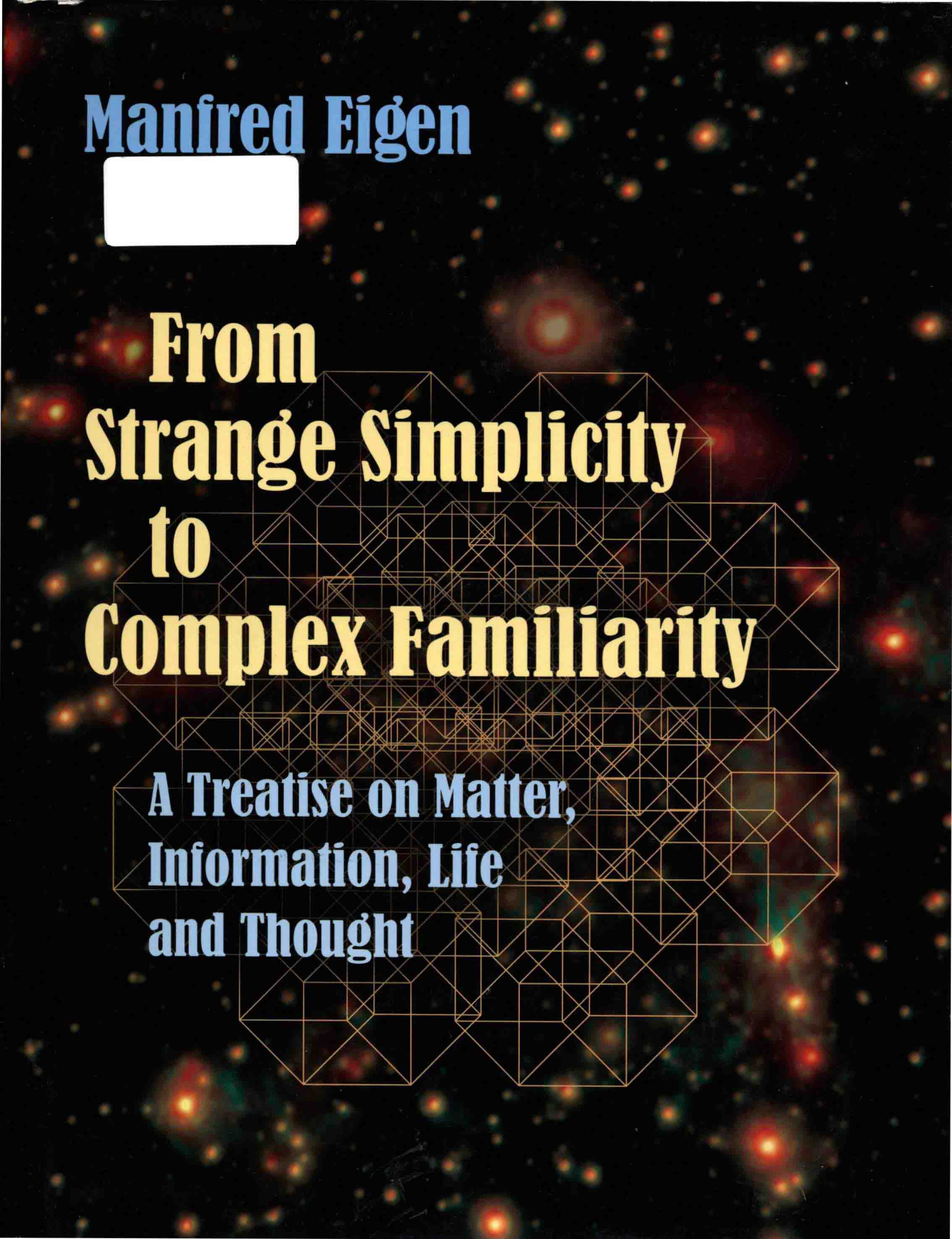

Manfred Eigen

From Strange Simplicity to Complex Familiarity

A Treatise on Matter, Information, Life and Thought

From STRANGE SIMPLICITY *to* COMPLEX FAMILIARITY

A Treatise on Matter, Information, Life and Thought

MANFRED EIGEN

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FROM STRANGE SIMPLICITY
TO COMPLEX FAMILIARITY

To

Richard Lerner

who has been President of The Scripps Research Institute throughout the last 25 years while at the same time remaining a creative chemist and having many new ideas, such as the invention of antibody libraries and their use in the pharmaceutical industry – with many thanks for being my host and for providing an atmosphere that enabled much of this book to come into being.

I owe especial thanks to my partner, Ruthild Winkler-Oswatitsch, for her indefatigable assistance in the preparation and completion of this book, a project that I cannot imagine would have succeeded without her contribution and which gives me a welcome opportunity to acknowledge nearly fifty years of working closely together.

Chapter 1, Matter and Energy,
is dedicated to Murray Gell-Mann,
one of the greatest physicists of our time,
who revolutionised our ideas on elementary matter.

Chapter 2, Energy and Entropy,
is dedicated to John Ross,
who broke up the limits of classical "statistical" mechanics by using theory and experiment to study mechanisms of complex reactions far from chemical equilibrium.

Chapter 3, Entropy and Information,
is dedicated to Manfred Schroeder,
who as a physicist and acoustician was the first to fasten the ties between acoustics and information theory.

Chapter 4, Information and Complexity,
is dedicated to Albert Eschenmoser,
one of the leading contemporary synthetic organic chemists,
who identified and reproduced rare biological compounds, thereby explaining abstract information in terms of chemical complexity.

Chapter 5, Complexity and Self-Organisation,
is dedicated to Leslie Orgel,
who over many years – originally in close contact with the late Stanley Miller – showed how the roots of life can be found in molecular biology.

Acknowledgements

This book originated some 15 years ago when I retired from my position at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany. Let me start by thanking the Max Planck Society and its presidents for supporting my work during some 50 years of active scientific research. With regard to this book, my thanks include in particular the Society's current president, Peter Gruss, and my colleagues at the Göttingen Institute for generously allowing me continued use of space and facilities at the Institute after my retirement. At the same time I should like to express my gratitude to the Scripps Research Institute and its president, Richard Lerner, for hosting my extended annual stays at La Jolla, California. There I have enjoyed a unique scientific atmosphere in the field of molecular biology, which exerted a catalytic influence upon large parts of the manuscript, which I often referred to as the "Scripps book".

By European standards, Göttingen's University is not particularly old. It was founded in 1737 by George II, King of England, who at the same time was Elector of Hanover (which explains his involvement in German academia). Göttingen, one of the first secular universities in Europe, became eminent as a centre of the Enlightenment in Germany. Its scientific tradition is based on mathematics; in physics it was the birthplace of quantum mechanics, and in chemistry it was associated with pioneers such as Wöhler and Windaus. From early on it housed one of the most important libraries in Europe, which caused Benjamin Franklin to come to Göttingen for an extended stay – not in order to study *in* its university library, but rather to study the library itself. Today Göttingen is also the home of numerous research institutions at which these disciplines are also represented. The Göttingen Academy of Science, today still a meeting place for scientific discussion in an almost family atmosphere, has left its mark on Göttingen as a town of science.

La Jolla can be seen in a similar way. Its strongest field is modern biology. This was started by institutes like the Salk and the Scripps and has been perpetuated by the university, which is one of the youngest, but also among the largest, in the USA. Scientific discussion often leads to surprising new ideas. However, La Jolla also offers seclusion and time to oneself. For the thinking and writing that went into this book, the two places – Göttingen and La Jolla – were ideal. Now let me turn from places to people.

This book owes much to my partner Ruthild Winkler-Oswatitsch, who has been closely associated with my work over forty years, and to Paul Woolley, whose contributions in editing the manuscript were especially valuable. Without their dedicated support this book would never have seen the light of day. Furthermore, I thank my friends and former colleagues Peter Richter and Peter Schuster for contributing the two articles that appear in Appendices A1.2 and A4. Peter Richter also devoted much time to thoroughly checking the equations in the page proof.

The preparation of the manuscript received invaluable aid from many persons. Claus-Peter Adam, occasionally supported by Hartmut Sebesse, transformed my hundred-odd manual sketches into well-designed computer-graphic art. Guido Böse, and in part Bernhard Reuse, were most helpful in unearthing the literature references quoted in the text. Most of the reproduction and photographic work was provided by Peter Goldmann, Irene Böttcher-Gajewsky and Heidemarie Wegener. I am particularly grateful to Ingeborg Lechten, who did most of the typing work, in which she showed special skill in setting up complicated mathematical formulae. Anja Zembrzycki, assistant to Peter Vogt in La Jolla, contributed valuable text-processing in later phases of the book's preparation. Josephine Stadler, assistant to Stefan Hell in Göttingen, managed the text transfer between various computer systems and organised numerous print-outs. Last-minute assistance with the computer files was kindly given by Heinz Winkler, Svea Steinhauer and Silvia Schirmer. Paula Foley, assistant to the president of the Scripps Institute, provided help in many aspects of the daily work. All this technical assistance was indispensable in the production of the final manuscript, and I owe a great debt of gratitude to all those involved, including many not mentioned here.

A contributing factor of great importance for this book has been the continuous discussion with colleagues and friends all over the scientific world – exchanges that have covered a great breadth of problems, spanning from fundamental physics to biology and the relationship between them. This is the skein of ideas underlying this book, which accordingly starts with a description of fundamental physical principles. The two cartoons in Section 1.2 related to Einstein's theory of relativity refer to a letter of Einstein's that is in the possession of the Einstein Archive at the Hebrew University of Jerusalem. The physics chapters (1 and 2) stimulated many discussions about biology with physicists, such as the one with Richard Feynman mentioned in the text, or later ones with Hermann Haken, John Wheeler, Leonard Susskind, David Gross and others about analogies between physics and biology. In this connection I should mention my studies of James William Rohlf's excellent textbook *Modern Physics from α to Z^0*, which provided many suggestions for dealing with the problems in Chapter 1. In this connection, I also cherished numerous discussions with my son Gerald, who is a practitioner in experimental particle physics. Reinhard Genzel informed me of his newest results about a black hole at the centre of our galaxy (see Section 1.7). Rudolf Kippenhahn supplied me with the newest data on spectral shifts observed in distant galaxies, and Theodor Hänsch provided me with new results in laser physics (see Figure 3.9.3). With Hans-Joachim Queisser I had a very stimulating exchange of ideas on possible mechanisms of an evolution of our universe. The mathematician Andreas Dress, founding director of a joint Institute of Mathematical Biology (in Shanghai) of the Chinese Academy and the Max Planck Society, was of great help in formulating some of the problems in mathematical terms, while the theoretical physicist Walther Thirring of Vienna University was a stimulating partner in the discussion of physical models.

Against the backdrop of physics, this book moves on to deal with chemical and biological topics. At my home Institute I received much help from Mary Osborne in obtaining material. Karl-Ernst Kaissling of the Max Planck Institute for Ornithology at Seewiesen supplied us with many examples of pheromones (Section 4.1). We also enjoyed discussions with Brigitte and Harald Jokusch.

In chemistry, it was the Swiss school that made the deepest impression on me. I was fortunate in being able to spend much time during my La Jolla stays in personal contact with Albert Eschenmoser, who like me regularly spent time at the Scripps Institute. Chapter 4 takes up many of the problems we discussed. Other members of the Zürich School – André Dreiding, Jack Dunitz, Giulio Arigoni and Martin Quack – joined this round. Kurt Wüthrich, who also spends much of his time at La Jolla, is another participant. And then there are the many scholars who are or were based at La Jolla: the late Francis Crick, Sydney Brenner, the late Leslie Orgel, Gerald Joyce, Gustav Arrhenius, Peter Vogt, Paul Schimmel, Kyriacos Nicolaou (who kindly provided Figure 4.1.6), Gerald Edelman and (in earlier times) the late Stanley Miller. However, that list should go on to include the names of many colleagues whom I met at various places, of whom I can mention only a few, such as David Hubel, the late Sol Spiegelman, Rudolf Rigler, Jean-Pierre Changeux, Larry Loeb, Alex Rich, Fritz Melchers, David Rumschitzki, the late Shneior Lifson and Hans Wolfgang Bellwinkel. I cannot name all of them, but they are all included in my thanks.

Let me add one final remark. The person who had the greatest influence upon my work was the late Leslie Orgel. He reviewed much of his own work about the complexity of evolution in a late paper that was prepared for posthumous publication by Gerald Joyce, who also wrote an obituary in *Nature*. Leslie's earlier pupil, the late Christof Biebricher, who joined my group at Göttingen, provided numerous sophisticated experimental verifications of ideas that originated in our common work.

Last but not least, let me include the editors of Oxford University Press in my acknowledgements. I have never experienced such a pleasant cooperation between publisher and author, and have been delighted with the patience shown to me – which I needed, as the content of the book touches many fields and gave rise to many a delay as I followed up, or read up, on some new idea. The working relationship with Sönke Adlung at OUP was invariably cordial and understanding – as it is among friends.

Thanks to all of those mentioned by name – and to many others!

Prolegomenon

The seemingly all-embracing title of this book might create the impression that it is going to deal with (almost) everything. This is by no means my intention. In order to avoid any misunderstanding concerning what this book is about, the reader is invited to start by reading these introductory remarks before proceeding to the main text. One can even start by reading the conclusion at the end of the book (depending on how one likes to read detective stories).

The focal point of this first volume is the concept of information, which is meant to include both the quantitative and the qualitative (or semantic) aspects of information, thereby providing a link between physics and biology. Why, then, do I start in the first chapter by talking about the elementary states of matter, ranging from particle physics to cosmology? And if I think that matter constitutes an important part of my subject, why do I not leave its description to the experts in the field? In fact, I strongly suggest that the reader consult other writings on modern physics for a better understanding of what I in many cases only can hint at. My reason for starting with the physics of matter is to emphasise the difference in the ways of thinking that we encounter when we try to gain an understanding of the physical nature of elementary, inanimate matter as compared with the complex states of animate matter.

Elementary structures are uniquely fixed *a priori* by physical principles. The structures of living entities, by contrast, are results *a posteriori* of a protracted evolutionary process. They are a means to an end. It is true that the realisation of animate matter requires certain (molecular) structures upon which the higher-order structures are built, but the guiding principle is function rather than structure. The periodic tables of quarks and leptons reflect fundamental physical symmetries that are given *a priori*, in a way similar to that in which the periodic table of the chemical elements reflects the immediate consequences of those symmetries. In contrast, the table of the genetic code does not offer any obvious *a priori* principle, although it, too, possesses a logical structure. Where symmetries or logical principles are found in biology, they usually turn out to be of an *a posteriori* nature, in that they arise from a functional advantage that they offer, rather than from a more general principle that requires them to be the way they are. In this way, they also reflect their own historical origin.

Given this fact, it may seem surprising how much physical regularity is still involved in Nature's design of life. Here I do not so much mean the material structures that we discover. Of course, these are made of molecules, and these must fulfil the physical and chemical criteria of existence and stability, which in turn are the result of physical laws. However, this is the realm of biochemistry and biophysics, and it answers questions such as that of how a protein should be designed for functional activity, or how a permeable membrane can best be constructed. The problem I wish to address is a different one: it is that of the design of the unimaginably complex blueprints of the living state that have now been continuously in existence for some 4000 million years. How did this information originate, and how could it eventually bring about structures as complex as the human brain? This question is a special version of an unsolved mathematical problem: how can problems of exponential complexity be solved within polynomial time? The solution in this case, of course, has to be found by physical means. This is what I call the "physics of biology". It differs from the physics of inanimate matter and also from what we call biophysics, i.e. the physics behind the structure and function of all the "gadgets" that operate in a living organism.

If we ask a biologist how the miracle of life was able to originate on our planet, he will most probably refer to Darwin. He will refer to the myriads of small steps in an evolutionary process. The great developmental biologist Theodosius Dobzhansky once stated: "Nothing in biology makes sense except in the light of evolution." The fact that life had to evolve was already widely accepted in Darwin's time, but before Darwin no mechanism had been suggested that could place such a process on a durable, rational basis. Darwin provided this mechanism: the principle of natural selection. I cannot get away from the impression that physicists have somehow never accepted natural selection as a true physical principle. Even though it has at last been exonerated from the (completely false) accusation of being tautological in character, its physical foundation has remained suspect up to the present day. Erwin Schrödinger spoke explicitly of his regret that biologists had to accept the validity of Darwin's principle while for him, as a physicist, Lamarck's ideas seemed so much more attractive. And in the six volumes of the *Lexikon der Physik*, a remarkably well-edited reference work that appeared in Germany a few years ago, one finds under "Darwin" only a biography of the physicist Sir Charles Galton Darwin, a grandson of the famous naturalist. Nevertheless, Charles Darwin's contemporary, the physicist Ludwig Boltzmann, praised him as the man of the century, calling the 1800s the "century of Darwin".

The biologist, on the other hand, has problems with accepting "natural selection" as a principle based on physics. Ernst Mayr, the doyen of 20th-century biology, called it a "biological theory". This would certainly have been correct if, at the same time, he had not explicitly contrasted it with "physical theory", which "can be written down in mathematical terms". I cannot agree with this distinction, and I am not even sure that Darwin himself would have agreed with it. If I understand Mayr correctly, he was referring to the incredible complexity of any biological situation, which cannot be accounted for other than by "biological experience"; however, theories always refer to an abstraction of reality.

Take, for example, quantum mechanics, the hallmark of theories in 20th-century physics. It makes general assertions, such as particle–wave dualism and fundamental "uncertainty" in the description of physical processes in space and time, and these have far-reaching consequences for the behaviour of matter at the elementary level. Owing to its mathematical exactitude we are able not only to obtain detailed insight into the structure of matter, but also to see the consequences of this theory when we perform experiments under strictly defined initial and boundary conditions. This has created a new understanding of the physical world, which includes a deep understanding of chemistry – despite the fact that certain chemical systems may be too complicated for carrying out precise calculations. Quantum mechanics as such provided a deep physical understanding of chemistry without putting experimental (and theoretical) chemists out of their job.

In the same way, I see the usefulness of a physical understanding of biology. It will allow us to apply the stringency of theory directly to systems of defined composition and structure in a manner testable by experiments. In this way it will provide us with precise knowledge about fundamental mechanisms of selection and evolution. Yes, selection and evolution are processes of self-organisation, based on non-linear dynamics in macromolecular systems that have certain reactive properties. In this book, we are going to see what properties are required in order to endow these systems with information-generating behaviour. We shall visit the new physical world of information space, where systems emerge out of randomness and stabilise themselves by reproductive feedback and – through a series of (first-order as well as critical) phase transitions – end up as highly adapted systems, developing all sorts of functions.

To what overall functions are they adapted? The answer is: existence – under any habitable environmental conditions! In this respect, a theory with workable solutions for the existence of life is just as fundamental for the existence of life as quantum mechanics is for the existence of matter. Such a theory can be formulated in definite terms and applied for definite initial and boundary conditions. The existence of life, then, is dependent on the existence of conditions for self-organisation of information-gathering systems. This can be, and has been, tested experimentally in chemically relevant environments.

Now let me be somewhat more concrete: The physical basis of natural selection is to be found in non-linear molecular dynamics. But how can selection for a certain performance – often some very "unphysical" property – be based on the physical mechanisms of dynamical behaviour? Selection must be an internally self-organising process; there is no external selecting agent other than selection pressure for existence, exerted by the environment. Hence, the internal feedback mechanism of selection must include some relationship that brings the idea of purpose onto the physical level of dynamics. The magic word that does this is "information", used here in the sense both of absolute quantity, representing "entropic complexity", and of semantic quality, representing "specified complexity". The latter turns out to be uniquely linked to reproduction. If it is to offer any advantage, specified information must be capable of (1) conservation, (2) proliferation, (3) variation and (4) selection. The common factor that links all these four requirements is *error-prone replication*.

Information – more precisely, semantic information – represents a particular choice from among a tremendous variety of alternative structures with finite lifetime. Replication, as an inherent autocatalytic property of the class of material information carriers, is the only way to conserve such semantic information, which otherwise would disintegrate without any hope of recovery. Being autocatalytic in nature, replication automatically results in the proliferation of this conserved information. Proneness to error introduces the requisite variation. Selection arises as a consequence of replication under conditions of growth limitation. Both the stability of information and the selection of advantageous alternatives require that the error be kept below a defined threshold value. Violation of the error threshold causes selection in the form of a phase transition in information space. All these properties can be described by a system of non-linear differential equations which, according to a theorem of Perron and Frobenius (Chapter 4), can be shown to be generally solvable.

Can such a straightforward physical process bring about anything as complex as the human brain? A positive answer rests on the fact that the evolutionary process as a whole is practically unlimited – even though any individual step may represent only very slight progress. Natural selection utilises *advantage*, regardless of whether the advantage is the result of a property at the molecular level or the higher level of a complex integrated network of molecules, cells or even organisms.

"Problem-solving without knowing the problem" sets almost no bounds to the complexity of the problem-solving system. Thus, systems can arise that appear to behave in a highly logical way. However, logic of this kind is an *a posteriori* property, that is, it has arisen in response to a selective requirement.

Here we see most clearly the difference between the "physics of biology" referred to above and the physics of matter. Consider an elementary structure, such as an atom. The atom is a direct and inevitable consequence of general natural laws that already embody the logic and symmetry of its structure. This structure reflects in an inevitable manner the cause of its existence. Consequently, it is not dependent upon "historical" events. Up to the level of atoms and small molecules, there is no alternative to unique solutions. However, their "simplicity" gets stranger and stranger the more we try to approach the origin of matter.

In this respect, biological structures are completely different. They result from protracted processes whose history is reflected in the variant chosen – one among a huge variety of complex structures – which ultimately becomes selected. The solving of each problem of adaptation can proceed along many alternative paths and may