1 Scientific Foundations of Medicine – Remarks on the Concepts of Entropy and Order in Physics, Biology and Medicine

1.1 On the Concept of Entropy in the Scope of Physics

The concept of entropy is a fundamental concept in physics. It is contained in every substance and is correlated with the degree of order of systems. This dark concept has been interpreted mainly by stochastic theory and deterministic dynamics. Ilya Prigogine, one of the pioneers in the field of irreversible thermodynamics, introduced a 1989 lecture entitled "What is Entropy?" with the statement, "A very strange concept."[2] According to Ruelle, entropy is a measure of the amount of randomness in a system. Entropy is generated but cannot be destroyed. According to the second law of thermodynamics, entropy increases in a closed system. Cramer put it this way: "The second law of thermodynamics can be formulated briefly and trivially as "it goes downhill".[3]

Energy transitions obey the second law of thermodynamics. This law was formulated in the 19th century in connection with the development of steam engines. According to the first law of thermodynamics, the different forms of energy are convertible into each other. However, these energy equivalences are only theoretically convertible into each other, because according to the second law, it is not possible to convert thermal energy into mechanical energy without energy losses. The German physicist Clausius pointed out that there are processes in which energy is conserved (fulfillment of the first law), but its reversal is impossible. It was also Clausius who introduced the concept of entropy. He concluded that entropy is generated by irreversible processes, that it can only assume increasing positive values and that it would only remain unchanged in a borderline case with a reversible process.

Isolated systems evolve spontaneously towards their thermodynamic equilibrium, which is thus defined as a state of maximum entropy: $dS/dt=P$ (entropy production) = 0.

Thus, entropy is also a measure of the energy loss of a system. At the same time, it is a measure of the irreversibility of processes: Any future macroscopic state of an isolated system can only have equal or higher entropy, and any past state only equal or lower than the present state. Reversal of this change of state is not possible. Since energy flows are directed in time, entropy thus also represents a measure of time, a measure of the passage of time.

All irreversible processes, therefore, generate entropy. Ludwig Boltzmann interpreted the inevitable increase of entropy as an expression of progressive disorganization and as a development towards a more probable state of a higher disorder.

2 Prigogine, I.: What ist Entropy? Naturwissenschaften 1989, 76:1-8.
3 Cramer, F.: Chaos und Ordnung. Insel 1993, S. 31.

From this, it was suggested that the expansion of the universe could provide a rationale for irreversible time. Harrison derived a measure for the entropy of the world from the ratio of the number of photons to the number of baryons in the cosmos.[4] According to estimations, there are in the universe on every baryon, i.e., on the basic components of the matter, i.e., protons, neutrons, etc., 108 to 109 photons. Thus, the cosmos consists, for the most part, of light. From this ratio of 1 baryon to 10^8 or 10^9 photons and in view of the fact that the few baryons are still further annihilated, the conclusion was drawn that the universe must die from heat death in the near future because the largest part of the entropy is already produced. In the mechanistic view of the 19th and the beginning of the 20th century, the idea of the world as a big machine work prevailed and so it is not surprising that a gloomy utopia of an inescapable heat death for the universe penetrated more and more deeply into the consciousness of the people and influenced also decisively the art around the turn of the century. Almost 100 years later, Harrison wrote: "A few decades ago, when scientists discussed the universe, they would predict in hushed tones the eventual heat death of the universe, imagining how everything would wither and die and entropy would rise inexorably to its final height...".[5]

But it is not yet so far.

For stable thermodynamic systems, the principle of minimal entropy formation is valid. The dynamics of these systems are characterized by an extensive linearity and their state is close to a state of equilibrium and is therefore called stable. The systems of life, on the other hand, are in a non-equilibrium state and the processes taking place in them are irreversible and non-linear. The time structure in Newtonian physics is a reversible one and all processes within the scope of this physics are reversible. According to Newton, an unaccelerated body remains in a state of uniform motion. However, this was an idealized assumption by Newton, because in reality all bodies are either accelerated or decelerated. Moreover, they do not move without friction. Only an ideal pendulum, i.e. one that swings without friction continues its motion for all eternity.

In the progressing 20th century, the concept of entropy rose to an "indicator of development" (Prigogine) or also to an "arrow of time" (Eddington). For all isolated systems, the future represents the direction of increasing entropy.[6] In the meantime, the entropy concept has also gained importance outside physics and especially in technology, information theory, biology.

Ludwig Boltzmann and others gave entropy a statistical meaning and interpreted the irreversible increase of entropy as an expression of a growing molecular disorder. This is because isolated systems would spontaneously evolve toward states of increasing probability, and thermodynamic equilibrium, after all, represents a state of greatest probability.

A relation between entropy S and thermodynamic probability W was derived by Boltzmann as follows:

$$S=k_B x \ln W$$

4 Harrison, E. R.: Kosmologie. Die Wissenschaft vom Universum. Darmstadt 1983.

5 Harrison, E. R., zit. nach F. Cramer, F.: Der Zeitbaum. Insel-Verlag 1993, S. 54.

6 Prigogine, I., Stengers, I: Dialog mit der Natur. Neue Wege naturwissenschaftlichen Denkens. Piper-Verlag München, 1986, 5. Auflage, S. 311. Prigogine, I.: Vom Sein zum Werden. Zeit und Komplexität in den Naturwissenschaften. Piper-Verlag München, 1980, 2. Aufl.

In this approach, the thermodynamic probability corresponds to the number of microstates belonging to the same macroscopic state. Through the Boltzmann constant k_B, entropy is related to energy and temperature.[7]

Entropy is thus a measure of the probability of a state: If a macrostate is realized by many microstates, the entropy is high. If there are few microstates, on the other hand, entropy shows a lower value. Thus, the concept of entropy has to do with the concept of probability of a state. Entropy increase means the transition of a system from a less probable state to a more probable state.

High entropy is thus probable, and a state of low entropy is improbable.

In the further development of the concept of probability, entropy corresponds to the number of questions that have to be answered with a "yes" or "no" to be able to describe the state of a system.

Thus, the concept of entropy is also linked to the concept of information. Whether both terms ultimately express the same thing is an open question. Entropy corresponds to the number of bits. This is because the probability of finding a system in a certain state is related to the number of available possibilities.

In a game of dice, a single roll offers six possible outcomes, two dice already offer 36 possibilities, and so on. Entropy corresponds to the logarithm of the number of possibilities and the number of bits corresponds to the logarithm of the number of possible states.

Entropy is the counterpart of energy.

Entropy is 0 when we know everything about a system. Entropy is maximum when we know nothing about the system.

Consequently, entropy measures our lack of knowledge about the behavior of molecules in a system. In ideal systems which are completely closed to the outside: No information is lost, and no information is discarded. The behavior of the system is thus reversible. As far as we know, all fundamental laws of physics, including electromechanics, are reversible. But where does the irreversibility come from? The irreversible behavior has its logic in the fact that order changes into disorder. In open systems, information must inevitably be lost to the environment. The behavior of open systems is not reversible for these reasons. Physicists also speak of the fact that the phase volume of these systems can decrease.

Possibly an indication of the teleological or rather teleonomic direction of the world can be derived from this.

In a container filled with a gas and completely closed, the movement of the molecules is equally probable, i.e., the gas is in an approximately homogeneous state. Homogeneous states are states of high entropy. The maximum of entropy corresponds to the state of lowest structuredness and highest disorder.[8] The order of the gas molecules corresponds to the average behavior of a huge number of molecules. Every possible arrangement of the gas molecules is equally probable. The statistical mechanics describes the average behavior of the molecules. The ordered behavior of the gas as a whole is leveled in the range of an average value. This behavior does not correspond to the behavior of a single molecule. However, the energy of the whole system always remains the same. The macrostate of the system corresponds to the percentage of microstates belonging to this macrostate. Order structures in this system can only

7 Penzlin, H.: Das Phänomen Leben. Grundfragen der Theoretischen Biologie. Springer Spektrum 2014, S. 160.
8 Penzlin, H., a.a.O., S. 160.

stabilize if the possibilities of the molecules to move or interact with each other are limited in some way. Thus, the buildup of order is only possible in thermodynamically open systems. The loss of degrees of freedom of motion and interaction in thermodynamically open systems is accompanied by a loss of information to the environment. Thermodynamically open systems must therefore be open to the exchange of matter and energy with the environment. Such energy-consuming thermodynamically open systems were called dissipative systems by Prigogine. They represent a necessary condition for the establishment of order in complex biological systems.

1.2 Importance of Entropy in Living Systems

Living systems are, as said at the beginning, thermodynamically open for the exchange of matter and energy – in this way, they ensure a low entropy in their interior by exporting entropy to the environment. In this way, they create the conditions for the establishment of order inside them, while increasing disorder elsewhere, i.e., outside. The systems of life correspond to systems of a high degree of order, low entropy and high potential energy, a state which must be maintained under permanent energy consumption.

According to Ebeling,[9] the necessary entropy export is based on three mechanisms:

1. heat release,
2. mass transfer with the environment, and
3. conversion of substances within the organism.

The fact that every organism gives off heat to the environment is of great importance for its survival, because the organism gets rid of a part of its surplus energy by giving off heat. It has been found out, for example, that in the course of the development of a chick from an egg, for example, a heat energy of approx. 80 kJ and thus a correspondingly large entropy is given off to the environment.[10] An amoeba absorbs higher-order substances, digests them and uses them to maintain its organization. In return, it emits heat to the environment, i.e., it spreads disordered energy. The planet Earth absorbs energy from the sunlight for the energy metabolism of the plants and radiates heat for it into space. The system Earth absorbs from the sun a heat flux of 10^{17} W, the temperature of which is 5800 K. The Earth radiates back to the outside about the same amount of heat of 10^{17} W, whereby the temperature amounts to then only 260 K. This value corresponds to the heat radiation of the Earth. The basic mechanism, according to which our Earth frees itself from entropy, consists physically in the absorption of high temperature photons and the emission of low temperature photons. Our planet emits on average $4x10^{14}$ entropy units (Watt Kelvin) per second as entropy export to the background radiation.[11] Thus, the Earth exports entropy into space. This planetary metabolic mechanism is a fundamental requirement for self-organization.

9 Ebeling, W., Freistel, R.: Physik der Selbstorganisation und Evolution. Akademie-Verlag Berlin 1982, S. 82.
10 Penzlin, H., a.a.O., S. 164.
11 Ebeling, W.: Chaos-Ordnung-Information. Deutsch Taschenbücher-Verlag Harry Deutsch Thun, Frankfurt am Main 1991; S. 16.

The complex pattern formations in the processes of the oncogenes, which start with a low structured fertilized ovum and finally develop into structurally highly differentiated living beings, are contrary to the second law of thermodynamics with the increase of entropy. But Boltzmann expressed the assumption early on that the entropy theorem could be broken in living systems.

Carl Friedrich von Weizsäcker doubted that the entropy growth must necessarily mean a structure reduction. The evolution of structure is even a direct consequence of the second law.[12]

Today, following Prigogine, one tends to the view that in the building up of forms in a living system, only one summand of the entropy decreases, that this decrease would be finally overcompensated by the increase of other summands, so that also here in the balance the entropy would increase.

According to Prigogine, the entropy change of any system can be divided into:

- Entropy production d_iS inside a system in the wake of the irreversible processes taking place there, and

- into the entropy flow d_eS across the boundaries of the system into the environment or out of it according to the following formula: $S = d_iS+d_eS$.

For reversible processes, dis = 0. For irreversible processes, $d_iS > 0$.

For living systems, it can be stated in summary that the increasing entropy in these systems in the wake of irreversible processes is compensated by removal to the environment.

1.3 Entropy and Self-Organization

The paradox "Carnot or Darwin"[13] could be brought closer to a solution only when one began to study the behavior of systems far from equilibrium in their behavior, i.e., in a state where there are no linear relations between the general fluxes and forces. Ilya Prigogine, in his studies on the thermodynamics of irreversible processes, was able to show so immensely impressively that systems can evolve to stationary non-equilibrium states with an approximately linear behavior even under conditions far from equilibrium.[14] However, a permanent supply of energy is required to maintain this state. At a further distance from the equilibrium state, for example in the wake of changes in the boundary conditions of the system, such states at which irreversibility occurs are subsequently reached. Under the prevailing conditions of nonlinearity, instabilities that can lead to the spontaneous formation of new spatial, temporal, or spatiotemporal patterns and structures are possible. Biological systems thus form new shapes at a supercritical distance from the equilibrium state under a supply of high-quality energy. Systems that undergo transitions to such states are called self-organizing systems.

Examples of self-organization can be found in the fields of chemistry, physics, astronomy, and in all living systems. The term self-organization originates from Ebeling and is defined as follows: "By self-organization, we mean an irreversible process

12 Cited from Penzlin, H., a.a.O., S. 161.
13 Callois, R.: La dissymétrie. In: Cohérences aventureuses. Paris 1973, S. 198.
14 Ebeling, W.: Chaos-Ordnung-Information, a.a.O., S. 17.

that leads to more complete structures of the overall system through the cooperative action of subsystems. Self-organization is the elementary process of evolution which can be understood as an unlimited sequence of self-organizing processes. In this sense, the processes on earth and in the cosmos are usually evolutionary processes that can only be understood in the context of their history, i.e., the whole chain of causative self-organization processes. Processes of self-organization often develop from kinetic transitions, which can occur with increasing deviation from equilibrium at certain critical parameter values."

According to Ebeling, the theory of self-organization is based on the following four theories.[15]

1. The thermodynamics of irreversible processes. It describes the global and local balances of energy, entropy, momentum, and of quantities of matter.
2. The nonlinear dynamics of order parameters, which deals with the solution of nonlinear differential equations for the characteristic quantities of the processes.
3. The stochastic theory, which works with macroscopic order parameters, but considers them as fluctuating quantities and deals with the existence of a probability distribution and an equation for this quantity.
4. Statistical theory, which works with probability distributions for the microscale state of the system.

A fundamental thermodynamic requirement for self-organization, as described above, is the export of entropy. Only those processes that can free themselves from the entropy generated internally by irreversible processes are potentially capable of self-organization.

In any case, the property of self-organization can, at this time, only be explained in terms of physical parameters, although it is a physical attribute of matter. We know a whole series of physical systems that have the property to spontaneously form specific spatial and temporal patterns under certain conditions. This requires a certain degree of global cooperation. A simple example of self-organization in the inorganic realm is provided by phase transitions during the transition of a liquid into a solid or a gas. This is the case when water freezes into ice.

A ferromagnet is functionally composed of a large number of largely ordered microscopic magnets which have only a few degrees of freedom in their alignment. In this state, the metal is magnetic. When the iron is heated, the heat causes these miniature magnets to swirl in all directions. After cooling, the metal regains its magnetization properties. Another example of self-organization in the inorganic range is the phenomenon of superconductivity of metals near absolute zero. At this low-temperature range, materials can lose their electrical resistance. This makes them superconducting. As we all know, electricity is generated by the flow of electrons. At temperatures near absolute zero, the flowing electrons slip into a cooperative state of large-scale organization. The electrons now behave as a single electron, and they move in the form of a highly organized quantum wave pattern. Similar large-scale organization patterns can also be observed in liquid helium.

Well-known examples of spontaneously evolving dissipative structures in the inorganic domain are the Bénard instability and the Belusoff-Zhabotinsky reaction. In the case of Bénard stability, the thermal motions within a liquid lead to sponta-

15 Ebeling, W., a.a.O., S. 42-43.

neously occurring roll-like patterns: If a homogeneous liquid layer is heated from below, then, when a critical value is exceeded, the typical hexagonal convection rolls develop in the wake of a heat exchange between the hotter liquid layers in the bottom region and the cooler ones further up. These typical convection currents are the result of coherent movement patterns of millions and millions of molecules.

Such self-organization phenomena in liquids are only possible because energy has been introduced into the system from outside in the form of thermal energy. In these examples, the externally supplied thermal energy does not, as one might expect, lead to an even more violent mobility of the liquid molecules and thus to an increase in disorder, but on the contrary to the spontaneous formation of order structures.

A chemical example of spontaneous self-organization in the field of chemistry is the Belusoff-Zhabotinsky reaction, i.e. the oxidation of an organic acid (malonic acid) with potassium bromate in the presence of a catalyst. This reaction proceeds discontinuously. Typical patterns, such as spiral waves, occur spontaneously. The interesting thing about this reaction is that initially homogeneous states are replaced by spontaneously occurring spatiotemporal patterns with a clear long-range order.

Such transitions to a more complex phase are accompanied by symmetry breaking: Water that one drinks from a glass exhibits rotational symmetry. If you put the glass in front of the window in winter, the water naturally freezes: Ice crystals form and the rotational symmetry is lost because the crystal surfaces now define a preferred direction in space. Because symmetries in the universe are broken at low temperatures, and because the universe continues to degrade from a very hot initial state, the history of the universe runs over a sequence of symmetry breaking.

Self-organization can therefore occur in systems far from equilibrium at all levels of reality. One can say that self-organization leads to more complex spatial, temporal, or spatiotemporal forms. Self-organizing systems are open to their environment. The new emerges spontaneously. It is theoretically explainable, but it is not exactly predictable in detail.

The slow heat method of the universe predicted by the prophecy of the second law could thus be contrasted with the counter-design of a universe that could creatively create ever new orders at all stages. Self-organization thus represents a fundamental physical principle. Matter therefore has, in principle, the property of self-organization in all its stages. However, even with this knowledge, this question is far from answered: Why does self-organization exist and why does life exist? The answer to these questions about the why does not fall within the original field of natural science. This inherent property of matter softens the contrast between "dead" and "living" matter at least a little bit. The assumption could impose itself that matter could be inherent to some kind of a remotely acting potential that would elude an exclusively physical interpretation. F. Cramer assigns to matter a priori an idea of its self-organization, an idea for the unfolding of its blueprints, and he expressed the conjecture that the idea of human consciousness could already have been present as a possibility at the big bang.[16]

According to Plato, ideas exist outside of matter. They needed matter to be able to manifest themselves, and Aristotle, who argued with the rigid matter concept of a Democritus, had formulated the concept of "entelechy". The physicist Erich Jantsch

16 Cramer, F.: Chaos und Ordnung. Insel-Verlag 1993, S. 229.

summarized his thoughts on self-organization thus:[17] "The one-sided application of the Darwinian principle of natural selection even today often leads to the idea of a "blind" evolution which produces any possible nonsense and finds out what is capable of life by coping with the environment and competition ... intuitive attempts to apply the basic principles of self-organization, as they apply to chemical and prebiotic evolution, also to higher stages of evolution have led to astonishingly realistic descriptions of the dynamics of ecological, sociobiological and sociocultural phenomena ... This new picture of knowledge which is primarily oriented to models of life rather than mechanical models, brings change not only in science. It is linked thematically and in the nature of knowledge to those other events that signaled a meta-fluctuation at the beginning of our century. The basic themes are the same everywhere. They can be summarized in terms of self-determination, self-organization, and self-renewal, in the recognition of a systemic interconnectedness of all natural dynamics over space and time, in the logical primacy of processes over structures, in the role of fluctuations that suspend the law of mass and give a chance to the individual and his creative invention, in the openness and creativity of evolution, finally, that is neither predetermined in its emerging and passing structures, nor in its final effect. Science is in the process of recognizing these principles as general laws of a natural dynamic. Applied to man and his systems of life, they are thus an expression of a natural life in the deepest sense. The dualistic division into nature and culture is thus abolished. In the reaching out, in the self-transgression of natural processes lies a joy that is the joy of life. In their interconnectedness with other processes within a comprehensive evolution lies the meaning, which is the meaning of life".

Our world is a non-equilibrium world. The universe is evolutionary in its essence. This evolutionary concept not only appears at the level of biological systems, but it also permeates the physical world at all levels of organization. Consequently, this principle is also present at all organizational levels of our body: starting with the networks of proteins inside the cell, the dynamic DNA structures, through the cellular associations and the large physiological integrity-maintaining systems, and from there into the networks between body, soul, and spirit. This principle also plays an important role in the development, progression and even treatment of disease. It reflects a universally effective principle in health and disease alike.

1.4 Significance of the Entropy for the Concepts of Medicine

Based on a thermodynamic approach, tumor diseases initially represent stationary systems in the early stages and non-stationary, chaotic non-equilibrium systems in the further course. Typical for malignant tumors is an increased cell turnover compared to the cell turnover rates of the surrounding host tissue: Malignant cells undergo their cell cycle processes faster, they divide faster, and in the wake of an increasing genetic instability they form new cell clones at an accelerated rate. On the other hand, due to a deficient supply of blood and nutrients to the tumor tissue, a considerable number of tumor cells die. Such an accelerated dynamic of cell turnover rates can be attributed to an increase in entropy d_iS inside the non-equilibrium system of an accelerated growing malignant tumor. Malignant and rapidly growing

17 Jantsch, E.: Die Selbstorganisation des Universums. München 1982, S. 34f.

tumors have a tendency to move further away from an initially existing, still approximate steady-state nonequilibrium condition. Typical morphological features of a malignant tumor are lower differentiation and less diverse patterning compared to the more highly differentiated feature maps of normal, healthy tissue.

Under the microscope, the pathologist often sees islands of widely differentiated and ordered cell assemblies on the tumor tissue which can be detached from areas of highly disordered cell assemblies. Consequently, any such described tumor cell cluster must have a higher d_iS than the surrounding tissue. Thus, they must also be assumed to have lower potential energy. And last but not least, there is therefore an entropy gradient between the tumor and the surrounding tissue: the faster a tumor grows, the greater the entropy export from the tumor to the surrounding tissue must be.

Fast-growing and particularly malignant tumors thus export disorder and entropy to the surrounding tissue. In rough approximation it is to be assumed: The faster a tumor grows, the more entropy it must export to the surrounding area.

The continuously produced surplus of entropy, the export of disorder into the environment requires a high degree of compensation capacity from the organism, the capacity of which can reach its limits. Entropy is related to temperature and energy via the Boltzmann constant. From a thermodynamic point of view, a tumor continuously withdraws energy from the organism and thus a growing potential for differentiation and diversification. In the early stages of a tumor, a small, limited entropy export to the outside is still to be assumed. In the later advanced stages and especially in the stage of diffuse metastasis, the whole system of the organism is finally involved in the out-of-control entropy balance. Malignant tumors require a lot of energy and in return export entropy, i.e., disorder, into the organism. Some of the entropy generated by the tumor is exported to the outside as heat. It is not uncommon to measure elevated temperatures in tumor patients.

Many patients report to the doctor that at the very beginning of their illness, there was a general feeling of malaise, an indefinable feeling of illness: "I felt that something was wrong with me," is a common phrase that cancer patients describe to their doctor in this or a similar way as an early sign of their tumor disease. In most oncology textbooks, patients are advised to take such vague symptoms seriously because they may be signs of a manifesting tumor disease. In the early stage of tumor disease, systemic aspects of such a disease may already become conspicuous, which may seem worth considering. Tumors, diseases in general, are not local phenomena.

Whether and to what extent such considerations of diseases, especially tumor diseases, could open up new perspectives remains to be seen. However, the comparison of two different systems in the organism seems to be worthwhile: On the one hand, a rapidly growing tumor with its balance of entropy and energy and a resulting export of disorder. On the other hand, the initially still stationary non-equilibrium system of the organism, which, in the course of a tumor disease, is increasingly burdened by the entropy export from the interior of the tumor and, in the language of synergetics, is virtually enslaved, until the organism could finally, in the final stage of the disease, come close to a thermodynamic state of equilibrium which can no longer guarantee a continued existence.

1.4.1 Entropy and banal Flu Infection: An Example

A healthy organism is approximately in a stationary non-equilibrium state, i.e., a state with a constant entropy production and an equally constant entropy flow to the outside. The entropy-generating irreversible processes in the organism, as we have seen, create order, on the one hand, to export a plus of disorder on the other hand.

Stable steady states can also be established in systems far from equilibrium. If these systems are in a stable state, the principle of minimal entropy production[18] applies to them. At a distance from the equilibrium state, for example, as a result of changes in the boundary conditions, irreversible processes come more and more into the foreground. These are characterized by increasing non-linearity. As a consequence, increasing instabilities of the system can be observed: With increasing distance from the equilibrium state, the system shows violent fluctuations.

Out of the phases of increasing instability, the system as a whole may branch into new steady states characterized by new pattern formations. Such branching points, from which nonlinear systems take new states, are also called bifurcation points.

Diseases can also start from such bifurcation points, namely when the organism moves away from its stationary non-equilibrium state, which is characterized by a low entropy production. Consequently, the state of minimal entropy production can be called "health". In this state of high order, the organs are, according to Gadamer, "silent".

Now let a patient suffer a banal infection, let's assume a harmless flu virus. The patient does not feel very ill, only a little tired and dull: his organism has moved little from the original stationary non-equilibrium state of minimal entropy production. With a few aspirin tablets, perhaps a cough syrup, and equipped with a considerable supply of tissues, he goes to his office as usual and completes his most important appointments as well as possible. He comes home in the evening or afternoon possibly a little earlier than usual, where, equipped with a chest compress, he retires early to bed and wakes up the next morning already in much better condition. After three or four days, he is fully recovered: The disease has disappeared without any noticeable traces which means: his organism has returned to its previous stationary non-equilibrium state. His neighbor, on the other hand, has caught the real flu: he has a high fever, he coughs incessantly, his tongue is thickly coated, his palatine tonsils are massively swollen, and he feels stitches in his chest with every breath. He feels so ill that he cannot leave his bed. His secretary has to cancel all appointments, including quite important ones. The family doctor has to come. He listens to the chest and finally thinks that there is the beginnings of pneumonia, and he prescribes, among other things, a proven antibiotic. It may have taken a whole week before the man was able to get out of bed, at least for a short time. It may have taken two weeks for him to feel really fit and fully able to work again. This young, physically fit, and athletically active man had thus come through the real flu. His organism then needed almost four weeks to return to its previous steady state of non-equilibrium. The illness had taken considerably longer than that of his neighbor, because he had suffered from severe fevers and pneumonia, and his system had survived the illness without any consequences.

18 Prigogine, I. cited from Penzlin, H., 1947, S. 165.

Another employee of the company, however, had suffered a much worse fate: his flu, which at first seemed quite harmless, had taken a very severe course. What had initially appeared to be a banal viral flu had been complicated by an additional bacterial infection.

The initially seemingly banal viral flu had been considerably complicated by an additional bacterial infection caused by dangerous antibiotic-resistant germs. An initial antibiotic therapy turned out to be ineffective. A combination treatment with other more effective antibiotics was subsequently used. This patient underwent severe bacterial pneumonia with sepsis. Unfortunately, the germs circulating in the blood became attached to the heart valves, leading to bacterial endocarditis. The patient had to be treated in the intensive care unit for three weeks. Here, it was possible to control the sepsis. However, it turned out that one of his heart valves had been severely damaged by the circulating bacteria and had become insufficient. As a result of this defective heart valve, the patient suffers from severe heart failure: it is now very difficult for him to climb just the ten steps to his apartment. A replacement of his defective heart valve in a cardiac surgery clinic is imminent. After his illness, this patient is not able to reach the original stationary non-equilibrium state with minimal entropy production. Rather, his organism has assumed a new steady state non-equilibrium state that differs from the previous one by a much higher entropy level. It is no longer the previous, approximately stable non-equilibrium state of minimal entropy production. Rather, it has been replaced by a state of higher entropy and a lowered degree of order.

From the point of view of chaos theory, which we will discuss in more detail later, one could say that after the disease its state trajectories have swung to the center of a new attractor.

Now we will assume the following worst case: An acquaintance is said to have received a heart or liver transplant some years before. The patient feels well after the transplantation, he pursues his profession and is active in sports. A permanent treatment with immunosuppressive drugs is necessary to prevent a possible transplant rejection. These drugs result in a weakening of his immune system. This man was also a victim of the flu epidemic. Possibly as a result of his weakened immune system, this patient suffers a particularly severe bacterial infection that eventually leads to life-threatening sepsis. The patient is treated in the intensive care unit for five weeks using all medical skills. In view of lung failure, the patient has to be ventilated by machine. After the clinical condition initially appears to improve, a rapidly progressive insufficiency of his transplanted heart develops, and the patient dies after six weeks in a state of multiple organ failure that can no longer be controlled. This patient's organism had also been in a stationary state of non-equilibrium prior to this influenza illness. However, as a result of the transplantation and required continuous immunosuppressive therapy, his organism had been in a state of higher entropy and lower order. Even before this catastrophic influenza illness, the patient had been generally susceptible to infections. For this reason, quite a few antibiotic treatments were necessary. His condition had already been characterized by sometimes violent and prolonged fluctuations around his non-equilibrium state. His system had settled down to a quasi-stationary steady state under clearly non-equilibrium conditions. However, this steady state had been characterized by changes in boundary conditions with increased fluctuations in the system. In the course of increasingly frequent and increasingly severe infections, his system had moved further and further away from the original state of equilibrium. In the wake of the frequent antibiotic treatments, there were also considerable disturbances of the digestive system with frequent diarrhea and a number of other disturbances and secondary diseases. After the final and catastrophic infection, the entire system went out of balance: the system was no longer resistant to ever-stronger fluctuations. The entropy production increased exponentially, and one complication led to the next, finally bringing the system to an ever greater distance from its original steady state, from where a return to the previous state was no longer possible: The system was irreversibly on its way towards another state of lower order. In the course of the final disease, vital systems eventually failed and ceased to function at an increasingly rapid rate. The failure of one system had an accelerating and irreversible effect on the failure of other systems. Under the condition of progressive organ failure, the state developed in the direction of a maximally increasing entropy. Physically, this person died a heat death in a thermodynamic equilibrium state. On the level of chaos theory, this human died as a consequence of a unification of his state trajectories towards the center of a new strange chaotic attractor. On the level of information theory, this human died because the informational networks on the level of cells, organs, and the whole organism could not transmit semantic contexts anymore.

On the level of the human being, a family father died with this man, leaving a woman with two small children stunned.

2 Systems of Life Exist on the Edge of Chaos

The word “chaos” comes from the Greek and designates the open status, the gaping, or also the emptiness. According to many creation mythologies, this emptiness, the nothing, is the original ground of becoming, from which the ordered ultimately emerged. In the ancient cosmogonies, in the pre-Socratic era, in the mysticism of the East, and also in the biblical story of creation, the desert, the infinite emptiness above boundless waters, is the original ground of all becoming. Chaos and cosmos, the unformed and that which is closed into an ideal form, thus stand in a complementary ontological context to each other. The principle of complementarity reflects a universal principle: It designates fundamental phenomena in the quantum realm, for example in the form of wave-particle complementarity, it appears in biological systems at various places, for example in the KL-complementarity of complex molecules, at the key-lock complementarity between antigen and antibody or between cell receptor and antigen. Indeed it reflects the relationship between health and disease in the context of the organism in its wholeness. Chaos is a tremendously complex phenomenon that is fundamental to reality. Schelling saw chaos as a “metaphysical unity of potencies.[19]

When orders decay, chaos arises. Complex evolving systems pass through chaotic states during phase transitions, which can subsequently stabilize again to form new order structures. Thus, chaos and order have a close, complementary inner relationship in biological systems. Thus, health and disease can be understood as temporally different functional manifestations of the same fundamental dynamics. Phases of chaotic transitions are characteristic for all diseases, as will be shown in more detail. The temporal modeling of chaotic transitions gives the different diseases their specific signatures. For example, a number of infectious diseases, especially in childhood, are characterized by feverish and often crisis-like courses. Intervals of fever episodes of three or four days are typical for courses of malaria. Children who have overcome an infectious disease are subsequently immune to the causative pathogens for life: From the chaotic fever crisis that has been overcome, a lifelong immunity has established itself as a new ordering structure. The disease had both to offer: A chaotic crisis fever episode and a lifelong protection derived from it.

Disease processes are not exactly predictable in terms of severity and duration for the affected person for reasons of principle. In medicine, only statistically based probability statements are possible.

Children’s illnesses are often accompanied by a violent fever, which, as quickly as it came, often subsides just as quickly. Children usually recover quickly. In a few children, however, the course of the illness may well be more threatening and involve serious complications, for example, if a febrile childhood illness has been complicated by meningitis. Even with the resources of modern medicine, bacterial meningitis can lead to a dramatic course with severe neurological sequelae, even a

19 Cramer, F.: Chaos und Ordnung, Insel Verlag (1993), S. 158.

fatal outcome. Despite all efforts, some of the affected children remain disabled for life.

Like all processes in living systems, the course of disease is not deterministic, and the dynamics of living systems are characterized by nonlinear differential equations:

The equations of motion in the domain of classical Newtonian physics are time reversible: +t = -t. In classical physics, time has a reversible form. The number of information formed in a reversible process is exactly equal to the number of information lost: The total amount of information always remains the same in a reversible process.

The movements of objects in the scope of classical physics follow a linear process. Linearity means that the change of an influencing quantity in a system leads to a fixed change of magnitude of the system properties analogous to a simple equation: y=x+1. This equation corresponds to a straight line in a Cartesian coordinate system.

If, on the other hand, there is a relationship between two variables corresponding to y=x2 or y=x3, then we speak of a nonlinear function. Such a function does not correspond to a straight line in a Cartesian coordinate system. Nonlinear functions take the form of parabolas or even more complicated curves.

The basics of mathematical modeling of nonlinear processes were created by the French physicist Henri Poincaré already in 1892.[20] Poincaré had dealt, among other things, with the question of the stability of our solar system. Newtonian physics had explained the motion of two orbiting planets by the power law, according to which the gravity must decrease with the inverse square of the distance. These equations were also true for the orbits of two bodies, for example for the orbit of the Earth around the sun. For any idealized two-body system, the orbits are stable and also follow Newton's equations exactly.

However, it turned out that Newton's equations were unsolvable for the calculation of the orbits of three bodies, for example, if the force effect of the Sun on the Earth-Moon system was to be calculated. Such mathematical approaches were solvable only if methods of stepwise approximations with summation of correction terms were used helpfully. Poincaré made the discovery that even after minute perturbations, some planetary orbits showed an unpredictable, i.e., chaotic behavior. In 1963 the American meteorologist E. N. Lorenz, who was engaged in mathematical weather models, resorted to the basic mathematical features of Poincaré's approaches. Lorenz made attempts at mathematical models of weather forecasting with the help of non-linear equations. His calculations were based on equations limited to six decimal places. If these equations were rounded off only slightly, i.e. to three places after the decimal point, his computers gave partly completely different predictions, although it had obviously been a matter of only very slight changes of the numerical sequence! At that time, classical physics still tacitly assumed that such minor changes could be extrapolated without any problems and without changing the final results decisively. Lorenz finally came to the realization that the progressive iteration (repetition) of equal step sequences in nonlinear processes at the end of these step sequences could lead to an exponential enlargement of apparently minimal chang-

20 Poincaré, H.: Les méthodes nouvelles de la mécanique céleste. Paris (1892). Cited from Cramer, F.: Chaos und Ordnung, Insel-Verlag 1993, S. 159.

es.[21] One explanation for this behavior lies in the sensitivity of complex systems to small changes in initial conditions. The Lorenz attractor named after him shows a butterfly shape characteristic for weather forecasting: Here, corresponding system states pass through characteristic loop patterns in the course of time. The system of an attractor is globally stable, but locally not exactly predictable, just as the local weather is not completely predictable. Similar chaotic motion patterns follow, for example, the trajectories of two frictionless coupled and freely swinging pendulums: If both pendulums swing in a constant ratio to each other under a dosed energy supply, the trajectory of the double pendulum initially follows a periodic swing mode. If, however, the pendulum is pushed even more strongly, completely chaotic and unpredictable oscillation patterns are following.

In deterministic chaos, the sentence "Similar causes produce similar effects" thus has only limited validity.

In medicine, we are dealing with multiparameter systems which are even more complex than the system of the double pendulum. The cause and the course of a disease are always influenced by several triggering and inhibiting factors. As a result, the initial state of a disease and its course cannot be precisely determined. An exact prediction of the course of a disease would theoretically only be possible if the initial state were known with exact precision. Moreover, not only disease-specific factors play a role in the course of a disease, but also a multitude of individual potentially contributing factors, for example, possible pre- and concomitant diseases, function, status, fitness of the immune system, psychological, and even social factors as well as the biography of a person in its entirety.

Non-linear, feedback processes are therefore potentially chaotic and react extremely sensitively to changes in the initial conditions. In this context, Lorenz is said to have spoken of a butterfly effect, which is quoted again and again: Even the beat of a butterfly's wings could cause a complete change in a large-scale weather situation.

On the other hand, the French physicist La Place had previously put forward the thesis that science could one day be able to predict the entire fate of the universe with a single mathematical equation if it had researched its starting point precisely enough. Such a strict and radical reductionist worldview has meanwhile disproved itself. It is the world view of a car mechanic.

Life processes run unsteadily and in feedback loops. The curves and lines of living structures are characterized by fractal forms. Both Newton and Leibniz were already familiar with curves that were steady but not differentiable. In 1890, Peano succeeded in the representation of an immensely complex curve which took up the area of a sheet of paper and thus had the character of a surface. About 70 years later, Mandelbrot dealt with the measurement problem, and he investigated the complexity of such curves. The best-known representation of a curve of a complex system is the Mandelbrot figure named after him with the Julia sets surrounding it and controlled by it. The Mandelbrot figure resembles the shape of an apple man and is therefore often called "apple man". In the areas of the chaotic edges of this Mandelbrot figure with its fractal dimensions, with higher and higher resolution, finer and finer images of Julia sets are displayed. In the Mandelbrot process, i.e., the transition from order to chaos, the so-called "Feigenbaum number" ... $\Delta = 4.669201$ ... appears as a constant. This irrational number corresponds to a universal constant which is

21 Lorenz, E. N.: Deterministic Nonperiodic Flow. J. Atmos. Sci 20 (1963), S. 130.

supposed to occur at all erratic transitions in nature. It is therefore compelling to assume that this "fig tree number" should also play a role in medicine and there, especially in the case of erratic courses of disease.

The fractal lines and geometric objects, which appear especially in the transitional areas between order and chaos, are of impressive aesthetic appeal – after all, they seem to reveal a large and possibly fundamental aesthetic category behind these fractal dimensions.[22]

The principle of nonlinearity is of fundamental importance for biological systems and thus also in many systems relevant for medicine.

In the course of nonlinear processes, time reversal, as in classical physics, is no longer possible. This means on a more general level that the amount of information at the beginning of a process does not correspond to the amount of information at its end. Rather, new information is always formed in the course of the processes. It is characteristic of the complex systems of life that they are able to develop new and previously unforeseeable properties that cannot be explained from the properties of the system components: Complex biological systems can thus emergently develop new properties. The phenomenon of emergence, which has many facets, also plays an important role in the course and treatment of diseases, as we will show.

In attempting to explain the phenomenon of emergence, radical reductionism seems to have reached its limits because it cannot explain the emergence of new things from its parts. Emergence is a holistic phenomenon and refers to the system as a whole rather than its parts.

Disease processes typically develop nonlinearly in their temporal progression. In their spatiotemporal pattern formation, the time symmetry between past and future is broken. In the course of most diseases, almost time-symmetric or quasi-periodic patterns can often be observed in addition to chaotic patterns. Recurrent fever episodes in the course of severe infectious diseases often show quasi-periodic patterns under changing antibiotic regimes: A patient with a known chronic lung disease suffers from a lung inflammation. He is treated with antibiotics according to the bacteriologically determined pathogen spectrum. Under this regime, the infectious agents are initially brought under control: The fever, which was high at the beginning, drops, and the strongly elevated laboratory chemical inflammation markers steadily decrease. The patient appears to be recovering from his severe illness. The relatives at the bedside are full of hope and the doctors are confident. But some of the bacteria have survived the antibiotic therapy and have become resistant. These resistant pathogens are now multiplying anew and at breakneck speed. The fever and the inflammatory markers rise again. The patient suffers a setback, he breathes heavily, struggles for air, and every breath hurts. The oxygen saturation in the blood drops as a sign of his insufficient breathing. The doctors decide that the patient needs artificial respiration. The disease has entered another fever cycle. Another antibiotic combination is tried. This also initially succeeds in bringing the high fever and the inflammatory signs, which have again risen sharply, to a standstill. The patient was successfully weaned off the ventilator. But again, some bacteria have survived the antibiotic cannonade and have become resistant, and the next

22 Mandelbrot, B. B.: Towards a Second Stage of Indeterminism in Science. Interdisc. Science Rev. 12, 1987, S. 117-127. Mandelbrot, B. B.: Les Objects Fractals. Paris (1975), Mandelbrot, B. B.: The Fractal Geometry of Nature. San Francisco 1982.

fever cycle is imminent and must be passed through. Such described courses can be described as almost commonplace in intensive care units. This patient is now considerably weakened by his repeated flare-ups of pneumonia, and his immune system is severely affected. If it is not possible at this stage of the disease to finally eliminate the remaining bacterial pathogens with an even more potent and effective antibiotic combination, there is a danger in this temporally advanced stage of the disease and after several periods of high fever attacks that the system as a whole could take an abrupt and final turn into a chaotic phase and thus enter a state of irreversibly progressing multiorgan failure. In the course of the infectious disease, the patient's organism had been exposed to higher and higher fluctuating swings around its non-equilibrium state under the fever attacks and repeated antibiotic therapies. The recurrent and quasi-periodic flare-ups of his infectious diseases had finally entered a transitional state, which marked the direction of irreversible organ failure and finally the end of the patient. Nonlinear disease processes can at times exhibit astonishing internal and external stability: Chronic diseases from the field of rheumatic forms can persist for months or sometimes even years without detectable changes in their condition at a largely stable level without acute episodes of disease. Other courses of chronic disease may be quasi-cyclical, presenting only one or two episodes of the disease per year. Thereafter, the symptoms of the disease subside rapidly and without leaving any noticeable damage, for example to the joints. Some patients only have to take medication in an acute episode of such a disease and after the inflammatory symptoms have subsided, they are almost symptom-free and able to cope with stress. However, we are also aware of other clinical pictures from this group of diseases. After a first or second relapse, they remain at the level of a permanent steady state and without further acute relapses. After a first relapse, other diseases take the form of a continuously progressive or chronic-aggressive course, as we know it from certain diseases of the chronic hepatitis group. Diseases can be characterized by episodes of approximately linear, steady, and reversible and thus rather smooth courses, they can change from such a relatively stable situation with linear or quasi-cyclical and often lasting for years into phase transitions with irreversible changes of their course directions quite abruptly. These phase transitions with an irreversible change of direction are also called bifurcations. In the course of most disease patterns, disease-intrinsic, i.e., disease-specific and extrinsic factors, such as the immune status, pre- and concomitant diseases, but also an externally introduced effective therapy, interact.

In most cases, therefore, these are mixed forms where quasi-linear progressions alternate with discontinuous non-linearity. Like all nonlinear systems, diseases are characterized by an intrinsic instability to even minor variations of the initial conditions.

2.1 Attractors at the Center of Health and Disease

The trajectories within the scope of Newtonian physics follow steady trajectories. Typical for nonlinear dynamics are abrupt changes in direction, random movements, and a high sensitivity of the systems to changes in the initial conditions. The dynamics of these complex systems are the subject of chaos theory which has become one of the most fruitful branches of modern science. It is to be expected that it will also play an important role in future medicine. The scope of chaos theory includes not only weather observations but also many modern disciplines, from the shock waves of supersonic aircraft to the often-chaotic stock markets, and from the chaotic rhythmicity of heartbeat and electrical brain activity to the physiological fluctuations of blood pressure to the rhythmic metabolism of hormonal systems to the global systems of the numerous control and regulatory circuits in our organism.

The different flow patterns of fast-flowing water have inspired artists at all times. The genius Leonardo da Vinci also intensively studied the flow properties of water. He succeeded in creating fascinating and lifelike depictions of turbulence and vortex formation in flowing water. One of his drawings impressively recreates the turbulent dynamics in a torrent with a sketch of almost geometrically grouped vortex patterns. Leonardo succeeds in his drawings with the representation and pictorial presentation of a sublime inner power and beauty of chaos which, at his time, could only be sensed intuitively but not yet mathematically modeled. Turbulence is a typical property of chaos. The phenomena of turbulence are important for many fields of science, starting with astronomy, aviation, and meteorology to medicine. Moderate turbulences are physiologically detectable in the peripheral blood vessels or in the area of the heart valves in every healthy person, strong and flow-relevant turbulences in the area of the heart valves, on the other hand, can be indicative of insufficient heart valves or arteriosclerotic vasoconstrictions.

Turbulence is also a matter of the right measure. Stationary turbulence is also called attractors.

The occurrence of turbulence in flowing water depends primarily on its flow characteristics or the flow velocity of the water. When streams and rivers show a low water level in summer, the water surface is smooth. When we were children, we would bounce pebbles over the surface of the water and whoever had the most bounces won. We often made small ships out of paper and placed them on the water where they were carried along by the sluggish and steady current. After a heavy downpour, the water flows faster, the current speed increases, and the first whirlpools can be observed. The flow velocity is now no longer uniform and steady, but rather the first eddies form at the edges of the banks, and if you were to put a boat into the water, it would drift away at different speeds, depending on whether it was in the middle of the current or near the bank. If it got into such a whirlpool, it would possibly turn in circles until the paper is soaked and it finally sinks at the same place. The water particles in the river thus exhibit different velocities and different patterns of flow velocities from place to place. In some places, the water flows steadily and smoothly and in other places, an object is buffeted back and forth on the surface. The different paths and the lines of motion of our little ship on the surface of the water could be noted by points on a map or marked in an imaginary space. Mathematicians call such a space a state space. In the case of slow and almost uniform flow conditions, the locations marked for the path of the shuttle would lie approximately in a straight line. In the case of faster and faster flow conditions and in the case of ripping flow conditions we would get abrupt changes of motion and partly bizarre curves.

The flow in a stream or in a river is, in reality, never completely uniform and smooth. Often stones, branches, or tree trunks lie in the way and lead to eddies and turbulences. We observe that these vortex formations in the vicinity of an obstacle can model impressive and amazingly stable ring-shaped structures. Such vortex formations, also called attractors, correspond to spontaneously arising dynamical patterns of order within the nonlinear dynamics of flowing water. The different states through which a dynamical system passes are called trajectories. The manifold forms of motion of the water particles are thus mapped onto specific trajectories. If a water particle would be in the area of a turbulence with a vortex, its trajectory would turn into approximately circular, but never completely equal trajectories.

The trajectories of the individual water particles thus swing towards an attractor, i.e., towards a relatively stable form of motion within a dynamic system.

Attractors as mathematical objects represent specific regions in phase space towards which the trajectories of the system processes converge. They can have the form of a point, but they can also form complex geometrical shapes, for example, periodic loop patterns. These are called limit cycles. However, they can model much more complex mathematical entities, such as a torus. Attractors can have complex fractional geometries.

Mathematically, an attractor comprises a finite set of states through which a system can pass. In reality, however, the states are never exactly the same, but always similar: Satellites never return exactly to their starting point on their orbit around the Earth but always deviate from it by a greater or lesser amount. The orbital curves of the satellites thus do not follow an exact circular path in an exact periodicity; they do not arrive exactly at their starting point after an orbit around the Earth, they only approach it with more or less large deviations. Such a behavior is called ergodicity. If, for example, one would lead an imaginary section through an exactly deterministic circular process, one would always hit only one intersection point, since all points of the process are located on this one and ideal circular line. An attractor, on the other hand, is the constantly changing values from nonlinear processes. In quasi-periodic processes, for example in the orbit of a satellite around the Earth, one obtains a large number of different intersection points, in the extreme case with an infinite number of quasi-periodic passes also an infinite quantity of intersection points. In the case of quasi-periodic processes, a whole network of intersections would be displayed if one wanted to represent them in phase space. Such lattice networks, also called homoclinic tangles, once caused Poincaré to say: “Things are so bizarre that I cannot bear to think about them any further”.

Circular or even approximately circular, i.e., quasi-circular, processes are called limit cycles. An example of a limit cycle is the pendulum motion of a mechanical clockwork: as the pendulum approaches the highest point of its swing path, it slows down its speed more and more and comes to rest for a short time at this highest point. From this resting point, it then moves in the opposite direction, gaining speed again until it reaches the lowest point of its path at maximum speed, and then moves again towards the highest point on the opposite side, its speed decreasing. In an ideal Newtonian world, the pendulum would continue to swing like this for eternity. The pendulum thus moves back and forth between velocity extremes, with the velocity at the two highest points farthest from its center position approaching zero. Under ideal conditions in a vacuum and without friction losses, the pendulum’s swinging back and forth can be represented as a complete circular form in state space. If the pendulum is given an additional impulse by a strong push, it increases its velocity accordingly, the pendulum swings further, and the diameter of its circular form increases. Under realistic conditions, however, the air resistance must be included in the calculation, i.e., the pendulum swings against the air resistance and loses energy. With time, its deflections become smaller and smaller, the speed slows down. In the real state space, the pendulum describes a spiral motion inwards due to these continuous energy losses until the pendulum finally comes to rest in a center point with zero momentum and zero deflection. This center, towards which the pendulum moves, is called an attractor by mathematicians. Attractors thus exert a kind of attraction force on dynamic systems. In a mechanical clock exactly adjusted by the clockmaker, the pendulum receives a shock and thus an energy supply at regular intervals. This energy supply is exactly timed to the oscillation modes. This means that the clock does not slow down with time and does not need to be readjusted. The clock thus always indicates the exact time.

We have seen that an almost frictionless swinging pendulum describes an almost uniform circular motion for all runs. The pendulum motion follows a dynamically stable limit cycle.

Limit cycles occur in many places in nature. Population studies of predators and prey provide an impressive example of such a limit cycle. For example, a farmer is raising carp in a pond for the Christmas feast. Unfortunately, the farmer has a malicious neighbor who secretly adds some pike to his fish stock during the night. For the pike, the carp pond is a set table and with the large supply of carp, they multiply magnificently. Eventually, their population virtually explodes. At some point, however, what must happen is that the number of pike increases, and the number of carp decreases accordingly. The pike no longer find enough prey, they have to tighten their belts, their appetite for pleasure diminishes, and with it their reproduction declines because their food source threatens to dry up. The carp have survived the worst, and they reproduce rapidly. This, however, increases the food supply for the pike again and their numbers increase, and the game begins anew. Thus, an oscillation mode is formed between predator and prey, similar to a pendulum swing. From year to year periodically once the carp and then the pike reach their highest population numbers. It is known from studies that the numbers of pike and carp always approach their original limit cycle. Even if a disease nearly wipes out the carp, under improved conditions the population will spiral closer to its original limit cycle. Such systems are thus remarkably stable in their inherent dynamics.

Limit cycles, i.e., periodic or quasi-periodic processes, play the role of a clock generator for numerous metabolic processes in many places in our organism. Their oscillation modes can indicate health and disease, which we will discuss in more detail.

2.2 Attractors and Internal Clocks in the Organism

In chronobiology, limit cycles play an important role. A large number of biological and thus medically relevant functions in the organism are subject to rhythmic fluctuations. For example, we organize our daily routine according to a circadian rhythm with wakefulness (2/3) alternating with sleep (1/3). Sleep disturbances make us ill in the long run.

The menstrual cycle of women comprises about 28 days.

Circadian rhythms are ubiquitous and occur in every cell, in unicellular organisms, plants, and throughout the animal kingdom. One of their essential functions is to adapt to a light-dark rhythm. In complex organs, these cellular clockworks must be coordinated with each other, i.e., their periodic cycles must be coordinated to a common limit cycle, to a superordinate circadian "master clock". In the last few years, a series of sensational publications have appeared on the subject of biological clocks and the genes that control the rhythmicity or periodicity of these clocks.

Fundamental and vital for the integrity of the organism are the cell division processes, which follow an almost 24-hour rhythm: During mitosis, the DNA is divided among the daughter chromatids. The cell cycle comprises four different phases: In continuous proliferation, cells enter interphase after cell division, consisting of the G1 phase (Gap-1), S phase (S = synthesis), and G2 phase. The G1 phase is characterized by cell growth and the synthesis of proteins and nucleotides needed as building blocks for DNA duplication. In the S phase, DNA is replicated, RNA and proteins are synthesized, and in the subsequent G2 phase, RNA and proteins are again synthesized. In a rapidly growing animal cell, a cell cycle takes approximately 24 hours, with the G1 phase accounting for 5-12 hours, the S phase for 6-8 hours, the G2 phase for approximately 3-4 hours, and mitosis for 0.5 to 1 hour. Cells have the ability to leave the cell cycle temporarily or permanently and enter the G0-rest phase. We know this property from the no longer dividing nerve or muscle cells. Deprivation of growth factors or nutrients can also cause cells to enter the G0 phase. Normally, continuous protein and RNA synthesis takes place throughout the interphase. These continuous growth processes of the cell are only briefly interrupted during the M phase (mitotic phase).[23] In a normal cell population, not all of the cells participate in proliferation. Thus, a proportion of cells remain in the G0 phase until they eventually die or enter proliferation correspondingly later. The proportion of cells that actually proliferates is called the "growth fraction". It is also important to know that cells enter the cell cycle only in response to specific signals from the G0 phase.

The physiological cell division processes are of vital importance to the integrity of the individual and are of the highest sensitivity. It goes without saying that each and every step from one phase to the other must take place only under the strictest control. Entry into the next phase is released only after the preceding phase has been subjected to intensive control and properly completed. In case of error messages, the cell cycle is stopped to give the cell time to repair possible DNA damage or to stop the cell cycle altogether and enter programmed cell death (apoptosis). Another checkpoint is located at the end of mitosis and finally verifies the proper division of the cell. The decision to pass a checkpoint or to stop the division process at such a checkpoint is regulated by external growth factors and the internal clockwork of the cell. The function of this internal clockwork is regulated by so-called cyclins and the cyclin-dependent kinases ("cyclin Dependent Kinases, cDK"). These cDKs are comparable to processors that coordinate extracellular and intracellular signals, thus guaranteeing undisturbed passage through the various cell division stages. The activity of cDKs is regulated by phosphorylation and their catalytic unit becomes active only when associated with regulatory subunits, cyclins. The name cyclin indi-

23 Dörner, Zellproliferation und Tumorwachstum. In: Wilmanns, W., Huhn, D., Wilms, K.: Internistische Onkologie. Thieme-Verlag (2000), S. 93-100.

cates the periodic activity of these proteins. This is because the cyclines only become active periodically as part of the cell cycle mechanisms. External signals can also have a regulating effect on this clockwork.[24]

One of the characteristics of tumor cells is that their cell division processes have more or less escaped regulation by external signals or by their internal clockworks.

We also know that circadian rhythms are genetically determined. Such "clock genes" have been identified, for example, in the fruit fly (Drosophila melanogaster), the golden hamster, the mouse and other animals.[25] In humans, clock genes (hPer1, hBmal1) have been shown to be rhythmically expressed in the skin and mucosa. This shows that every cell has such "clock genes".

"The master clock is thought to be located in the central nervous system at the base of the third ventricle.[26] Special nuclear areas in the anterior hypothalamus (nucleus paraventricularis, nucleus suprachiasmaticus) have been assumed to be biological timers that are independent of day and night. Desynchronization experiments speak for even more of such timers, which can decouple under certain pathological conditions. Aschoff spoke of a "mother clock, of several daughter clocks and coupled oscillating subunits".[27] We also know, for example, that melatonin has the functions of a "time hormone". After all, we know that it plays an essential role in time displacement and in adaptation problems after intercontinental flights and during shift work. Sleep disorders are typical disturbances of the circadian rhythm. The attractor of the circadian rhythm is deformed by pathological sleep behavior. It has been found that in depressive patients the experience of time can often be profoundly disturbed. Blood pressure is also subject to circadian rhythms and usually falls during the night. It is not surprising that infarctions occur twice as often in the morning hours than during the rest of the day.

One of the more recent branches of this research is chrono pharmacology which deals with the behavior of a drug in the body under the aspect of the temporal structuring of the organism and draws conclusions from this for the form of administration of pharmaceuticals: The right drug must not only be administered in the right dose but also at the right time in order to develop an optimal effect. It was already known more than 300 years ago that asthma attacks preferentially occur at night. These nocturnal asthma attacks are caused by complex interactions of different circadian rhythms consisting of hormonal, biochemical, and cellular functions.

Basic biological rhythms also control the breathing rhythm, the heartbeat, the change between different sleep stages, and rhythmic modeling of brain wave curves, but also periodic generation and control processes in the hematopoietic, hormonal, and immune systems. The order structures of the human body are organized by complex networks of rhythmic and periodic patterns.

It was also possible to prove that only a few tens of thousands of rhythmically discharging nerve cells in the above-mentioned nucleus area of the nucleus suprachiasmaticus, which is also called the "master clock", took over the function of a co-

24 Wagener, Ch.: Molekulare Onkologie: Entstehung und Progression maligner Tumoren. Thieme-Verlag Stuttgart (1999), 2. Aufl., S. 117.

25 Lemmer, B.: Zirkadiane Rhythmen und klinische Pharmakologie. Internist (2004), 45:1006-1020.

26 Lemmer, B., Bjarnason, G. A., Jordan, R. C., Wood, P. A. et al.: Circadian expression of clock genes in human oral mucosa and skin: Association with specific cell-cycle phases. Am J Pathol (2001): 158:1793-1801.

27 Aschoff, J.: Gesetzmäßigkeiten der biologischen Tagesperiodik. Dtsch Med Wochenschr (1963): 88:1939. Aschoff, J.: Circadian clocks. North-Holland Publ Comp, Amsterdam (1965): Lit Gross, S. 28, S. 50-53.

ordinated pacemaker with a period duration of approximately 24 hours. From there, signals are transmitted to the peripheral organs via the autonomic nervous system or the endocrine system. In turn, retroactive signals from the periphery reach the central nervous system, where these incoming messages, for example, messages about food intake, are processed.

At the center of molecular biological clocks are four genes and the proteins they encode, namely:

- Per 1 (“period”),
- Tim (“timeless”),
- Clock (“circadian locomotor output cyclus kaput”) and
- Bmal1 (“brain and muscle”).

The protein products formed by these genes have either an inhibitory or activating effect on the functions of other genes. The synchronized activity of a comparatively small number of nerve cells is thus capable of combining such a complex interplay of neuronal, humoral, and cellular associations in the organism into a concerted whole that is coordinated down to the smallest counterpoints.[28]

Among the circadian rhythms in the field of hormonal systems, the hormones cortisol and ACTH, which are formed on the pituitary-adrenal axis, have been the best studied in recent years. The pituitary gland produces the hormone ACTH which stimulates the adrenal cortex to produce the stress hormone cortisol. Typical for the circadian cortisol profile are maximum high concentrations in the morning at the time of waking and minimum concentrations in the first half of the night around midnight. Concentrations of this hormone can vary by a factor of 10 during the day. The concentrations of cortisol measured in the course of 24 hours show only slight deviations in their determined values from day to day, and they follow periodic patterns which, mathematically speaking, build up an approximately ring-shaped limit cycle. Such a limit cycle attractor is astonishingly stable and only slightly susceptible to disturbances. We all know it: Those of us who get up every day at 06:00 or 07:00 and go to work, wake up the first days on vacation also exactly at these times and many find it difficult to fall asleep again after waking up. Only after a few days does the body get used to the new conditions and the vacation really begins.

The circadian rhythm of the stress system described above can also be modulated and changed by environmental factors, such as light, sleep, or by different food intakes. It is known that the ingestion of a meal leads to a rapid rise in cortisol. However, this food-induced cortisol increase is also dependent on the time of day. For example, a steak ingested around noon leads to a different increase in cortisol levels than if a steak of the same size was ingested in the evening.

The duration and intensity of sleep at night also have a modulating effect on hormone status: sleep deprivation during the night, for example, leads to an increase in cortisol levels on the following day. The light-dark cycle exerts a modulating influence on cortisol production via the hormone melatonin, which is produced in the pineal gland. Last but not least, psychological factors also exert a considerable influence on the pituitary-adrenal axis. Healthy individuals who know that they have to get up early the following morning show a steeper increase in ACTH and cortisol levels in the last hours before waking up because their master clock is alerted prematurely.

28 Schultes, H., Fehm, H. L.: Zirkadiane Rhythmen in der Endokrinologie. Internist (2004), 45:983-993.

Thus, the limit cycles of circadian rhythmicity are on the one hand surprisingly stable and on the other hand quite adaptable to changing environmental conditions, which is a typical feature of the high adaptability of complex biological systems.

Persistent or repeated distortions of physiological attractors or limit cycles can result in severe metabolic disturbances: It is known, for example, that disturbances of circadian rhythmicity in the region of the pituitary-adrenal axis may be involved in the development of a so-called metabolic syndrome. This syndrome includes fatty liver and other metabolic pathologies. A consequence of this metabolic syndrome is also the development of insulin resistance, i.e., a precursor to diabetes mellitus. This shows the often ominous way in which disturbances in the circadian rhythm of messenger substances, for example stress hormones, can lead to serious metabolic diseases.[29] What is equally thought-provoking is the clear scientific evidence that disturbance-free circadian rhythmicity can be of great importance for cognitive abilities.[30]

The hormone thyrotropin (TSH) as the most important functional regulatory variable of the thyroid gland, is produced in the anterior pituitary gland and stimulates the thyroid gland to produce the thyroid hormones T3 and T4. The secretion of TSH is stimulated by another hormone from the hypothalamus, TRH (thyrotropin-releasing hormone), and inhibited by dopamine. The production of hormones usually occurs via cascades and via the interplay of activating and inhibiting factors. TSH is secreted in a distinct circadian rhythm and rises steeply in the evening hours around 8:00 pm to reach a maximum between midnight and 4:00 am. Thereafter, there is a continuous decline until a minimum is reached in the noon hours. Its circadian rhythmicity is characterized by a pulsatile secretion with a mean pulse frequency of about two hours. During the evening surge, pulse-encoded TSH secretion increases, forming the basis of the circadian surge.

Acute sleep deprivation leads to significantly higher nocturnal levels; physical stress, a catabolic metabolic state, and even fasting for several days can almost completely abolish the circadian rhythms of TSH.[31]

Circadian fluctuations in glucose metabolism have been known to physicians for many years. The so-called dawn phenomenon, which is characterized by a pathological reduction of insulin sensitivity in the early morning hours, has become the focus of attention. This phenomenon is not detectable in metabolically healthy individuals: In healthy individuals, maximum glucose tolerance and insulin sensitivity are found in the early morning hours, which continuously decreases again in the following hours. Here, diurnal fluctuations in the circulating concentrations of cortisol and growth hormones, which act as insulin counter-regulators, are thought to play a significant role.

As expected, insulin secretion in the islet cells of the pancreas shows a circadian rhythm with a clear morning peak. The hormone systems of insulin on the one hand and cortisol and the growth hormone on the other thus have an antagonistic effect on the circadian rhythm of the blood glucose values. In reality, however, the relationships are far more complex because a large number of other effectors would also have to be taken into account.

29 Schultes, B., Fehm, H. K.: Zirkadiane Rhythmen in der Endokrinologie. Internist (2004), 45:983-993.
30 Seeman, T. E., McEwen, B. S., Singer, B. H., Albert, M. S.: Increase in urinary cortisol excretion and memory declines. McArthur Studies of successful aging. J Clin Endocrinol Etab (1979), 82:2458-2465.
31 Schultes, et al., a.a.O.

The activity of the immune system is also modulated by various circadian rhythms and limit cycles: the concentration of white blood cells (granulocytes), for example, is subject to diurnal fluctuations.

Recent research suggests that mental illness may also be linked to disturbed day-night rhythms: Psychiatrists have known for a long time that the day-night rhythm of depressive patients can be permanently disturbed. In many depressed patients, mood swings are most pronounced in the morning hours with listlessness, fatigue, and loss of appetite ("morning low"). These findings are important to clinicians because they provide the basis for chronotherapeutic treatment methods that can be used to treat depression via the track of rhythm-mediating systems.

What should be shown is the complex interplay of different hormonal systems, some of which interact agonistically, others antagonistically. This interplay gives the systems a high degree of dynamic stability on the one hand and a maximum of reactivity to changes on the other. The circadian rhythmicity of the individual hormones models its own specific limit cycle, or the typical form of an attractor. In the immeasurably large number of hormones active everywhere in metabolism, countless attractors interact and interpenetrate each other. This results in complex attractor structures, even whole attractor landscapes, which model what is commonly called health or disease.

The heartbeat is the best-known biorhythm of all. It stands as an archetype for life itself. In rhythmic sequence between systole (contraction of the heart muscle) and diastole (relaxation and return flow of venous blood from the periphery to the heart), blood is pumped through the circulatory system. Many millions of cardiac muscle cells must be precisely coordinated in time and space to ensure a sufficient circulatory system. The coordination of the cardiac muscle cells is achieved by electrical signaling in a hierarchically structured system of neuronal pacemaker units. From there, the signals are transmitted to the cardiac muscle cells. The so-called sinus node, located in the right atrial region at the junction of the superior vena cava, has the function of a primary pacemaker center. This node is made up of specialized cardiac muscle cells that have the ability to depolarize spontaneously and can excite themselves electrically. This happens about 60-80 times per minute in an adult at rest. In the case of well-trained persons, resting pulses of less than 50/min. or even less than 40/min. can be registered. A special property of the sinus node is the immediate repolarization after depolarization which is made possible by special HCN channels (Hyperpolarization activated Cyclic Nucleotide gates) in the cell membrane. From here, the electrical excitation spreads through the muscles of the atrium and reaches another pacemaker center, the AV node located between the right atrium and the right ventricle. If the sinus node fails, the AV node takes over the pacemaker function as a secondary pacemaker with a natural frequency of approx. 40-50/min. From the AV node, the current reaches the muscles of the heart chambers via special conduction pathways, the so-called Purkinje fibers. If the function of the AV node is also disturbed, a ventricular rhythm of approx. 25-40 beats/min is finally established.[32] In case of a disturbance of the excitation propagation, it is therefore always the structure with the next higher natural frequency, which then takes over the pacemaker functions as a heterotopic automation center.

32 Schrader, J., Gödecke, A., Kelm, M.: Das Herz. In: Pape, H.-Ch., Kurtz, A., Silbernagl, S.: Physiologie. Thieme-Verlag (2014), S. 171-212.

Each of these hierarchically structured pacemaker centers generates quasiperiodic electrical signals in the form of limit cycles. These attractors are coupled to further attractors, so that a dynamic complex system of a network of interpenetrating attractor patterns is created. This system, which consists of attractors of different periodicities, guarantees functional integrity that lasts for decades and an incredible ability to adapt to changing stresses on the heart – from a quiet nap on the sofa to an ultramarathon run. The sinus curves of the approx. 60-80 electrical excitations per minute never show exactly the same frequency; it is always the well-known quasi-periodic oscillation and contraction patterns that maintain dynamically stable and yet responsive system states on the edge of chaos. In this respect, the pulse beats palpable at the neck or at the wrist are never stereotypically the same. Rather, pulse waves that are stereotypically always palpable in the same way may indicate a disease of the cardiovascular system.

2.3 From mathematical models to a deeper understanding of the dynamics of diseases

We tried to illustrate the role of limit cycles, specific forms of attractors, in the circadian rhythms of different systems in the organism. Boundary cycles, i.e., attractors, play an essential role wherever it is a question of maintaining dynamic non-equilibrium states that are adaptable to different requirements.

On a dynamic systemic approach, innumerable attractors of different patterns interpenetrate in the functional networks of both the healthy and the diseased organism. Complex mathematical structures, even entire attractor landscapes, emerge from the interaction of these manifold dynamic patterns. These show similar forms and pattern formations from person to person but are individually different. One could imagine the organism as a tremendously complex structure of countless attractors, and dynamic pattern formations, interacting with each other. These patterns change their forms from moment to moment and yet in their totality, they represent the unmistakable identity of an individual. The attractors interact at all levels and stages of the organism, starting with the networks of proteins in the cells, through the organs, to the interaction of these organs and systems in the organism as a whole. A healthy organism is based on the stability and flexibility of its fluctuating equilibrium states at all levels, from the organs down to the molecular networks of proteins and genes. These equilibrium states must be robust and stable against disturbing external influences on the one hand and at the same time functionally adaptable to changing conditions.

We tried to show that the different states a system can assume in the course of time can be mapped point by point onto trajectories. In quasi-periodic systems, these trajectories return to the vicinity of their starting point, thus forming quasi-cyclic loops.

We know a whole series of such quasi-cyclic disease patterns. We have mentioned some of them. According to Virchow's cellular pathology, diseases originate at the level of the cell and no longer in a defective mixing ratio of the body fluids. However, diseases and courses of diseases are not only characterized by their cellular or molecular biological abnormalities, rather the dynamics of their course marks an additional and intrinsic feature of diseases. Just as in the technical disciplines of science or especially in meteorology a multitude of different patterns of attractors are mathematically modeled, more detailed attempts at mathematical modeling of the various disease patterns could prove fruitful for medicine. After all, such models contain a direct, pictorial visualization of the dynamics of a disease process. This could possibly deepen the understanding of diseases.

2.4 Complex Regulatory Systems in the Organism

2.4.1 Remarks on the Circulatory System as a Complex Control System

The interaction of the functional components of the circulatory system is ensured by complex control systems: The functional principles of the circulatory system and the interaction of heartbeat with the peripheral vascular system under the influence of nervous and hormonal effectors are discussed in an excellent, expert and scientifically exhaustive textbook of physiology by Pape et al. with rich illustrations. It is also very edifying for a physician who has been working as a clinician for many years to hold such a fact-rich yet fluently written textbook in his hands.[33] At rest, the heart transports between 2.8 and 4.2 liters per minute through the large circuit between the left ventricle and the right atrium. The same amount of blood flows through the small circuit between the right ventricle and the left atrium. The vascular system comprises a blood volume of about 5 liters. In diastole, i.e., the flaccid phase, the heart withdraws about 70-80 ml from the veins near the heart and pumps it back into the arteries with each systole, i.e., with each heartbeat, whereby the pressure in the arteries rises to over 100 mmHg. This high pressure is a consequence of the low distensibility of the arterial walls and the high flow resistance in the peripheral sections of the vascular system. The used blood finally enters the venous system via the vessels with the lowest caliber in the peripheral exchange system, namely the capillaries, which supply the tissues with oxygen and nutrients. At this capillary exchange level, the vascular tree branches out and multiplies its surface area up to 1,000 square meters! This area, which is extremely important for the exchange of nutrients, is 500 times larger than the surface area of the body. Ohm's law of physics applies to the flow conditions of blood in the vascular system, according to which the blood ejected from the heart flows through the resistance of the peripheral vascular system as a result of the pressure difference between the arterial and venous systems. According to this law, the flow time volume increases with the pressure difference between the arterial and venous system and decreases with the flow resistance. Short-term regulation of arterial blood pressure occurs via circulatory reflexes that are neuronally triggered and follow the principle of negative feedback. Baroreceptors, nerve pressure transducers, play an important role in this process.

These baroreceptors are located in the area of the so-called carotid sinus, i.e., at the dividing point of the great carotid artery and close to the aortic arch, whereby their free nerve endings lie in the layers of the vessel walls and can thus be activated by the dilatation state of the vessels. They are therefore located directly on the arteri-

33 Pape, H.-Ch., Kurtz, A., Silbernagl, S.: Physiologie. Thieme-Verlag (2014), S. 171-212.

al high-pressure system, and they have an inhibitory effect on the sympathetic autonomic nervous system. In these stretch receptors, the most important physiological parameters of cardiac function, such as heart rate, cardiac output, and mean arterial pressure, are registered, encoded, and transmitted to the central nervous system. Acute blood loss, for example, results in a drop in blood pressure. This drop in blood pressure is registered by the aforementioned baroreceptors and transmitted to the brain via several circuit relays. From there, the peripheral sympathetic tone is reflexively activated, resulting in an increase in the frequency and stroke volume of the heart and an increase in peripheral resistance. This reflex arc enables rapid and controlled counter-regulation in the event of a short-term drop in blood pressure.[34] In the case of permanent changes in blood pressure, for example in hypertension, the baroreceptors adapt to the new blood pressure level. The system thus readjusts its control variables. In the language of synergetics, the system adapts to new order and control parameters in this way. Changes in control variables, and changes in control and order parameters can result in illness, in the case discussed, hypertonia, i.e., permanent high blood pressure.

Other systems are involved in the regulation of blood pressure, which cannot be discussed further here. For example, kidney function, salt and water balance, and a multitude of other hormonal factors play an important role.

2.4.2 Homeostasis and the Role of Feedback Mechanisms in Complex Regulated Systems of the Organism

The term “homeostasis” refers to the maintenance of a stable internal environment in the body. Homeostasis is maintained by complex physiological control and regulatory systems that function on the basis of response and feedback loops.

In its simplest form, a control system consists of three components:

1. input signal
2. controller
3. output signal

The controller is programmed to receive, process, and respond to signals. In the language of synergetics, such a control system monitors the regulated variables or controlled variables, which according to Hermann Haken are referred to as order and control parameters.[35] However, physiological control systems in the organism are far more complex than the three components of a simple control system mentioned above: The input signal is the value of a controlled variable that is registered by a sensor or receptor. If the actual value of the controlled variable is too far from the setpoint or if it moves outside the permitted range, the sensor is activated, which sends a signal to the controller. In the controller, the incoming data are processed and evaluated with regard to their significance. A corresponding response signal is then transmitted. This signal alters physiological processes with the aim of readjusting the controlled variable to the permitted values within the range of the setpoint.

34 Ehmke, H.: Das Kreislaufsystem: In: Pape, H-Ch., Kurtz, A., Silbernagl, S.: Physiologie. Thieme-Verlag (2014), S. 214-265.

35 Haken, H.: Erfolgsgeheimnisse der Natur. Synergetik: Die Lehre vom Zusammenwirken. Rowohlt-Verlag (1995). Haken, H., Haken-Krell, M.: Entstehung von biologischer Information und Ordnung. Wissenschaftliche Buchgesellschaft (1989).

Nerve cells usually serve as controllers or data processing centers, but endocrine cells, i.e., cells of the immune system, also play a role.

Walter Cannon, one of the fathers of American physiology, observed in the 1920s that the same chemical signal could produce different effects in different tissues, and he concluded that "homeostatic agents can have antagonistic effects in one area of the body while acting cooperatively in another".[36]

Feedback means that the result of a chain of events with causally linked effects is transmitted back to its starting point and fed in there or, more simply, that the control of a system is modulated by feedback about the current state. The advantage of this type of control is that unexpected disturbance variables can be taken into account in the control process. Another advantage is that the components of the control system can work somewhat inaccurately without missing the setpoint (at least on average).

In the organism, it is not only simple variables that are controlled, such as blood pressure, the pH value of the cell, the glucose concentration or other metabolic parameters in the blood or muscle length. Complex processes, such as pregnancy, fertilization, the growth of an embryo or fetus, organ differentiation, food intake and digestion and, last but not least, the reception and processing of sensory stimuli as well as the motor activity of the musculature as a whole, are also subject to strict control mechanisms. Control processes can last only milliseconds, as in the case of a specific movement, but they can also take many years, as in the case of growth, for example. Feedback loops can have an activating or inhibiting effect on a chain of events.

How successfully a system maintains its state of homeostasis depends primarily on the sensitivity of the system. In the process of negative feedback, the controller keeps the actual value as close as possible to the setpoint. However, if disturbance variables repeatedly cause deviations, negative readjustments can be triggered in the opposite direction, so that wave-like fluctuations of the actual value around the setpoint can be observed. If disturbance variables occur suddenly and abruptly, the deviations can be particularly severe in response. In a stable system, however, they soon subside again.

Negative feedback loops have a homeostatic effect, i.e., they support the system, stabilize the regulated variables and they maintain homeostasis.

In oncology, especially in the field of cell kinetics of malignant cell clusters, such inhibitory and stabilizing feedback loops are disabled by the omission of the so-called contact inhibition. As a consequence, the growth and cell division behavior of these degenerated cells becomes increasingly rapid and chaotic.

Positive feedback loops, on the other hand, do not have a homeostatic effect. This is because their response still reinforces the original stimulus. As a result, the value of the regulated variable moves even further away from the setpoint. This triggers a control loop in which the reflex response becomes larger and larger, and the system can eventually get completely out of control. In a positive feedback mechanism, which is rather rare in biology and medicine, we are dealing with mechanisms of self-reinforcement. An example of such positive feedback and self-reinforcement is the depolarization of a nerve or muscle cell. Here, the permeability of the cell membrane for Na+ ions (sodium) is increased. The resulting increased Na+ influx

36 Cannon, W.: Organization for Physiological Homeostasis. Physiological Review (1929): 9:399-443.

depolarizes the membrane further and further.

We are all familiar with the patellar tendon reflex as an example of a simple feedback mechanism: the physician strikes the patellar tendon which lies below the kneecap with his reflex hammer and thus triggers a stretching stimulus. This stretch stimulus leads to an elongation of the tendon and muscle. This signal is transmitted via sensitive nerve pathways to the spinal cord, which acts as a regulator. From there, an output signal is sent via motor nerve pathways to the periphery, i.e., to the quadriceps muscle, which responds within fractions of a second with a muscle contraction.

Feedback mechanisms are therefore active at all levels of the organism: from the level of genes and proteins to the level of the cell via the organs to the complete organism. The accelerated growth behavior of a malignant tumor can thus be understood as a consequence of insufficient feedback loops. Feedback processes also play an important role in the transcription of information on the DNA, whereby the proteins formed in the course of the reading mechanism can have an inhibitory or activating effect on the DNA.

Disturbances within the regulatory systems are often causes of diseases:

Elevated morning fasting blood glucose levels indicate defective regulation of glucose metabolism. After a carbohydrate-rich meal, the blood glucose level rises physiologically and sends a signal to the insulin-producing cells of the pancreas. In the regulator cells of the pancreas, the current blood glucose levels are registered and compared with the current state of metabolism. As a result of this evaluation, a signal is sent out to release the hormone insulin. Under physiological conditions, the amounts of insulin secreted are fairly closely matched to the glucose concentrations in the peripheral image. Insulin promotes the uptake of glucose into muscle cells. This is followed by cascade metabolism of the glucose molecules. These are degraded to CO^2 and water, producing energy-rich phosphates ATP (adenosine triphosphate). Adenosine triphosphate, ATP, is a central energy supplier of the cell.

A counterpart of insulin is the hormone glucagon. Both molecules oscillate in their own cycle in the cell depending on the energy demand: If the glucose level in the peripheral blood drops too much, the pancreas secretes the hormone glucagon which acts antagonistically to insulin and ensures an increase in the blood glucose level. This hormone is responsible for the adequate supply of sugar to the cells. It stimulates the release of sugar molecules from the glucose stores of the cells. The hormones insulin and glucagon, which act antagonistically to each other, thus ensure in feedback loops that the concentration of glucose in the peripheral blood always remains within a physiological range. In reality, however, the situation is far more complex since a large number of other factors are involved in regulating blood glucose levels:

In so-called juvenile diabetes type 1, the hormone insulin is missing and must therefore be supplied by insulin injections. In type 2 diabetes, sufficient insulin is still present in the early stages. In this case, there is insulin resistance, i.e., the insulin cannot dock at the insulin receptors of the cells and pass on the signals from there for the uptake of sugar molecules from the blood into the cells. In the case of insulin resistance, a precursor to diabetes, an important control loop is therefore disturbed: The input signal "increased blood glucose levels" should physiologically be followed by an output signal "increased uptake of glucose into the muscle cell", but this does not happen in these cases. This paves the way for manifest diabetes if insulin resistance persists.

The first step in the regulatory mechanism is therefore always the activation of a receptor. Receptors are often complex proteins on the cell membrane or inside the cell. For example, chemoreceptors register the pH value. Osmoreceptors register osmolarity. The thermoreceptors as temperature sensors or the baroreceptors as pressure sensors should be mentioned. The proprioceptors which register the relative position of the body or body parts in space are also important. Finally, the mechanoreceptors for pain, vibrations, or touch should also be mentioned. All these sensory receptors are programmed for a certain threshold value. This refers to a minimum stimulus intensity that must be exceeded to trigger a reflex or a stimulus response.

2.4.3 The Acid-Base Balance as an Example of a Regulated System

The maintenance of a precisely adjusted acid-base balance is decisive for the global balance of the organism. This balance must be within very narrow limits because most of the biochemical processes of life, such as the kinetics of enzymes or the signal chains for intra- and extracellular communication, can only take place within a precisely adjusted pH range. The proton H+ plays an important role in the chemistry of the acid-base balance although it is the cation with the lowest concentration in the extracellular fluid. Acids can release H+ ions. Bases take up H+ ions. The pH value indicates the strength of an acid or base and corresponds to the negative decadic logarithm of the proton concentration. In healthy individuals, the pH value in arterial blood is 7.40 with a narrow physiological fluctuation range of ± 0.03 to ± 0.05 units. The pH of arterial plasma thus lies between 7.37 and 7.45. A lower value is referred to as acidosis, and a higher value as alkalosis. The bicarbonate and phosphate buffers act as physiological buffers.

Both strong and weak acids occur in metabolism: HCL (hydrochloric acid) is a strong acid that is formed in the stomach. H2SO4 is formed during the oxidation of the SH-groups of the amino acids cysteine and methionine. Weak acids include, for example, pyruvic acid which is formed when sugar is metabolized, and fatty acids which are formed when fat is burned. Strong bases are normally absent from the metabolism. Among the most important bases are bicarbonate and ammonia which can bind an H+ ion. Some negatively charged proteins (albumin, hemoglobin) can also accept protons. They are therefore counted among the weak bases. Protons in very low concentrations exert important influences both inside and outside the cell on enzymes, receptors, and on the ion channels in the cell walls: A chemical reaction of ions with amino acids, for example, leads to a change in the electrical charge and consequently to a change in the electrostatic attraction of individual protein sections. This in turn leads to a change in the shape and thus also the function of the entire molecule.

Similar and quite comparable processes take place at the ion channels of the cell walls: Glucose (sugar) is degraded in the so-called citrate cycle to pyruvic acid in the form of energy-rich phosphates. In the case of insufficient oxygen supply, for example under heavy muscular strain during sport, this pyruvic acid can no longer be completely consumed, and lactic acid is formed. This dissociates into H+ ions and lactate ions. As a result, intracellular acidosis sets in. In turn, the cell tries to release