new species or higher taxa. He accepted Gould's and Eldredge's (1977) criticism of phyletic gradualism, which according to him had much in common with Simpson's (1944) view, based on palaeontological data, of the different rates of evolution (Wright, 1982). Wright agreed with Simpson's rejection of Goldschmidt's thesis (1940) that speciation and the origins of higher categories depend on types of mutations that have nothing in common with the changes that occur within species. Opposed to grand speculations, he held that though genetics at the time bore directly only on evolution in populations, phenomena at the higher level should be explained as far as possible, "as flowing from observed phenomena of genetics in the broad sense, including cytogenetics, before postulating wholly unknown processes" (ibid.). Unlike Goldschmidt he did not use his developmental genetic experiments for the proposition of new mechanisms for large evolutionary changes. But by rejecting Goldschmidt's intuitive and superficial argumentation of the spatial re-organization of chromosomes as requirement for speciation and Goldschmidt's claim that the germ plasm as a whole controls "a definite reaction system, which then is not a mosaic of separate effects but a single developmental system controlled as a whole by one agency" (Goldschmidt, 1940), Wright developed a far-sighted model of hierarchical integrated genetic systems in the body with evolutionary implications (1941a):

"[Goldschmidt] seems to hold that the conception of the organism as an integrated reaction system requires a corresponding *spatial* integration of the germ plasm and that essential change in the reaction system can thus come about only by repatterning of the chromosomes. To others, a *temporal* integration is all that is necessary, or even possible, with the chain reaction as the simplified model. Within the organism as a more or less integrated reaction system, there is a hierarchy of subordinate reaction systems, each with considerable independence, as shown by capacities for self-differentiation. Thus there must be partially isolated reaction systems for each kind of organ and for each kind of cell. It is difficult to see how any spatial pattern in the germ plasm can operate in determining these, but there is no theoretic difficulty with a branching hierarchic system of chain reactions in which genes are brought into effective action whenever presented with the proper substrates, irrespective of their locations in the cells. There is no limit to the number of reaction systems that can be based on the same set of genes, and such systems may obviously evolve more or less independently of each other."

As a possible mechanism for generating organisms with an alternation of generations in evolution (such as coelenterates which alternate between medusae and polyps), he suggested a gradual suppression of one reaction system (e.g. of the fixed phase) and elaboration of that of the free phase.

To conclude, Wright opened up new paths of testable quantitative investigations in his developmental-genetic studies as well as evolution. His developmental genetics and his new evolutionary theory, the shifting balance theory, did not contradict experimentally and theoretically well supported genetic theories though the shifting balance theory caused strong controversy with Fisher whose "theory of dominance" it called into question (see e.g. Wright, 1929). Wright's view that properties of biological systems are the results "of chemical combinations, of gene combination, course of ontogeny etc.", and that the examination of these systems should be based on clearly defined properties of the components in order to be scientific (Wright, 1935) has proved superior to holistic approaches to biological systems such as Goldschmidt's. Wright placed his research in a framework of logical reasoning which resulted in the farsighted speculation that a systems approach should be related to the regulation of hierarchical genetic subsystems which might provide a possible mechanism for development and evolution. His seminal work on developmental genetics and his reflections on biological systems contributed to progress in these fields. In addition I argue that Wright's decision not to propose theories about those mechanisms on the basis of existing experimental data, finds its rationale in the fact that the scientific tools for their elucidation were not yet available (Morange, 2010, see also Falk, 2009).

Outlook

Loeb's reductionist research project unified approaches of physiology, genetics and embryology with the aim of finding physico-chemical (molecular) explanations for all life processes including evolution. This project was later continued in molecular biology, a synthesis of physico-chemical and biological fields. Though the molecular approach has been highly successful and indispensible for higher level investigations, up to the present day properties of biological systems cannot be fully explained on the molecular level alone.

Goldschmidt's anti-reductionist approach to development and evolution, in which he treated biological systems as a whole and not composed of separate integrated components, was methodically flawed; his crucial experiments either non-reproducible or too vague to serve as a basis for further research. His widely propagated attempt to integrate physiology, genetics, development and evolution turned out to be a dead end.

Sewall Wright combined a reductionist approach in which he considered the analysis of genes and genic action in development crucially important – conducting experiments to this end – for any higher level investigations with farsighted speculation on relating properties of biological systems to the regulation of hierarchical genetic subsystems. His suggestion to base the study of biological systems on clearly defined properties of the components has proved superior to holistic approaches which start examinations from systems as a whole.

Generally, progress in biology has been achieved by replacing inefficient or incorrect concepts and methods by better ones, by opening up new lines of research, and by integrating formerly disparate fields of research. According to Michel Morange (2010), steps to a meaningful integration of developmental-genetic mechanisms and evolution started mainly in the 1970s and 1980s, when the isolation of developmental genes and the characterization of gene-regulatory-networks became technically possible. The development of modern biology in the 19th century began by separating, at least methodically, formerly integrated lines of research. Later on several of these different fields were united again by integration. A pre-requisite for these successful integrations was sufficient knowledge of the parts. Attempts to integrate them at a too early stage proved futile.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.ydbio.2011.02.020.

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