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INTRACELLULAR MECHANISMS OF ADAPTATION AND SELF-REGULATION IN SELF-ORGANIZING NETWORKS: THE ROLE OF CHEMICAL TRANSDUCERS

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This paper describes mechanisms of intracellular and intercellular adaptation that are due to spatial or temporal factors. The spatial mechanisms support self-regulating pattern formation that is capable of directing self-organization in a large class of systems, including examples of directed intercellular growth, transmitter production, and intracellular conductance changes. A balance between intracellular flows and counterflows causes adaptation. This balance can be shifted by environmental inputs. The decrease in Ca^{2+}-modulated outward K^+ conductance in certain molluscan nerve cells is a likely example. Examples wherein Ca^{2+} acts as a second messenger that shunts receptor sensitivity can also be discussed from this perspective.

The systems differ in basic ways from recent diffusion models. Chemical transducers driven by membrane-bound intracellular signals can establish long-range intercellular interactions that compensate for variable intercellular distances and are invariant under developmental size changes; diffusional signals do not. The intracellular adaptational mechanisms are formally analogous to intercellular mechanisms that include cellular properties which are omitted in recent reaction–diffusion models of pattern formation. The cellular models use these properties to compute size-invariant properties despite wide variations in their intercellular signals.

Mechanisms of temporal adaptation can be derived from the simplest laws of chemical transduction by using a correspondence principle. These mechanisms lead to such properties of intercellular signals as transient overshoot, antagonistic rebound, and an inverted U in sensitivity as intracellular signals or adaptation levels shift. Such effects are implicated in studies of behavioral reinforcement, motor control, and cognitive coding.

1. Introduction. This paper discusses several basic issues concerning the processing of patterned data by individual cells and by networks of cells. These issues can be loosely grouped under three general headings. (I) Pattern registration without noise or saturation. This heading includes phenomena such as neural short term memory and the maintenance of morphogenetic patterns with properties such as sensory adaptation, con-

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trast enhancement, and self-regulation. (II) Pattern learning by parallel sampling sources. This heading includes phenomena such as environmentally directed growth, enhanced transmitter production, and altered conductance or other receptor sensitivity changes in response to intercellular signals. (III) The establishment of long range order in intercellular interactions by chemical, as opposed to electrical transducers. These mechanisms lead to such phenomena as intracellular adaptation, overshoot, antagonistic rebound, and transient sensitivity changes in response to input fluctuations. Such phenomena occur regularly in psychological experiments on reinforcement mechanisms, but are still not recognized to be adaptational effects due to the action of chemical transducers. The issues are often motivated below by neural examples, but they apply equally to other biological systems, and therefore have a universal significance.

We start by noting that certain phenomena, which have often been treated as central biological facts—e.g. self-regulation (Wolpert, 1978)—are automatic properties of deeper design principles; e.g. pattern registration. One reason for this oversight in earlier work seems to be the omission of cellular structure from many models of cellular interactions, including the popular reaction–diffusion models. The results herein argue that cells have been chosen as an ubiquitous evolutionary design for important functional reasons, and that cellular structure should be reintroduced into cellular models.

We then suggest some mechanisms of intracellular processing that have analogs in mechanisms of intercellular processing by networks of cells; e.g. intracellular adaptation of photoreceptors (Baylor *et al.* 1974a, b; Baylor and Hodgkin, 1974; Normann and Werblin, 1974) vs intercellular adaptation due to lateral inhibition of retinal bipolar cells (Cornsweet, 1970; Werblin, 1971). These intracellular mechanisms can be interpreted as network interactions among intracellular components; e.g. of the cell membrane as a network of macromolecules. The homology between intracellular and intercellular network properties helps to clarify how several levels of hierarchical cellular organization can stabilize and regulate each other.

2. Pattern Registration, Intercellular Adaptation, and Self-Regulation. All cells face the *noise-saturation dilemma*, which can be solved either by intercellular mechanisms, or by homologous intracellular mechanisms. The dilemma can be stated as follows. Let a pattern of inputs $(I_1, I_2, \ldots, I_n)$ excite a collection of cells $v_1, v_2, \ldots, v_n$. All cells *in vivo* experience a certain amount of noise, and all cells possess only finitely many excitable sites. If the inputs in the pattern are too small, they get lost in the noise. If they are too large, they can turn on all the excitable sites in all the cells; that is,

saturation of the sites occurs, and the cells become insensitive to differences and fluctuations in the input sizes. How can cellular systems balance between the two equally deadly, but complementary, extremes of noise and saturation?

The answer in terms of intercellular mechanisms is that competitive interactions between the cells, or their inputs, cause the cells to automatically retune their sensitivity in response to fluctuations in the size of feedback signals or inputs (Grossberg, 1970, 1973, 1977, 1978a; Sperling, 1970). When this solution is modelled, it automatically has properties of sensory adaptation and self-regulation in special cases. Thus, satisfying the design principle of accurately registering a pattern without noise or saturation implies properties of adaptation and self-regulation as consequences. This is not evident in recent models of self-regulation (Gierer and Meinhardt, 1972; Meinhardt and Gierer, 1974; Wolpert, 1978) if only because these models do not include the mass action laws that express cellular structure. The simplest example of the intercellular solution is reviewed below in order to motivate its intracellular analog. This example makes our first point in an idealized setting, or gedanken experiment. Once the point is made, a full understanding can be achieved by classifying related possibilities that differ in their choice of rate constants, interaction strengths, and other parameters. Papers in which this classification has been undertaken are referenced below.

Suppose that n cells v_i are given, and that each cell v_i is subjected to an input $I_i(t)$, $i=1,2,\ldots,n$. Let B be the total number of excitable sites in v_i; let $x_i(t)$ be the number of excited sites at time t; and let $B-x_i(t)$ be the number of unexcited sites at time t. Suppose that excited sites spontaneously become unexcited at rate A. Also let unexcited sites be excited by mass action at a rate jointly proportional to their number $B-x_i(t)$ and the input intensity $I_i(t)$. Then

$$\dot{x}_i = -Ax_i + (B-x_i)I_i, \tag{1}$$

with $0 \leqq x_i \leqq B$, $i=1,2,\ldots,n$. Each x_i in (1) saturates at B as each I_i increases. How can this be prevented? Often the information in an input pattern $(I_1, I_2, \ldots, I_n)$ resides in the *relative* input sizes $(\theta_1, \theta_2, \ldots, \theta_n)$, where $\theta_i = I_i I^{-1}$, and $I = \sum_{k=1}^{n} I_k$ is the total, or background, input activity. For example, in vision these relative sizes are the *reflectances* (Cornsweet, 1970) of the pattern. More generally, testing how well the ratios $x_i x_j^{-1}$ match the ratios $\theta_i \theta_j^{-1}$ provides a measure of how sensitive the cells are to differences in their inputs. Otherwise expressed, we test how well the system *factorizes* the data $(\theta_1, \theta_2, \ldots, \theta_n)$ about pattern from the data I about total activity.

This factorization property seems to underlie a variety of neural processes, e.g. chromaticity vs luminosity information in vision; information about the order with which list items occur vs information about their performance velocity; cue information about an individual event vs its ability to arouse performance (Grossberg, 1978b).

In order for each v_i to compute a ratio θ_i, it must know what *all* the inputs are. Writing $\theta_i = I_i(I_i + \sum_{k \neq i} I_k)^{-1}$, it is clear that increasing I_i increases θ_i and that increasing any I_k, $k \neq i$, decreases θ_i. In other words, I_i "excites" θ_i, as in (1), whereas all I_k, $k \neq i$, "inhibit" θ_i. Thus the inputs must compete at each v_i in order to prevent saturation and thereby compute the "reflectances" θ_i. When this intuition is expressed by mass action dynamics, (1) is replaced by

$$\dot{x}_i = -Ax_i + (B - x_i)I_i - x_i \sum_{k \neq i} I_k. \tag{2}$$

The new term $-x_i \sum_{k \neq i} I_k$ says that excited sites at v_i (which number x_i) are inhibited at a rate proportional to the total inhibitory input $\sum_{k \neq i} I_k$. In neural terminology, the inputs form a feedforward, or nonrecurrent, on-center (excite v_i) off-surround (inhibit all v_k, $k \neq i$) interaction pattern (Fig. 1). The off-surround automatically changes the *gain*, or decay rate, of the

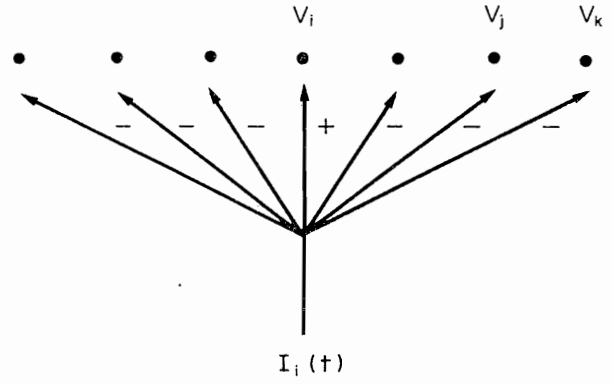

Figure 1. Cellular networks undergoing feedforward competitive mass action interactions automatically retune their sensitivity using gain control by their competitive signals

system by multiplying x_i. This multiplication of x_i by inputs is called a *shunt* in neural terminology. Thus (2) describes, in neural terms, a nonrecurrent shunting on-center off-surround interaction. In general terms, (2) describes a feedforward mass action competitive network.

In response to fixed reflectances $(\theta_1, \theta_2, \ldots, \theta_n)$ and a fixed background

input I, system (2) approaches the equilibrium activities

$$x_i = \frac{BI_i}{A+I} = \theta_i \frac{BI}{A+I}. \tag{3}$$

Thus no matter how large I becomes, $x_i x_j^{-1} = \theta_i \theta_j^{-1}$. There is no saturation because competitive signals automatically retune x_i's sensitivity as I increases. Equation (3) has several other interesting properties. For example, (3) factorizes x_i's response into a term depending only on the pattern weight θ_i and a term $BI(A+I)^{-1}$ depending only on the total activity I. Consequently, the total activity $x = \sum_{k=1}^{n} x_k$ satisfies

$$x = \frac{BI}{A+I} \leqq B. \tag{4}$$

The maximum value B of x is independent of the number n of cells, by contrast with system (1), where the maximum value of x is nB. I call this property *normalization*. In cellular competitive networks, normalization, or an approximate version thereof, underlies self-regulation, or the invariance of form under size changes (changes of n); cf. Wolpert (1974). The main point of (3) and (4) is that normalization occurs in system (2) given any choice of pattern $(I_1, I_2, \ldots, I_n)$. System (2) also has the special property that it preserves the relative sizes $(\theta_1, \theta_2, \ldots, \theta_n)$ of the inputs in the activity pattern $(x_1, x_2, \ldots, x_n)$. This is generally false. Indeed, one of the important lessons to be learned from cellular competitive systems is that their transformations of inputs into activities can be extremely varied even though a similar mechanism normalizes them all. As a simple example, normalization continues to hold if parameter B in (2) is replaced by an arbitrary positive number B_i at each v_i. Then the inequality $x \leqq B$ is valid with $B = \max_i B_i$. In the absence of inhibitory interactions, we could only conclude that $x \leqq \sum_{i=1}^{n} B_i$. However each choice of the parameters B_i alters the transformation of inputs into activities. Thus the normalization property depends on the existence of competitive interactions coupled into cellular mass action laws, whereas details of the transformation from inputs to activities depends on particular choices of parameters.

When feedback networks are considered below, the conclusion will again be that normalization depends on the competitive geometry and the cellular mass action laws, but not on the choice of input pattern or on the exact form of the feedback signals. Such a conclusion does not hold, for example, in the reaction–diffusion model of development that was pro-

posed by Gierer and Meinhardt (1972) and Meinhardt and Gierer (1974). For example, their model requires a special choice of signal function, namely a sigmoid signal, to achieve self-regulation [see discussion after (11)]. Different choices of signal function can dramatically alter the pattern transformations that a cellular network can execute, and this is one means whereby such networks can be designed to carry out different tasks. However, the choice of signal function is not the mechanism behind their normalization property.

Adaptation due to intercellular competition is illustrated by writing I_i in logarithmic coordinates as $K=\log I_i$ and the off-surround input as $L=\sum_{k\neq i} I_k$. Then (3) can be rewritten as

$$x_i(K,L)=\frac{Be^K}{A+e^k+L}. \tag{5}$$

By (5), a shift in L shifts x_i's response curve—i.e. its region of maximal sensitivity—without causing any overall sensitivity loss—i.e. compression of x_i's response interval $[0,B]$. If L is changed from $L=L_1$ to $L=L_2$, then the shift is

$$S=\ln[(A+L_1)(A+L_2)^{-1}] \tag{6}$$

since

$$x_i(K+S,L_1)=x_i(K,L_2) \quad \text{for all } K\geqq 0; \tag{7}$$

cf. Werblin (1971). In summary, the saturation problem is overcome by feedforward cellular systems undergoing competitive interactions.

Equation (2) is the simplest example of a feedforward cellular competition, but considerable information is now available concerning how more general choices of parameters, as in

$$\dot{x}_i=-A_ix_i+(B_i-x_i)\sum_{k=1}^{n} I_kC_{ki}-(x_i+D_i)\sum_{k=1}^{n} I_kE_{ki}, \tag{8}$$

$i=1,2,\ldots,n$, influence the transformation from input pattern $(I_1,I_2,\ldots,I_n)$ to output pattern $(x_1,x_2,\ldots,x_n$; Ellias and Grossberg, 1975; Levine and Grossberg, 1976; Grossberg, 1978c). In (8), C_{ki} is the excitatory interaction strength from v_k to v_i, E_{ki} is the inhibitory interaction strength from v_k to v_i, and x_i can fluctuate between a maximum value of B_i and a minimum

value of $-D_i \leqq 0$, where 0 is scaled to be the passive equilibrium point which x_i approaches after all inputs are shut off. Equation (8) includes arbitrary rate parameters and feedforward competitive geometries. When these parameters are varied, the network can induce the following transformations of the input pattern into the activity pattern, among others: inward and outward peak shifts, spurious peaks and peak splits, curvature and edge detection, amplification of pattern matches, attenuation of pattern mismatches, noise suppression, and variable sensitivity at variable adaptation or nonspecific arousal levels. Of course, normalization cannot subserve these properties if the inhibitory interactions are chosen too weak.

Equations such as (8) are familiar in a neural context, where the equation for a cell's activity, or voltage $V(t)$, often has the form

$$C\frac{\partial V}{\partial t} = (V^p - V)g^p + (V^+ - V)g^+ + (V^- - V)g^-. \tag{9}$$

Here C is a capacitance, the constants V^p, V^+, and V^- are passive, excitatory, and inhibitory saturation points, and g^p, g^+, and g^- are conductances that can be changed by inputs (Kuffler and Nichols, 1976). We adopt the convention that $V^+ > V^p \geqq V^-$. Then the voltage $V(t)$ satisfies $V^+ \geqq V(t) \geqq V^-$. Equation (8) can be written in the form (9) by rescaling time so that $C=1$, rescaling the voltage so that $V^p=0$, and then setting $V=x_i$, $g^p=A$, $V^+=B_i$, $V^-=-D_i$, $g^+=\sum_{k=1}^n I_k C_{ki}$, and $g^- = \sum_{k=1}^n I_k E_{ki}$, for each $i=1,2,\ldots,n$.

In many biological problems, feedback signals occur in addition to feedforward inputs. Such signals are, for example, needed to keep short term memory traces active after sensory inputs terminate (Grossberg, 1973, 1978b). They are also common in models of morphogenesis where they make possible the maintenance of morphogenetic patterns (Gierer and Meinhardt, 1972; Grossberg, 1976, 1978a; Lawrence *et al.*, 1972; Meinhardt and Gierer, 1974). The simplest feedback cellular competitive system is

$$\dot{x}_i = -Ax_i + (B-x_i)[f(x_i)+I_i] - x_i\left[\sum_{k\neq i} f(x_k) + J_i\right], \tag{10}$$

$i=1,2,\ldots,n$. Term $(B-x_i)f(x_i)$ describes how a positive feedback signal $f(x_i)$ from v_i to itself excites the unexcited sites $B-x_i$ by mass action. The inhibitory term $-x_i\sum_{k\neq i} f(x_k)$ describes the switching-off of excitation at v_i by competitive, or inhibitory, signals $f(x_k)$ from all v_k, $k\neq i$ (see Fig. 2). Term I_i is the total excitatory input, and term J_i is the total inhibitory input at v_i. Again our gedanken experiment considers a system with

broadly distributed inhibitory signals and unbiased rate parameters. How should the feedback signal $f(w)$ be chosen as a function of cell activity w to guarantee useful transformations of input patterns into activity patterns $(x_1, x_2, \ldots, x_n)$? In particular, what choices of $f(w)$ suppress noise but can store useful activity patterns? This problem was solved in Grossberg

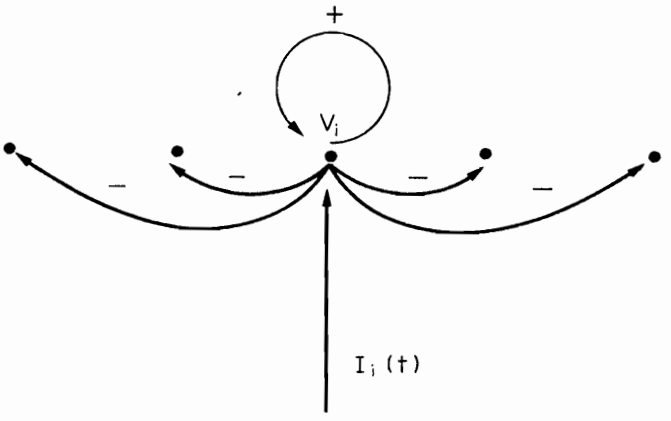

Figure 2. Cellular networks undergoing competitive feedback self-regulate as they transform the input pattern before storing it

(1973), which should be consulted for details (or the review in Grossberg, 1978b). For present purposes, it is important to realize that *all* non-trivial choices of signal function $f(w)$ lead to normalization of the total activity $x(\infty)=\lim_{t\to\infty} x(t)$ as time increases, despite the fact that different signals can dramatically alter the transformation from input to activity pattern. The normalization is due to the combination of competition and cellular mass action laws, not to the statistics of the signals. This result differs from the phenomena reported to hold in the morphogenetic model of Gierer and Meinhardt (1972, p. 34). In their model, neither cell saturation nor inhibitory automatic gain control occur. For example, in one form of the Gierer and Meinhardt model, the excitor $x(\omega, t)$ obeys the reaction–diffusion equation

$$\frac{\partial x}{\partial t} = -Ax + Bf(x)y^{-1} + C\frac{\partial^2 x}{\partial \omega^2} + D. \tag{11}$$

In (11), the positive feedback term $f(x)$ is chosen to be either a power or sigmoid function of x. There is no saturation term in (11), since $f(x)$ is always monotone increasing. Term $(B-x_i)f(x_i)$ in (10) plays the role of $f(x)$ in (11). Note that $(B-x_i)f(x_i)$ is not monotone increasing, since it equals zero when $x_i=B$. Term y^{-1} in (11) describes the effect of inhibitor

$y(\omega, t)$ on excitor $x(\omega, t)$ by multiplying the positive feedback term $f(x)$; increasing inhibitor attenuates positive feedback. By contrast, in (10), inhibitory signals appear in negative feedback terms, such as $-x_i \sum_{k \neq i} f(x_k)$, that have no analog in (11). Meinhardt and Gierer claim that self-regulation can occur if $f(x)$ is a sigmoid signal function, but not if $f(x)$ is a power signal function. Since a sigmoid signal can be approximated by a power signal at small values of x, it would appear that self-regulation in (11) depends on the saturation, or insensitivity, of the sigmoid signal at high excitor levels. It seems doubtful to me that the exquisite self-regulation of biological patterns is caused by insensitivity of a signal function to the high activity levels in these patterns, especially if cellular systems automatically retune themselves to achieve an operating range that maximizes their sensitivity.

3. Adaptive Resonance between Dipole Fields. An alternative picture of self-regulation can be summarized by the phrase "adaptive resonance between dipole fields" (Grossberg, 1978a, b). The normalization property is only one ingredient in this picture. When the normalization property holds among a collection of cells, it defines these cells as a functional unit, or channel. This channel rapidly recalibrates all its inputs and feedback signals until they equilibrate at an intracellular activity range within which the internal biochemistry of each cell can sensitively react. Within this range, the channel computes relative activities, or ratios, whose spatial distribution across the channel's cells depend on details of tissue design, such as the choice of intercellular signal functions and interaction pathways. Tuning the operating range of the functional unit is a basic theme of the systems, and is related to their self-regulatory capabilities. Tuning can be achieved by such mechanisms as nonspecific shunting of interaction pathways by enzymatic activation, or restriction of the cell subgroups that are permitted to interact after a prescribed developmental stage. As an example of the latter strategy, Grossberg (1978a) considers a system whose cells each contain an intracellular dipole—cf. cAMP and cGMP—of competing reactions; e.g. formally set $n=2$ in (10) and let x_1 and x_2 be the activities of competing intracellular processes. Such a cell can normalize its internal activity and can store arbitrary relative sizes of x_1 and x_2 even after the cell is isolated. When the intracellular dipole interactions are gated by slowly varying chemical transducers, a variety of subtle new effects can occur, such as an inverted U in the sensitivity of the dipole as a function of its total input size. See Section 10 below.

A dipole field is said to exist among a collection of cells, each of which possesses an intracellular dipole, when corresponding ends of all the dipoles are capable of interacting via positive or negative cellular feedback,

as illustrated by (10). A dipole field is thus composed of two parallel recurrent subfields joined by competitive dipole interactions. The subfields define functional sub-units, and the dipoles compute relative activation levels between these sub-units. In the context of sensory neurophysiology, an example of an intercellular dipole is a pair of competing on-cells and off-cells, and the dipole subfields are recurrent on-center off-surround networks that join on-cells to on-cells and off-cells to off-cells (Grossberg, 1976, 1980).

An important theoretical issue is how do pairs of interacting dipole fields retune each other's operating levels to maximize each field's sensitivity to the other field's signals, whether during uninterrupted development, or during development after ablation experiments? I suggest that interfield tuning is often achieved by matching mechanisms that are activated when either field sends developing contacts to the other field, and that self-regulating connections can be the result of such interfield tuning processes even if the internal dynamics of the separate dipole fields do not completely self-regulate. For example, syncytium formation during sea urchin gastrulation (Gustafson and Wolpert, 1967) can be viewed as a matching process whereby pseudopodia from certain mesenchymal cells adhere to certain ectodermal cells. The selective pseudopod formation of mesenchymal cells and the selective adhesiveness of ectodermal cells are field properties that set the stage for this matching process. The development of the rectinotectal map in *Xenopus* can also be viewed as a matching process between two spatial maps (Keating, 1978; Meyer and Sperry, 1978).

Laws for the directed growth of connections between dipole fields are illustrated for the case of syncytium formation in Grossberg (1978a). These laws are of the form considered in Section 5 below. When matching between two dipole fields occurs, a dynamic state is elicited that I call an adaptive resonance. The adaptive resonance locks the match into a globally stable configuration via several feedback processes. When mismatch occurs, processes of unstable competition for connection sites, reset of the dipole patterns by interfield signalling, and motion of connections in gradient fields can occur until the best possible match is attained. An analogous tradeoff between resonance and reset seems also to occur during the development of cognitive codes (Grossberg, 1980), but the reset mechanisms in cognitive examples cause shifts in the transmission characteristics of extant neural pathways rather than relocation of these pathways. Both types of example seem to obey similar formal laws, however. This paper aims at clarifying and extending some of the interrelationships between these ubiquitously occurring formal laws.

4. Absolute Stability of Competitive Systems with Adaptation Level. The results concerning (10) have been significantly generalized since 1973, leading to a mathematical method that is defined for *every* competitive system, where a competitive system is any autonomous system $\dot{y}=f(y)$, $y=(x_1, x_2, \ldots, x_n)$, that remains in a bounded region R of $\mathbb{R}^n$, and such that

$$\frac{\partial f_i}{\partial x_j}(y) \leqq 0 \quad \text{if } i \neq j \text{ and } y \in R.$$

This method explicates the idea that a competition can be understood by keeping track of who is winning it. By doing so, one shows that every competitive system induces a decision scheme, which can be used to analyse whether the competition will undergo pattern formation (Grossberg, 1978d, 1978c) or sustained oscillations (1978d) as time goes on. In particular, Grossberg (1978e) proves that all competitive systems which can be written in the form

$$\dot{x}_i = a_i(y)[b_i(x_i) - c(y)], \tag{12}$$

$y=(x_1, x_2, \ldots, x_n)$, undergo global pattern formation if $a_i(y)$, $b_i(x_i)$, and $c(y)$ satisfy mild conditions. Global pattern formation means that, given any nonnegative initial data $y(0)$, the limit $y(\infty)=\lim_{t\to\infty} y(t)$ exists. Otherwise expressed, arbitrary local signals $b_i(x_i)$ and amplifications $a_i(y)$ can be synthesized to generate and store global patterns if there exists an adaptation level $c(y)$. In particular, any competitive cellular system

$$\dot{x}_i = -A_i x_i + (B_i - x_i)[f_i(x_i) + I_i] - (x_i + C_i)\left[\sum_{k \neq i} f_k(x_k) + J_i\right] \tag{13}$$

can be written in the form (12) by choosing

$$a_i(y) = x_i + C_i \tag{14}$$

$$b_i(x_i) = -A_i - I_i - J_i + (x_i + C_i)^{-1}[A_i C_i + I_i + (B_i + C_i) f_i(x_i)] \tag{15}$$

and

$$c(y) = \sum_{k=1}^{n} f_k(x_k). \tag{16}$$

Thus global pattern formation occurs in (13) no matter how the parameters A_i, B_i, and C_i, the signals $f_i(x_i)$ and the inputs I_i and J_i are chosen. I call the persistence of pattern formation under parametric changes *absolute stability* of pattern formation. The absolute stability property amply illustrates that cellular competition is a robust design framework in which to study biological pattern formation.

Generalizations of (13), such as the feedback analog of (8), namely

$$\dot{x}_i = -A_i x_i + (B_i - x_i)\left[\sum_{k=1}^{n} f(x_k)C_{ki} + I_i\right] - (x_i + D_i)\left[\sum_{k=1}^{n} g(x_k)E_{ki} + J_i\right], \quad (17)$$

$i = 1, 2, \ldots, n$, have also been analysed (Ellias and Grossberg, 1975; Levine and Grossberg, 1976; Grossberg, 1978a, d). They are capable of transforming the input pattern in various ways, such as generating hysteresis, lateral masking, slow drifts, and travelling waves in the spatial locus of maximal activity. If $C_{ki} \neq 0$ for some $k \neq i$, then (17) is not a competitive system in the mathematical sense. However, in all the physically interesting systems of this form that have been considered, the spatial extent of excitatory feedback is narrow relative to the spatial extent of negative feedback. For present purposes, the most important conclusions are that competitive feedback interactions in cellular networks solve the noise-saturation dilemma, are capable of normalization, and can be classified in terms of their underlying decision schemes.

These results are satisfying as far as they go, but they also focus our attention on three related questions: To define a competitive network, there must exist two types of signals, excitatory signals and inhibitory signals. In many situations, extracellular signals of these two types are known to occur; for example, in mammalian visual cortex (Creutzfeldt, 1976) and in the slime molds (Bonner, 1967; Keller and Segal, 1970). How is the noise-saturation dilemma solved when intercellular excitatory and inhibitory signals do not both occur? In particular, consider photoreceptors in a vertebrate retina. Photons act as one type of extracellular inputs to these cells, actually as inhibitory inputs since they hyperpolarize the cells. What input source supplies the competitive interactions that prevent saturation? One might hope that these interactions are derived from neural feedback via the horizontal cells. However, such feedback does not always appear to exist, and in any case, functionally isolated photoreceptors have been shown capable of sensory adaptation (Baylor and

Hodgkin, 1974; Baylor *et al.*, 1974a, b; Normann and Werblin, 1974). Finally, even in situations where competitive intercellular interactions now exist, we must ask how the individual cells of ancestral organisms were able to accurately register patterned data before these interactions evolved, as they presumably must have to guide the evolution of the interaction pathways? Such questions strongly point to the existence of intracellular mechanisms to supplement, and sometimes even to supplant, intercellular schemes for dealing with noise and saturation. In any case, they motivate us to formally overcome noise and saturation even if only one type of intercellular signal exists.

5. Nonstationary Prediction and Pattern Learning: Directed Growth, Production, or Sensitization. Our goal is to show that a single intracellular mechanism can solve the noise-saturation dilemma and can guarantee unbiased spatial pattern learning under very general conditions. The latter property builds on previous theorems concerning systems that are capable of pattern learning. These systems were originally derived from postulates concerning classical conditioning (Grossberg, 1964, 1967), but gradually it became clear that they solve a universal problem about nonstationary prediction that includes examples of enhanced transmitter production (Deutsch, 1972; Eccles, 1964; Grossberg, 1969a, 1974), postsynaptic sensitization (Grossberg, 1974; Woody *et al.*, 1976), and directed growth (Grossberg, 1978a) as special cases. The same laws can formally hold in examples of all these processes despite the possible existence of different chemical interactions to realize the laws in special cases. The laws impose a canonical ordering for computing certain vital operations—e.g. spatial averaging, temporal averaging, preprocessing, transduction, and gating of signals. If this ordering was invented at a particular stage of evolution, then it could be adapted to any later evolutionary specialization in the following sense: Any number of cells, activated by arbitrary data preprocessing, and sending out signals that might be influenced by arbitrarily complex system-dependent transduction rules, can simultaneously learn an arbitrary spatial pattern without asymptotic bias due to each other's signals.

The laws were first defined and analysed in this generality in Grossberg (1969b, 1971, 1972a). They have the following form.

$$\dot{x}_i = A_i x_i + \sum_{k \in J} B_{ki} z_{ki} + I_i \tag{18}$$

$$\dot{z}_{ji} = C_{ji} z_{ji} + D_{ji} x_i, \tag{19}$$

where $i \in I$, $j \in J$, and I and J are arbitrarily large sets of indices. In a neural setting, function $x_i(t)$ is the short term memory (STM) trace of cell (population) v_i and $z_{ji}(t)$ is the long term memory (LTM) trace of the axon (population) e_{ji} from v_j to v_i. The terms A_i, B_{ji}, C_{ji}, and D_{ji} are continuous functionals; that is, they can depend on the history of all the system's variables x_i and z_{ji} up to the present time. Functional A_i is the STM decay rate of x_i, and C_{ji} is the LTM decay rate of z_{ji}. Functional B_{ji} is the performance signal carried by the pathway e_{ji}. It is gated by z_{ji} on its way to v_i, yielding a net effect of $B_{ji}z_{ji}$ on $\dot{x}_i$. All such signals are summed (spatially averaged) to yield a total effect $\sum_{j \in J} B_{ji}z_{ji}$ of intercellular signals on v_i. Functional D_{ji} is a learning signal carried by the pathway e_{ji}. The function z_{ji} is computed at the interface between e_{ji} and v_i—e.g., the synaptic knob or postsynaptic membrane—where it takes a time average (via C_{ji}) of the product of learning signal D_{ji} and postsynaptic STM trace x_i. Both the signals B_{ji} and D_{ji} are nonnegative—in neural examples they often represent spiking frequencies or other signals that are derived from suprathreshold potentials—and B_{ji} is related to D_{ji}. The inputs I_i form the pattern to be learned. In special cases, z_{ji} can represent the rate of producing presynaptic transmitter, the strength of intercellular connections from v_j to v_i, or the postsynaptic sensitivity at v_i in response to signals from v_j.

Unbiased pattern learning in a general anatomy can be proved in two main steps. The first step will be reviewed because it provides insight into why the intracellular mechanism works and what it means. This step is summarized by saying that "pattern variables and total activity variables factorize". To achieve this, it is assumed that *local symmetry axes* exist, or that signals and decay rates can depend on their sampling cell v_j but not on the sampled cells v_i, $i \in I$. Then (18) and (19) are specialized to the systems

$$\dot{x}_i = -Ax_i + \sum_{k \in J} B_k x_{ki} + I_i \tag{20}$$

and

$$\dot{z}_{ji} = C_j z_{ji} + D_j x_i. \tag{21}$$

To see why factorization occurs, suppose that the inputs I_i form a spatial pattern $I_i(t) = \theta_i K(t)$. Define the pattern variables $X_i = x_i(\sum_{k \in I} x_i)^{-1}$ and $Z_{ji} = z_{ji}(\sum_{k \in I} z_{jk})^{-1}$. Then (20) and (21) imply

$$\dot{X}_i = \sum_{k \in J} E_k(Z_{ki} - X_i) + F(\theta_i - X_i) \tag{22}$$

and

$$\dot{Z}_{ji} = G_j(X_i - Z_{ji}). \tag{23}$$

The coefficients E_j, F, and G_j are $E_j = B_j z_j x^{-1}$, $F = Kx^{-1}$, and $G_j = D_j x z_j^{-1}$, where the total STM and LTM activities $x = \sum_{k \in I} x_k$ and $z_j = \sum_{k \in I} z_{jk}$ and input $K = \sum_{k \in I} I_k$ obey the equations

$$\dot{x} = Ax + \sum_{k \in J} B_k z_k + K \tag{24}$$

$$\dot{z}_j = C_j z_j + D_j x. \tag{25}$$

By (22) and (23), all the effects of the total input K are absorbed into the coefficients E_j, F, and G_j. Because all these coefficients are nonnegative, term $F(\theta_i - X_i)$ describes the tendency of X_i to approach θ_i, term $\sum_{k \in J} E_k(Z_{ki} - X_i)$ describes the tendency of X_i to act as a nonlinear center of mass that responds to all the pattern weights Z_{ji}, $j \in J$, and term $G_j(X_i - Z_{ji})$ describes the tendency of each Z_{ji} to approach X_i. The size of the coefficients determines the sensitivity of X_i or Z_{ji} to these influences, and thus the rate with which the pattern variables respond to them. If the coefficients are sufficiently large, then X_i approaches θ_i and each Z_{ji} approaches X_i. The net effect is that Z_{ji} approaches θ_i. Viewed from v_j, the LTM pattern $(z_{ji}: i \in I)$ becomes proportional to the input pattern $(I_i: i \in I)$. In examples of directed growth, this means that the connections from v_j to v_i, $i \in I$, ultimately match the morphogenetic source pattern $(I_i: i \in I)$. In examples of classical conditioning, the transmitter production rates or postsynaptic sensitivities match the pattern defined by the unconditioned stimulus (UCS). See Grossberg (1969b, 1972a) for mathematical details.

The factorization property is the basis of the universality of this mechanism. For example, suppose that (21) describes the effect of the morphogenetic pattern $(x_i: i \in I)$ on the intercellular connections $(z_{ji}: i \in I)$ from v_j to $\{v_i: i \in I\}$. A connection from v_j to v_i can start to form only after $D_j x_i$ becomes positive. Functional D_j is the expected value that a growing pathway will reach v_i from v_j. The product $D_j x_i$ is the expected value that a connection will form due to a statistically independent interaction between growing pathways and v_i's ability to anchor them via x_i's activity (adhesiveness). Functional D_j can depend on the history of the system, in particular on past activity levels of v_j and on the medium in which connections grow, according to any law that is nonnegative and continuous in time. Such complexities can easily lead to uncontrollable

instabilities in a poorly designed system. Because D_j appears in (23) only through the coefficient G_j, however, the laws (20) and (21) overcome this difficulty. The LTM trace Z_{ji} is inexorably drawn towards X_i no matter how complex D_j is, since the size of D_j merely determines the rate with which this attraction manifests itself.

Having noted some of the benefits of factorization in self-organizing networks, we must now ask a sobering question. System (20) and (21) does not include the saturation terms that are ubiquitous in cellular systems. How can we transform a system in which saturation can occur into a system of the form (20) and (21), in which saturation does not occur, to recover the benefits of factorization? This question can be refined by noting that all the signals B_j and D_j in (20) and (21) are excitatory; there is only one type of signal. Saturation can therefore be overcome in this system only by an intracellular mechanism. What intracellular mechanism overcomes saturation and simultaneously yields the factorizing from of (20) and (21)? Can such a mechanism be interpreted as a competitive scheme among intracellular components? The next section answers these questions in the affirmative.

6. Conservation of Antagonistic Gates in Signal Transducer Channels. The desired mechanism can be motivated as follows. Suppose that we try to write the STM equation (20) including a saturation term $(H-x_i)$. Omit the input term I_i momentarily. Then

$$\dot{x}_i = -Ax_i + (H-x_i)\sum_{k\in J} B_k z_{ki}. \tag{26}$$

Suppose that we could transform (26) into a competitive equation, much as we transformed (1) into (2). Then corresponding to each excitatory term $B_k z_{ki}$, we would need an "off-surround" of inhibitory terms $B_k \sum_{m\neq i} z_{km}$. Then (26) would be replaced by

$$\dot{x}_i = -Ax_i + (H-x_i)\sum_{k\in J} B_k z_{ki} - x_i \sum_{k\in J} B_k \sum_{m\neq i} z_{km}. \tag{27}$$

Unfortunately, this equation is physically meaningless. There is no physical mechanism whereby a term z_{km} with $m\neq i$ can influence x_i, since x_i is computed in v_i whereas z_{km} is computed at the interface of e_{km} with v_m, which is not near v_i. Equation (27) violates the *locality* of the dynamics; there is no way for z_{km} to jump from e_{km} to v_i. How can we recover the effect of term $\sum_{m\neq i} z_{km}$ without violating locality? This is possible if we

think of z_{ki} as participating in a competitive process on an intracellular level whose total activity L_k self-regulates, or is conserved. Then, just as $\sum_{m \neq i} z_{km}$ is complementary to z_{ki}, so too is $L_k - z_{ki}$ complementary to z_{ki}, or alternatively $L_k - B_k z_{ki}$ is complementary to $B_k z_{ki}$, but on an intracellular level. We can therefore rewrite (27) in either of two ways:

$$\dot{x}_i = -Ax_i + (H - x_i) \sum_{k \in J} B_k z_{ki} - x_i \sum_{k \in J} B_k (L_k - z_{ki}) \tag{28}$$

or

$$\dot{x}_i = -Ax_i + (H - x_i) \sum_{k \in J} B_k z_{ki} - x_i \sum_{k \in J} (L_k - B_k z_{ki}). \tag{29}$$

Both of these processes are manifestly local. Because the terms $\pm x_i \sum_{k \in J} B_k z_{ki}$ cancel in both (28) and (29), (28) can be written in the form (20) as

$$\dot{x}_i = -(A + \sum_{k \in J} B_k L_k) x_i + H \sum_{k \in J} B_k z_{ki}, \tag{30}$$

and (29) can be rewritten in the form (20) as

$$\dot{x}_i = -\left(A + \sum_{k \in J} L_k\right) x_i + H \sum_{k \in J} B_k z_{ki}. \tag{31}$$

Thus locality, a solution to the noise-saturation dilemma, and the factorization property are all achieved by (28) or (29). A similar device works when inputs I_i are included. Then (28) is augmented to

$$\dot{x}_i = -Ax_i + (H - x_i)\left[\sum_{k \in J} B_k z_{ki} + I_i\right] - x_i\left[\sum_{k \in J} B_k (L_k - z_{ki}) + (M - I_i)\right] \tag{32}$$

which can be rewritten in the form (20) as

$$\dot{x}_i = -\left(A + M + \sum_{k \in J} B_k L_k\right) x_i + H \sum_{k \in J} B_k z_{ki} + HI_i; \tag{33}$$

and (29) is augmented to

$$\dot{x}_i = -Ax_i + (H - x_i)\left[\sum_{k \in J} B_k z_{ki} + I_i\right] - x_i\left[\sum_{k \in J} (L_k - B_k z_{ki}) + (M - I_i)\right], \tag{34}$$

which can be rewritten in the form (20) as

$$\dot{x}_i = -\left(A + M + \sum_{k \in J} L_k\right)x_i + H \sum_{k \in J} B_k z_{ki} + HI_i. \tag{35}$$

The physical meaning of (32) can be summarized as follows. At the interface between e_{ji} and v_i, there exists a population of L_j sites that act to gate the signal B_j from e_{ji} before it can reach v_i. These sites can be in either of two complementary states. At any time, z_{ji} of these sites are in one state, and the remaining $L_j - z_{ji}$ sites are in the complementary state. The total number, L_j, of sites in either state is conserved. A similar conservation law divides the total number H of postsynaptic sites into unexcited sites $H - x_i$ and excited sites x_i. The signal B_j couples the two pairs of conserved antagonistic processes into two parallel, competing channels that change the balance of excited sites x_i through time. In particular, B_j interacts with the z_{ji} sites to turn on unexcited sites $H - x_i$ of the v_i process by mass action, as in term $(H - x_i)B_j z_{ji}$. Signal B_j also interacts with the complementary $L_j - z_{ji}$ sites to turn off excited sites x_i of the v_i process by mass action, as in term $-x_i B_j(L_j - z_{ji}$; see Fig. 3). The

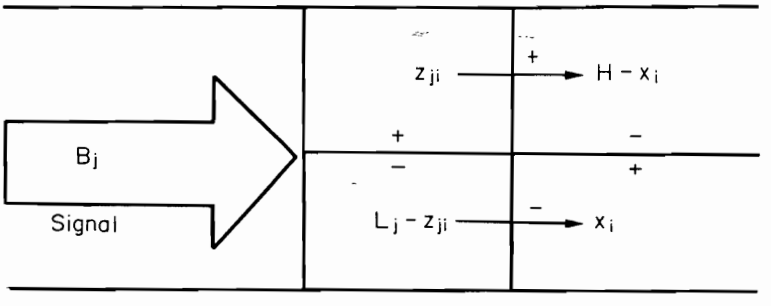

Figure 3. Flow-counterflow balance prevents saturation on an intracellular level and permits factorization of pattern data from total activity data

net effect of turning on signal B_j is thus to balance a flow against a counterflow. If we interpret z_{ji} and $L_j - z_{ji}$ as the expected values of competitive processes in an intracellular network, then B_j acts to non-specifically shunt, arouse, or tune this network into interacting with the

complementary H sites; cf. Grossberg (1973). Otherwise expressed, B_j enzymatically activates the flow and counterflow according to mass action laws.

The balance between flow and counterflow can easily elude experimental detection. This is because the net effect of flow $(H-x_i)B_jz_{ji}$ and counterflow $-x_iB_j(L_j-z_{ji})$ is the term

$$-B_jL_jx_i+HB_jz_{ji}. \tag{36}$$

The LTM trace z_{ji} appears in (36) only as a gate of the excitatory signal B_j. Inhibition appears in (36) only as a gain change of x_i by B_jL_j. The net effect of B_j on x_i is thus to excite x_i and to speed up x_i's rate of averaging signals. In particular, if x_i is the membrane potential of a nerve cell v_i, and the sites L_j occur within the membrane of e_{ji} or v_i, then measuring the potential x_i in response to the signal B_j will not reveal the existence of conserved antagonistic sites in the membrane. Instead, one might conclude that B_j has a purely excitatory effect on v_i. A more direct measure of membrane dynamics would be needed to reveal the complementary flows. In cases where the flow is realized by an inward flux of an ion (e.g. Na^+ or Ca^{2+}) and the counterflow is realized by an outward flux of a different ion (e.g. K^+), then the balance between flows can be measured by ionic probes, and also provides a new functional insight into why the complementary ionic fluxes exist.

Equation (34) has a similar physical interpretation. The terms $(H-x_i)B_jz_{ji}$ and $-x_i(L_j-B_jz_{ji})$ can be interpreted as follows. As in (32), signal B_j couples the sites z_{ji} to the sites $H-x_i$ to cause an excitatory flow $(H-x_i)B_jz_{ji}$. By contrast with (32), all the z_{ji} sites which remain unactivated by B_j contribute to the counterflow $-x_i(L_j-B_jz_{ji})$. A site in the z_{ji} population is committed to the counterflow until it is enzymatically activated by B_j. We can therefore interpret term B_jz_{ji} as being proportional to the fraction of z_{ji} sites that are activated by B_j.

Equation (34) will be used as the basis for the remainder of the paper, since it has properties that generalize to situations where equation (32) seems to be inadequate.

7. Shifting the Flow Balance by Learning. We must now ask the same question about (21) that we did about (20): How can its factorizable form be recovered despite the existence *in vivo* of saturating interactions? A formal solution is to write the LTM equation as

$$\dot{z}_{ji}=-C_jz_{ji}+(N_j-z_{ji})D_jx_i-z_{ji}(P_j-D_jx_i) \tag{37}$$

and then to cancel the terms $\pm z_{ji} D_j x_i$ to rewrite (37) in the form (21) as

$$\dot{z}_{ji} = -(C_j + P_j) z_{ji} + N_j D_j x_i. \tag{38}$$

The net effect on (38) of the flow–counter-flow balance in (37) is an excitatory coupling of signal D_j to x_i that is time-averaged by z_{ji}.

Each of the equations (34) and (37) exhibits a balance between two complementary flows. The relationship between these flows is diagrammed in Fig. 4. Note that whereas the LTM sites that are "on" excite the STM

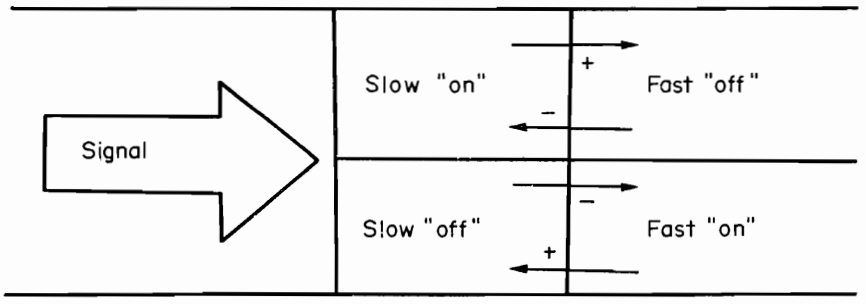

Figure. 4. Two parallel negative feedback loops among fast and slow variables stabilize the temporal shifts in flow–counter-flow balance

sites that are "off", the STM sites that are "off" inhibit the LTM sites that are "on"; and that whereas the LTM sites that are "off" inhibit the STM sites that are "on", the STM sites that are "on" excite the LTM sites that are "off". The net effect is two negative feedback loops acting in parallel between the "fast" STM process and the "slow" LTM process.

Consider a situation in which the fast flow is realized by an inward ion flux (e.g. Na^+ or Ca^{2+}) and the fast counterflow is realized by an outward ion flux (e.g. K^+). Then equation (37) describes a slow shift in the balance of these two flows that is enzymatically driven by the signal D_j. The effect of learning in this example is to increase the flow (inward ion conductance) and to decrease the counterflow (outward ion conductance) in response to a later signal of unit size.

Data has been collected that is qualitatively compatible with this concept. A long-lasting potentiation of cellular response in cells of the sympathetic ganglion of the bullfrog has been traced to a change in ionic conductance (Schulman and Weight, 1976), and in several molluscan preparations (*Anisodoris nobilis*, *Helix pomatia*) it has been shown that potentiation is due to depression of a late outward K^+ current that is dependent on a prior influx of Ca^{2+} (Eckert and Lux, 1977; Eckert and Tillotson, 1978). Such a coupling between inward and outward ion fluxes is

compatible with the idea that they share a conserved process. Although the present formalism represents the flow and counterflow as simultaneous processes, they can clearly act sequentially on a fast time scale without disturbing the main conclusions.

8. Long Range Order Due to Chemical Transduction of Signals: Action Potential vs Diffusion. The property of local symmetry axes guarantees factorization, but it also imposes a strong constraint on intercellular signals, since each signal source v_j then sends the same signals B_j and D_j to all signal sinks, v_i, $i \in I$, until the signals are gated by the LTM traces z_{ji}. This property is hard to justify if, for example, the distances between v_j and all the v_i, $i \in I$, are not the same. How can factorization be recaptured when each v_j can send different signals to the several cells v_i, $i \in I$?

An answer was given in Grossberg (1972a). It is reviewed herein because its relevance to a larger class of problems concerning developmental biology has since then become clearer (Grossberg, 1978a), and because the solution was not until now reconciled with the noise-saturation dilemma. The original answer suggested new functional reasons why:

(1) intercellular signals are sometimes carried by chemical, rather than electrical, signals; and

(2) intracellular signals are sometimes carried by the cell membrane, rather than by signals that traverse the cell body cross section. In nerve cells, these properties suggest a basic reason for the existence of action potentials and chemical transmitter substances.

If the path weights b_{ji} from v_j to v_i are arbitrary positive numbers, then (20) is generalized to equation

$$\dot{x}_i = -Ax_i + \sum_{k \in J} B_k b_{ki} z_{ki} + I_i, \tag{39}$$

in which the temporal variation of the signal from v_j to v_i is described by B_j, but the net signal along e_{ji} is $B_j b_{ji}$. How can we transform (39) so that spatial pattern learning is unimpaired despite the biases introduced by arbitrary path weights b_{ji}? It is easy to formally do this, but then we must ask what the transformation means physically. Formally, we need only to transform (39) and its companion LTM equation to a system in which no biases b_{ji} occur; namely,

$$\dot{x}_i = -Ax_i + \sum_{k \in J} B_k w_{ki} + I_i \tag{40}$$

and

$$\dot{w}_{ji} = -C_j w_{ji} + D_j x_i \tag{41}$$

which is the same as (20) and (21) except that it uses the notation w_{ji}, rather than z_{ji}, for the LTM trace from v_j to v_i. Comparison of (39) with (40) imposes the definition $w_{ji}=b_{ji}z_{ji}$. But then (41) imposes the following equation for z_{ji}:

$$\dot{z}_{ji}=-C_jz_{ji}+D_jb_{ji}^{-1}x_i. \tag{42}$$

Thus if path weights b_{ji} gate the performance signals B_j in (39), then unbiased pattern learning occurs if path weights b_{ji}^{-1} gate the learning signals D_j in (42).

At first broach, using $D_jb_{ji}^{-1}$ in (42), rather than D_jb_{ji}, might seem unintuitive. A mathematical analysis (Grossberg, 1972a) shows, however, that unbiased pattern learning cannot be achieved in a general anatomy if (42) is replaced by

$$\dot{z}_{ji}=C_jz_{ji}+D_jb_{ji}x_i. \tag{43}$$

It will now be shown that b_{ji}^{-1} in (42) has a natural physical interpretation, in addition to its useful formal property. This physical interpretation will be developed with nerve cells in mind, but since it depends on a simple dimensional argument, it can be generalized to other types of cells. Equation (43) also has a physical interpretation. The two interpretations describe classes of cells that utilize different mechanisms for carrying intracellular signals.

It is well-known that the action potentials, or spikes, that carry electrical signals along axons e_{ji} are determined by electrical and ionic events that occur across the axon circumference, which in turn is proportional to axon diameter. Let R_{ji} equal the (average) diameter of the axon (population) e_{ji}. The main hypothesis leading to b_{ji}^{-1} in (42) is that

$$b_{ji}=\lambda_jR_{ji} \tag{44}$$

or that the total signal strength, or ionic flux, across the axon is proportional to axon diameter. This hypothesis is compatible with the classical assumption that the action potential is an all-or-none event that propagates nondecrementally along the axon. For example, in mammalian A-type axons (myelinated, somatic axons) extracellular recording shows that spike amplitude increases linearly with axon diameter (Ruch *et al.*, 1961, p. 73). Suppose that after the signal in e_{ji} propagates down the axon

circumference, it reaches the synaptic knob, where it disperses throughout the cross-sectional area of the knob; for example, as ionic or electronic fluxes, or processes that are triggered in parallel with these fluxes. Let the rate of change of the LTM density at the interface between e_{ji} and v_i be proportional to the signal density. Finally, let the total effect of the signal on the postsynaptic cell be determined by mass action; that is, the total signal is proportional to the product of signal density, times LTM trace density, times cross-sectional area of the knob.

These simple mass action rules generate (39) and (42) as follows. Signal strength is proportional to R_{ji}, or to b_{ji}. The cross-sectional area of the knob is proportional to R_{ji}^2. Hence signal density at the cleft is proportional to $R_{ji}R_{ji}^{-2} = R_{ji}^{-1}$, or to b_{ji}^{-1}, as in (42). Thus

$$\text{(signal density)} \times \text{(LTM density)} \times \text{(area of knob)} \cong R_{ji}^{-1} x_{ji} R_{ji}^2 \cong b_{ji} z_{ji},$$

as in (39).

The above conclusion depends on a membrane-bound signal to yield (42). By contrast, a mechanism whereby signals propagate throughout the cross-sectional area of the axon—such as a diffusion—cannot produce unbiased learning given arbitrary path weights, or at least such a mechanism is still unknown. The difficulty here is that signal strength is proportional to R_{ji}^2, signal density is proportional to one, and the rate of LTM density change is proportional to one. The total signal is proportional to

$$\text{(signal density)} \times \text{(LTM density)} \times \text{(area of knob)} \cong b_{ji}^2 z_{ji}.$$

Thus we are led to the system

$$\dot{x}_i = -Ax_i + \sum_{k \in J} B_k b_{ki}^2 z_{ki} + I_i \tag{45}$$

and

$$\dot{z}_{ji} = -D_j z_{ji} + E_j x_i, \tag{46}$$

which can be written in terms of $w_{ji} = b_{ji} z_{ji}$ as

$$\dot{x}_i = -Ax_i + \sum_{k \in J} B_k b_{ki} w_{ki} + I_i \tag{47}$$

and

$$\dot{w}_{ji} = -D_j w_{ji} + E_j b_{ji} x_i. \tag{48}$$

This system cannot achieve unbiased pattern learning given arbitrary positive b_{ji} (Grossberg, 1972a).

The above observations suggest that the action potential interacts with chemical transducers in a manner that can compensate for differences in axon diameter, at least within a range of diameters such that (44) and the conversion into signal densities hold. More generally, membrane-bound intracellular signals and chemical transducers can work together to establish functionally strong long-range intercellular interactions even if the structural pathways between the cells become smaller as a function of intercellular distances. This compensatory transformation does not exist if intercellular signals are elctrical and are carried passively, or electrotonically, within cells.

The membrane–chemical diad describes an intercellular signalling mechanism that is radically different from diffusion. It is suggested in Grossberg (1969a, 1978b) that this property is one aspect of a general design principle called *spatiotemporal self-similarity* which allows cells to learn patterns from each other whose coded meaning is invariant under the massive changes in their mutual distances due to development and growth. Otherwise expressed, spatiotemporally self-similar cells are functionally disengaged from the Euclidean geometry in which they sit, and functionally embedded in a network geometry that allows them to establish developmentally stable long-range interactions.

9. Long-Range Order and the Noise-Saturation Dilemma. Can a system that experiences the noise-saturation dilemma be written in a factorizable form in which long-range order occurs, as in (39) and (42)? The answer is "yes" if we use (34) as a guide. When the transformation in (32) is formally applied to both the STM and LTM equations, it yields a system that does not seem to admit a sensible physical interpretation. The transformation in (34), by contrast, yields the system

$$\dot{x}_i = -Ax_i + (H - x_i)\left[\sum_{k \in J} B_k b_{ki} z_{ki} + I_i\right] - x_i\left[\sum_{k \in J} (L_k - B_k b_{ki} z_{ki}) + (M - I_i)\right] \tag{49}$$

and

$$\dot{z}_{ji} = -C_j z_{ji} + (N_j - z_{ji}) D_j b_{ji}^{-1} x_i - z_{ji}(P_j - D_j b_{ji}^{-1} x_i), \tag{50}$$

which is physically interpreted in the same fashion as (34) and (37), and which can be rewritten in the form (39) and (42). Thus system (49)–(50) overcomes the noise-saturation dilemma, establishes long-range order, and factorizes in an essentially arbitrary anatomy that can experience arbitrary data preprocessing and simultaneous convergence of arbitrarily many sampling sources. At the present time, these are the only equations known to imply all these basic properties.

10. Temporal Adaptation: Overshoot, Rebound, and Inverted U. The adaptation that occurs in (49) and (50) is *spatial* adaptation due to competition between spatially distributed sites, despite the fact that all the sites might exist in a single cell. There can also exist *temporal* adaptation within single cells. Temporal adaptation is the phenomenon that is typically called "intracellular adaptation". Below it is shown how such a temporal mechanism is derived from the gating law $B_j z_{ji}$ by applying a correspondence principle. The derived mechanism can adapt or not depending on the relative sizes of two decay rates. The mechanism also implies other properties, such as temporal overshoot, rebound, and variable sensitivity as a function of the adapting level, that have been reported in another place (Grossberg, 1969a, 1972b, 1975), but without stressing their interpretation as adaptational effects. A new property describing the simultaneous rebound of all differentially active cells in a field in response to a nonspecific event (e.g. arousal, hormone) will also be derived.

The simplest intercellular transduction rule converts an output signal S from one cell into a proportional input I to the receiving cell, viz., $I=kS$, where $k>0$. The law whereby cell v_j converts the signal B_j into an input $B_j z_{ji}$ to v_i is of this type, with $S=B_j$ and $k=z_{ji}$. Transduction can, for example, convert an electrical input into a chemical output, an input of photons into an electrical output, and so on. Given this physical interpretation, the law $I=kS$ describes the *gating* of S by k. Data describing the gating effect of transmitter on signals in various neural preparations is described in Čapek *et al.* (1971), Esplin and Zablocka-Esplin (1971), McCandless *et al.* (1971), and Zablocka-Esplin and Esplin (1971). When the transducing agent is released, degraded, or otherwise eliminated by the transduction process, there must exist a mechanism whereby it can be replenished, so that the rule $I=kS$ can be at least approximately maintained through time. If we interpret k as the amount of transducer and kS as the rate at which it is eliminated, then we are led to the following law for the temporal evolution of the amount m of available transducer:

$$\frac{dm}{dt}=A(k-m)-BmS. \tag{51}$$

The term $A(k-m)$ in (51) says that the amount m of transducer attempts to maintain the level k. It does this by producing transducer m at a rate Ak that is proportional to k, and by feedback inhibition of the production rate at a rate $-Am$ that is proportional to m. The term $-BmS$ in (51) says that the amount of transducer is reduced at a rate proportional to its elimination. When $m \cong k$, this term is proportional to I, as desired. Thus (51) is the law that "corresponds" to the law $I = kS$ when depletion of transducer can occur.

Temporal adaptation of the signal BmS can be explained as follows. Let a signal of constant size $S = S_0$ be applied during a time interval $[0, T]$ that is sufficiently long for $m(t)$ to approach its equilibrium value m_∞. Setting $dm/dt = 0$ in (51), it follows that

$$m_\infty = \frac{Ak}{A + BS_0}. \tag{52}$$

Not surprisingly, m_∞ is a decreasing function of S_0, since more transducer is eliminated if the input that activates it is greater. By contrast, the intercellular signal at time $t = T$ has size (approximately)

$$Bm_\infty S_0 = \frac{ABkS_0}{A + BS_0}, \tag{53}$$

which is an increasing function of S_0. Thus although the amount of available transducer decreases, the net signal increases because the signal S is coupled to m by mass action. Suppose that at time $t = T$, the signal suddenly increases in size to $S = S_1$. If $m(t)$ is a slowly varying function of time, then in the time interval immediately following $t = T$, the intercellular signal is

$$BmS_1 \cong Bm_\infty S_1 = \frac{ABkS_1}{A + BS_0}. \tag{54}$$

In (54), S_0 acts as an adaptational baseline against which S_1 is evaluated, just as I in (3) acts as an adaptational baseline against which I_i is evaluated. In (3), the baseline is due to fast spatial interactions across a parallel network of cells. In (54), the baseline is due to slow temporal interactions within a serial intracellular gate. If the rate with which $m(t)$

changes is just as fast as the fluctuation rate of $S(t)$, then temporal adaptation does not occur; it is due to the slow rate of $m(t)$ relative to $S(t)$. For example, the fact that cones adapt better than rods in the *Necturus* retina (Normann and Werblin, 1974) does not, by itself, imply that their transduction mechanisms are different; a difference in relative rates could suffice to explain this.

A similar explanation shows how a sudden increment in $S(t)$ from S_0 to S_1 can cause a transient overshoot in the intercellular signal. Immediately after the increment, (54) holds, but then $m(t)$ slowly approaches its new asymptote $Ak(A+BS_1)^{-1}$. Thus the signal BmS rapidly jumps from (53) to (54), and then slowly decays to the asymptote

$$\frac{ABkS_1}{A+BS_1}. \tag{55}$$

More subtle effects occur if two transducer channels, C_1 and C_2, lead to output signals that mutually compete before they are further processed (Fig. 5). For mathematical convenience, the inputs to each of the two channels are broken up into two summands: an input I that is commonly shared by both channels—this is the adaptation level—and the net additional input J that one of the channels, say C_1, experiences—this is the phasic, or test, input. The following statements have been proved, among others (Grossberg, 1972b).

Let both channels equilibrate to constant positive levels of I and J. In particular, after competition of signals occurs, only C_1 elicits a net output signal. Then

(I) a sudden decrement in J can cause the cessation of the C_1 output and a transient rebound output from C_2;

(II) a sudden increment in the adaptation level I, by itself, can cause the cessation of the C_1 output and a transient rebound output from C_2;

(III) the absolute size of the C_2 rebound, given a fixed decrement in J, is an inverted U function of the adaptation level I.

Quantitative formulas and predictions describing these and various other effects are derived in Grossberg (1972b) concerning a class of experiments about behavioral reinforcement. For example, property (I) helps to understand how a reduction in conditioned reinforcer input J to one incentive motivational channel can activate the complementary channel and serve as a basis for counterconditioning; e.g. fear reduction can elicit transient relief, or removal of consummatory goal cues can elicit frustration. Property (II) shows how a novel event, by nonspecifically increasing the adaptation level I, can also activate a specific process like countercon-

ditioning. Property (III) shows how the adaptation level can modulate the effect of rewarding inputs according to an inverted U function, and predicts the existence of two types of emotional depression, an under-aroused and an overaroused syndrome with significantly different symptoms, at the two ends of the inverted U. We now note that these results

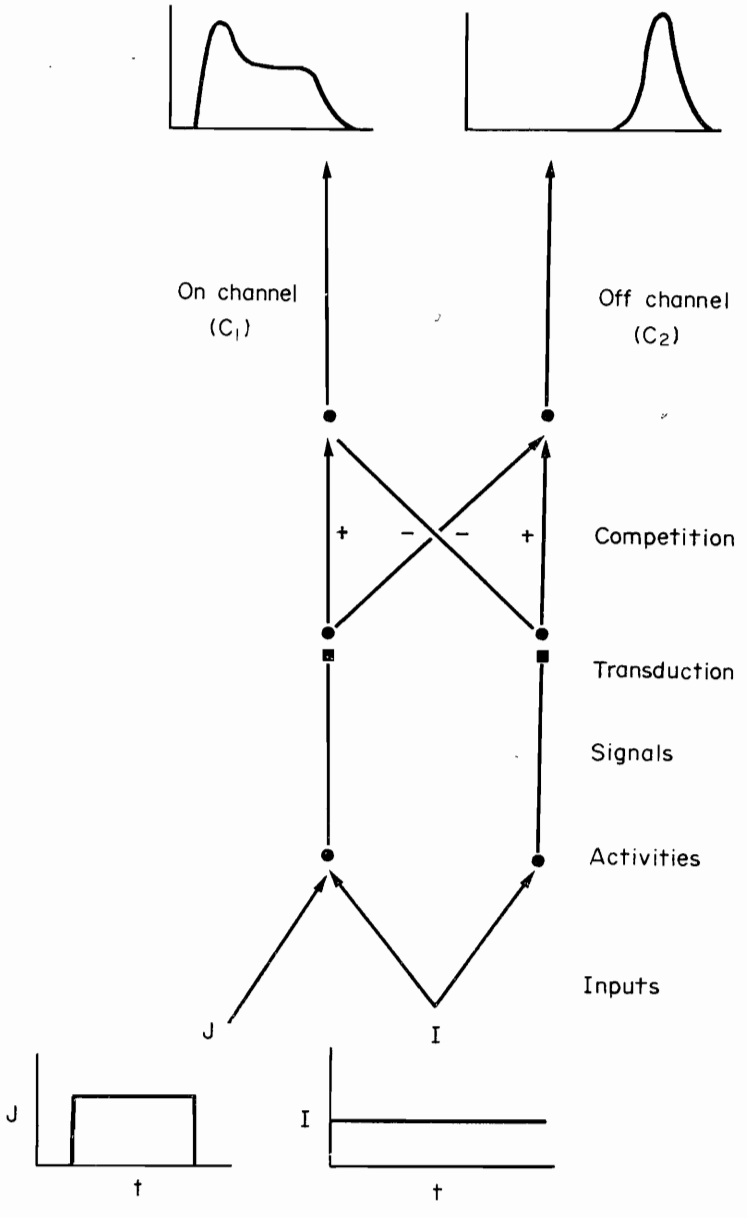

Figure 5. On-cell off-cell dipole: Onset of the phasic input J causes on-cell overshoot followed by a persistent on response; offset of the phasic input J causes off-cell transient rebound

have a more general application to situations wherein chemical transducers can be depleted by a slower process than the signal fluctuation rate.

For example, suppose that the motor command cells that control agonist and antagonist muscles compete after receiving transduced phasic and tonic signals. Analogously, suppose that feature detectors in a sensory

cortex are arranged in on-cell off-cell dipoles, so that onset of a phasic sensory cue persistently turns on its on-cell, whereas offset of this cue transiently turns on the off-cell, which thereupon can sample a pattern to be learned in response to cue offset (Grossberg, 1976, 1980). In either case, we will show below that an unexpected or novel event can simultaneously rebound the activities in *all* the on-cell off-cell dipoles by causing an increment in non-specific arousal across all the cells. In the case of motor control, this rebound can simultaneously brake hundreds of muscles by matching the antagonist rebound to the size of the prior agonist command. In the case of sensory or cognitive processing, the rebound can simultaneously and differentially suppress those activities across the feature detectors whose signals caused the unexpected event. In both cases, the arousal event—which is controlled by a one-dimensional command—can exquisitely reorganize the pattern across a high-dimensional field of cells by actualizing a type of probabilistic logic in real time; namely, if a certain degree of "on" activity implies an unexpected event, then it is transmuted into a comparable degree of "off" activity.

To see this, let the phasic input to a given on-cell have intensity J and the tonic input to both on-cell and off-cell have intensity I. The steady-state potential in the on-cell is then $x_1 = \alpha(I+J)$ and in the off-cell is $x_2 = \alpha I$. Let each cell generate a proportional signal, for simplicity. Then signal $S_1 = \beta(I+J)$ and signal $S_2 = \beta I$. Each signal is gated by its transducer m_1 or m_2, respectively, whose steady state values are

$$\bar{m}_1 = \frac{Ak}{A+BS_1} \quad \text{and} \quad \bar{m}_2 = \frac{Ak}{A+BS_2}, \tag{59}$$

respectively. Now rapidly change the arousal level to $I^* > I$, while holding J fixed. The new signal values rapidly approach $S_1^* = \beta(I^*+J)$ and $S_2^* = \beta I^*$, respectively. To achieve a rebound from on-cell to off-cell, the gated signal to the off-cell must exceed that to the on-cell shortly after the arousal level changes. If m_1 and m_2 change slowly, then this will occur if

$$S_1^* \bar{m}_1 < S_2^* \bar{m}_2. \tag{60}$$

By (59), inequality (60) is equivalent to

$$I^* > I + \frac{A}{\beta B}. \tag{61}$$

The crucial observation is that inequality (61) is independent of J. Thus if the arousal increment exceeds $A\beta^{-1}B^{-1}$, then *all* dipoles will be simultaneously rebounded. Moreover, the rebound size is matched to the initial on-cell activity because

$$S_2^*\bar{m}_2 - S_1^*\bar{m}_1 = \frac{AB\beta^2 kJ[I^* - I - A\beta^{-1}B^{-1}]}{[A+\beta BI][A+\beta B(I+J)]}, \tag{62}$$

which is a monotone increasing function of J.

Unfortunately, such explanations have been overlooked by the experimentalists who do reinforcement, sensory, and motor experiments. In the reinforcement area, for example, experimentalists continue to cite the descriptive theory of Rescorla and Wagner (1972) and to perform experiments based on that theory (Dickinson and Pearce, 1977). It is to be hoped that as the adaptational properties of chemical transducers in competing channels are recognized, experiments will be designed to test the sharper distinctions that these properties describe, both in neural and nonneural tissues.

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