Genetics and Epigenetics of Neural Function: A Model

Michel Kerszberg
Institut Pasteur, Neurobiologie Cellulaire
France

Abstract

■ A neural model for one- or few-trial irreversible behavior learning such as occurs in imprinting is introduced. It is assumed that synaptic connections in the relevant parts of the central nervous system are initially set up in a largely, but not totally random fashion, as a result, for instance, of differential cell–cell adhesion. The behavior to be learned is then sometimes exhibited, but not in a reproducible, mature way. During early neural activity, active postsynaptic neurons may, however, deliver a putative retrograde trophic factor to some of their afferent synaptic boutons. This is taken to occur according to a Hebb-type rule. At a later stage, only those synapses that have accumulated enough trophic factor are stabilized selectively. We show explicitly how this process may lead to a perfectly wired circuit. The calculations indicate that if the connections were relatively well defined from the beginning, then random pulses at the inputs suffice for this refinement process to take place. This is analogous to the maturation of neural circuits under spontaneous electrical activity (*unsupervised* learning). If the initial connections are "fuzzy," however, well-defined patterns of activation are needed at the inputs so that selective stabilization leads to a correct functional system (the model now behaves in an *instructionist* mode). Experiments suggested by the model are discussed, and involve the manipulation of afferent inputs, of the initial synapse distribution, or of the stabilization phase. ■

INTRODUCTION

The central nervous system (CNS) of a newborn animal exhibits remarkable abilities, which develop, often spontaneously, into mature behavioral patterns. Thus, many birds develop a normal song even when reared in isolation; others, however, whose song is not obviously more complex or variable, require specific auditory inputs (Kroodsma 1982): they must *learn* to sing. This entails a period of relative vulnerability and increased dependence on congeners.

The statement has often been made that maturation and learning are indispensable because our genetic system cannot possibly code for the complete CNS wiring diagram; one could likewise argue there is not enough genetic information available to describe the full arrangement of the body's atoms! Such statements neglect the fact that ontogenesis is, after all, effected by extremely elaborate and polyvalent cellular mechanisms operating under the control of what may actually amount to relatively few genes. I shall argue in the next section that because of this, the genetic specification of complex neural wiring diagrams down to the level of individual neurons might, in fact, be possible *in principle*. The lack of flexibility of such a specification will also be apparent from the example I shall sketch; and thus, although the full CNS of, say, mammals, *could* be entirely specified by very few genes, with no outside influence, we shall also see that it would not be tenable to advocate this view seriously.

On the whole, then, the question as to why some capabilities of the CNS have to be learned, and others do not, remains to a large extent open; it is surely reasonable to imagine, however, that an evolutionary advantage is gained from learning, or, at least, from a maturation phase, and that the improvement comes in terms of flexibility and reliability. In this work I will examine in some detail how this may sometimes come about.

My main thesis will be that certain forms of learning, at least, combine the intrinsic security afforded by genetic mechanisms, together with the flexibility of learning processes, in the following way. A wiring diagram is initially set up, but in a fuzzy way, through the agency of genetic factors, which are postulated to regulate the differential probabilities with which various neuron classes form connections with others; because of this probabilistic feature, the emphasis is drawn away from individual neurons, toward neuronal *groups*. Later, through the selective provision of trophic support to those synapses that satisfy a Hebb-like condition, certain terminals are stabilized and others are eliminated. The final result depends on the initial wiring, but also on the input patterns with which the system is fed during the stabili-

zation phase. These input patterns represent the contribution of the environment to the maturation process, which is, thus, under the combined control of endogenous mechanisms and external stimulation.

Note that, in this approach, attention is concentrated naturally on neural assemblies as a result of the imperfect nature of the original circuitry: assemblies are actually *needed* for the model to work.

The third section will be devoted to a description of the type of learning behavior I should like to study here, as illustrated, for example, by bird song acquisition. In the fourth section the biological premises I shall use will be described, and the model then defined; the fifth section contains a brief derivation and a discussion of the results. The perspectives these open for further research are examined in the sixth section. Finally, the experimental predictions this work leads to are summarized in the last section.

Why Learning?

In this section, I should like to develop a specific scheme whereby the wiring diagram of the CNS might be completely defined on a genetic basis, down to the individual neurons' level, in a biochemically plausible, but evolutionarily impossible way. This will bring the question of "Why Learning" into sharper focus: one will henceforth be motivated to introduce a model in which the shortcomings of a purely genetic construction may be overcome.

As mentioned in the Introduction, ontogenetic phenomena are believed to proceed through the multiplicative, combinatorial effects of control genes acting on batteries of constitutive and other control genes (Britten & Davidson 1969). What could the role of specific genes controlling CNS development then be? One possible answer is that these genes might simply provide a *unique* set of molecular labels on every neuron's surface. Once each neuron was individually identified, the membrane molecules encoded for or controlled by the label genes could regulate such characteristics as neuron morphology and the adhesion of a neuron's growth cone to other neurons' membranes, thereby establishing the final wiring diagram. Neurotransmitter and receptor types would also be fixed, thus determining the sign and other features of the connections. Now, assuming two alleles per "brain gene" locus, unique specification of a complete labeling for n neurons would require $m = \log_2 n$ loci, that is, a few tens of loci only! The labeling proper, for example, setting up the activity pattern of these and other genes in each identified neuron, could then be effected by the developmental machinery itself, using the allele information embodied in the m loci. Of course, such a scheme strongly limits the possible connectivities, but, more seriously, it inevitably introduces a variety of drastically severe point mutations (those of the genes coding for the "high-order" labels, which may affect the labeling of large classes of cells), and this is not evolutionarily credible: such an unstable scheme simply introduces too many possibilities for quick, dramatic change. Furthermore, while complete circuit predetermination might make sense for highly stereotyped behavioral patterns, it becomes disastrous when adaptability is required. This balance between "nature" and "nurture" will be further discussed in "Further Perspectives" in the context of evolutionary theory.

Sensitive Periods in Learning and Selective Synapse Elimination

Some forms of learning (e.g., imprinting, or song acquisition in birds) present rather unique features: they occur early in life, lie under strong genetic dependence, and are characterized by *sensitive periods* (Marler & Terrace 1984), after which exposure to correct stimuli will no longer lead to successful skill retention. I propose a model that may be appropriate for this type of learning. In the past, although many models have dealt with epigenesis of neural systems, little attention has been paid to the interaction of epigenetic and *genetic* factors (Linsker 1986). Also, previous models were concerned mainly with setting up cognitive maps (Willshaw & von der Malsburg 1976); while the distinction was never made between imprinting-like phenomena and other types of cortical plasticity (Bischof 1983). Here I examine the developmentally timed emergence of *collective function* and *behavior* in neural assemblies under the combined influence of genetic and epigenetic determinants. The genetic component is responsible either for *spontaneous maturation* of behavior or for *unsupervised learning* of stable behavioral patterns; but the model also allows learning in an *instructionist*-type, input-driven mode in which the genetic component may be bypassed partially or altogether.

My starting point will be the assumption that certain genes do not specify neural circuits completely, but code instead for the *probability* that some connections will initially be established. Such statistical wiring entails a conceptual shift, emphasizing neuronal *groups* instead of single neurons, since a single cell cannot be representative of a statistical distribution. It also leads of course to almost—but not quite—random initial performance. During early neural activity, however, active postsynaptic neurons provide oncoming synapses with a putative *trophic factor* (TF) (Purves & Taghert 1987); there follows a period during which synapses that have absorbed little TF are eliminated (Purves & Lichtman 1980; Changeux & Danchin 1976; Stanfield 1984). Calculations on a single group of neurons will show how this process can lead, with great likelihood, to a perfectly wired structure. In a system rather sharply defined genetically, spontaneous, random activity suffices: as mentioned, this is analogous to maturation of neural circuits under spontaneous activity (Hubel & Wiesel 1962; Shatz & Stryker

1988; Galli & Maffei 1988); however, if the initial wiring is too fuzzy or even wrong, as will be likely when the past evolutionary environment for the behavioral trait under consideration has been highly variable, neural activity needs to be *biased* strongly through selective presentation of early stimuli for learning to take place. Learning by selective stabilization thus permits not only fine tuning, but complete functional correction as well. Surprisingly, however, I also find that if competition among synapses for trophic support is too fierce, learning can actually *fail*.

A synaptic retraction phase sculpts the CNS lastingly; less powerful learning mechanisms such as synaptic strength adjustment (Hopfield 1982) may be unable to correct whatever deficiencies appear at this stage: this suggests that behavioral refinement through synaptic elimination may be related to sensitive periods, a prediction that could be tested experimentally, for example, in the honeybee's first orientation flight (Brandon & Ross 1982).

In the following sections I define the model more completely, and sketch the results' mathematical derivation. I then discuss the outcome, mainly with the evolution of behavior in mind.

A Model

Consider a group (Edelman 1978) G of N_G neurons receiving N inputs from each of two other groups, A and B (see Figure 1a). Assume, for illustration, that its owner's fitness is increased if G detects $A \wedge \bar{B}$, that is, G should fire if and only if A is firing and B is not. This happens if A synapses have a net excitatory effect, while B synapses are globally inhibitory, and the threshold for G firing is somewhat positive. Such simple circuits can surely be built under exclusive genetic guidance; but, as complexity increases, this becomes less and less plausible: the required evolutionary time is prohibitive, and flexibility is insufficient, as previously discussed. I now construct a model that illustrates how the situation might be improved on both counts if one assumes inheritance of connectivity *probabilities* and relies on epigenetic "learning" processes for fine tuning. The hypothesis of differential, probabilistic connectivity is based, in particular, on the observation of analogue neurons, for example, in *Daphnia magna* parthenogenetic clones (Levinthal, Macagno, & Levinthal 1976), which indicates that the connectivity is determined only partially by genetic mechanisms. The model must allow for probability encoding that could be sharp (the probabilities are close to 0 or 1, i.e., the circuitry is effectively under genetic control) or loose (probabilities not very different from ½). We thus imagine that N is large and that a fraction $p_{A+} = ½ + \beta$ of the connections impinging from A is excitatory; for convenience, we also take $p_{B-} = p_{A+}$. Of course, $p_{A-} = p_{B+} = ½ - \beta$. A slight bias β can evolve quickly, when the appropriate genetic variance exists.

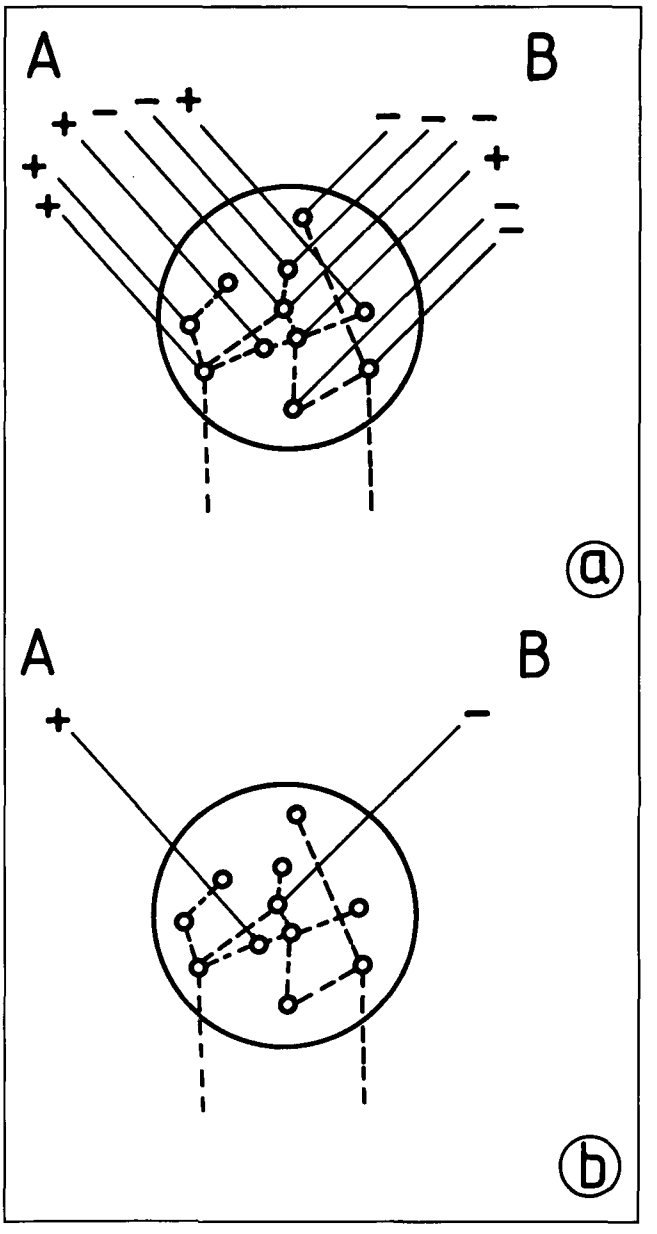

Figure 1. Hypothetical neural circuit used to demonstrate how selective synapse stabilization may lead to functional refinement in neural groups. (**a**) Before stabilization, a large number of afferent connections impinge on the group. There is a *bias* in the sign of the connections: in this case there are somewhat more excitatory connections from afferent A and inhibitory connections coming from B (this could be realized through various biologically plausible mechanisms: see text). The dashed lines denote interneuronal and output connections, which are assumed to be stable from the outset. The system is now subjected to inputs from A and B. (**b**) After stabilization, the only afferent inputs remaining are those that have received a sufficient amount of trophic factor from their postsynaptic neuron. This is assumed to take place according to a Hebb-type rule of correlated activities. It is shown in the text how the probability for various connections to survive varies in time, thus leading to improved functioning of the circuit. Here only one excitatory A-afferent, and one inhibitory B-afferent remain, a much sharper situation than in (**a**).

For instance, inhibitory links could be built by synapses adhering preferentially on inhibitory interneurons in G; differential adhesion suffices for this, as mediated, for example, by neural cell-adhesion molecules (NCAM) (Edelman 1983). Other cues (Dodd & Jessel 1988), such as substrate adhesion molecules, may produce related effects in a very different manner. This will not be discussed here in any detail. Note that various ways of actually realizing inhibitory or excitatory stimulation may lead to differing predictions; in what follows, I shall assume that the neurons in G have, for the most part, a net mutually excitatory effect; it is the afferent A- and B-synapses themselves that have a variable probability of being either excitatory or inhibitory.

Built in such a probabilistic way, the circuit functions erratically, since G's total weighted input is at most of order β, whatever A and B. Let us now show qualitatively how *selective* elimination, combined or not with training, increases this figure dramatically (the calculations are performed in the next section; see Figure 1b). I assume that the stabilization and functioning of the afferent synapses (but *not*, in this simple example, that of the G-synapses) depends critically on the retrograde delivery of TF by postsynaptic neurons. The idea is that with $\beta > 0$, even if inputs from A and B are random, neurons in G fire slightly more often when $A \wedge \bar{B}$ than otherwise; when active, they supply TF to firing excitatory synapses [Hebbian reinforcement (Hebb 1949)]: thus A_+ connections are favored, and will be protected when the developmental program calls for synapse elimination, which therefore enhances circuit discrimination.

The notion of activity-dependent release of trophic factors is not as yet well established experimentally. The concept is surely strengthened by various lines of evidence demonstrating synthesis of nerve growth factor (NGF), one of the most commonly mentioned putative trophic factors, by the targets of NGF-sensitive neurons (Shelton & Reichardt 1984), and the presence of NGF receptors on the membrane of these neurons (Davies, Brandtlow, Heumann, Korsching, Rohrer, & Thoenen 1987). However, there is no incontrovertible evidence for activity-triggered release itself (Henderson 1986). I shall proceed here on the assumption that such evidence should ultimately be produced.

In contrast to the A_+ terminals, preferential survival of B_- synapses would seem to require anti-Hebbian behavior, that is, delivery of TF from an active neuron to an inactive inhibitory connection (we shall not explore in detail the alternative suggestion that *active* inhibitory synapses might be reinforced by hyperpolarized postsynaptic neurons; the ensuing predictions can be worked out and will seldom differ significantly from those reached here). Evidence pointing in the direction of certain inactive synapses being preferentially stabilized has been found recently (Callaway, Soha, & Van Essen 1987), and we shall postulate such reinforcement; note, however, that it can be dispensed with if the system is built initially with a large overall excess of inhibitory connections, and G neurons have a suitably lowered firing threshold: sheer numbers then ensure survival of an inhibitory synapse, *unless* excitatory ones are reinforced.

What happens if $\beta \leq 0$? Correct wiring can still be achieved, but input presentation must be selective, so that, more often than not, A fires while B is silent. Then again, A_+ synapses will be reinforced, as they are those which fire most. Thus, "loose" circuitry can be trained to perform operations it was not programmed for, as the need arises; but the closer β is to $-\frac{1}{2}$, the harder the conversion. In an evolutionary perspective, it is interesting to note that the need to "train" immature circuitry through selective input presentation could lead to rapid coevolution of largely unspecific cortical structures and of parental "teaching" behavior (see "Further Perspectives").

CALCULATIONS AND RESULTS

I now sketch the calculations that support the above claims. If an A- or B-synapse fires with probability α in the presence of an oncoming action potential (A or $B = 1$), and $1 - \alpha$ otherwise (A or $B = 0$), then the normalized sum $s = S/N$ of all instantaneous inputs on G is essentially a random variable with Gaussian distribution $P_{AB}(s)$: its average is $2N\beta(2\alpha - 1)(A - B)$ and its variance is $4N\alpha(1 - \alpha)$. Assume the probability for a given G-neuron to fire is a function of s only, namely a sigmoid $F(s) = 1/\{1 + \exp[(T - s)/Q]\}$ where T is G's threshold and Q is a measure of its noisiness and global selectivity; the total firing probability is

$$X(A,B) = \int_{-1}^{+1} P_{AB}(s)F(s)ds \simeq \int_{-\infty}^{+\infty} P_{AB}(s)F(s)ds$$

Once firing, a neuron can deliver a limited amount of TF to, say, $2c$ active excitatory or silent inhibitory synapses. Thus, when only A is "on," the probability for an A_- synapse to be "eligible" is $E_{A-}(A = 1, B = 0) = (1 - \alpha)X(1, 0)$. Now, if $N \simeq cN_G$, that is, few synapses impinge on any neuron, all can obtain TF when eligible. $N \ll cN_G$ corresponds to poor early innervation and will be ignored; on the other hand, $N \gg cN_G$ is interesting and implies *competition* among synapses: abundant types such as A_+ and B_- are *disadvantaged* by competition—more of them are eligible simultaneously. To account for this, I shall normalize eligibilities in the case $N \gg cN_G$, dividing $E_i(A,B)$ (where $i = A_+, A_-, B_+$, or B_-) by $\Sigma_i E_i(A,B)p_i$.

How much TF is actually received depends on the frequencies of inputs A,B, as controlled by sensory environment, internal factors, and/or "teacher." I define input probabilities $I_{\bar{A}\bar{B}} = \epsilon$ (no external stimulation), $I_{A\bar{B}} = (1 - \epsilon + 2\delta)/3$, and $I_{\bar{A}B} = I_{AB} = (1 - \epsilon - \delta)/3$; δ is the bias in favor of input $A \wedge \bar{B}$. The likelihood, per

input presentation, that an i-synapse gets a unit of TF is readily computed:

$$T_i = I_{A\bar{B}}E_i(1,0) + I_{AB}E_i(1,1) + I_{\bar{A}\bar{B}}E_i(0,0) + I_{\bar{A}B}E_i(0,1)$$

from which one can evaluate the (binomial) distribution for the number x of TF units accumulated over M input presentations. With the simple hypothesis that a synapse's chance to survive is roughly $1 - exp(-x/R)$, this yields average relative survival rates

$$S_i = 1 - (1 - T_i + T_i e^{-1/R})^M$$

It is now easy to find the probability P_s that, if all synapses retract at time M save one from A and one from B, the right configuration is obtained; thus, the odds for *one* A_+ connection to remain are

$$P_s^A = \left[1 + \frac{1 - 2\beta}{1 + 2\beta}\frac{S_{A-}(1 - S_{A+})}{S_{A+}(1 - S_{A-})}\right]^{-1}$$

In similar fashion, one can evaluate P_s^B, the probability that only one B_- synapse is stabilized; finally $P_s = P_s^A P_s^B$. Here we have assumed that only $N_f = 2$ synapses escape elimination (one from A, another from B); cases where more synapses survive could also be treated, for example, $N_f \simeq N_G$. It is important to note here that final functional performance depends critically on a delicate balance between firing thresholds and number as well as strength of the remaining synapses; here we assume no threshold or synapse strength adjustment: we must then make sure that an approximately equal amount of inhibitory and excitatory synapses is finally stabilized. This could be achieved, for instance, by assuming that the two synapse types each require a *different* TF and that roughly the same quantity of both substances is initially present.

Figures 2 and 3 display the variation of P_s as a function of M, for various balances of genetic *vs.* epigenetic determination. P_s is always substantially larger than $(\frac{1}{2} + \beta)^2$, the outcome of *random* elimination. In favorable situations (large enough β and δ), P_s quickly approaches 1. Figure 2 illustrates the case of unbiased, or spontaneous ($\delta = 0$) input activities influencing the response of a neuronal group whose wiring is biased through $\beta = 0.3$. The diamonds correspond to the case of strong initial innervation, leading to competition among synapses: we see that learning proceeds very slowly, as P_s does not rise much with increasing M (the elapsed time before synapse elimination). The crosses indicate what happens for an optimal level of initial innervation; here learning is very efficient and the probability P_s that the final wiring is functional increases quickly with M. In Figure 3, we study the selective stabilization of initially random input synapses in the presence of *nonrandom* input activities. One sees that insufficient input bias will lead to system failure; relatively large input biases, on the other hand, can result not only in successful functioning of initially random systems, they are even capable of "correcting" *wrongly* ($\beta < 0$) connected systems. These analytical calculations are supported by direct computer simulations of selective stabilization in neural assemblies (Kerszberg, Dehaene, & Changeux 1989).

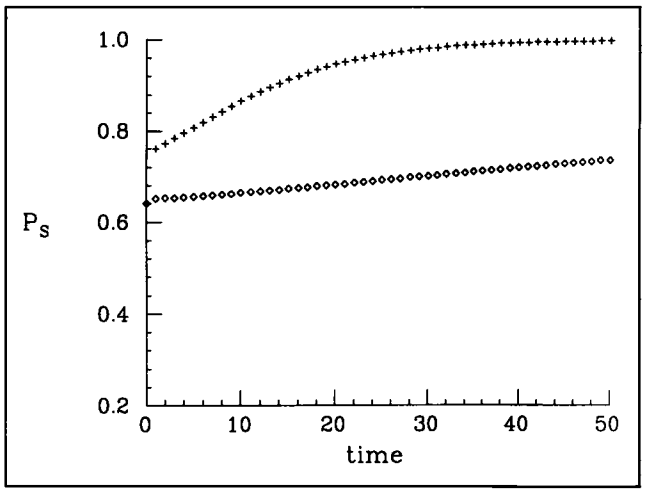

Figure 2. Probability for selective synaptic retraction to produce functional circuitry when it occurs after a given activity period. Parameters here and in Figure 2: $N = 40$, $\alpha = 0.9$, $T = 0.2$, $Q = 0.5$, $R = 0.1$ (see text); in addition $\beta = 0.3$, $\epsilon = 0.25$, $\delta = 0$. This corresponds to the random, spontaneous activity of a genetically "biased" neuronal group. (◇) strong initial innervation, leading to synapse competition and very slow learning: (+) weaker initial innervation, success probability increases rapidly to 1.

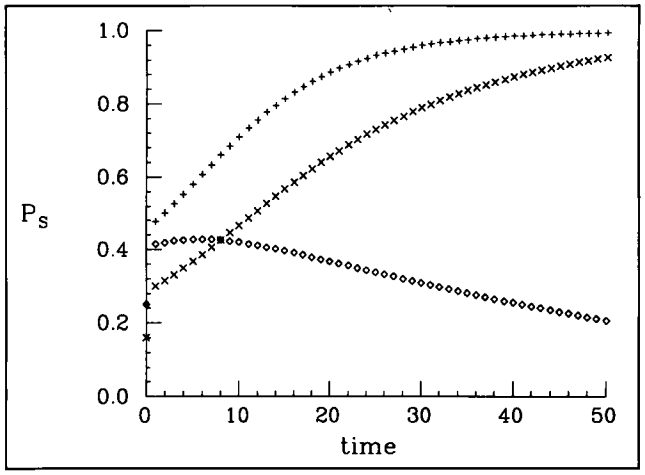

Figure 3. Effect of nonrandom inputs on learning. (◇) Genetically uncommitted neurons ($\beta = 0$) subject to not very specific inputs ($\epsilon = 0.50$, $\delta = 0.40$): teaching fails but note maximum around $M = 6$, due to *partially* correct wiring; (+) $\epsilon = 0.25$, teaching succeeds because of sufficient input bias. (×) Same as +, but with $\beta = -0.1$. Initial connections are mainly of the *wrong* sign, but system "reeducation" is seen to occur.

FURTHER PERSPECTIVES

Our results are just meant as an illustration of possible mechanisms for the evolution of functional neural pathways. More intricate circuitry could be established either

with the use of additional connection biases further *down* in the system (i.e., more β-like parameters), or by exploiting the biases already present in the outputs of *upstream* neural groups (induced δ-like biases). Combined with features such as synaptic plasticity (Tsukahara 1981) and turnover (Chang & Greenough 1982), asynchronous potentiation (Larson & Lynch 1986; Winson & Dahl 1986), axoaxonal contacts (Kandel & Schwartz 1985), neuronal death (Clarke 1985), or reentrant signaling (Edelman 1978), such processes could lead to very elaborate responses.

Subtle feedback loops may also emerge in sensorimotor systems. If we assume random spontaneous activity of motor neurons, and genetically preset biases in the way they are initially connected to muscles, a newborn's movements will exhibit certain regularities; these "directed" motions will in turn induce biases in the inputs to sensory systems. Simultaneous, mutually assisted fine tuning should then occur under favorable circumstances. Such a phenomenon might play a role in imprinting (Halliday & Slater 1983). The model could also explain why, while preference for the imprinted stimulus can be "unlearned" in certain circumstances, it will always emerge again in a multiple-choice experiment (Bischof 1983). The unique (and drastic) nature of early imprinting, resulting in a one-time elimination of synapses, would make it essentially nonerasable: it leaves a structural mark on the CNS, while "ordinary" learning, which mainly—but not only—modulates existing synapses, may not do so to the same extent (Chang & Greenough 1982; Purves, Voydovic, Magrassi, & Yawo 1987).

Phylogenetically ancient circuits are delicately adjusted, built under genetic control, and apt to be specialized; the skills they confer may become obsolete in an unstable world. More recent structures are likely to have parameters such as $\beta \simeq 0$: they are not very specific but adaptable, and therefore need the refinement provided by learning ($\delta > 0$). Among other factors, δ depends on parental behavior, which itself has an important genetic component (Marler & Terrace 1984). In (β,δ,M) space, starting with nonzero, purely "environmental" δ, natural selection can operate and β, δ grow: a smooth adaptive landscape is initially available for this to happen, as P_s increases progressively. The landscape may later sharpen itself as the fitness of fast learners (low M) improves (Baldwin 1896). The optimal parameters are ultimately functions of environmental variability. The interplay between β, M ("nature"), and δ ("nurture") thus opens interesting perspectives, which I hope to explore in the future.

CONCLUSIONS

Let me summarize my conclusions and predictions. If the model proposed here is correct there must exist a strong correlation between the occurrence of phenomena such as irreversible imprinting, on the behavioral level, and synapse elimination on the neurobiological one. The correct formation of synapses should depend on the easily controlled presence of appropriate inputs, but also on the existence of genetically determined structural features such as differential probabilities for cell–cell adhesion and moderate initial innervation. This is also open to experimental manipulation, for example, by application of NCAM antibodies (Rutishauser, Gall, & Edelman 1978), or by upsetting potential morphogen gradients. The very course of the elimination phase could itself be modified: providing exogenous amounts of trophic factor (Njå & Purves 1978) or artificially maintaining TF synthesis (Henderson 1986) during known elimination phases should largely *suppress* imprinting and imprinting-like phenomena.

The question of cell adhesivity mutants is also of great interest. NCAM or other cell adhesion mutants should exhibit modified learning abilities. Adhesivity changes occurring through such mutations may clearly be *small*: as such they are of potential evolutionary significance, in probable contrast to the *large*, drastic CNS mutations known, for example, in *Drosophila* (Dudai 1985).

Finally, we have explored only one in a series of possible variant models, using a particular form of Hebb reinforcement, and a special way of initially setting up differential connectivities. Analyzing in detail the alternative possibilities pointed out in the text should lead to a multiplicity of final wiring diagrams for a specific functional activity, or, perhaps more interestingly, to the impossibility of realizing certain functions using some ill-chosen sets of rules. These questions will be examined in more detail in forthcoming work (Kerszberg, Dehaene, & Changeux 1989).

Note

Reprint requests should be sent to Dr. Michel Kerszberg, Institut Pasteur, Neurobiologie Cellulaire, 25 rue du Dr. Roux, 75724 Paris Cedex 15, FRANCE.

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