THE ORGANIC CODES

An introduction to semantic biology

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THE MICROSCOPE AND THE CELL

The cell theory and the theory of evolution are the two pillars of modern biology, but only the latter seems to be the object of ongoing research and debates. The cell theory is generally regarded as a closed chapter, a glorious but settled issue in the history of science. The emphasis today is on cell experiments, not on cell theory, and there is no doubt that one of our greatest challenges is the experimental unravelling of the extraordinary complexity that has turned out to exist in the cellular world. At various stages of this book, however, we will see that the experimental results suggest new ideas, and at the end of the book it will be possible to combine them in a new model of the cell. This is because cells are not only what we see in a biological specimen through the lenses of a microscope, but also what we see through the lenses of a theory. The cell, after all, is a system, and understanding the logic of a system requires some theorising about it. And since this theorising has a long history behind it, let us begin by retracing the main steps of that intellectual journey. This chapter shows that the concept of the cell had to be imposed on us by the microscope because it was unthinkable in the world-view of classic philosophy. And after that intrusion, the concept has gradually changed and in so doing it has changed our entire approach to the problems of generation and embryonic development. But this historical journey is not without surprises, because it will take us toward an idea that all definitions of life of the last 200 years have consistently missed. The idea that epigenesis does not exist only in embryos but in every single cell. That the phenotype is always more complex that the genotype. That epigenesis is a defining characteristic of life.

The cell theory

The idea that all living creatures are made of cells has changed more than anything else our concept of life, and is still the foundation of modern biology. This great generalization was made possible by the invention of the microscope, but did not come suddenly. It has been the culmination of a collective research which lasted more than two hundred years, and in order to understand it we must be aware of the main problems that had to be solved.

Let us start with the microscope. Why do we need it? Why can't we see the cells with the naked eye? The answer is that the eye's retina itself is made of cells. Two objects can be seen apart only if their light rays fall on different cells of the retina, because if they strike the same cell the brain receives only one signal. More precisely, the brain can tell two objects apart only when their images on the retina have a distance between them of at least 150 μm (thousandths of a millimetre). The cells have average dimensions (10 μm) far smaller than that limit, and, even if an organism is stared at from a very close distance, their images overlap and they remain invisible. It is therefore necessary to enlarge those images *in order to increase their distance on the retina*, and that is where the microscope comes in.

Enlargements of 5 or 10 times can be obtained with a single lens (the so-called simple microscope) but are not enough for seeing the cells. Substantially greater enlargements require a two-lens system (a compound microscope) and the turning-point came in fact with the invention of that instrument. The first two-lens optical systems were the telescopes, and the idea of a compound microscope came essentially from them. In 1610 Galileo made one of the first compound microscopes with the two lenses of a telescope, and in 1611 Kepler worked out the first rules of the new instrument.

The invention of the microscope brought about an immense revolution in science. It led to the discovery of an entirely new world of living creatures that are invisible to the naked eye, the so-called *micro-organisms.* The microscopists of the seventeenth century were the first men who saw bacteria, protozoa, blood cells, spermatozoa and a thousand other *animalcula*, and gradually realised that the large creatures of the visible world are actually a minority in nature. The micro-organisms make up the true major continent of life, and their discovery changed our perception of nature to the very core.

Unfortunately, the microscopes of the seventeenth and eighteenth centuries had a basic structural defect. Lenses that are made of a single piece of glass cannot focus in one point all the light rays that cross them, and their images are inevitably affected by aberrations. The rays that traverse the periphery of the lens, for example, do not converge with those that cross the central part, thus producing a *spherical aberration.* Likewise, the rays which have different colours (or frequencies) converge at different distances from the lens giving origin to *chromatic aberrations.* Because of these distortions, people could see only isolated cells, such as bacteria and protozoa, or plant cells, which are separated by thick cellulose walls, but could not see cells in animal tissues. It is true therefore that in those centuries people saw many types of cells, but the microscope was showing that the smallest units of plants (the compartments that in 1665 Robert Hooke called *"cells"*) are not seen in animals, and it was impossible therefore to think of a common structure.

The discovery that cells exist in all organisms required a new type of microscope, and this came only in the nineteenth century, when the aberration obstacle was overcome by the introduction of *achromatic lenses.* These are made of two or more pieces whose geometrical forms and refraction indices are such that the aberrations of one piece are precisely compensated by those of the other. The first achromatic microscope was build by Giovanni Battista Amici in 1810, and with this new instrument came a systematic revision of all that the microscope had revealed in previous centuries. In 1831 Robert Brown discovered that plant cells contain a roundish refracting mass that he called the *nucleus*, and inside the nucleus it was often possible to see an even more refracting structure that later became known as the *nucleolus.* In 1839 Matthias Schleiden and Theodor Schwann compared plant embryos (which do not have the thick cellulose walls of adult tissues) with animal embryos, and discovered that their microscopic structures are strikingly alike. They are both made of nucleated cells, hence the conclusion that the cell is a universal unit of the living world. This idea brought down the century-old barrier between plants and animals and represents the first part of the cell theory: *all living creatures are made of cells and of cell products.*

Any new idea, however, raises new problems, and in this case the main issue was about the mechanism by which cells are generated, a topic where Schleiden and Schwann made a proposal that turned out to be completely wrong. They suggested that cells originate with a mechanism which is somewhat similar to crystal growth, and which they called *free formation.* The daughter cells were supposed to come from germs or seeds in the nucleus that would grow inside the mother cell like crystals in a saturated solution. The discovery of the true mechanism required many other years of research, and came essentially from embryology studies. In the earliest stages of development it is often possible to see all the cells of an embryo, and, as their number grows, one can realise that they always contain nuclei whose size and shape are practically constant. This means that cells never go through a germ-like stage, where they would have to be smaller than nuclei, and must be produced by a process that keeps their basic structure invariant, i.e. by a process of *replication.*

In 1852 Robert Remak explicitely rejected the free-formation idea and concluded that *"Cells always come from the division of other cells."* In 1855 Rudolf Virchow reached the same conclusion by studying a great number of normal and pathological adult tissues, and condensed it with the motto *"omnis cellula e cellula".* The final version of the cell theory is therefore the combination of Schleiden and Schwann's first theory with the conclusion of Remak and Virchow: *"All living creatures are made of cells and of cell products, and cells are always generated by the division of other cells."*

The problem of generation

At the very centre of biology there are two complementary problems: *"How does an organism produce an egg?"* (the problem of generation), and *"How does an egg produce an organism?"* (the problem of embryonic development). These questions have been debated since antiquity – both Hippocrates and Aristotle wrote at length about them – but only the microscope made it possible, in the nineteenth century, to make the crucial observations that led to a solution.

With the cell theory, organisms became *societies of cells*, and the problem of generation became the problem of understanding which and how many cells are forming the germ of a new individual. Botanists believed that any seed had to be fertilised by a high number of pollen grains, and it was widely held that the greater that number the stronger would be the resulting plant. The same thing applied to animals, where it was again thought that an egg had to be fertilised by many spermatozoa, each carrying a fraction of the hereditary material, because it was *an experimental fact* that an egg is always surrounded by a multitude of spermatozoa at fertilisation, and it was taken for granted that a single spermatozoon could not possibly carry all the hereditary traits of the body.

It was Oskar Hertwig, in 1875, who solved this problem. By studying sea urchins, animals which are particularly suitable for microscopy studies because of their transparency, he noticed that eggs contain a single nucleus before fertilisation and two nuclei immediately afterwards. He realized that the second nucleus had come from a spermatozoon, and therefore that a *single* spermatozoon can fertilize an egg. Hertwig's discovery was completed in 1879 by Hermann Fol, who managed to inject many spermatozoa into a single egg, and found that in this case development is always abnormal, thus proving that fertilisation can and must be realised by a single spermatozoon.

This however was only a first step. The idea that fertilisation is brought about by the union of one spermatozoon and one oocyte is important, but does not solve the problem of generation. We still need to understand why spermatozoa and oocytes are the only cells that are capable of generating a new individual. What is it that gives them such a power? That makes them so different from all other cells of the body? Once again the answer came from microscopy studies, but new techniques had to be developed first. The decisive innovations were more powerful microscopes (microscopes with a higher resolving power) and the deployment of staining techniques. The dye eosin, for example, gives a pink colour to the cytoplasm while haematoxylin makes the nucleus intensely blue, and a high-resolution microscope reveals that the blue dye of the nucleus is concentrated in discrete bodies that were called *chromosomes* (coloured bodies).

The new technology made it possible to discover that chromosomes undergo spectacular conformational changes and elegant movements (the *chromosomes' dance*) during cell division, a process that Walther Flemming called *mitosis.* But the most significant discovery was the demonstration that the entire chromosome set is divided in two identical parts during mitosis, one for each daughter cell, which strongly suggests that chromosomes are the carriers of hereditary characters. At this point there was only one missing piece in the generation puzzle, and that came with a discovery made by Edouard Van Beneden in 1883. Van Beneden found that in the worm *Ascaris* there are four chromosomes in almost all cells, but only two in their sexual cells (the gametes). And he pointed out that maternal and paternal chromosomes are brought together in the fertilised egg (the zygote) to produce again a cell with a full complement of four chromosomes. Van Beneden, however, published the data without comments, and did not ask why gametes have only half the chromosomes of all other cells.

It was August Weismann, in 1884, who understood the meaning of Van Beneden's discovery, and concluded that sexual cells must undergo a very special division that halves their chromosomal set, so that the union of two gametes at fertilisation could restore the normal (diploid) number. This special division was called *meiosis* in order to distinguish it from normal mitosis, and in 1890 Oskar Hertwig proved the experimental reality of meiosis by describing in detail all its phases. This, then, is what distinguishes the sexual cells from all the others and gives them the power to generate a new individual: *only sexual cells divide by meiosis.*

Weismann gave the name of *somatic cells* to those that divide only by mitosis (and are thus destined to die with the body), and called *germinal cells* those that can divide both by mitosis and meiosis. These are potentially immortal, because they can have descendants for an indefinite number of generations.

The discoveries of fertilisation, meiosis and germinal cells, in conclusion, made it possible to give a precise answer to the generation problem in cellular terms: *the generation of a new individual starts with two meioses, when gametes are formed, and is realised at fertilisation, when a zygote is formed.*

The problem of embryonic development

The most elegant experiment in the history of embryology was performed some 2400 years ago by Aristotle. He opened the shell of chicken eggs at different incubation days, and carefully described what he saw: the white spot on the yolk that marks, at the very beginning, the point where the future embryo is going to appear; the tiny brown lump that starts pulsating at the third day and later will turn into a heart; the greatly expanded vesicles that will become eyes; the entangled red vessels that descend into the yolk and branch out like roots; and the thin membrane that wraps everything up like a mantle.

On the basis of these observations, Aristotle concluded that in a developing embryo organs not only increase in size, as Hippocrates had said, but also in number. Embryonic development, according to Aristotle, is an *epigenesis*, a chain of one genesis after another, where new structures and new functions appear at various steps. During embryonic development, in short, *the complexity of the system increases.*

Almost 2000 years later, around 1660, Marcello Malpighi repeated Aristotle's experiment, but with an important difference. He was the first man to watch a developing embryo under a microscope, and what he saw led him to a very different conclusion. The area where blood vessels are destined to appear, for example, is apparently empty to the naked eye, but under the microscope is full of capillaries. Aristotle had concluded that blood vessels appear *ex novo*, but according to Malpighi he had been betrayed by his own eyes. Could he have used a microscope, he would have realised that organic structures are present even when they are not yet visible. Malpighi therefore reached the conclusion that an embryo's development is not an epigenesis but a *preformation*, a growth of forms that already pre-exist in the fertilised egg.

The theory of preformation was enthusiastically accepted by almost all naturalists of the seventeenth and eighteenth centuries. Swammerdam, Leeuwenhoek, Leibnitz, Réaumur, Spallanzani, Boerhaave, von Haller, Bonnet and many other great scientists declared themselves convinced preformationists, and this not only for experimental reasons but mainly for theoretical ones. They did know the laws of geometrical optics and were aware that their microscopes were affected by aberrations, but the existence of living creatures that are invisible to the naked eye could not be disputed, and was leading to an extraordinary conclusion. The great idea of preformationism was the principle that *the infinitely small is as real as the infinitely large*, and this meant that it is always possible to explain living structures with smaller structures. Such a conclusion was indeed legitimate at the time, because there was no atomic theory in physics and chemistry, but once again it was the microscope that decided its destiny.

The technological evolution of microscopy eventually made it possible to observe even the earlier stages of development, and it became clear that very young embryonic structures are totally different from adult ones. In 1828, Karl Ernst von Baer published *On the Development of Animals*, a monumental treatise of comparative embryology that ended once and for all any version of preformationism. Von Baer showed that in animal species there is a common stage of development where the entire embryo is nothing but a few sheets of organic matter, or *germinal layers* (ectoderm, mesoderm and endoderm). And the evolution of these basic structures clearly showed that embryonic development is not only a growth process, but also a continuous emergence of new tissues, and a series of three-dimensional movements that deeply transform the shape of the developing embryo.

With the advent of the cell theory, embryonic growth was immediately accounted for by a sequence of cell divisions. A fertilised egg becomes 2 cells, and then 4, 8, 16, 32, 64 and so on. With 10 divisions the cell number is about a thousand, with 20 is a million, with 30 is a billion, with 40 is a thousand billion, and so forth. For the fifty thousand billion cells of an adult human body, therefore, all that is required is 45-46 cell divisions. The difference between an adult body and a fertilised egg, however, is by no means a mere question of cell numbers. Fifty thousand billion eggs, whatever their arrangement in space, would never make a human being, and it is clear therefore that during development cells must become *different* from the fertilised egg. Embryonic develoment is accompanied therefore by a hierarchy of differentiation processes (which in man produce more than 200 types of cells).

During development, furthermore, the external shape and the internal anatomy of an embryo undergo many transformations before one can start recognising the familiar features of adult life. These changes are brought about by migrations, tubulations, invaginations and foldings of many types, and are collectively known as *morphogenesis.*

The discoveries of cell growth, histological differentiation and morphogenesis, in short, gave a precise answer to the problem of embryonic development in cellular terms. *Embryonic development is a true epigenesis and consists of three fundamental processes: growth, differentiation and morphogenesis.*

The two versions of the cell theory

The great philosophers of antiquity discussed quite a number of world views, such as the atomic theory, determinism and indeterminism, relativity and evolution, and yet none of them conceived the cell theory, which makes us wonder why. The fact that they did not have the microscope does not seem to be decisive from a conceptual point of view. Even atoms cannot be seen, and yet the atomic theory was explicitely formulated. The problem is therefore the following: *Why could ancient people think about atoms but not about cells?* The idea that matter can be divided into particles is suggested by many facts of daily life: a house is made of bricks, a desert is made of grains of sand, drops of rain can be turned into a river, and so on. Why not add that organisms are made of micro-organisms?

The reason is that in this case the ancients found themselves up against an overwhelming obstacle, because experience shows that a mother is always bigger that the embryo which is born from her. Life on Earth must come therefore from above, not from below, from a superior Being – God or Mother Nature – not from small insignificant microbes. In such a situation the microscope was absolutely indispensable to force us to see the cells, to impose their existence on us, because without this violence our minds would never have been able to believe them. The cell theory has undoubtedly been one of the great revolutions in the history of thought, perhaps the greatest of all, and yet one can still hear the suggestion that it is not a real scientific theory because it has a purely descriptive nature. According to this view, the theory is but a record of the empirical fact that all living beings are made of cells, and that every cell derives from a pre-existing one.

In reality, this happens because the cell theory can be expressed either in a *weak* or in a *strong* version. The theory can indeed be reduced to a mere description of life when it is formulated by saying that "*All* known *living organisms are made of cells*." In this case it has no predictive power and no falsifiable consequence. But there is also a strong version that does represent a true falsifiable generalization of the empirical facts, and therefore a true scientific theory. It is the statement that "*All* possible *living organisms are made of cells*."

The first version is a mere acknowledgment that cells exist, at least on our planet. The second one states that cells are the fundamental components of *all* forms of life, including extraterrestrial and artificial life. It states that cells are the *logical* units of the living world, just as atoms are the units of the physical world. The strong version of the cell theory, in other words, declares that life does not exist without cells, and represents therefore a definition of life itself: *life is the state of activity of cells and of cellular systems.*

The very first problem of biology, the question *"What is life?"*, becomes therefore *"What is the cell?"* In order to answer this, however, we must recall the answers that have been given in the past to the question *"What is a living organism?"*

Mechanism

There are at least two good reasons for saying that modern biology was born in Europe in the first half of the seventeenth century. One is the discovery of the new world of micro-organisms. The other is the formulation of the first great paradigm of biology: the idea that *every living organism is a machine.* This concept – known as *mechanism* – found in René Descartes its most outstanding advocate, but in reality it was the result of a collective convergence of ideas by scholars of many European cities. From antiquity up to the end of the Renaissance, machines had been built with the sole purpose of obtaining practical benefits, but in the seventeenth century this view was enlarged by two fundamental novelties.

The first is that machines started to be seen not only as a means for changing the world, but also as an instrument for studying it. In order to look into a microscope, and accept the reality of micro-organisms, one must first of all *believe* in what one is seeing, trust that the instrument is not producing optical illusions (as some were saying) but is revealing structures that do exist in the real world. The second novelty of the seventeenth century is that machines became not only an instrument of knowledge but also *a model* of knowledge. The idea was developed that to understand the human body it is necessary to divide it into parts, and to study the functioning of its smaller components, just as we do with machines.

"A healthy man is like a well functioning clock, and an ill man is like a clock that needs repairing." This statement by Descartes is a perfect summary of mechanism, and inspired a radical transformation of medicine. Anatomy ceased to have a purely descriptive role and moved towards physiology and pathology. A physician did not have to rely on the books of Hippocrates and Galen but on experience, as any good mechanic does. The revolution of mechanism cut deeply into every aspect of European thought. Even the concept of God changed, and the Omnipotent became the Supreme Mechanic, the creator of the laws that govern the "machine" of the universe. And God is to universe what man is to machine. This idea inspired a complete separation of thought and matter and found its highest

expression in Descartes' dualism, in the distinction of *res cogitans* and *res extensa*, i.e. in a total divorce of mind from body. It was the beginning of modern philosophy.

It has been said (and it is likely) that no great cultural revolution can be a sudden event. It must necessarily be preceded by a long period of incubation, possibly in unlikely places and by the hands of unimpeachable players. In our case, many historians suspect that the cultural mutation of mechanism appeared in the first centuries of the Christian era, and was nursed in monasteries. In a world that was increasingly falling apart, those were the only places where a remnant of civilisation was kept alive, by cutting bridges with the outside and by living in self-sufficient communities. But in those places economic independence was only a means to the goal of spiritual life, and machines started to be built so that time could be subtracted from labour and dedicated to prayer and meditation.

Machines were no longer instruments of slavery but tools of liberation, a gift from God, and it became important therefore to understand them, to improve them, and to build new ones. The machine culture was particularly nursed in Benedictine abbeys, but gradually it went outside their walls, spread into neighbouring urban communities, and entered the shops of artisans and artists. And finally it also knocked at the doors of universities.

Whatever did happen in those centuries, it is a fact that with the beginning of the seventeenth century a completely new type of machine started appearing: tools that served no practical purpose, and were used only for the demonstration of theoretical principles (a typical example was the inclined plane that Galileo built in order to illustrate the laws of motion). In the eighteenth century, furthermore, machines appeared that were even more useless and bizarre, like Jacques de Vaucanson's mechanical duck (that flapped its wings, quacked, ate and expelled artificial faeces) or the "Writer" of Pierre Jacquet-Droz, an automaton that could dip his pen into an inkwell, shake off the ink and write Descartes' phrase *"Cogito ergo sum"* (Figure 1.1).

These machines were apparently built for amusement, and could easily be mistaken for toys, but in reality they were the equivalent of our artificial intelligence computers. Machines that were announcing the new philosophy with the disarming tools of utopia.

The chemical machine

The mechanical concept of nature spread very quickly in seventeenth century Europe, but not without conflict. Opposition came from virtually all quarters, and it was violent. Apart from the rejection by Aristotelian academics, there was a new science that was slowly

Figure 1.1 The "Writer", built in the middle of the eighteenth century by the Swiss inventor Pierre Jacquet-Droz, is a beautiful automaton sitting at a writing desk that dips his pen into the inkwell, shakes off the excess ink, and writes Descartes' famous motto *"Cogito ergo sum."* The automaton is still fully operational and survives in a Neuchâtel museum.

emerging from the night of alchemy and regarded the human body essentially as a seat of chemical reactions. The heirs of the alchemists were determined to leave magic behind, but had no intention of accepting the “mechanical” view of nature, and one of chemistry’s founding fathers, Georg Ernst Stahl (1659-1731), launched an open challenge to mechanism. His thesis was that organisms cannot be machines because they possess a *vis vitalis* that does not exist in the mineral world. Stahl was the first to make a clear distinction between organic and inorganic chemistry, and challenged mechanism with three arguments:
(1) It will never be possible to obtain a synthesis of organic compounds in the laboratory because inorganic materials are devoid of *vis vitalis*.
(2) What is taking place inside living organisms are real transmutations of substances and not movements of wheels, belts and pulleys.
(3) Living organisms cannot be machines because machines do not suffer.

The first objection encouraged a long series of experiments on the *in vitro* synthesis of organic compounds, and was clamorously falsified in 1828, when Friedrich Woehler obtained the synthesis of urea in the laboratory. It is interesting to notice that Woehler himself was a convinced vitalist, and wrote with dismay that he was witnessing *“The great tragedy of science, the slaying of a beautiful hypothesis by an ugly fact”* (this shows that the first vitalists – quite differently from their later followers – fully accepted the principle of experimental falsification).

The second objection of Stahl had a stronger basis, and forced mechanists to change the very definition of *living machine*. In the course of the eighteenth century, in fact, the view that organisms are *mechanical machines* gradually turned into the idea that they are *chemical machines.* This smooth change of perspective went hand in hand with the development of a new engine, an apparatus that was exploiting the chemical reactions of combustion to produce mechanical movements. It was the steam engine that brought together the two sciences, and both mechanists and vitalists realised that a chemical machine is not a contradiction in terms, as had been thought, but a reality.

The third objection of Stahl, the idea that machines do not suffer, has never been overcome, and even today is a major obstacle on the road towards artificial life. Descartes wrote that only human beings suffer because only they have a soul, while animals are merely *mimicking* the expressions of pain, but very few took seriously such an extravagance. It became increasingly clear therefore that an organism cannot be a mere mechanical machine, and eventually the concept of the chemical machine was universally accepted.

In the nineteenth century, the study of the steam engine was pushed all the way up to the highest level of theoretical formalism, and culminated with the discovery of the first two laws of thermodynamics: the principle that energy is neither created or destroyed, and the principle that the disorder (or *entropy*) of any closed system is always on the increase. This second principle had a particularly traumatic impact, because it appeared to expose an irreducible difference between physics and biology. In any closed physical system disorder is always increasing, while living organisms not only preserve but often increase their internal order.

The standard reply that organisms are not closed but open systems is of little comfort, because one needs to understand *how* they manage to keep their highly organized state. Eventually however the answer was found and came from two hypotheses:
(1) Living organisms must continuously exchange matter and energy with the environment (the idea of *biological perpetual motion*).
(2) The internal order of organisms is preserved because the disorder produced by their chemical reactions is continuously pumped outside them.

In order to remain alive, in other words, organisms must be in a perpetual state of activity (their cells work even when they sleep), and must continuously pump out the excess entropy of their reactions. In the words of Erwin Schrödinger (1944), they eat not only matter but also order. Towards the end of the nineteenth century, in conclusion, a living organism came to be seen essentially as a *thermodynamic machine*, i.e. as a chemical machine that must be continuously active in order to obey the laws of thermodynamics.

The computer model

Towards the end of the eighteenth century, just as the chemists' critique was giving way, another opposition to mechanism arose and gave origin to a new version of vitalism. This movement started as a spontaneous, almost instinctive, reaction of many biologists to a veritable absurdity that mechanists wanted to impose on biology. It was a revolt against preformationism, the idea that adult structures are already preformed in a *homunculus* within the fertilised egg. In 1764, Charles Bonnet explicitly launched the great challenge of preformationism: *"If organised bodies are not 'preformed', then they must be 'formed' every day, in virtue of the laws of a special mechanics. Now, I beg you to tell me what mechanics will preside over the formation of a brain, a heart, a lung, and so many other organs?"*

The challenge was clear, and in order to avoid preformationism biologists were forced to conclude that the *formative force* required by Bonnet in order to account for embryonic development must indeed exist. It was an embryological, rather than a chemical, force, very close to Aristotle's *inner project*, but it also was given the name of *vis vitalis.* Preformationism, as we have seen, was definitely abandoned in 1828, when von Baer's monumental treatise showed that embryonic development is a true epigenesis, as Aristotle had maintained, i.e. a genesis of new structures and not a simple growth of pre-existing structures. Once again, mechanists were forced into admitting that the concept of a "living machine" had to be modified in order to account for the reality of embryonic development, but this time a solution turned out much more difficult to find, and throughout the whole of the nineteenth century the claim of vitalism appeared unsurmountable.

The answer came only with genetics, and more precisely with the discovery that life does not consist only of matter and energy but also of *information.* In 1909, Wilhelm Johannsen made a sharp distinction between the visible part of any organism (the *phenotype*) and the part that is carrying hereditary instructions (the *genotype*), and argued that a living being is not a monad but a dual system, a diarchy, a creature that results from the integration of two complementary realities. Unfortunately, Johannsen's message was either ignored or misunderstood, and it was only the computer, with the distinction of *hardware* and *software*, that turned the *phenotype–genotype* duality into a comprehensible and popular concept.

What matters is that the genotype – the biological software – is a deposit of instructions and therefore is potentially capable of carrying the project of embryonic development. This was the long-awaited answer to vitalism, and the computer became therefore the new model of mechanism. In reality, the new model of a living machine is not the computer that we encounter in our daily life, but an ideal machine known as *von Neumann's self-replicating automaton.*

John von Neumann, one of the founding fathers of computer science (it was he who invented the central processing unit), asked himself if it is possible to design an automaton that is capable of building any other automaton (a *universal constructor*), and in particular an automaton that builds copies of itself (a *self-replicating machine*). His great contribution was the demonstration that such machines are *theoretically* possible (Figure 1.2). In practice, a von Neumann's self-replicating machine has never been built because of its complexity (it requires more than 200 000 components), but the proof that it *could* be built amounts to saying that it is possible, and proves therefore that a machine is capable of replication (Marchal, 1998). Von Neumann announced these conclusions in 1948, and his work inspired a completely new research field that today is already divided into disciplines and is collectively known as *artificial life.* A parallel, but different, field is that of *artificial intelligence*, and it is important to keep them apart. Artificial intelligence studies characteristics that in real life appeared at the end of evolution, whereas artificial life simulates what appeared at the beginning (Sipper, 1998; Tempesti *et al.*, 1998).

In the field of artificial life we are today at a level that organic life reached about 4 billion years ago, at the time of the so-called primordial soup, but the interesting thing is that we could actually witness the origin of this new form of life with our own eyes. This is the last frontier of mechanism, the borderline beyond which the dream could become true.

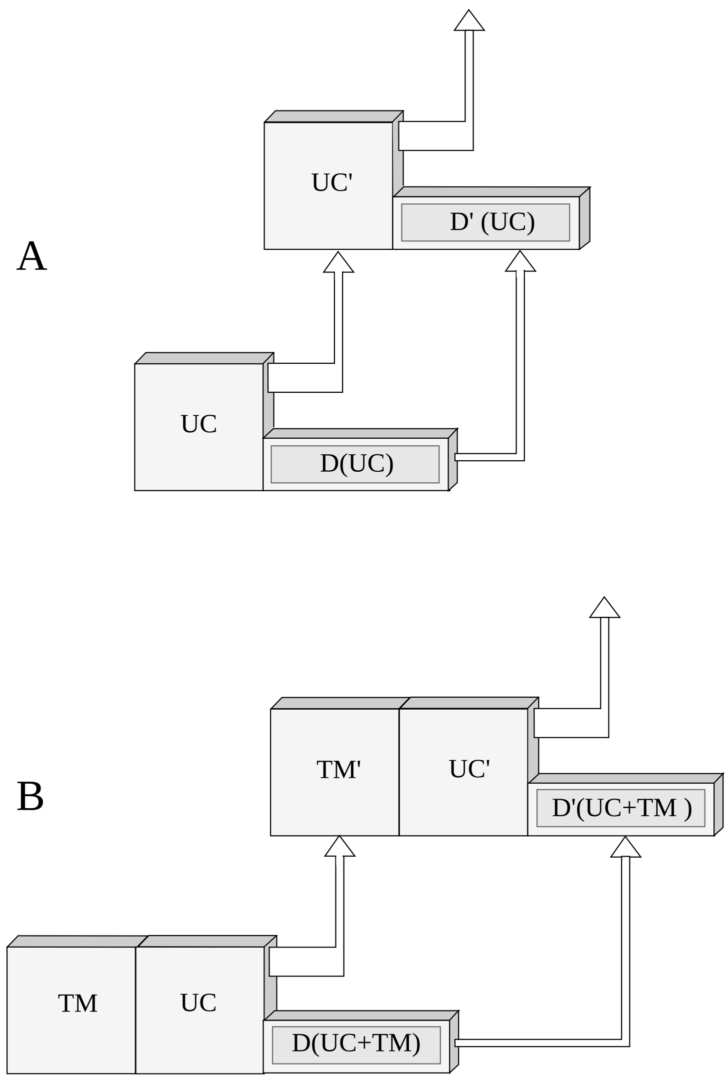

Figure 1.2 Von Neumann's self-replicating machine.
(A) A universal constructor UC can use its own description D(UC) to build a copy of itself, UC', and of its description D'(UC).
(B) A universal constructor UC can include a universal computer, for example a Turing machine (TM), and build a copy of the entire system from its description D(UC+TM).

The autopoietic cell

Artificial life is an entirely new approach to the fundamental problems of biology, because it allows us to study life in a totally different way, i.e. by building machines that have some of its properties. It must be underlined, however, that silicon-based life is utterly different from carbon-based life because artificial molecules and artificial cells are made of electronic circuits and are therefore two-dimensional creatures. This explains why biologists have not abandoned more traditional approaches, and the search for a proper definition of organic life has never stopped. In this field, an important step forward was made in 1974 by Francisco Varela, Humberto Maturana and Ricardo Uribe, with the paper that introduced in biology the concept of *autopoiesis.*

In order to illustrate their idea, Varela and Maturana used the tale (already exploited by Alexander Oparin) of a green man from Mars who comes to Earth and wants to discover what kind of life exists on our planet. He makes a long list of terrestrial objects but is not so sure about their living status, and asks a farmer to help him. The farmer takes a look at the list and immediately divides the objects in two columns, living at the left and not-living at the right:

man	*radio*
tree	*motor car*
mushroom	*computer*
mule	*robot*
hen	*moon*
coral	*tide*

The green man is surprised by such a display of confidence, and asks the farmer to tell him by which feature he could pick up the living so quickly. The farmer takes two objects at random – mule and hen – and say that they are alive because are capable of *"movement"*, but the green man is not convinced. Coral and tree do not move but are definitely alive. At that point the farmer suggests *"irritability"*, or *"the ability to react to stimuli"*, but again the answer fails. It is true that man and mule react to a needle's puncture, but tree and coral remain indifferent. The farmer then shouts *"Reproduction!"* but immediately has to change his mind because the mule does not reproduce. And yet his two columns are absolutely correct. But why? What is it that he knows without being aware of knowing? The farmer needs to think it over, and asks the green man to come back the next day. Then he starts thinking.

Trees lose their leaves in autumn, and produce them again in springtime, by growing new ones from the inside. And animal hair does the same thing: it grows from within. The farmer knows that when he is starving his body weakens and becomes thinner, but as soon as he starts eating again his growth goes back to normal. And it is always an internal activity that keeps the body growing. At this point he has understood, and is ready to answer the green man.

All the objects of the right column – radio, motor car, etc. – are not capable of repairing themselves, while those of the left column are alive precisely because they have this property. Now the green man is satisfied and agrees with him. The second principle of thermodynamics had been discovered even on Mars, and green men knew that an organism must be in a perpetual state of activity in order to be alive. Not only must a body be capable of repairing itself when something breaks down, but it must be repairing itself all the time, it must always be demolishing and rebuilding its own structures, i.e. it must be capable of *permanent self-production*, or *autopoiesis.*

Varela and Maturana add that autopoiesis must be a property of every living system, including its smallest units, which means that any cell can be represented by a scheme that illustrates its continuous transformation of external matter into cellular components (Figure 1.3). When production is equal to demolition, a cell is in a stationary state (*self-maintenance*); when production is greater than demolition, a cell grows and eventually divides itself into two (*self-reproduction*). Varela and Maturana arrive in this way at a definition of the living system in general and of the cell in particular: *a physical system is alive if it is capable of transforming a flux of external matter and energy into an internal flux of self-maintenance and self-reproduction.*

This definition, as we have seen, is an automatic consequence of