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Introduction

The broadest and most complete definition of Life will be – The continuous adjustment of internal relations to external relations.

Herbert Spencer

The truths of cybernetics are not conditional on their being derived from some other branch of science. Cybernetics has its own foundations.

W. Ross Ashby

Among the most fertile ideas introduced into biology in recent years are those of cybernetics … control theory obtrudes everywhere into biology.

Peter B. Medawar

THE DEVELOPMENT OF BIOLOGICAL CYBERNETICS

I watched a kestrel from a building high on the Citadel overlooking Plymouth Sound. It hovered at arms' length from the window in a stiff breeze, holding its position for long periods so perfectly that one could not detect the slightest movement of its head. To maintain this static hover, its wings beat quickly, varying a little in frequency and angle to adjust to the buffeting breeze, as it watched intently for any movement of prey on the ground below. It reminded me of Gerard Manley Hopkins' lines from his poem The Windhover: 'how he rung upon the rein of a wimpling wing'. Occasionally the bird sheared away: 'then off, off forth on swing'; to return again and take up its position as before, as if to dispel any doubts I might still have of its control in the air. 'The achieve of, the mastery of the thing!'

In the same way our control systems master the continuous variation in the environment in which we live, holding steady a host of different internal processes against the continuous fluctuation of external change. In warm-blooded creatures, control over temperature is within a degree of 37°C. The precise control over our internal temperature is just as astonishing as the kestrel's control of flight but, unlike the kestrel in flight, the continuous adjustment of temperature is invisible to us, and is therefore often overlooked. The kestrel hovers, its wings beating rapidly, its tail making continuous small adjustments, working hard to keep its eye steady for prey. But we are all but oblivious of the subtle and continuous adjustments of our own thermal regulation, through the many changes in temperature of a typical day; leaving a warm house on a winter's morning, or running to catch a train, or returning home and climbing into a hot bath. All these activities shift temperature from its preferred setting, and their effects are neutralised to keep internal temperature constant.

It is as if a guiding hand magically regulates the control of each process in the inner workings of the body. When applied to the hundreds, if not thousands, of control mechanisms, the effect can be called *The Wisdom of the Body* [1], the title given by Walter B. Cannon (1871–1945) to his account of the concept of homeostasis. His discovery of the mechanisms by which sugar and salt, temperature and oxygen are kept constant in the living body led him to the general principle that he called 'homeostasis'. This remains the single most important concept in our understanding of the physiology of animals and humans.

Yet it was the Frenchman Claude Bernard (1813–1878) who had earlier recognised the 'constancy of the internal environment' (see [2]), and his interpretation was more eloquent. He wrote that this equilibrium 'results from a continuous and delicate compensation established as if by the most sensitive of balances', with the consequence that 'the perpetual changes in the cosmic environment do not touch it; it is not chained by them, it is free and independent'. It is this meaning of homeostasis that we shall take from Bernard's writing, with an outcome that, significantly, has less to do with the constancy of control than the capacity to resist external variation. Throughout evolution, the gradual liberation of living organisms from their susceptibility to the continuous fluctuation of the major environmental variables has been made possible by their increasingly complex functionality. By such adaptations, their internal workings became protected more completely from everything that varies outside the body. Control mechanisms work continuously to achieve internal constancy by countering external change, just like the 'windhover' in a breeze.

Of course, both definitions mean the same thing, and the illusion of constancy obscures what must be done to achieve it.

PROCESSES AND THINGS

Some aspects of natural features in the world around us are more accessible than others. An oak tree is a large and immovable 'thing', with elements of which we are well aware: a trunk, branches and leaves. But 'processes' are less accessible, such as the rate at which water is transpired from roots to leaves, before being evaporated into the air. At any particular moment in time, an oak tree is perceived as a 'thing'; it grows slowly, and measurements are required over a long time period to determine its growth curve. Growth is a 'process', as it can only be measured with respect to the passage of time. So 'things' are tangible, but 'processes' are invisible and happen over time, and so are much less accessible. To access a 'process' requires that we make observations of a 'thing' at intervals over time, and make a graph of its progress with respect to time. We then draw a line between the points, and assume that interpolation can tell us what happened in the intervals between measurements. This involves an assumption, but we can make more frequent observations to give a more accurate depiction of the rate of growth, and so visualise the 'process' more clearly. After all, it is what organisms *do*, rather than what they *are*, that is more important, so the focus of our study should be change due to 'processes', rather than a static 'thing' approach. Conrad Waddington (1905–1975), the inspirational biologist, made a clear distinction between a 'thing' approach and a 'process' approach to understanding life, saying that the 'things' we see are simply 'stills' in a movie, which we can access in various ways [3]. To understand growth, we must turn changes in size or number into a movie.

The second problem in studying growth is that the agents of the control of growth are not well known. That is not strictly true because endocrinology is all about the agents of control, and we know that various hormones are involved in the control of growth. But the feedback mechanisms responsible for control consist of several essential components that include a sensor of the controlled process, an adjustable goal setting and a comparator where a sensed rate and the pre-set goal come together to determine whether there is an error. In those control mechanisms that are known and understood, the seat of control may take a lifetime's work to find and involve just a few cells. The organs of control are not like other organs; they are small, obscure and are not recognisable by what they do. This makes them extremely difficult to investigate. It took 70 years to discover the mammalian thermostat, and much painstaking research to understand its operation, once its seat was known.

Such difficulties legitimise another approach, which is to apply the principles of control theory and assume the minimal form that a control mechanism could take, given its output. It is then possible to create a hypothetical control mechanism that is able to account for the observed output. Then, by experimentally perturbing the growth process, various forms of behaviour become apparent. These can then be used as a basis for elaborating the form of the hypothetical control mechanism required to produce each new aspect of behaviour. So this has been the approach taken here to tell the story of growth as an invisible process controlled by inaccessible mechanisms.

CONTROL MECHANISMS AND THEIR ORIGINS

Maia is the story of an idea, and its development over 30 years, which provides a different approach to understanding the control of biological growth. Key to this approach is an experimental method of accessing growth control output which would be normal in control engineering, but is much less common in biology. To observe the output of a homeodynamic system when it is at rest is uninformative, because the controlled process or state is stable and constant. Perturbation is necessary in order to deviate the system from equilibrium and then observe the response of the control mechanism as it restores the equilibrium. Understanding then lies in interpreting the characteristic oscillatory output.

As already mentioned, a control mechanism has three basic components. The first is a goal, or preferred setting, that represents some ideal rate or state that is optimal for the organism. The second is a comparator by which the actual state of affairs in the present is compared with the goal setting. The difference between them constitutes an error. The third is the controller that provides the means of minimising the error. It is unclear how such a mechanism might have evolved, because the components are interdependent and it appears that none would have survival value on its own.

Homeostatic mechanisms have grown in number and complexity throughout evolution, giving mastery of the environment to those animals, such as the mammals, in which internal control is highly developed. It has enabled animals to withstand change, keeping processes constant; as steady as the eyes of the 'windhover', focused on its prey, before it plunges to the ground. Homeodynamic mechanisms control the inner workings of all organisms, from protozoans to mankind. The workings of a single cell are reputed to be regulated by a thousand control mechanisms, regulating the operation of the genome, metabolic pathways, osmoregulation and so on. But it is the increase in the number and sophistication of homeodynamic systems that enables the most complex organisms to become 'free and independent' of the changes around them. From the Khoikhoi in the tropics to the Inuit of the Arctic, the human brain is regulated at an equable 37°C. This trend of increasing freedom from environmental change is called 'anagenesis' and has been apparent for at least half a billion years: a driving force in the progress of evolution towards greater complexity and adaptive functionality.

Each cybernetic mechanism is defined by a goal setting, a preset state or rate or a set point. Its purpose for life is to maintain some state or process close to a setting. Each goal is an item of memory that is not necessarily stored in the brain, and is not simply remembered, but is referred to frequently to determine errors and maintain control. Control mechanisms are sometimes referred to as 'error minimisation systems', always working to reduce the difference between actuality and the goal setting. What is more, these goals are self-adjustable to meet increases in work load, adapting to change throughout the lifetime of the organism.

Together, the organism's homeodynamic goals constitute a diffuse body of extra-genetic information. Collectively these preferenda are life's purposes, providing the template by which an organism maps to its ever-changing habitats. It is this body of cybernetic information, and the mechanisms that continually refer to it, that fit an organism to its particular ecological niche and make its life possible. If one needs to reconsider the idea, one does not have to look further for a 'life force', for when prescribed preferenda, along with their coupled feedback mechanisms, no longer refer to their pre-set goals, there can be no life. What is curious, but completely understandable, is that evolution is blind and mechanistic, and so cannot create anything capable of meeting a future purpose; has it created myriads of homeodynamic machines that each incorporate direction, drive and future purpose? These are teleological mechanisms.

The science of control is cybernetics and all homeodynamic systems operate according to its principles. A.A. Lyapunov (1911–1973), the Russian mathematician, recognised that 'control, in its broadest sense, is the most universal property of life, independent of form' and that it must be possible 'to describe living systems from a cybernetic point of view'. He saw cybernetics as a concept central to biology, by providing the underlying principle of self-regulation.

Norbert Wiener (1894–1964) was an eccentric, stout and short-sighted polymath; a child prodigy driven by his father. He became a leading mathematician of his time, who wanted to make a telling contribution to the outcome of World War II. This he did by his work on the automatic directing of anti-aircraft fire, which led him to develop his ideas on the theory of control. In 1948 he brought them together in the book *Cybernetics*, for which he is best known. It also marked the birth of a discipline and the name he gave it, in what was the first theoretical treatment of the subject. Wiener's book had the subtitle *Control and Communication in the Animal and the Machine*, which linked the theory of control in technology with that in biology. The link was primarily due to Wiener's collaboration over many years with his friend Arturo Rosenblueth (1900–1970). Significantly, he had previously been the colleague and collaborator of Walter Cannon, and the connection ensured that there would remain close links between cybernetics and homeostasis.

THE EMERGENCE OF BIOLOGICAL CYBERNETICS

The Macy Conferences established cybernetics as a multidisciplinary concept. They were held in New York from 1946 until 1953 and were designed to explore the implications of the recent discovery of cybernetics. There were three British-based scientists who contributed to these meetings, and who brought news of the fast-growing field of cybernetics back across the Atlantic. They were William Grey Walter, W. Ross Ashby and J.Z. Young; each of them spread the word and incorporated the central ideas into their work and through their books. Grey Walter's paper at the 1953 Macy Conference was on *Studies on the activity of the brain*, Young's paper at the conference in 1952 was on *Discrimination and learning in Octopus*, while Ashby's paper at the same conference was on *Homeostasis*. Grey Walter was the first to show that simple control devices could learn and produce lifelike behaviour, while Ashby developed an electronic analogue which he called a Homeostat. For Young, homeostatic principles became important in his work on the brain of the octopus. He made homeostasis the overarching concept in his great volume *The Life of Mammals* [4], which has been a textbook for generations of zoologists. In the first chapter he traced its significance for the reader, as a thread that runs throughout the volume. Over 40 years later, Elaine Marieb adopted a similar focus in her medical textbook *Human Anatomy and Physiology* [5], with sections on homeostasis in each chapter. In this way, generations of students have been introduced to homeostasis as a vital concept with which to understand life.

Nevertheless, the term 'cybernetics' has become less used, because the word has been corrupted to create jargon such as 'cyberspace', 'cyborg', 'cybermen' and 'cybernaut'. Cybernetics is now more often thought of as a branch of control theory, but Wiener chose his term so carefully that it would be a pity to lose one so full of meaning. 'Cybernetics' is derived from the Greek word *kybernetes*, meaning steersman, recognising that the earliest feedback mechanisms were the 'steering engines', or servo-mechanisms, designed to steer ships. He also wanted to acknowledge the first theoretical work on feedback mechanisms, published in 1868 by James Clerk Maxwell (1831–1879) in a paper entitled *On governors* [6]; 'governor' was a Latin corruption of *kybernetes*. Maxwell's paper was on the centrifugal governor, credited to James Watt, which controlled the steam engines of the Industrial Revolution, preventing 'hunting' and 'runaway'. So one cannot avoid the conclusion that there are good grounds for reverting to Wiener's original term.

Cybernetics is an important part of 'systems theory', which includes the study of any system that can be thought of as a group of related elements organised for a particular purpose. The abstraction is valuable in recognising the properties of systems like networks, hierarchies and feedback loops. The concepts of systems theory transcends many disciplines, as they are portable and can be applied wherever control is involved. Norbert Wiener developed the theory of cybernetics to direct anti-aircraft guns, but the same theoretical understanding was soon applied to the control of distribution of electricity from power stations, and provides insights into Parkinson's disease. It is the extraordinary versatility of the central ideas of cybernetics that makes them so powerful. Here examples from technology and everyday life will be used to make the cybernetic behaviour in animal and human biology more accessible.

FOCUS ON GROWTH AND ITS CONTROL

Despite the generality of cybernetics in biology, here the focus is on growth and its control in biology. The tendency of living things to increase in size is one of the defining features of life. J.Z. Young (1907–1997) wrote, ‘The study of growth consists largely in the study of the control and limitation of growth.’ Failure to impose control is potentially disastrous, whether the unfettered growth of cells that causes cancer, to growth in the number of people who inhabit the Earth. Each shows the consequences of regulatory systems out of control. Nevertheless, cybernetics and biological growth took a longer time to come together than might have been expected. In the 1940s, when the young Peter Medawar (1915–1987) was boldly assembling the ‘laws of biological growth’ [7], he showed why the measure of growth called the ‘specific rate’ is physiologically the most appropriate measure of growth. He hinted that, as it is constant in populations of single cells, it reflects the rate of the underlying biosynthetic processes, when teased from their cumulative product. Yet in the 1970s, cancer researchers were still trying to understand growth in a cumulative sense rather than as a rate-controlled process. Nor did they see the value of perturbation in order to understand control and its failure. Ross Ashby’s Law of Requisite Variety stated that, for any homeodynamic mechanism, disturbance is neutralised by a response that gives a stabilised outcome. To neutralise disturbance, and restore the equilibrium, a counter-response is required to achieve a balance of opposing forces. Perturbation is the novel element to the approach taken here: an approach that is natural to a cyberneticist, but has not been so for students of biological growth.

The idea developed here became the Maia hypothesis, named after the Roman goddess of growth and increase. In temperate northern climes, the spring outburst of growth occurs predominantly in the month of May, to which Maia gave her name. The approach considers growth as a controlled process: a hypothesis that demonstrates and aims to explain growth control from a cybernetic perspective. Apart from perturbation, a subtle difference in approach is to think of growth not so much as the maintenance of constancy, but rather as the resistance of internal processes to external change.

The first few chapters deal with the problem of biological growth in general terms, together with the origin and application of cybernetics to biological processes. ‘Growth’ means increase in cell size together with the multiplication of cells by which animals and plants grow in size, but also the growth of populations of free-living cells and organisms. Enlargement in size and increase in population number are both referred to as growth, and involve processes that are analogous and homologous. Rather than distinguishing between them, the aim is to consider growth in its broadest sense, and to draw together the physiology and ecology such that the understanding of one can inform the other.

The products of growth and replication grow arithmetically in the same way (Chapter 2); growth is a multiplicative process of the kind seen in nuclear fission or in the increase in money through compound interest. Growth accelerates at an increasing rate because the products of growth also grow. The products of replication also replicate, whether through the increase in number of cells within a tissue, or the individuals within a population. This is exponential growth, which makes populations double in size at regular intervals. However, unlimited exponential growth becomes unsustainable and can have dire implications for survival. For this reason, mechanisms have evolved which limit growth and multiplication, thus avoiding problems of excess and instability. Everyday examples abound, from the growth of the bacteria that sour milk, to the spread of duckweed over a pond in summer. Such growth can be compared to a forest fire, which spreads at an accelerating rate, doubling in size every 30 seconds or so at first, although it must eventually burn out for lack of fuel. We know that biological growth must ultimately be constrained, as exponential growth cannot be sustained indefinitely. But is limitation due to external factors, or to some internal mechanism, or both?

We must begin to look at the part played by self-regulating systems, first by considering the simplest kind of control systems (Chapter 3). The familiar systems for heating a home are used to illustrate the analogous thermoregulatory system of warm-blooded animals (Chapter 4). A wealth of examples of homeostasis are drawn upon in athletes and astronauts, racehorses and bumble bees, to illustrate the subtleties of adaptation.

THE MAIA HYPOTHESIS

Then we see Maia as a single loop control mechanism. Using simple model organisms, and an experimental design incorporating perturbation, it is possible to observe the oscillatory output of the control mechanism (Chapter 5). So the approach is primarily experimental, and the principal novelty is the development of a method that makes it possible to isolate the output of growth control mechanisms. The work was carried out on cultures of simple organisms in the laboratory. The first is the marine hydroid *Laomedea flexuosa* (frontispiece) and the second a marine yeast *Rhodotorula rubra*. The essential part of the experimental design is the requirement to perturb the growth of the organisms, and then isolate the consequences of having done so. Using low levels of toxic inhibitors proved the simplest way to deviate growth from its preferred or goal setting, so that graduated loadings could be imposed upon the control mechanism to reveal variations in the control responses to inhibitory load. Initially the Maia hypothesis is a method by which growth data can be expressed as the oscillatory output that is typical of feedback mechanisms (Chapter 5). This reveals the richness of output behaviour by which organisms may overcorrect at low levels of loading, neutralise inhibition at higher levels or become overloaded when the capacity to counteract is exceeded.

The concept of homeostasis was central from the outset. Biological cybernetics focuses upon homeodynamic systems which are responsible for control in biological systems. Such systems are dedicated to serving the inbuilt purpose of maintaining the process at some preferred rate or state. For the life of the organism, they maintain a homeodynamic equilibrium but, for the biologist, this condition is uninformative as to the workings of the mechanism responsible. The equilibrium must be disturbed and deviated from its goal in order to see the response necessary to restore it to its goal setting. This reveals the characteristic oscillatory output of the feedback mechanisms responsible for homeodynamic control of growth. The growth rate output of perturbed organisms, and the output of simulation models incorporating feedback, were so similar and characteristic of cybernetic mechanisms that there was little doubt that the Maia hypothesis was correct. At low levels of perturbation, equilibrium was quickly restored; at higher levels, recovery was slower; and at even higher levels, the capacity of the control mechanism was exceeded and finally overwhelmed at a level that coincided with lethal levels of the toxic inhibitor.

Most of what is known about cybernetics comes from man-made feedback mechanisms, whose designers start with a blank sheet of paper when creating such systems. The study of biological control mechanisms requires what is called ‘reverse engineering’; the system exists within the organism and the researcher must find out its properties by deducing them from the output of the system. As investigation proceeds, the model comes to represent more accurately the system within the organism. A systems approach is a necessary escape from the limitations of reductionism, as the properties of the whole system are not to be found in its constituent components, but require