

# **OPTIMALITY PRINCIPLES IN BIOLOGY**

**ROSEN**



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IN BIOLOGY**

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## PREFACE

DESPITE the existence of an increasing number of excellent elementary texts dealing with mathematical biology, I have felt for many years that important gaps still exist. The nature of these renders difficult any approach to this field by the interested student without excessive effort on his part. This book was written in an attempt to fill, or at least reduce, some of these gaps. Specifically, it is intended (*a*) to exhibit simply at least some of the basic interrelationships between apparently diverse areas of mathematics, physics, biology and the social sciences, (*b*) to indicate to the student where important unsolved problems lie relatively close to the surface, (*c*) to describe in some detail the mathematical tools with which these problems may be attacked, and finally, (*d*) to encourage the reader to attempt to formulate and solve these problems. An attempt has been made to write the kind of book which I would have liked to have had available when I first resolved, many years ago, to arrive at a mathematical understanding of the refractory but fascinating enigmas of biology.

These aims have made it necessary, and I believe desirable, to strive for breadth rather than depth. In my opinion, there is a need to indicate specifically and to bind together into a conceptually coherent whole, the analogies, the similarities and the common unifying threads that underlie a score of apparently diverse specialities. Once this has been done, the many hundreds of specialized texts should then be consulted and mastered by the interested student. Until this has been attained, a mass of excessive detail will only hinder the student's understanding, and make his task more difficult.

It is hoped that specialists will appreciate this point of view, and not criticize too harshly the inevitable sketchiness and oversimplification implicit in such a programme. I have tried to correct for this by means of bibliographic references and explanatory notes at the end of each chapter, which indicate supplementary reading for the material presented in the main text. Many omissions nevertheless remain, but it is hoped that

enough detail is given to represent with reasonable accuracy a clear overall picture.

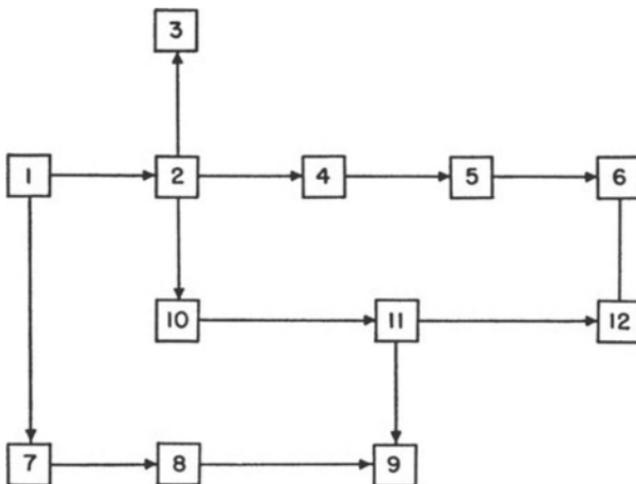
Any biologist will notice that most of the strictly biological references are at least 20 years old, and that they deal with questions which preoccupied an older generation of biologists. The spectacular rise of molecular biology, which has characterized the direction of growth of the biological sciences in the past two decades is ignored; DNA is never mentioned. However, it must be pointed out that the older problems have merely been displaced and not solved by the recent developments at the molecular level. These problems involve the very core of biological organization and development: homeostasis, ontogenesis, phylogenesis. It is important for biology that these problems are not lost sight of; it is hoped that a restatement of the old problems in a new terminology may provide at least a small impulse in the direction of *rapprochement*.

More important, perhaps, has been the decision to adhere as far as possible to continuous and deterministic (as opposed to discrete and/or stochastic) models. This may disturb some readers, inasmuch as many of the biological problems which are dealt with must ultimately fall back on the genetics of populations, which is discrete and stochastic. The justification for this approach is the same as that which allows the kinetics of chemical systems to be described by differential equations. It has been impossible to avoid entire mention of discrete and stochastic models; therefore reference is made to the perceptron, stochastic learning theory, and dynamic programming. However, the discussion of these matters is heuristic in nature; it is intended to indicate how such models relate to the primary subject matter, and to challenge the reader to investigate them further on his own. Only one brief reference is made to McCulloch-Pitts nets, and none at all to the theory of finite automata and its extensive application to problems of 'self-organization' which dominate much of the current interdisciplinary work. Fortunately, an excellent introduction to such finitistic models is available (M. Arbib, *Brains, Machines and Mathematics*, McGraw-Hill, New York, 1964), and the reader is urged to consult this text and the references cited therein.

Mathematically, the book has been directed towards the advanced undergraduate or beginning graduate level. A few

somewhat more esoteric words, like 'topology' or 'compactness' logically intrude themselves into the development at various points, and it is in the student's interest to retain them, despite the fact that one cannot digress long enough to explain them in detail. Occasionally reference is made to other texts for technical results which would take the reader too far afield to develop directly. It is felt that such references, too, provide a didactic service, since part of the art of interdisciplinary work is an intelligent use of supplementary text; this is not achieved without practice, and practice does not come from books which are entirely 'self-contained'.

The diagram below indicates the main logical interrelationships between the various chapters of the book, and should help the reader to organize the many diverse ideas discussed. There are other more subtle logical relationships which have not been indicated; these may not be apparent until the book has been read through. Indeed, the book will not have conveyed its maximum benefit until it has been read through several times.



## ACKNOWLEDGMENTS

It is a pleasure to record here my indebtedness to the friends and colleagues who have aided me in the preparation of the manuscript. Foremost is the debt that is owed to Nicolas Rashevsky who suggested that I undertake this task, and painstakingly reviewed the manuscript at a time when he had better things to do: but far more important than this is the scientific legacy created by his industry and his achievements, which I hope may find some reflection in these pages. At the start of his work, mathematical biology was a small collection of diverse theoretical curiosities. His work has transformed mathematical biology into the coherent and burgeoning research discipline which it is today.

I am indebted to my colleagues M. Arbib, C. Ehret, P. H. Greene, H. D. Landahl, H. G. Landau, H. M. Martinez and E. Trucco for their critical reading of the manuscript, their comments, and suggestions (all of which were appreciated even though not all were implemented). Thanks are also due to Mrs. Janyce Nasgowitz for typing the draft from incomprehensible notes, and to Mr. N. Wolfe, who prepared the figures.

Finally, I would like to acknowledge the support of the U.S. Public Health Service and the U.S. Air Force in their support of much of the research described herein.

ROBERT ROSEN

## GENERAL CONSIDERATIONS

### 1.1 Optimality in Science and Engineering

THE idea that nature pursues economy in all her workings is one of the oldest principles of theoretical science. The development and ramifications of this idea, from the time of the Greeks to the present day, makes a fascinating study in itself. Notions of 'economy' or optimality, come readily to those who personify nature, or who see in natural laws the workings of a divine intelligence. To such individuals, nothing could be more natural than to expect that the processes of nature are carried out in a manner which is, in some sense, the best possible. Indeed, entire metaphysical systems, have been based on such ideas.

However, the idea of optimality, or economy, is difficult to make quantitative in a general way; each individual aspect of natural law seems to require special consideration. There are, nevertheless, a number of guiding principles which apply to optimality considerations throughout the sciences. Consider briefly what is meant by saying that some form, or process, or design, is optimal. It may be helpful for the moment to look at human engineering problems, from which, of course, ideas of optimality were originally abstracted; for example, consider what a design engineer would regard as an optimal solution of some problem with which he is concerned.

A human engineer is generally faced with the problem of designing a structure able to perform a given task, set within a given operating context, say designing a bridge. Each possible structure which solves the problem necessarily carries with it a certain cost, which is conveniently measured in some common kind of currency, such as dollars or kilowatt hours (such a common currency is necessary so that competing solutions may be compared). The optimal solution is the one or ones which will meet all the conditions of the problem, i.e. will carry out the given task within the given context, with the minimum cost. The first

principle that is seen emerging is, that in any study of optimality which is at all quantitative, one must be able to specify a well-defined class of competing solutions to the problem at hand, and to each such solution a cost must be assigned, in such a manner that the costs of the various competing solutions are mutually comparable.

Obviously the solution, which is optimal in a given context, will depend on the class of competing solutions, and on the specification of the cost of each solution. A design for a bridge, for example, may be optimal if it is specified that the bridge is to be built out of a particular kind of steel; but if the use of a lighter or stronger metal is allowed in construction (thereby enlarging the set of competing designs), it may be found that the previous solution is no longer optimal. The task of finding the optimal solution may be called selection (or artificial selection), for reasons which will become apparent.

In the language of mathematics we say that over the set of competing solutions to a given problem there is given a function (called the cost functional), which associates to each element of that set an element belonging to a totally ordered set of costs or values. The problem of finding the optimal solution is then the problem of finding that solution corresponding to the *minimum* cost. In other words, problems of optimization in human engineering design can always be formulated in principle as mathematical minimum problems<sup>1</sup>. Such problems are well defined mathematically, and in the next chapter the mathematics of such problems is discussed in detail.

## 1.2 Optimality in Physics

In physics there are a number of excellent examples of problems of this type, which it will be of value to discuss and compare briefly here (although more detailed discussion must be deferred until the appropriate mathematical techniques are developed in the next chapter). There are a full half-dozen different examples which have been of great importance to the development of theoretical physics and which deserve mention in this regard.

The first of these, historically, is Fermat's Principle of Least Time. This principle dominates the science of geometrical optics, and states that a ray of light, moving through an arbitrary

medium (whose refractive index may vary from point to point, for example) will follow, out of all possible paths, that path for which the transit time of the ray is a *minimum*<sup>2</sup>. It will be noticed that Fermat's principle is exactly of the form that has been considered. This is first of all a well-defined problem; namely, to move a light ray from an initial point to a terminal point through a general optical medium. Secondly, with this problem a well-defined set of possible solutions can be associated; namely, the set of all physically possible paths which join these points. Finally, with each path a number can be associated which represents in some sense the cost expended by a light ray moving along that path; namely, the elapsed time of transit of the ray. Fermat's principle tells us then that the optimal path is that path for which the cost (i.e. the transit time) is least, and that the optimal path is the one which will actually be exhibited in nature.

The next physical principle of this type which should be mentioned here is, in a precise sense, a mechanical analogue of Fermat's principle, and is known as Maupertuis' Principle of Least Action. This principle has to do with the motion of mechanical systems, and it asserts in its most general form that a mechanical system, out of all possible paths consistent with the conservation of energy, will move along that path which minimizes the mechanical quantity known as action. In those systems in which kinetic energy, as well as total energy, is conserved, and on which no net external forces are applied, this principle reduces to the statement that, of all admissible paths of the system, consistent with conservation of energy, the system will move along that particular path which minimizes the time of transit<sup>3</sup>. The analogy to Fermat's principle is clear, and indeed is of deep theoretical importance<sup>4</sup>.

In Maupertuis' principle there is again a set of possible solutions to a well-defined mechanical problem (namely, the set of all paths of a system consistent with conservation of energy), to each element of which is associated a number (the action) representing a cost, expended in following that path. Maupertuis' principle tells us that the optimal path is the one for which the action is minimized, and that this optimal path is the one actually followed by the system.

The third of the optimality principles in physics makes an interesting contrast with the Maupertuis principle just described.

This is known as Hamilton's principle, and is perhaps the most important optimality principle in theoretical physics. This is also a mechanical action principle, as is that of Maupertuis. It resembles the latter principle in that, to each element of a set of possible paths of a mechanical system, it associates the action corresponding to that path as a cost. However, it differs from the Maupertuis principle in the admissible set of possible paths which are allowed; in the latter principle the paths chosen are those consistent with the conservation of energy. The paths considered by Hamilton's principle are those which arise through the process of what are called virtual displacements, in which the time is held fixed and only the space co-ordinates of the system are varied (subject to the constraints on the system). The two sets of paths corresponding to the two principles are, in general, different because there is no reason why a path arising from a virtual displacement should be consistent with energy conservation. Thus, despite the other similarities between these principles, they differ greatly in their application. Hamilton's principle is by far the more powerful (the principle of Maupertuis in fact can be inferred from it) and, as stated before, forms a cornerstone on which a major part of theoretical physics rests.

The contrast between the principles of Maupertuis and Hamilton shows, in a particularly striking way, how the character of an optimality problem depends on the precise definition of the set of possible solutions, even when the cost function is held fixed. Naturally, the same result may be expected when the cost function is changed and the set of solutions held fixed.

Other important areas in physics in which problems of the same form arise may be mentioned here, but need not be discussed in any detail. An interesting example arises in the general theory of relativity, in which the actual path of a material particle, travelling between two points in a force field, corresponds to the line of minimal length (geodesic) which connects these two points [remembering that, as a result of the correspondence between fields of force and the curvature of the space in which the particle moves, the lines of minimal length are not (as in Euclidean space) ordinary straight lines].

Mathematically, the problem of determining the geodesic, or curve of minimal length, which joins two points on a given surface, is a one-dimensional problem, and may be directly

generalized to higher dimensions. The two-dimensional generalization of this problem is to find and characterize the surface(s) of minimal area bounded by a given closed curve in three-dimensional space. This is the *Problem of Plateau*. Plateau's problem is also closely connected with a minimality principle in physics, because any thin membrane, such as a liquid film, bounded by a closed contour in space, tends to assume a configuration of minimal surface area. This can be directly proved from the fact that a virtual displacement performed on such a film (considered as a mechanical system in equilibrium) does no work (see Section 2.10). The tendency of thin films to assume configurations of minimal area has direct application to biology, having been applied to a number of interesting problems in organic form<sup>5</sup>.

#### *Exercise*

State explicitly the set of solutions and the cost function of the last two optimality problems.

It is evident that considerations relating to economy or optimality, in the strict sense in which these terms have been used above, are of great importance in a wide variety of situations in the physical sciences. It is also important to point out, in this context, a further consequence of the fact that optimality problems arise so often in different physical contexts:

' . . . in almost every field of physics [optimality] principles can be used to express the "equations of motion" [of physical systems], whether they be Newton's equations, Maxwell's equations, or the Schrödinger equation. Consequently, when [such a] principle is used as the basis of the formulation, all such fields will exhibit, at least to some degree, a structural analogy. When the results of experimentation show the need for alteration of the physical content in the theory of one field, this degree of analogy has often indicated how similar alterations may be carried out in other fields . . . [for example], by describing the electromagnetic field by [a Hamilton principle], it is possible to carry over the methods of particle quantization to construct a quantum electrodynamics. . . .'<sup>6</sup>

It will be seen how the same advantages of a consistent formulation of the type illustrated above also accrue to a wide variety of biological problems; this, indeed, is the main task of the present monograph.

### 1.3 Optimality and Selection in Biology<sup>7</sup>

Attention is now turned to the main question: How do optimality principles appear in the biological world, and how may they be reduced to a manageable and useful mathematical formalism? It must first be asked why, apart from theological or aesthetic bias, any kind of optimality principle should be expected to be manifest in the organic world. In physics, indeed, it was impossible to otherwise justify optimality principles, such as those of Fermat or Maupertuis, until it became pragmatically clear that these principles worked. In biology, however, it is possible to give at the outset a coherent, if qualitative, argument which will to some extent justify a search for such principles in biology, and help in their formulation. This argument is based on the phenomenon of natural selection, and the pressure which selection exerts on nearly every aspect of the structure, function, and performance of biological individuals.

What is natural selection? Roughly and heuristically, natural selection is regarded as the outcome of a competition (or, in more Darwinian terms, a 'struggle') for the conditions of existence between those individuals or processes which happen to find themselves together in the same set of environmental circumstances. Intuitively, it is seen that those individuals which can, in some sense, compete more effectively than others, will be more likely to survive this competition, both as individuals and also, more importantly, in the production of progeny. If one now supposes (*a*) that the competitive superiority of these individuals, relative to the given environmental conditions, can be transmitted to the offspring of such individuals, and (*b*) that the given environment is held constant for a sufficient time, then the total population will become enriched in individuals possessing the advantages in question, and ultimately those forms representing a competitive disadvantage will tend to disappear from the population; this can be shown rigorously in simple situations<sup>8</sup>. The fundamental point to notice with regard to natural selection is that all types of competitive advantage, regardless of their initial nature, are ultimately translated into differences in fecundity (providing our assumptions (*a*) and (*b*) are satisfied), and it is these differences in fecundity which ultimately result in the predominance of the advantageous forms after a sufficient time has elapsed<sup>9</sup>.

On the basis of natural selection, then, it may be expected that biological organisms, placed for a sufficiently long time within a specific set of environmental circumstances, will tend to assume characteristics which are optimal with respect to those circumstances. This means that organisms tend to assume those characteristics which ensure that, within the specified environment, there shall be no selective disadvantage *vis-à-vis* the other organisms with which they compete.

It is now possible to make the fundamental hypothesis that biological structures, which are optimal in the context of natural selection, are also optimal in the sense that they minimize some cost functional derived from the engineering characteristics of the situation. This most natural assumption has been called the *Principle of Optimal Design*<sup>10</sup>, and most of the present work is devoted to exploring a few of its implications. In those cases where the Principle of Optimal Design is susceptible to direct check, its results have been in excellent agreement with biological observations. Usually, however, the appropriate cost functional is not immediately obvious; therein lies the art and the difficulty of the entire subject.

#### **1.4 Qualitative Considerations of Biological Optimality**

It has been shown that the optimality problems of physics and engineering possess a definite form. They must be formulated in such a way that a well-defined set of potential solutions may be constructed, and so that each of the potential solutions may be associated with a number representing the cost corresponding to that solution. Then one must find the solution to the problem which incurs a minimum cost. How, given the assumptions made concerning the relation between selection (fecundity) and optimality in biology, can principles of form and function of organisms be expressed within this framework?

One must begin, of course, by attempting to assess the various costs involved in specific biological problems. In the first place, it is known that any aspect of organic structure, such as an eye, an ear, or a vascular system, carries with it a kind of metabolic cost, which must be measured in some kind of uniform metabolic currency, common to all organisms. This cost represents, roughly, the energy expenditure required of the organism to construct and maintain the structure in question. Since an organism has only a

limited amount of metabolic energy available to it, other things being equal, one can argue that the structure (or structures) involving the least expenditure of metabolic energy (and otherwise consistent with the demands of the organism) will be the optimal structure. This much can be shown experimentally in special situations, e.g. in bacterial populations<sup>11</sup>.

Aside from the *intrinsic* cost, assessed by the inevitable expenditures for construction and maintenance, an *extrinsic* cost must also be considered arising from the pressure of selection. This cost is reflected in the over-all fecundity of organisms bearing the organ in question, as compared with (ideally) other organisms differing from those given only in the structure of that organ. As already shown, selection operates, in effect, by assessing a fine, or penalty, against an organism possessing an organ of lower competitive efficacy. The total cost of a particular structure, then, must be evaluated in terms of the algebraic sum of the extrinsic and intrinsic costs (multiplied, if necessary, by appropriate conversion factors to bring them to a common currency or dimensional form).

There are some qualitative features of this situation which may now be noted, and which may give some insight into the scope of the Principle of Optimal Design:

1. It is intuitively clear that for each organ type there exists an upper bound or threshold value  $\sigma_0$  such that, if the total cost of a particular organ of that type exceeds  $\sigma_0$ , the corresponding organism becomes inviable.

2. Let the total cost be denoted by  $\sigma$ , the intrinsic and extrinsic components of the cost by  $I$  and  $E$  respectively, so that  $\sigma = I + E$ . Now  $\sigma$ ,  $I$ , and  $E$  are all cost functions in the sense discussed above; that is, they each associate a number with each element of a set of possible designs or structures for a particular organ or activity.

3. If  $E$  is small and relatively constant over the total set of possible solutions, then the total cost  $\sigma$  of the competing designs becomes dependent on the intrinsic metabolic cost alone. For example, in an environment in which there is not much to see, the least expensive eye is the best eye. In an environment in which there is nothing at all to see, the best eye is no eye ( $I=0$ ), as in the well-known blind cave fish, which live in total darkness.

4. On the other hand, if the dominant term in the total cost is

$E$ , then in general the optimal solution(s) will be those which minimize  $E$ , even if  $I$  is not minimized simultaneously. If  $E$  is minimized by only a small number of possible designs in the given environmental circumstances, then, just as in the previous case, there will be only a small number of optimal forms, and the pressure selecting against the nonoptimal forms will depend on how sharp is the distinction in cost between the optimal forms and the others. In any event, it may be noted that when the selection pressure is high, then all organisms regardless of other differences between them, which are favoured by a particular environment, will tend to assume the same designs. This is known in ecology as the *Principle of Convergence*, or the *Law of Convergent Evolution*. Many examples of convergence can be given: the albinism and eyelessness of cave animals, whether fish, mammals or insect; the similarity in form of diverse carnivorous marine vertebrates (shark, barracuda, dolphin, ichthyosaur); the striking similarities between Australian marsupial forms and the corresponding forms of higher mammals in other parts of the world occupying analogous environmental situations; and hundreds of other examples which might be cited.

5. Conversely, if  $I$  and  $E$  are both small and approximately equal over the set of possible designs in a given environment, then there will be very little selection pressure and little reason for choosing one design over another. This results in a high degree of polymorphism, i.e. variation of form and design in organisms inhabiting a particular environment. These situations are important in evolution, for they can give rise to what is often termed adaptive radiation.

Indeed, despite its crudity, the present analysis shows that there is a close relationship between selection pressure in an environment and the level of convergence which is observed in the organisms inhabiting that environment. This can, in principle, be related quantitatively to the behaviour of the cost functions described, and ultimately can be expressed in terms of optimality. Roughly, strong convergence indicates a single, or a very few, designs which minimize these cost functions, and hence a strong selection pressure; many minima indicate weak selective pressure and a high degree of polymorphism. What is important to recognize is that all these ecological rules immediately appear as consequences of optimality principles, that these principles may

be formulated and investigated in a precise manner, and that they are capable of providing exact information in individual cases.

### Notes to Chapter 1

1. Some optimality problems are formulated most naturally as maximum rather than minimum problems (see Note 14, Chapter 11, and Section 12.3). However, the two kinds of problem are formally equivalent; the problem of minimizing the function  $f(x)$  is identical to that of maximizing  $-f(x)$ , and conversely. Most of the problems given here are concerned with natural minimum problems.

2. As shown in Chapter 2, the mathematical formulation of Fermat's principle and other optimality principles does not automatically insure the minimal character of the optimal solutions. All that is guaranteed is that the optimal solutions will all be stationary. However, in virtually all real physical problems, the actual optimum does indeed turn out to be a minimum (rather than an inflection point, a maximum, or other kind of stationary solution).

3. See Section 2.11, in Chapter 2. A useful heuristic version of this argument goes as follows: If  $T$ ,  $V$  represent respectively the kinetic and potential energy of the system, then the action of the system during a time interval of duration  $t$  may be taken as  $(T - V)t$ . Conservation of total energy means that  $T + V = \text{constant}$ . If kinetic energy is conserved as well, then  $T = \text{constant}$  and  $V = \text{constant}$  also. Therefore  $(T - V) = \text{constant}$ , and the action of the system becomes simply proportional to the transit time, as asserted.

4. Hamilton himself pointed out the analogy between these two variational principles in 1834 and emphasized the relation established by this analogy between classical mechanics and geometrical optics. Since geometric optics is a limiting case of the theory of wave optics, it has been suggested that Hamilton might have constructed the mechanical analogue to wave optics on the basis of this analogy. This mechanical analogue is today called *wave mechanics*, and was not discovered until Schrödinger derived his wave equation in 1926. For a development of wave mechanics from this point of view, the reader might consult the little monograph of H. T. Flint (*Wave Mechanics*, Methuen, London, 1929).

Indeed, many of the fundamental optimality principles of physics are closely related to one another. For instance, Hermann Weyl (*Space, Time, Matter*, Dover, New York, 1950, p. 244) shows how Fermat's principle may be derived from the formulation of general relativity in terms of geodesics.

5. See for example D'Arcy W. Thompson, *On Growth and Form*, (revised edition), Macmillan, New York, 1945, especially Chap. VII. For a physical discussion of the minimal character of liquid films, see G. Joos, *Theoretical Physics* (2nd edn), Hafner, New York, 1950, pp. 220-5.

6. H. Goldstein, *Classical Mechanics*, Addison-Wesley, Reading, Mass., 1950, pp. 46-47.

7. Justice cannot be done to this complex and manifold subject in the space of a few pages, therefore the reader is urged to consult the literature for further details concerning this cornerstone of biology. Two excellent review volumes, which may serve as a first approach to the literature, are the following:

'20th Century Darwinism', *Cold Spring Harbor Symposium on Quantitative Biology*, Vol. 24 (1959).

*Evolution After Darwin*, Vol. 1, 'The Evolution of Life'. Sol Tax (ed.), University of Chicago, Chicago, 1960.

Another very fine book is that of B. Rensch, *Evolution Above the Species Level*, Methuen, London, 1959. These works also constitute general references for the subsequent discussion of Chaps. 4-6.

8. This assertion is a special case of Gause's well-known *Principle of Exclusion* (see G. F. Gause, *The Struggle for Existence*, Williams & Wilkins, Baltimore, 1934), which states that two competing species cannot indefinitely share the same ecological niche; i.e. that one of them will eventually be completely displaced. For experimental work bearing on this principle see, for example, T. Park, 'Experimental Studies of Interspecies Competition', *Ecol. Monogr.*, 18 (1948) 265-308. (It should be noted that many ecologists do not accept the validity of the Gause principle, arguing that in nature no two species ever do share exactly the same niche.)

9. What is called 'fecundity', or net rate of production of off-spring, is roughly analogous to the term 'fitness' as used in population genetics. See Chap. 11, Section 11.4 and in particular Note 14.

10. The notion of optimal design is, of course, an old one, and permeates (at least in spirit) much of the older literature on quantitative biology (cf., for example, the extensive literature on honeycombs cited in D'Arcy Thompson, *op. cit.*, p. 525 *et seq.* The honeycomb still inspires important mathematical work related to optimality; see, for example, L. Fejes Tóth, 'What the Bees Know and What They Do Not Know', *Bull. Am. math. Soc.*, 70 (1964) 468-81. However, the first explicit statement of the Principle of Optimal Design in its general form is due to N. Rashevsky (cf. his *Mathematical Biophysics* (3rd edn), Dover, New York, 1960, especially p. 292 *et seq.* of vol. II).

Quite recently, geometrical ideas similar in spirit to those which appear in the literature on honeycombs have been employed to explain the symmetry of spherical viruses. See, for example, D. L. D. Caspar and A. Klug, 'Physical Principles in the Construction of Regular Viruses', *Cold Spring Harbor Symposium*, Vol. XXVII (1962), 1-24; 'Structure and Assembly of Regular Virus Particles' in *Viruses, Nucleic Acid and Cancer*, Williams & Wilkins, Baltimore, 1963, pp. 27-29; H. D. Mayor, 'Icosahedral Viruses—A Geometric Approach to their Maturation', *ibid.*, 63-67.

It might also be appropriate to note here that ideas of optimal design as a consequence of natural selection have also been invoked at the molecular level, in an attempt to attain some insight into problems connected with the origin of life. Such notions of 'molecular ecology'