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Disease Entities and Open Systems

Abstract

The so called mechanical world view outgrew Aristotle's interpretation of biological nature. However, today it becomes more and more obvious that the reductionist methodology leads to anomalies when applied on living systems. When we consider open systems which exchange matter and energy with the environment and maintain en extend their own organization, it becomes relevant to return to the old Aristotelian concepts. By way of examples from chemistry, biology and physics it will be demonstrated how such systems can develop into highly organised objects which require an Aristotelian description to be comprehensible. Such Aristotelian descriptions can be given a precise mathematical formulation by applying and extending modern non-lineair dynamic system theory.

Introduction

Man is a complex physio-chemical machine and human diseases may be considered as faults in this machine. Such faults in the human machinery, like those in machines constructed by ourselves, may be caused by defective constructions, by the influence of the environment or by wear and tear[1]. It is possible to define causal chains which lead from external factors to internal defects which in turn lead to observable symptoms. The physician is the service mechanic who is able to identify the faults and to restore the normal functionality of the machine. A good physician must have a deep knowledge of the human machinery, he must know its structure and functionality, and he must know about the kinds of load and strain that influence it and may threaten its stability.

Much of the progress of modern medicine is due to this mechanical picture of biological organisms. It is a simple and powerful analogy which has not yet been completely exhausted and probably never will because it is

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1. See Henrik R. Wulff: The disease Concept and the Medical View of Man. This Volume.

being continuously transformed and refined. In the 17th century when the mechanical world view appeared the machine concept was rather crude. Descartes, for instance, compared biological organisms with the beautiful fountains that could be seen in Parisian parks. The machinery involved was completely mechanical and could be described by Descartes' own physics. Today we know much more about mechanisms. We know that not only gravitational forces are involved. Since the formation of the mechanical world view we have achieved a deep understanding of nature on the atomic and molecular level and we are able to construct machines that are so complex that it is hardly possible to predict their behaviour. The machine metaphor of modern medicine is much more complex that the primitive ones used by iatrophysicists in the 17th century.

In spite of the fact that the mechanical conception of disease has been continuously refined and, as a consequence of this, is still a very productive and fruitful theoretical framework we have the feeling that it in some serious sense is defective, that it gives us only a rather limited view of the nature of human diseases. Furthermore, one may also argue that this inadequacy cannot be repaired by considering more and more complex systems of the same nature. It is not only a question of complexity, it is rather a question of our conceptual framework which in a sense leaves something important out of sight.

It has been argued by many writers that what is missing in our mechanical disease concept is the notion of homeostasis. Endocrinologists and experts in many other fields use this notion, and it is evident that the related concepts of self-regulation and stable equilibria are important. But these concepts can and have be added in a natural way to our ordinary notion of a mechanism. They do not in themselves lead to a new view of biological organisms. A deep study of self-regulating system was initiated by the English physicist James Clerk Maxwell in the last century. In his work on the stability of Saturn's rings and later in his important paper "On Governors" Maxwell developed the mathematical ideas which later led to modern control theory[2]. At the time when Maxwell wrote his paper mechanical engineers were well aware of control theoretical problems and they were familiar with many examples of control devices, the most important one being the centrifugal regulator of steam engines.

A steam engine equipped with a centrifugal regulator (figure 1) is a self-regulating system. When the load on the engine is increased a message is sent (mechanically) to the regulator which adjusts the valves of the engine and its power is increased. Maxwell introduced the concept of stable regulation in a precise mathematical way and he determined the conditions under which the

2. The earliest known device for feedback control is a float regulated Greek water clock from the third century B.C. But a theoretical understanding of such mechanisms had to wait until the works by Maxwell and others in the middle of the last century.
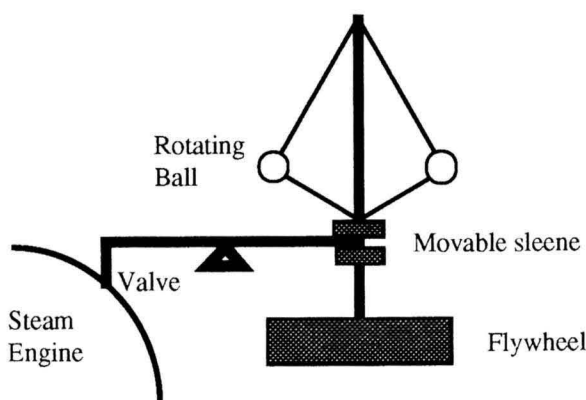
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Rotating Ball

Movable sleene

Valve

Steam Engine

Flywheel

Figure 1

governor regulation was stable.

Modern regulators are much more complex and elegant than the governor. In addition to mechanical signals it is possible to use thermal, chemical, electrical and many other forms of signals. Modern computer technology has made it possible to put low cost electronics and thermal regulators in houses, cars, power plants and human bodies. Control theory is a well-understood and mature scientific field which makes it possible for us to construct complex machines and devices. In this field notions like self-regulation, homeostasis and equilibrium are well-defined terms and they have been so for a rather long time. The field has matured since Maxwell's famous papers and today advanced control theoretical methods are applied in all technological fields. Control theory leads to a natural extension of our machine concepts. Advanced machines are self-regulating and tend to restore their state of equilibrium when they are disturbed. The car regulates its temperature within some normal limits during even excessive driving, the power plant produces electricity at a voltage level which lies within narrow limits. In a similar way heart rate, body temperature, blood pressure, and many other biological parameters are all kept within natural limits by biological regulators. A fault in the machine may as well be a defect regulator as a broken pipe line. All this is, or should be, old knowledge. The concept of homeostasis and other control theoretical notions are important and indispensable terms in a modern definition of physical as well as biological mechanisms.

Control theory leads to a natural extension of the mechanical models of disease. Complex machines as well as biological organisms contain many different kinds of interacting components or organs. They all serve different purposes, they regulate, store energy, transfer signals, etcetera. By this co-operation of a huge number of organs the whole system is kept close to a

state of equilibrium. Power plants and biological organisms are designed in such a way that they are able to cope with all kinds of threatening influences from the environment. Under normal working conditions they will stay close to their normal level of functioning and, in virtue of that, serve their ultimate purpose being it energy production or survival of the species. Only in extreme situations when influences from the environment exceed usual levels will the system, or the organism, break down.

Modern man-made machines are designed to work within certain natural boundaries, they are self-regulation systems which have a characteristic level of normal function and by modern scientific analyses it is possible to describe precisely how the system will behave in a neighbourhood of this stable state of normality. By analogy biological organisms may be understood as self-regulation systems which are able to restore their normal level of function when exposed to minor disturbances. As we do not know the design of biological systems it is part of biology to develop an understanding of nature's design, or to express it in another way, to define levels of normal function of biological organisms and organs. With such definitions available it may be possible to define disease entities in control theoretical terms. This does not by itself lead to any new conceptual framework.

A pre-mechanistic view of nature

A good way to get an idea of the limitations of our modern mechanical conception of biological organisms and related notions such as the disease concept is to go back to a pre-mechanistic view of nature. In the writings of Aristotle we find such an anti-mechanistic and also anti-reductionistic interpretation of biological nature. His main metaphor was not a mechanical device as Descartes' fountains which worked according to mechanical laws. Contrary to this reductionistic picture he focused on how biological organisms, say plants, developed and changed their forms according to a plan. For him changes were not only movements from one location to another. It also comprised changes from one structure to another one, as when seeds develop into plants. This is an important point. Modern natural science does in fact also describe how systems develop in time. If a governor regulated steam engine is pushed to increase its power the regulator will open its valves and it will slowly restore the normal level of function. This process in time can be described precisely in control theoretical terms. It is even possible to calculate the time it will take the system to return to normality. But during this process the system has maintained its internal structure. The laws governing it during the external strain and after it has returned to normality are the same. It is not this kind of changes Aristotle has in mind when he discusses how a seed develops into a plant or how bronze is transformed into a statue. Changes may be qualitative as well as quantitative. Some qualitative changes are of a very radical nature. When an organisms

dies or is born its internal structure is completely changed. Using a term from modern physics, we may characterise such changes as *symmetry breaks*. Symmetries characterising the new system are completely different from those characterising the old one.

According to Aristotle we need several notions of change to describe natural processes. But in modern natural science there exists only one kind of change which we can define precisely, namely *locomotion*. This was also the view of Descartes who claimed that all natural processes could be reduced to the interaction of corpuscles and it is true of modern physics where motion in space has been generalised to motion or action in phase spaces. Modern science is reductionistic in the sense that it tells us next to nothing about qualitative changes. It does not say much about what is going on when a substance goes from solid state to fluid form, or when a fluid goes from laminar to turbulent flow, or when a human being goes from a state of health to a state of serious illness. It is true that modern physics is able to specify conditions under which a flow will become turbulent or the behaviour of a mechanical device will be chaotic. But it does not tell us much about what actually is going on when these conditions are met. It is possible to describe the structure before the symmetry break and the structure after, but the process of transition and the states between the two new relatively stable structures are not well understood by modern science.

Aristotle did not give us any useful clue that might lead to a better understanding of the process of structure change or symmetry break. But we can learn from Aristotle to raise that question again and he also introduced some abstract philosophical terms which might guide us. A main task of Aristotle's philosophy was to describe qualitative and substantial changes as we see them in our daily life. To accomplish this he introduced some important distinctions, namely the distinction between *matter and form*, and between *actuality and potentiality*.

All existing mundane substances (e.g. plants, statues and human beings) consist of matter as well as form. A bronze statue is a piece of bronze with a certain form. It can be deformed into a circular container and thereby it ceases to be a statue. The same matter can be changed into many different forms and in that way be brought to serve quite different purposes. In a similar way a fluid can go from a laminar to a turbulent state of flow, or a human cell can change from a natural to a malignant state. By this transition the characteristic properties of the subject are being radically changed. The matter is not changed essentially but the form and thereby also the function is modified in an essential way. The subject has some potentialities related to its form and matter. These possibilities can be actualized if the subject is exposed to the right influences, or they may never be actualized if it is not effected in the right way. Substantial changes of a substance are of this form. It realizes some of the potentialities that are built into it. This kind of change

is entirely different form locomotion and, as mentioned above, it has not been given much attention in modern natural science.

Modern control theory has a lot to say about how to regulate a system when it is sufficiently close to an equilibrium. But it is almost silent when the system approaches a critical area of instability. In some sense this is strange because – as Aristotle's philosophy shows – many ordinary situations which are of greatest importance to us are in fact critical and unstable situation. This is the case with phenomena such as birth, death, outbreak of diseases, unfolding of flowers, etcetera – all symmetry breaking phenomena which constituted the prototypical examples for Aristotle. Aristotle gave a qualitative description of such structure shaping phenomena and he rightly emphasized that the laws that govern the process should be found in the structure of the systems under transformation. We need a quantitative theory of these phenomena.

Macroscopic changes in open, non-lineair systems

A first important observation is that these transitions from one kind of symmetry to another one are *macroscopic* properties of the system. It is the whole organism that becomes ill, it is the whole seed grain that is transformed into a whole plant, etcetera. It is true that human beings, plants, fluids, etcetera all are systems consisting of molecules, but the transitions from one structure to another cannot be defined on the microscopic level. It is a joint venture of the whole set of molecules. A rather trivial example is the emergence of convection patterns in a fluid which is placed between two plates with different temperatures.

If the plates have the same temperature the fluid will be homogeneous. One will not be able to differentiate between different locations within the fluid. But when the temperature of one of the plates is raised a very characteristic macroscopic structure will emerge. A characteristic convection pattern will suddenly appear (figure 2). If the temperature difference of the
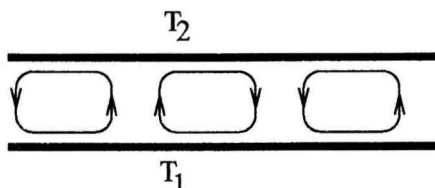

Figure 2

plates are kept constant this pattern will remain unaltered. At the global macroscopic level the system has changed radically, a new global symmetry has appeared. It is evidently impossible to discover these convection patterns by studying isolated water molecules. This pattern is due to the global

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interaction between molecules, and it is not a linear superposition of properties of water molecules. This transitional process from a homogeneous fluid to a fluid with a very regular convection pattern can only be described by applying macroscopic variables.

Another well-known hydrodynamical example is the transition from laminar to turbulent flow. Consider a viscous flow that passes a cylinder. When the Reynolds number increases the symmetry of the flow will change from laminar to various kinds of non-laminar flows (figure 3).

R = 0.01

R = 20

R = 100
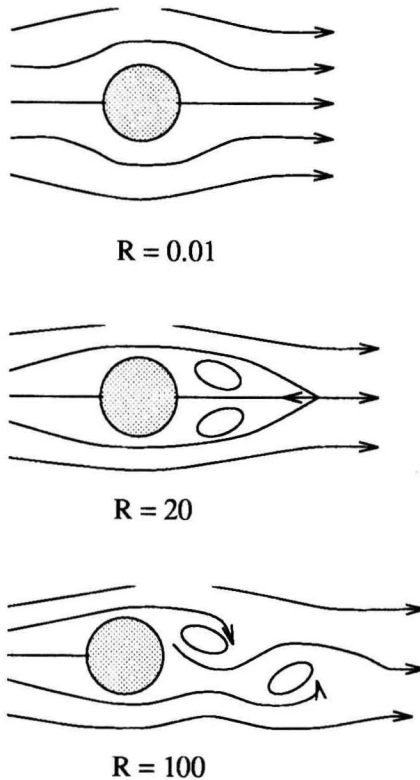
Figure 3

The flow is characterised by four macroscopic parameters, namely density (r), global velocity in front of the cylinder (V), diameter of cylinder (d) and viscosity (m). The relationship between these parameters defines the symmetry of the system. With respect to turbulence the Reynolds number

$$R = \frac{\rho \cdot V \cdot d}{\mu}$$

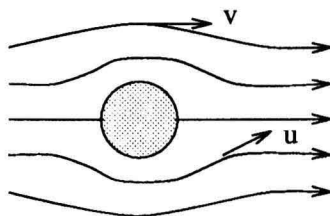is important. Its value determines the type of the flow.

Figure 4

A flow is a complex dynamical system that can be characterised by a vector field which varies with time. That is, we describe the flow by placing a velocity vector at each point in the fluid at a given time (figure 4).

The time variation of the vector field is described mathematically by differential equations in which the parameters r, V, d, m appear as characteristic macroscopic constants. A very large group of interesting physical, chemical as well as biological systems can be described in this way.

The pattern should be clear: the main symmetries of a system are defined by a set of macroscopic parameters. If these parameters are changed the system may suddenly break its symmetry and go from one characteristic structure to another one as when convection patterns or turbulence emerge in a fluid. At least at a phenomenological level the situation in medicine is similar. A healthy organism has a characteristic structure or, depending on our level of description, a hierarchy of structures (symmetries) which in some cases may be characterised by parameters. If these parameters are modified too much some of the symmetries may break down and the organism will develop a disease. The question we must pose is: Will it be possible to develop a satisfactory theory of these transitions? The modern theory of complex dynamical systems has produced results and concepts which might lead to a positive answer.

Another important feature of our examples is the fact that they are open systems. The convection pattern would disappear if we did not maintain a temperature difference between the plates, and the periodic turbulence would change if the Reynolds number were increased. We must supply the systems with energy or matter. Although the systems are in relatively stable states they would be destroyed if their energy and matter supply were stopped. In a similar way a biological organism would die if its food supply were cut off. So, the group of systems we are dealing with are *open systems far from equilibrium*. Furthermore, they are often *strongly non-linear* which among other things means that the principle of superposition does not in general hold[3]. A consequence of this is that properties of subsystems do not

3. For a further analysis of such systems see, for instance, Grégoire Nicolis, Illua Prigogine: *Exploring Complexity.* W.H.Freeman and Co, New York 1989.

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add up to properties of the whole system. Such systems are capable of changing their internal structure when exposed to certain environmental influences.

Open non-linear systems far from equilibrium have not been studied nearly as thoroughly in classical natural science as closed systems and they possess properties which in some sense contradict well established laws that hold for isolated systems. As they are open the second law of thermodynamics does not generally apply. Such systems can in certain situations decrease their entropy. The emergence of convection patterns is an example of this. Let S_{eq} be the entropy of a system in equilibrium, and let S be the entropy in some other state. Then the excess entropy

$$\Delta S = S - S_{eq}$$

is negative and increases to zero as time goes to infinity. Mathematically this means that the equilibrium is asymptotically stable and constitutes a *global attractor*: independently of which state the system starts from it must eventually approach the state S_{eq} (figure 5).

State with Entropy S_1

State with Entropy S_{eq}

State with Entropy S_2
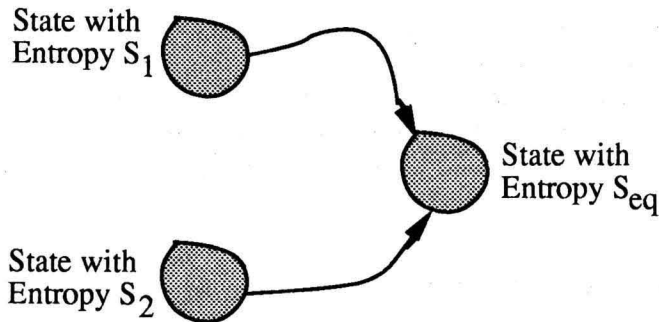
$\Delta S = S - S_{eq} \leq 0$ and $\dfrac{d \Delta S}{dt} \geq 0$, for isolated systems

Figure 5

Recall that according to Aristotle all mundane systems have some internal tendencies. Heavy systems will, if they are not supported, fall down in the direction of the centre of the Earth. Isolated systems are Aristotelian in the sense that if they are left to themselves, that is, do not exchange matter or energy with other systems, then they will approach the final equilibrium state with entropy S_{eq} and rest there for ever.

Another central Aristotelian claim is that subjects have certain potentialities they are able to realise if they are placed in the right environment. A seed grain will develop into a plant if placed in the right surroundings. It will actualise its internal potentiality. But it cannot change its species. Maybe

there are some degrees of freedom during the development, but it is not completely free to grow as it pleases and we can only to some degree influence its growth. It has some potentialities but not others. Open non-linear systems behave in a similar way. The fluid between two plates will necessarily develop convection patterns but it is free to select the orientation. In some cases the first cell in figure 2 will be clockwise in others it will be counter clockwise. But the system must realise one of the possibilities. It has no other choice (figure 6).
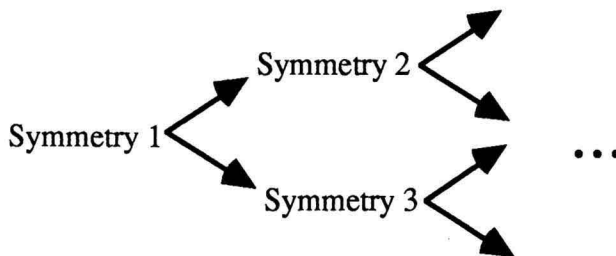
Figure 6

It will go from a state with only one possible symmetry to a state with two possible symmetries and when one symmetry has been selected it will stay in that state as long as the system is not disturbed too much. It is a locally stable state. This pattern of development into situations with more and more possible symmetries can be explained very nicely in the theory of complex systems.

Systems and irreversible changes

As our former examples show this tendency to bifurcate into systems with more and more possibilities is also related to the global parameters that characterise the system, for instance, the Reynolds number. Let us look at another example due to C. Zeeman[4]. As is well-known to you of course, the human heart is a pump which works in a specific way. Initially the pump is in a relaxed state, diastole. Then an electrochemical stimulus forces the its muscle fibres to contract and push out the blood. This starts slowly in order to ensure no damaging backflow. But suddenly, however, the fibres make one big contraction and thereby push most of the blood into the aorta. At this point the electrochemical stimulus ceases and the heart starts to fill again, first slowly and later quite rapidly. The whole process is repeated again and again. (figure 7)

We can develop a very simple model of this in the following way. Let x be a state variable which expresses the length of a heart muscle fibre, and let

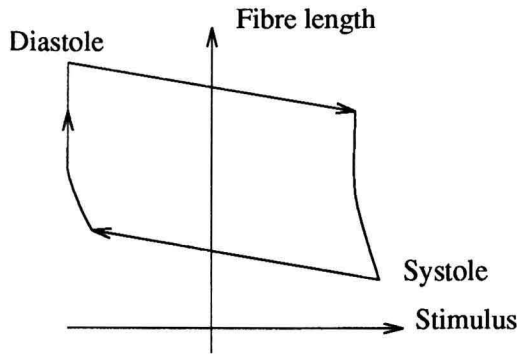4. C. Zeeman: Catastrophe Theory, Addison-Wesley, 1977.

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Figure 7

y be the stimulus. The time variation of these variables are interrelated in the following way:

1. The rate of stimulus change is proportional to the length of the fibre.
2. The rate of fibre change is negatively proportional to the stimulus and to its own length.
3. We need some un-linearity to take care of the sudden contraction and relaxation of the fibre.

These requirements lead to a system of equations of the following form:

$$x' = \mu[-y - (\frac{x^3}{3} - \alpha x)]$$

$$y' = \frac{x - x_0}{\mu}$$

These equations formalize how the change rates of fibre and stimulus are related to fibre length and stimulus. There are two parameters in the equations. The parameter a expresses the tension of the fibre, and μ is a kind of scaling. The equations have an asymptotically stable equilibrium in the point:

$$x_{eq} = x_0$$

$$y_{eq} = (\frac{x_0^3}{3} - \alpha x_0)$$

In order to understand how the relationship between fibre length and stimulus change in time let us look at figure 8 which gives the relationship between the variables x and y and the parameter a.

This surface actually passes through the (a,y) plane, but in order to make the figure more transparent we have lifted it a bit above the plane. When a is greater than zero the surface is folded such that a line parallel to the x-axis
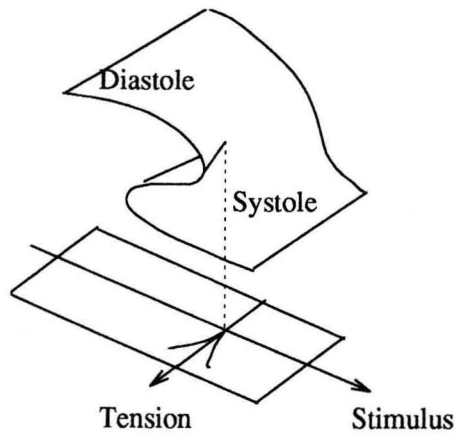
Figure 8

cuts it in three points, whereas it is not folded when a is less than zero. When a is big the distance between the upper and lower layer of the surface is big, and when a is negative there is only one layer.

The dynamics of the system is in an essential way determined by the shape of this surface which is called a *cusp surface*. When a varies from a negative value to a positive one the system's behaviour changes drastically. Consider the following (x,y) slices of the surface (figure 9).
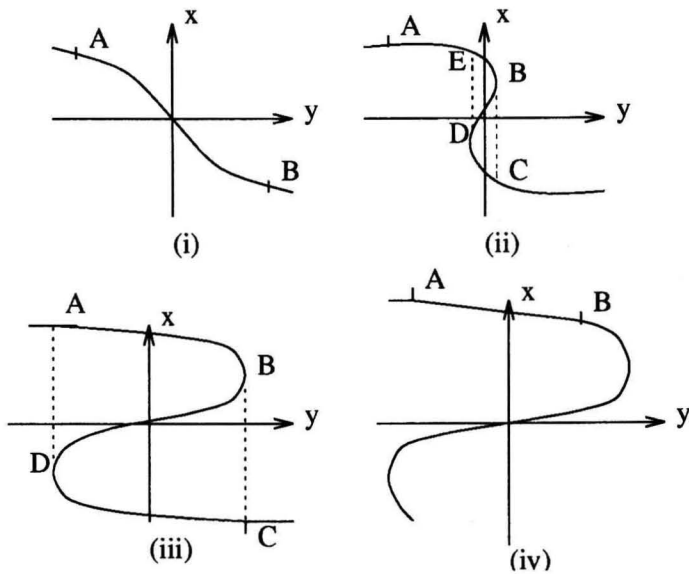

Figure 9

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Consider the case where a > 0. When x is on the upper branch of the cusp surface the stimulus increases until x jumps down on the lower branch. Then the stimulus decreases and x moves to the left until it jumps to the upper branch again. The whole process is repeated. The system performs a cyclic process again and again. This cycle process is stable in the sense that if the system initially starts a bit away from the cycle it will approach it in the limit. We call it a *limit cycle*.

When the parameter a is less than 0 the situation is quite different. The cusp surface only has one branch and x cannot jump. The heart cannot perform cyclic movements. It will approach an equilibrium and eventually stop. This is a general phenomenon which is typical for a very big group of dynamic systems depending on one parameter a (figure 10).
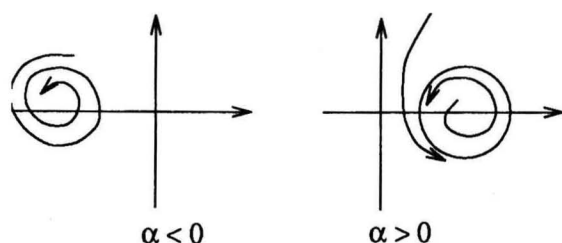

$$\alpha < 0 \qquad \alpha > 0$$

Figure 10

When the parameter is below a critical value the system has an asymptotically stable equilibrium, but when the parameter takes values above the critical value the equilibrium becomes unstable and a limit cycle appears. The amplitude of the limit cycle increases with the parameter. This is called a *Hopf-bifurcation*.

There are many other kinds of bifurcations , for instance, the *pitchfork bifurcation* where a stable equilibrium splits into two stable equilibria as the parameter a passes a critical value. In some cases one will observe more and more bifurcations as increases and, eventually, when a approaches another critical value the number of bifurcations will be infinite and the behaviour of the system becomes *chaotic* (figure 11).

These various possibilities can to some extent be classified by studying the global behaviour of the systems. So, modern global analysis of dynamical systems in a way gives flesh and blood to the Aristotelian claim that systems have some intrinsic potentialities which under suitable conditions may be realised. When a system in this way passes a critical value it grows in an *irreversible* way. It cannot turn back. The child cannot become a foetus again, the energy lost by friction cannot be recovered, and when a system has chanced from a stable state to a chaotic one its orbit in the past cannot be traced any longer. Consequently, the *direction of time* is important in these kinds of developments where the structural parameters of a system are changed. Time reversal does not in general make sense.
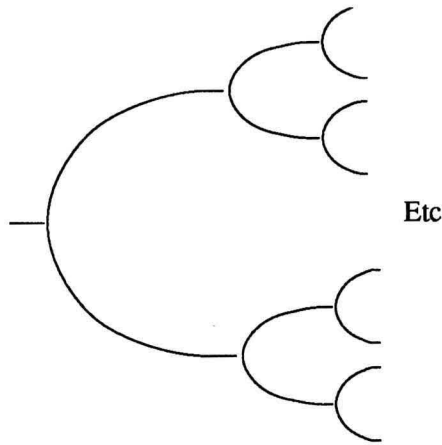
Figure 11

Unpredictable changes by a strange attractor

As we have seen dynamical systems behave in accordance which the Aristotelian claim. They have some inborn possibilities which are typical of their species. Depending of their relations to the environment they will realise some of these possibilities. They grow in a lawful way. A kind of growth which we are just beginning to understand. They may go from one stable state to another one but in some cases their behaviour may be chaotic. We observe chaotic behaviour all over the world and it is not necessarily an undesirable state, nor need it be unstructured. An interesting case is when a system oscillates between two attracting regions in an unpredictable way. To illustrate this first a couple of simple physical examples will be given and then, finally, we shall look at a medical application.

Consider a thin steel beam which is clamped in a rigid framework between two permanent magnets. When the beam is kept straight its distances from the magnets are equal (figure 12).
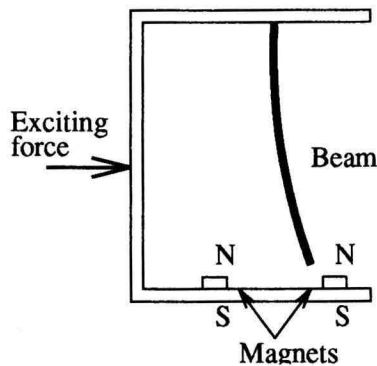

Figure 12

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When no external forces are present the beam settles with its tip close to one or the other of the magnets. There is an unstable central equilibrium position right between the magnets. But the slightest disturbance would cause the beam to oscillate and eventually settle down close to one of the magnets. Assume that the system is shaken periodically by an external force of the form:

$$b \cos \omega u$$

It can then be modelled by the following system of equations:

$$x' = v$$
$$v' = x - x^3 - av + b \cos \omega u$$
$$u' = 1$$

This system of equations is called the Duffing equations, named after G. Duffing who studied them at the beginning of this century[5].

We know that if the system is not disturbed there are three equilibrium positions of the beam. An unstable one right between the magnets and two stable ones close to one or the other of the magnets. But when the system is regularly disturbed it cannot settle down in any of the stable positions. It starts to oscillate between the attraction areas around the stable positions. It jumps back and forth between these regions in an unpredictable and chaotic manner (figure 13).
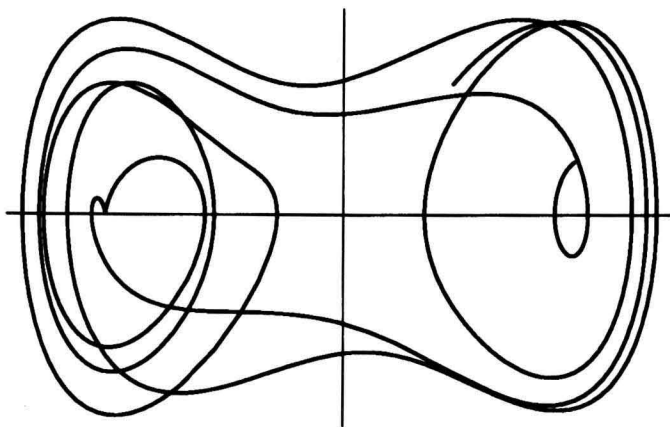

Figure 13

5. For a comprehensive discussion of this example see J. Guckenheimer and P.J. Holmes: Nonlinear Oscillations, Dynamical Systems and Bifurcations of Vector Fields, Springer-Verlag, New York 1983.

This is called a *strange attractor of the system*. The system is in fact behaving in a qualitatively predictable way as it oscillates around two stable equilibria, but its detailed behaviour is chaotic. It is impossible to predict when it will jump to the other attracting region and when it will leave it again.

Before we consider a medical application let us look at another strange attractor, the so-called Rössler attractor. The Rössler equations are the following

$$x' = -y - z$$
$$y' = x + ay$$
$$z' = bc - cz + xz$$

For the values a = 0.32, b = 0.3 and c = 4.5 of the parameters we observe the following chaotic attractor of the system (figure 14).
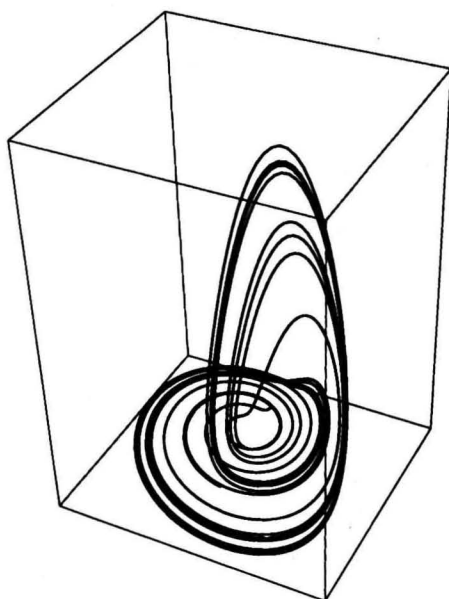

Figure 14

The system oscillates in an harmonic way but it is completely unpredictable whether it jumps or stays in the vertical plane. It the parameters are slightly changed the shape of the attracting region will change.

Medical application

Now to a medical application of chaotic dynamics. The following figure (figure 15) shows monthly reported cases of various childhood diseases in
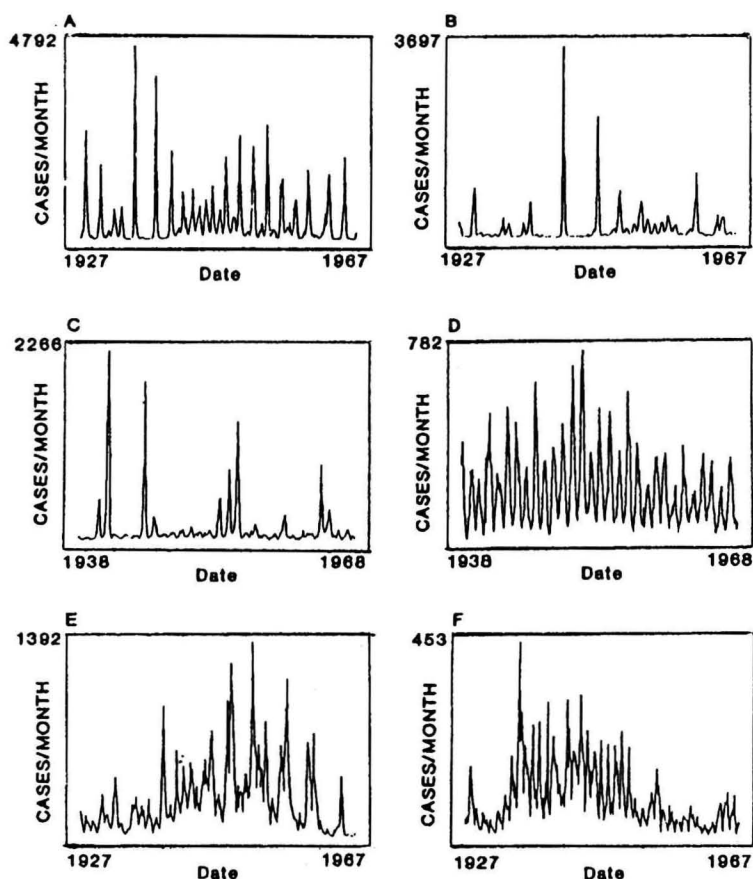
Figure 15

Denmark[6]. A is measles, B mumps, C rubella, D chicken pox, E pertussis, and F scarlet fever.

It is evident that the number of cases fluctuates in typically irregular ways which differ from one disease to another. Both frequencies and amplitudes vary with time. It is therefore natural to ask whether there is any underlying regularity in this variation or whether it is completely noisy. Let us look at measles and chicken pox. Let $I(t)$ denote the number of infected at time t. We plot the numbers $I(t)$, $I(t+T)$ and $I(t+2T)$ in a three dimensional co-ordinate system. T is 3 months. For measles and chicken pox we get the following diagrams (figure 16).

6. This and the following figures are from L.F. Olsen, G.L. Trutly, and W.M. Schaffer: Oscillations and Chaos in Epidemics: A Nonlinear Dynamics Study of Six Childhood Diseases in Copenhagen, Denmark, Theoretical Population Biology 33, 344-370 (1988).
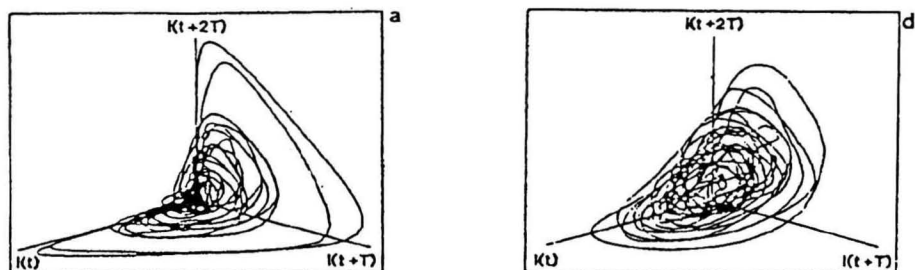
Figure 16

The measles curve looks very much like the Rössler attractor. Consequently, it is natural to expect that there is some kind of chaotic behaviour in the measles time series $I_m(t)$. The chicken pox curve looks more like a noisy limit cycle. This observation is further supported by constructing Poincaré sections and return maps.

A *Poincaré section* is a map of the intersection between the curve and some plane (or surface) that cuts all trajectories of the system. Such sections for the two diseases are shown in the next figure (figure 17).
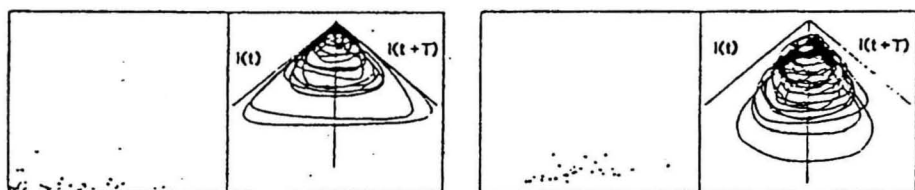

Figure 17

It is line like in the case of measles whereas it seems to be more space filling in the case of chicken pox.

Another technique to analyse the data is to construct *return maps*. That is done by plotting the position of the system after one cycle as function of its position at the beginning of the cycle. Return maps of measles and chicken pox are shown on the next figure (figure 18).

With some right one can say that the points of the measles return map seem to lie on a bent curve whereas the chicken pox map consists of randomly scattered points. This also supports the fact that the development of measles is governed by chaotic attractors while chicken pox corresponds to a noisy limit cycle oscillation.

It is not completely clear how these observations should be interpreted and the analysis is also problematic because, among other things, the random variables $I(t)$, $I(t+T)$ and $I(t+2T)$ definitely are stochastically dependent. Anyhow, there seems to be some deep difference between the dynamics of the two diseases which is worth studying further.
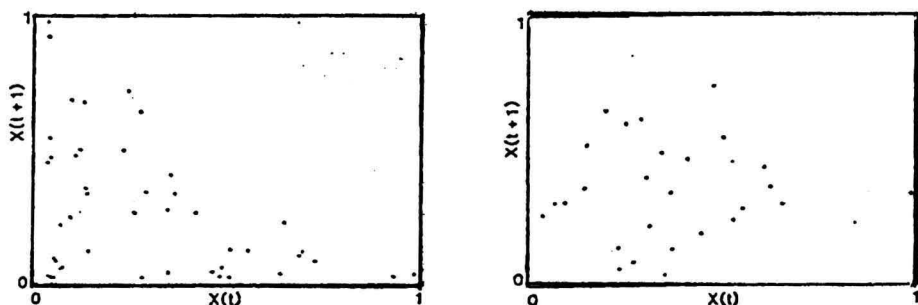
S.A. PEDERSEN

Figure 18

Conclusion

Let us now return to the disease concept. From what has been said it is evident that the mechanic conception of a disease entity is an extremely fruitful notion. Many diseases seem to have real essences in the sense of Locke. They are classified with respect to which sub-mechanism in the organism that is defect. The mechanism may be a homeostatic unit, a transmission line, an anatomical lesion, etcetera. The machine concept is a strong and useful metaphor and as the natural sciences develop the metaphor becomes richer and richer. Until now machines have mainly been considered as isolated system or systems not far from equilibrium. New developments in the theory of complex dynamical systems have made possible a beginning understanding of how open systems may undergo radical transformations. Usually, such transformations are irreversible and fundamentally new symmetries are created. In most cases it will be impossible to return to earlier symmetries in the same way as the newborn baby never will be a foetus again.

Breakouts of diseases are such irreversible, drastic and fundamental changes in the internal structure of the organism. Possibly, and hopefully, we might have reached a stage in the scientific development where we are able to transcend Aristotle and give content to his claim that systems or organisms have inborn potentialities. This might then lead to a better understanding of disease processes.