References and Notes

1. The terms membrane carrier, carrier, and transport system are used interchangeably in this article to signify a system obeying saturation kinetics, which facilitates the movement of specific compounds across the cytoplasmic membrane.
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3. C. R. Scriver, *N. Engl. J. Med.* **273**, 530 (1965).
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6. This specificity is not absolute. D-Methionine shows definite, though very low, affinity for the neutral amino acid carrier (*4*). Also, elimination of the α-hydrogen may yield compounds with detectable, albeit much reduced, affinity. In Ehrlich ascites tumor cells, *N*-methyl derivatives may be transported by a second carrier system that may be specialized for this cell type; compare (*2*).
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15. Interactions with position 1 are also interesting with respect to the physiological substrate galactose, which is also transported via the "glucose" system. This substrate is phosphorylated by galactokinase (E.C. 2.7.1.6) at position 1, and this is its reactive site. The fact that several structural modifications are permissible for transport can lead to the erroneous conclusion that binding to this site is not critical. Thus, 1-deoxy-D-glucose and a score of α- and β- (1-substituted) alkyl glucosides are transported. However, some puzzling exceptions are aurothio-D-glucose and β-thiomethyl glucoside, and these are not transported [B. R. Landau, L. Bernstein, T. H. Wilson, *Amer. J. Physiol.* **203**, 237 (1962)]. One interpretation of these data is that the thio derivatives could not be hydrogen bonded to a carrier protein, and this is strengthened by an analysis of various galactose derivatives (*13*). 1-Deoxygalactose and methyl-β-D-thiogalactopyranoside are not transported, but α-D-galactopyranosyl fluoride is. Since the deoxy or thio derivatives cannot form hydrogen bonds, whereas the fluoro analog can, it is suggested that hydrogen bonding to the one position is essential for transport. Only limited information is available on the specificity of galactokinase [F. Alvarado, *Biochim. Biophys. Acta* **41**, 233 (1960)]. The data available do emphasize the complementary nature of galactokinase and sugar transport specificities. Thus, derivatives at carbon-2 such as 2-deoxygalactose and talose (the 2-epimer of galactose) which are rejected by the transport system are phosphorylated by galactokinase. On the other hand glucose, the 4-epimer of galactose, is rejected by galactokinase.
16. PRPP, 5-phospho-α-D-ribosyl pyrophosphate (Fig. 3).
17. The kinetics of product inhibition indicate that the catalysis proceeds as an ordered sequential reaction. PRPP adds first to the enzyme, then adenine; PP_i leaves, then AMP [A. Kornberg, I. Lieberman, E. S. Sims, *J. Biol. Chem.* **215**, 417 (1955); R. D. Berlin, *Arch. Biochem. Biophys.* **134**, 120 (1969)].
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25. The actual concentrations used were (mmole/liter): tris hydrochloride, 50, *p*H 8.29; magnesium chloride, 2.0; PRPP, 0.1; and adenine, at its apparent K_m, 0.002. The enzyme was prepared from rabbit polymorphonuclear leukocytes isolated from peritoneal exudates. The cells were subjected to sucrose lysis after the method of Cohn and Hirsch [*J. Exp. Med.* **112**, 983 (1960)], and the enzyme was assayed directly from the soluble 8000*g* supernatant fraction. The AMP product was stable in this extract, which also contained no adenase, guanase, or xanthine oxidase. The enzyme specific activity was 0.02 unit per milligram of protein (1 unit = 1 micromole converted per minute). The sensitive assay was performed by chromatographic separation of substrate and product [R. D. Berlin and E. R. Stadtman, *J. Biol. Chem.* **241**, 2679 (1966)]. Paper chromatography of the reaction mixtures in three solvent systems indicated that adenine and AMP were the only radioactive compounds present.
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Information Theory in Biology after 18 Years

Information theory must be modified for the description of living things.

Horton A. Johnson

Several years ago *Science* published an article by E. N. Gilbert entitled "Information theory after 18 years" (*1*). In reviewing the contribution of information theory to communications engineering, Gilbert, though still hopeful, found that up to that time it had flourished on promises alone.

In biology the role played by information theory has been even more disappointing. Its introduction into biological thought in the early 1950's promised a calculus uniquely suited to the mathematical description of living systems. Now, after 18 years of symposia and published articles on the subject, it is doubtful whether information theory has offered the experimental biologist anything more than vague insights and beguiling terminology.

After reviewing some of these hopes and disappointments, I shall point out some new directions in which information theory might evolve to become a useful general calculus for biology.

Early Expectations

During the past 100 years, in which physical sciences have enjoyed such a profitable interplay between experiment and mathematical theory, the life sci-

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ences have developed without the benefit of a general quantitative theory. This is not to minimize the contribution of physicochemical theory, which has been invaluable in dealing with specific physicochemical phenomena in living organisms. I do not refer to this type of theory, but rather to a general method of analysis which would apply to an entire organism or group of interacting organisms. Such a theory would provide a means of bookkeeping much like thermodynamics, which, given an initial description of a system, will allow quantitative prediction about that system at some future time. Given, at time t_1, a steam locomotive with a certain amount of coal, energy bookkeeping will tell us how far up a hill the engine will be at a time t_2 when it runs out of coal. One would like to be able to do this sort of thing with a living system. Given the conditions of a living system at t_1, one would like to be able to make a quantitative prediction about that system at t_2, when it runs out of something or other. But what is that "something or other"? It will have to be a fundamental, essential, and measurable property of living matter.

Although free energy is such a property, thermodynamics has a limited predictive value in biology. It cannot tell us when a system is alive; it can only tell us when a system is *not* alive.

Structure or organization is much more definitive than free energy in this respect. For example, there are many possible arrangements of the atoms which make up an amoeba. Only a small fraction of the possible arrangements have sufficient free energy to support life. But of all the arrangements energetically compatible with life, only a very small fraction will have the proper spatial relationships or structural organization to form a living organism. Specific organization is a far more stringent determinant than free energy for defining a living system. This is why information theory has been so attractive to biologists; it provides a way of quantifying organization, and the maintenance of specific organization is the essence of life.

One of the first to recognize the potential significance of information theory in life sciences was Henry Quastler, who, within 4 years after the appearance of Shannon's celebrated paper in 1948 (*2*), edited a book on the applications of information theory to biology (*3*). This was particularly exciting because the concepts of macromolecular storage and transfer of information were just beginning to take shape, and information theory seemed to go hand in hand with the new molecular biology. Quastler pointed out, for example, that a single amino acid has about the information content of a word, and that a protein molecule has roughly the information content of a paragraph of English prose. The DNA in a mammalian cell has a capacity of about 2×10^{10} bits of information, which is equivalent to about 100 sets of the *Encyclopaedia Britannica.* To estimate the complexity of an entire organism was also of interest. One could simply say that the level of complexity or organization of an organism is measured by the number of bits of information needed to describe it. In 1955 Morowitz (*4*) estimated that about 2×10^{11} bits of information are required to describe an atomic map in three dimensions of the bacterium *Escherichia coli.* This result was in general agreement with the information content based on the physical negative entropy of *E. coli* as derived from calorimetric data.

Information theory seemed to be an exciting new way to measure a fundamental property of living things, and it was hoped that this would eventually lead biology into quantitative maturity. In the ensuing years, however, information theory never offered any real help in designing or interpreting an experiment, and this, after all, is the only measure of the significance of a theory. In principle, information theory seems to offer just what biology needs: a quantitative theory of organization. Why has it failed to find its place in the laboratory?

Deficiencies in the Existing Theory

One should expect that a theory developed specifically for the analysis of communications systems might not be in the best form for the analysis of biological systems. Yet biologists have been reluctant to tamper with information theory. If we are brash enough to look this gift horse in the mouth, we can find at least two features of information theory in its present form which make it incompatible with theoretical biology.

The present theory, defining information as a displacement from randomness or as negative entropy, deals only with the quantity of information or organization; it says nothing about the quality of that information. But, in biology, quality of information is just as important as quantity. Take, for instance, two rabbits in a box. The information in the box, measured as physical entropy, is about the same whether the rabbits are of the same sex or of different sexes. Yet the future of that biological system depends entirely upon the sexual quality of the information in it. Information theory misses the biological point completely.

Second, living things are open systems for information. Metabolism requires the extraction of negative entropy from the environment for the synthesis of highly ordered structures within the organism. At the same time, ordered structures within the organism are continuously being broken down. Thus there is a continuous but irregular flow of negative entropy, or information, through the organism. In order for a system of bookkeeping to have predictive value, it is important to define some sort of closed system in which a conservation rule can operate.

It is not sufficient to define biological information in physical terms only—that is, as negative entropy. It seems necessary to define it further in terms of a qualitative factor which is uniquely biological, and to recognize among the several species of biological organization those which are maintained in closed systems where conservation rules can be formulated.

Some Proposed Modifications

A qualitative factor. In biology some information is more important than other information, but information theory in its present form, wherein all structure or organization is viewed as physical negative entropy, cannot distinguish the significant from the trivial. Evidently the quantitative measure, information, must be modified by some sort of qualitative factor. This does not seem strange, after all, because in thermodynamics we are accustomed to measuring energy by an extensive factor, entropy, modified by an intensive factor, temperature. In the same way one might expect to modify the extensive property, negative entropy or information, by an intensive factor. This intensive factor will have to indicate the biological intensity of the physical quantity, negative entropy. It will have to state what part of the organization or information is biologically significant or purposeful.

This changes the problem enormously. Of the 2×10^{11} bits of physical information which Morowitz found in

Escherichia coli, how much was really vital or purposeful for the future of that organism? Most of it must have been trivial or even irrelevant to the future life of the bacterium. Every random orientation of a molecule, every momentary folding of a membrane, was included in his atomic map from which the information content was estimated. If all of the instructions necessary for the growth and maintenance of the organism were contained in its DNA, which has maximum coding capacity of 10^7 bits, then only about one part in 20,000 would be purposeful, and the intensive factor would be of the order of 10^{-4}.

Purposeful information is highly specific. Physical organization or negative entropy can be produced by metabolic processes which increase the entropy in the environment of an organism, but that biologically purposeful information which directs the synthesis of an enzyme or the assembly of a mitochondrion is of a very specific kind. Once lost, it cannot be recovered simply by turning low-entropy glucose into high-entropy carbon dioxide. Although a living organism is an open system for negative entropy (and therefore for information in the usual sense), it is a closed system for purposeful information—that specific structural information which directs life strategy, the synthesis of specific proteins, the structures of organs, reflexes, instincts, and so on.

By further limiting the definition of purposeful information to information which cannot be obtained metabolically from the environment, we gain an advantage in that we can now consider a closed system and thereby formulate a conservation rule which will have predictive value. We can say that a living system—a cell, a colony of cells, a multicellular organism—cannot maintain life without a certain minimum level of purposeful organization. If this is a sine qua non of a living system, and if this information cannot be renewed from the environment, then there must be a conservation of purposeful information within the living system. This is a one-way conservation law: purposeful information of a living system can increase but cannot decrease indefinitely.

A selection term. There is another kind of information which is not dealt with in communications information theory but which is essential for the description of living things. Returning to the two rabbits in a box, let us assume that the quality of information in the box is such that we have a biologically purposeful combination of animals. There is still one more requirement if the system is to have a biological future: the size of the box. If it is too large the rabbits may never find each other. Elements of a biological system must be sufficiently concentrated to interact. If the map of *Escherichia coli* were used to construct a single bacterium the size of a cucumber, and if the interstices were filled with inert helium molecules, everything would be in the proper relative positions and the total structural information would be the same, but the structure would not be alive. But if one were to sort out all of the helium molecules, the structure would collapse to its proper size and would begin to live. This sorting process increases the information in the organism. This kind of information, identical to the entropy of mixing, was not included in the original map. When a gas expands or diffuses into another gas, the entropy of the gas increases. In the biological case we are interested in a reverse process—the negative entropy of compressing elements of a system, of "unmixing" or sorting. We have said that proximity of certain elements of a living system is essential for life, so part of the negative entropy of sorting or concentrating is biologically purposeful information. A statement about a change in total purposeful information ΔI_t can be written

$$\Delta I_t = \Delta I_s + (\Delta n)\ (\log_2 a) \qquad (1)$$

where I_s is the purposeful structural organization, the information inherent in the elements of the system and their relative positions. The last term represents the change in purposeful concentration of those elements. The latter is written as the number of purposeful selections, Δn, multiplied by the information value of each selection; a is the number of alternatives from which a selection is made.

This statement says that the purposeful information in a living system consists of two moieties, (i) that of the elements themselves and their geometric arrangement relative to one another, and (ii) that of the concentration of those elements due to the sorting out of irrelevant elements.

A conservation rule. I have said that a certain minimum of purposeful information is necessary for the survival of a living system and that this purposeful information, by definition, must be maintained within the system and cannot be supplied by the environment. Therefore a continued loss of purposeful information is not compatible with life. For any living system under survival conditions

$$\Delta I_t/\Delta t \geqq 0 \qquad (2)$$

where I_t is the total amount of purposeful information in the system and Δt is a time interval which spans at least one generation of the individuals in the system. Combining Eqs. 1 and 2 gives

$$(\log_2 a)\ (\Delta n/\Delta t) \geqq -\Delta I_s/\Delta t \qquad (3)$$

Thus, purposeful structural information, as defined here, exists in a closed system. Being negative entropy in a closed system, it must decrease with time according to the second law of thermodynamics. That is to say, there will be continuous disordering of specific structure within the system. To compensate for the spontaneous disordering, there must be a continuous ordering or sorting process. Equation 3 states that new purposeful information must be generated within a living system by some sort of selection process at a rate (left-hand term) equal to or greater than the rate of decay of specific structural information (right-hand term).

In other words, the organization of a living system must be maintained at a certain minimum displacement from randomness. Thermodynamics tells us that this organization will drift toward randomness. This drift must, then, be opposed by self-organizing, selective processes which tend to recreate order. At this point we are forced to conclude that there can be no sustained life in the absence of a continuing selective process. This is a deduction from just two premises: (i) the definition of a class of information for which a living system is a closed system and upon which it is vitally dependent, and (ii) the second law of thermodynamics. We have, by these assumptions which seem to fit the facts, arrived at a fundamental property of living things which would not be directly deducible from physical laws alone.

Redundant and derivative information. There are further subdivisions of information which are essential in describing living matter. This time let us consider the amount of information in a stack of books, each a copy of Euclid's *Elements.* What kinds of information are represented here? If we define a purpose then we can decide what is purposeful and what is not. Let us say that the purpose is to set forth the relationships between the elements of plane figures. We can easily identify

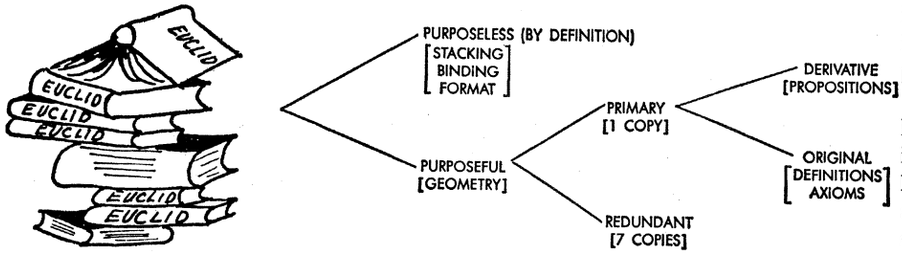

Fig. 1. Classification of information in eight copies of Euclid's *Elements*. These subdivisions must be recognized in biology, because their operational significance is very different.

some of the purposeless information—the materials of which the books are made, the colors of their covers, the order in which they are stacked, the format, the kind of type, the page numbers, and so on.

Having eliminated the purposeless information in the stack of books, we find that we can now further subdivide the purposeful information—the information which deals specifically with geometry (Fig. 1). Any one volume will give us as much of this information as all of them together. We can throw out all volumes but one and call the discarded purposeful information redundant. The single remaining volume contains what we can call nonredundant or primary information.

In this single volume there are 13 books containing proofs of nearly 500 propositions. These proofs are all logical consequences of the first few pages of the volume, those which list the 35 definitions, five postulates, and ten axioms. In principle, if any of the other pages were missing, the information on them could always be derived again from the original definitions, postulates, and axioms.

The proofs of the propositions, while not redundant, are not essential as long as the definitions, postulates, and axioms are intact. We can call the definitions, postulates, and axioms original information, and the propositions derivative information.

Similarly the entire output of a computer may consist of new, purposeful, and nonredundant information, but it is all derivative information, being the result of specified operations upon the original information contained in the program.

In biology, embryogenesis provides an analogous situation. All of the structural information of the developing individual is derived from a single egg, which contained all of the original information. The individual is an operational consequence, a derivative, of the original information. In a multicellular organism most of the cells are derivative—that is, they can be replaced from a store of original information in so-called stem cells. The original information is redundant, and the redundancy affords a certain protection, but redundant stem cells may be lost or errors may appear in their genetic material, until finally, when the last of the original information is gone, that part of the organism's information is gone forever. Circulating blood cells are derivative and are expendable, since the instructions for making more are in stem cells. But let an animal be irradiated to the point where his last stem cell is gone and he cannot recover.

Since this information, by our definition of purposeful information, cannot be taken from the environment, it represents negative entropy in a closed system and must, according to the second law of thermodynamics, decay with time. Since, once having been lost, it cannot, by our further definition of original information, be regenerated within the individual, the individual must undergo a continuous loss of original information with time. The outward manifestation of purposeful biological information is function. The definition of a class of original information suggests that, with the passage of time, all organisms must suffer a continuing loss of function.

Some Applications

Let me illustrate through several examples how these ideas might be put to work in experimental biology. Admittedly the problems are not as well defined as one would like, the quantities used are accurate only to within an order of magnitude or so, and numerical results are only first approximations. I present these examples only as a broad indication of some of the new directions in which information theory might profitably move.

Cell proliferation. First let us try Eq. 3 at the cellular level by considering a bacterial colony. Bacteria can be kept proliferating in a steady state in a so-called "chemostat," a device, designed by Novick and Szilard (*5*), in which the population size is kept constant by a continuous inflow of nutrient medium and an equal outflow of medium plus bacteria. The continuous washing out of bacteria allows the colony to remain indefinitely in logarithmic growth.

The conservation rule says that, as purposeful information is lost through entropic decay, purposeless information must be selected out. Selection, in terms of the chemostat, means a selective proliferation of relatively error-free bacteria to replace the error-free and error-laden cells swept out of the culture indiscriminately by the washout process. The washout rate will be the maximum rate at which error-free bacteria can replace error-laden organisms. The conservation rule defines a minimum washout rate that is compatible with a steady state and below which the colony will deteriorate. The minimum rate will be such that, for every bacterium which suffers a loss of purposeful information, one intact bacterium will be replicated and one defective bacterium will be washed out of the culture. If we knew the rate at which information is lost from the system, we could predict just what that minimum rate should be, but, as it is, we can only make a rough estimate. Novick and Szilard, using *Escherichia coli* in the chemostat, measured a mutation rate, resistance to T5 bacteriophage, to be 10^{-8} per bacterium per hour. If this mutation is the result of a single amino acid substitution, then it represents the loss of a single codon, or 6 bits of information, from the genetic message. If one can use this as an indication, then information is lost from DNA at a rate of about 1.6×10^{-9} bit per bit per hour. If the total purposeful information is of the order of the information content of the bacterial DNA, it is about 10^{7} bits per bacterium. Assuming these estimates to be reasonable, we find that information is lost at a rate of about 10^{-2} bit per hour per bacterium. If most mutations are deleterious to the future of the organism, then one can say that the bacteria turn from purposeful to purposeless elements at a rate of about 10^{-2} per hour. The

conservation rule says that purposeless elements must be sorted out as rapidly as they are formed, so at least 10^{-2} of the bacteria have to be washed out each hour. Since the good are washed out with the bad, the overall washout rate must be higher.

Novick did, in fact, find a minimum washout rate of about 10^{-1} below which the steady state could not be maintained (*6*). The numbers used in this estimate are rough approximations, so the agreement of the theoretical result with the experimental data proves nothing. But it does show that a conservation rule of the type stated in Eq. 3 *could* account for the observation.

It seems reasonable to conclude that, for any cell population or tissue, there must be a quantitative relationship between the rate of cell proliferation and the rate of information loss, and that, when information is not conserved by selective proliferation, that population must surely deteriorate. These rates are measurable, and, once they are known, the quantitative relationship between them could be useful in the laboratory. It is conceivable that one could calculate the cell proliferation rate necessary for functional stability of a given tissue, could predict the rates of informational and functional loss in tissues with slow rates of proliferation, and could predict whether a line of cultured cells would deteriorate with time.

Chemical homeostasis. There is a very different way in which information theory can be exploited in biology, through use of the concept that information is equivalent to negative entropy. Szilard (*7*) expressed this quantitatively, starting with the statistical definition of entropy $S_0 = k \ln W$, where S is the entropy of a system, W is the number of its possible microscopic configurations (Planck's complexions), and k is Boltzmann's constant.

The generation of one bit of information about the system halves the uncertainty of the number of possible complexions. $S_1 = k \ln (W/2)$, and the entropy change associated with one bit of information or one binary decision is

$$\Delta S = S_1 - S_0 = -k \ln 2$$

Since the entropy of the closed system cannot decrease, the entropy of the observer, who is part of the system, must increase by at least $k \ln 2$, and at Kelvin temperature T his free energy must decrease by at least $kT \ln 2$ units. Since Boltzmann's constant is of the order of 10^{-16} cgs unit, the energy cost of making observations (creating new information) is real but so small that it is of practical significance only in certain unusual cases. This consideration is rather like the relativistic correction, which always applies but is important only in describing something moving very fast. The energy equivalent of information always applies, but it is important only in describing enormous numbers of observations. (It is an interesting thought that this places an energetic constraint on Laplace's mechanistic determinism.) In living things there are control devices which are required to make so many observations that the energy expenditure becomes significant, predictable, and measurable.

The kidney is an example of an organ in which the energy cost of information gathering is of major importance. This concept has made possible the solution of a longstanding problem in renal physiology (*8*). The kidneys are second only to the heart in rate of oxygen consumption per weight, and accordingly they should be among the hardest-working tissues in the body. But in fact the only measurable work the kidneys do on their external environment is the osmotic work involved in concentrating urine to conserve water. This amounts to less than 1 percent of the energy input! That such an elegant device should have such a dismal thermodynamic efficiency has troubled renal physiologists for half a century. But the kidney's primary function is not to concentrate urine but to control the composition of the extracellular fluid, the critical environment in which all cells live. Information theory tells us that any control function, insofar as it involves the generation of information, requires energy. As, in the wake of metabolism, the extracellular fluid tends to deviate from its ideal composition, the kidneys must maintain a continuous surveillance over ions and molecules in the fluid and a continuous sorting out of unwanted particles. This is a matter of a very large number of observations, so large that the energy cost of generating information, until now only a theoretical curiosity, becomes significant.

The problem can be approached in this way. Purposeful sorting of particles requires that the kidney recognize each particle sorted, and in order to recognize a particle there must be some sort of coupling between the kidney and the particle, a kind of interrogation signal, if you will. Now what will be the minimum cost of generating such as signal? Information theory says that the simplest sort of observation, recognizing one of two equally probable things, cannot be accomplished for less than $kT \ln 2$ units of free energy. Multiplying this small cost by the vast number of selections made by the kidney over a period of time gives a power requirement which is large enough to put the kidney well on its way to respectable efficiency. But this cost per observation is an absolute minimum, based on a noiseless condition, and for a practical level of reliability in the presence of noise the cost will be even greater.

Regardless of the mechanism, recognition of a particle requires the generation of some sort of interrogation signal distinguishable from background thermal noise, which has a mean amplitude of kT, or 0.027 electron volt at body temperature. The reliability of the selection process is dependent upon the signal-to-noise ratio. The composition of the extracellular fluid is maintained within a range of about $\pm$ 5 percent. It can be shown that a signal-to-noise ratio of 3 gives a chance of less than 5 percent for errors due to random thermal perturbations. This level of reliability requires a recognition signal of at least $3 \times 0.027 = 0.08$ electron volt. Man's renal tubules select about 10^{22} ions (chiefly Na^+) per minute. The power requirement for recognizing these ions is $0.08 \times 10^{22} = 8 \times 10^{20}$ electron volts, or about 30 calories per minute.

The power consumption of the human kidneys is about 100 calories per minute. This gives an efficiency of about 30 percent, which, if the figure is correct, means that the kidney works more efficiently as a control device than the heart works as a mechanical pump. Its efficiency is as impressive as that of a diesel engine.

Why had this informational "work" escaped the notice of conventional thermodynamic analysis? Selection of sodium ions, for example, is equivalent to the momentary separation of ions into two classes: sodium and nonsodium. If these two classes were to remain separate, we would be aware of an increase in free energy resulting from the increased order due to the "sorting work" of the kidney. However, the ions and molecules selectively conserved are immediately remixed and returned to the extracellular fluid, so that the free energy generated by sorting is lost by the entropy of mixing and degraded to heat without ever appearing as a directly measurable increase in free energy.

Here information bookkeeping has given us some quantitative insight which had not been deduced from thermodynamic bookkeeping.

Aging and death. Earlier I defined a species of original information which, in contrast to derivative information, cannot be replicated by the organism once it is lost. This irreplaceable essential information is stored in the specific structure of certain molecules, cells, and organs. None of these structures is entirely stable, and each will have a finite rate of decay at any temperature above absolute zero. In other words, this species of irreplaceable information is negative entropy in a closed system and must, therefore, decrease according to the second law of thermodynamics. It is interesting to examine the possibility that the unavoidable, cumulative loss of original information or organization, with its resulting loss of function, might be the basis of the aging of living things.

A commonly used operational definition of age is the probability of death in a given time interval, or the age-specific mortality rate. The changing probability of dying with increasing age is called the Gompertz function.

If a complete set of essential, original information is necessary for the maintenance of life in an organism, then the probability that such a set of information will become incomplete with the passage of time should be equivalent to the Gompertz function for that organism. The rate of loss of original information will depend upon the intensity of the many and various perturbations which tend to disorder structures or molecules in the organism—for example, spontaneous thermal fluctuations in chemical bonds, ionizing radiation, or reactive chemical species such as free radicals and peroxides. The rate of decay of this information will also reflect the tendency of living things to avoid loss of information by molecular, cellular, and tissue repair mechanisms. If this essential original information is allowed to decay as a first order process, one obtains the probability of death as a function of time. Varying the redundancy of this information generates a family of theoretical Gompertz functions which fit closely the actual measured Gompertz functions of various mammals (*9*). This is, to be sure, no more than curve fitting and proves nothing. It does indicate, however, that what we observe as aging *could* be basically the decay of original information, and the curious fact of the different rates of aging in different mammals *could* be explained on the basis of different orders of redundancy of original information.

One last bit of insight. Although the individual must decay, the species need not. A man has as much purposeful information at age 20 as his father had at age 20 and as his son will have at age 20. In other words, the net change in information over a complete life cycle is zero:

$$\oint dI = 0$$

Going back to the conservation law, we find that the flow of information through successive generations must be acted upon by strong selective processes to compensate for the inevitable decay of information in the individual. One way to overcome this decay would be to select, at some time in the cycle, just one cell from an adult—one cell with a complete complement of original information—and then build up a new individual, a new set of derivative information, from that. The sex cycle, the periodic reduction to a one-cell stage, must result in an enormous sorting out of purposeless information. The selective process for the sperm is awesome. The mammalian sperm must swim what for its size is equivalent to many miles, through thick mucous, and, what is more, to qualify it must arrive at the finish line first in a field of more than 100 million. The sex cycle is more than a means of creating new individuals. It is a Maxwell's demon restoring negative entropy to the pool of original information at regular intervals in the history of a species.

Conclusion

Information theory has failed thus far to provide a useful calculus for experimental biology. This failure can be laid to the fact that information theory, in its present form, quantifies negative entropy, an extensive property. In thermodynamics the extensive property, entropy, must be modified by an intensive property, temperature, in order to signify the feasibility of a process. Similarly, in biology the extensive property, information or negative entropy, can have significance for the feasibility of a living process only if it is modulated by an intensive property which indicates the biological relevance or purposefulness of that information.

Futhermore, it is necessary to define operationally the several kinds of information in a living system. There are species of information for which a living system is a closed system. In such cases there can be established conservation rules which have predictive value.

With modifications such as these, information theory may yet become a useful system of theoretical biology. It may yet provide a way of coming to quantitative grips with such varied phenomena as cell proliferation, aging, and chemical homeostasis.

References and Notes

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