

Computer Models of Stroke Recovery: Implications for Neurorehabilitation

WILLIAM W. LYTTON, JEANNE M. STARK, DWAYNE S. YAMASAKI,¹ and SAMUEL J. SOBER

Departments of Neurology (WWL, SJS) and Anatomy (JMS, DSY)

Neuroscience Program (WWL, DSY)

University of Wisconsin

Wm. S. Middleton VA Hospital (WWL, SJS)

Madison, Wisconsin

The persistence of cortical plasticity in the adult can help explain functional recovery after stroke. Computer modeling tools developed to explain the process of early development of sensory systems can be extended to help us relate cortical plasticity to both behavior and to underlying molecular and cellular mechanisms. Computer modeling results suggest a two-phase recovery process, involving immediate alterations in activity patterns caused by the loss of the infarcted neurons ("dynamic plasticity"), followed by true plastic changes as the new activity alters synaptic weights between neurons. Recognition of these two phases suggests that timing of physiotherapy and pharmacotherapy may play an important role in their efficacy. *NEUROSCIENTIST* 5:100-111, 1999

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Causal links are nonintuitive in complex systems. In the realm of weather, a rogue current in the mid-Pacific can throw off your vacation plans on the Atlantic seaboard. In the brain, a drug or other intervention can have far-reaching and unexpected effects. The computer has proven a valuable tool for permitting predictions to be made in complex systems. This is done by making connections between different levels of organization (1). In the nervous system, these levels of organization can be identified anatomically and physiologically (Box 1) (2, 3). A major goal of computational neuroscience is to reach across these levels—for example, to explain and predict molecular effects at the network level or network effects at the behavioral level. Creation of these conceptual links is important in neurological disease because pharmacotherapeutic interventions are aimed at the molecular level, whereas clinical outcomes are sought at the functional, behavioral levels.

In the early 1950s, computer-science pioneer A.M. Turing developed a series of equations that help explain how the leopard got its spots (4). He noted that a chemical process marked by a difference in reaction rates with diffusing reactants could produce a variety of striped and spotted designs that could be responsible for a wide variety of biological patterns (5). The processes of evoked activity and activity-dependent plasticity present in the central nervous system can be viewed as "reactions"

that occur at different rates, resulting in the development of patterns such as ocular dominance and orientation columns (6). Given mathematical methods that can explain the development of patterns, it was natural to apply these methods to the problem of recreation of appropriate or inappropriate brain patterns after the disruption produced by a stroke.

Plasticity in the Adult Brain

The pioneering studies of Hubel and Wiesel introduced the concept of a critical period in brain development. They found that appropriate neural connections from the eye either formed during this period or did not form at all, leaving the animal visually impaired. Extrapolation from this result suggested the hypothesis that neural organization of primary cortex was largely fixed at some definable developmental stage, restricting adult plasticity to remote cortical areas where learning could still take place. Although lower vertebrates were known to recover function after central nervous system damage, such changes were not thought to occur in primates. However, evidence of substantial plasticity was found by Merzenich and colleagues (7-9), who demonstrated changes in primary sensory cortical maps in adult monkeys.

Cortical reorganization in adults has now been demonstrated in both somatosensory and visual areas. Most studies have looked at cortical reorganization in response to alterations of stimulus characteristics (for example, eliminating stimulation by removing a finger or altering the pattern of stimulation on a patch of skin by transplanting it to a different location). In general, cortical reorganization involves the shifting and resizing of cor-

¹ Current address: Forbes Norris ALS/MDA Research Center, California Pacific Medical Center, San Francisco, California, and Dept. of Biology, Sonoma State University, Rohnert Park, California.

Address reprint requests to: Dr. William W. Lytton, Department of Neurology, University of Wisconsin, 1300 University Ave., MSC 1715, Madison, WI 53706-1532 (E-mail: bill@neurosim.wisc.edu).

Level of Organization

Example studies

	Physiological	Computer Model
Behavior	grasping, visual pursuit	robotics, language simulations
Maps	reformation after peripheral or central ablation, or after cortical stimulation	map formation and reformation with Hebbian or other rules
Networks	assessment of receptive fields	neural network simulations
Cells	long-term potentiation, electrophysiology, sprouting	single neuron simulations - cable modeling
Molecules	pharmacology, receptors and ion channels	Hodgkin-Huxley kinetics, synaptic simulation

Adapted from Sejnowski and Churchland, 1988 [3]

tical maps so that heavily stimulated areas are well represented, weakly stimulated (or removed) areas lose representation, and similarly stimulated areas are represented together (10–15). In addition to peripheral manipulation, intracortical microstimulation can also cause rapid plasticity. After several hours of stimulation to a particular cortical site, surrounding neurons tend to have receptive fields similar to those of the neurons being stimulated (16–19). Although the “expressive fields” of the motor system are somewhat harder to define than the receptive fields of sensory systems, similar cortical changes and receptive field properties have been observed in motor cortex as well (20).

Similarly, in animal models of stroke, receptive fields of surviving cells expand and fill the space previously covered by the lesioned area (21). In the visual system, microelectrode recordings of surviving neurons have revealed dramatic alterations in receptive fields, including expansion, shift (asymmetrical expansion), and contraction (Fig. 1A) (22, 23). Changes in firing rates of these neurons were also found. Similar results have been reported in the somatosensory (24) (Fig. 1B) and motor cortex (25–27).

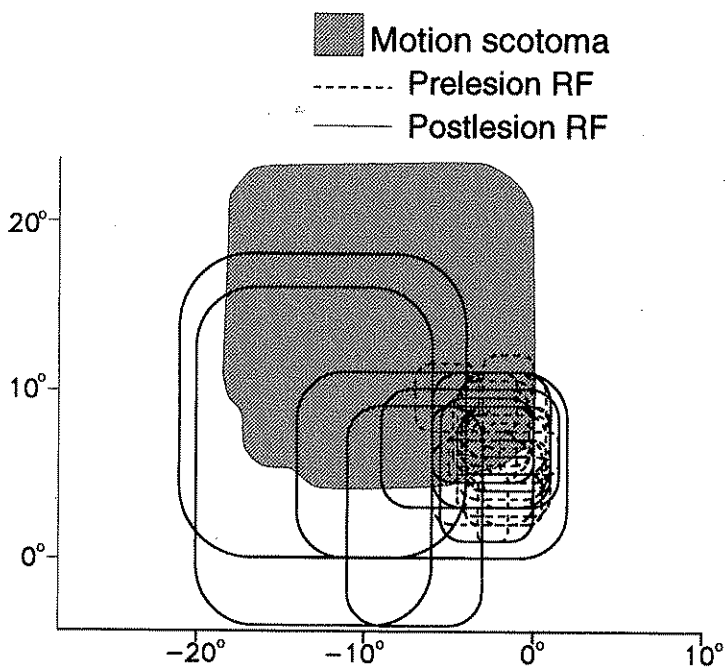
Dynamics of the Cortical Map

The basic concept of a dynamic cortical map, originally proposed by von der Malsburg (28–31), has been widely

adapted (32–35). The basic computer model comprises a set of inputs and the cortical layer (Box 2). Interactions between neurons in the cortical layer are defined not only by anatomical connectivity, but also by the dynamics of physiology (Box 3). The dynamics of neural activation are fast, with events occurring within milliseconds. A second level of dynamics is then built on top of this first level, occurring with much longer time constants (on the order of hours to days). This is the phenomenon of activity-dependent synaptic reorganization: the Hebb synapse (Box 4) (36). The distinction between the dynamics of physiology and the dynamics of synaptic reorganization is justified by the large difference in time constants between the two phenomena. However, the two phenomena are actually interacting, because synaptic reorganization is dependent on the physiology of activation dynamics and activation is dependent on the underlying anatomy that is being altered by synaptic reorganization (Box 4, *bottom*).

With regard to stroke, this observation, implicit in the general schema and made explicit by Reggia and colleagues (34, 37, 38), means that recovery from stroke will necessarily involve two phases. Immediately after the stroke occurs, the normal dynamic of the network is suddenly disrupted. Neurons no longer see their accustomed excitatory or inhibitory inputs from the ablated

A Middle Temporal (MT) Visual Area



B Somatosensory Cortex

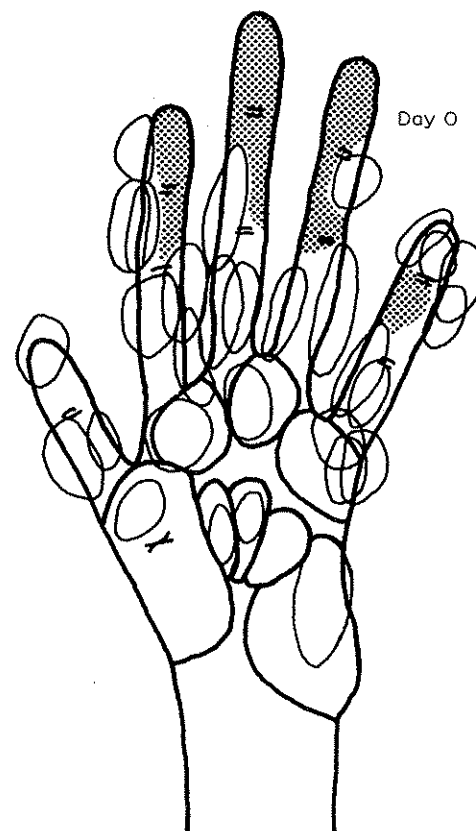


Fig. 1. A, Expansion of receptive fields in adjacent area of cortex after cortical ablation. Neurons are sampled from similar locations near the site of the lesion, although there is no way to resample the exact same neurons before and after lesion. Both the motion scotoma and the receptive fields of individual cells are graphed as degrees of visual field. (Reprinted with permission from Sober SJ, Stark JM, Yamasaki DS, Lytton WW, Receptive field changes following stroke-like cortical ablation: a role for activation dynamics. *J Neurophysiol* 1997;78:3438–3443. Copyright © 1997 The American Physiological Society.) B, Expansion of receptive fields is also reported surrounding an ablation in somatosensory cortex. Prelesion receptive fields are generally smaller, but are not shown in this figure. (Reprinted from *Progress in Brain Research*, vol. 71, Jenkins WM, Merzenich MM, Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke, pages 249–266, Copyright © 1987, with permission from Elsevier Science.)

area. Areas subject to lack of excitation would show a local version of diaschisis, the term used to describe distant reduction in brain activity caused by lack of accustomed activation from a lesioned area. Areas subject to lack of inhibition would show unmasking as previously ineffective subcortical projections are revealed. These changes in receptive fields and behavior might seem at first to be a result of plasticity (that is to say, a result of physical change in the connections of the neural circuit); actually, the only change in structure is the stroke itself, which removed a set of neurons from the circuit. We have characterized the results of this dynamic phase as “dynamic plasticity,” because it gives the appearance of an underlying change in structure consequent to the stroke but is, in fact, only a set of dynamic consequences (23).

The alterations of dynamic plasticity set the stage for the true plastic changes to the wiring of the neural cir-

cuit. Structural changes consequent to activity might include cell death from excitotoxicity and changes in synaptic strength related to coincident presynaptic and postsynaptic activity, as will be discussed below. Additional structural changes have nothing to do with activity but are instead the consequence of other tissue factors such as edema, resolution, extension of an ischemic penumbra, or spreading depression. Such factors are now also being included in computer modeling (39) but will not be discussed further here.

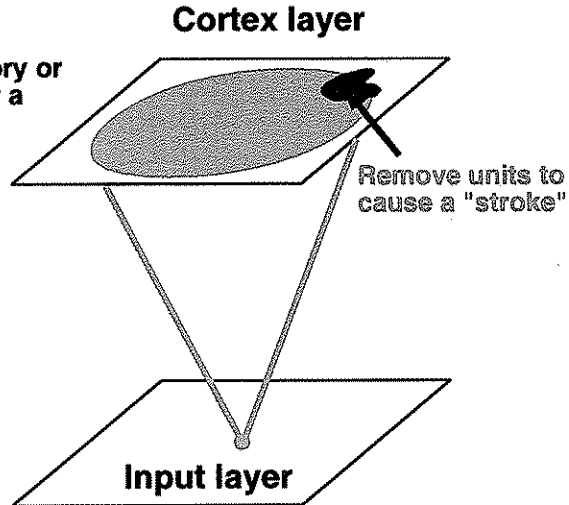
Phase 1: Dynamic Plasticity

As a first phase, neural reorganization after stroke will involve reorganization of activity (40, 41). In our previous study (23), we directly compared the predictions of a computer model of stroke with the immediate changes in receptive fields observed in remaining cells

Standard Computer Model

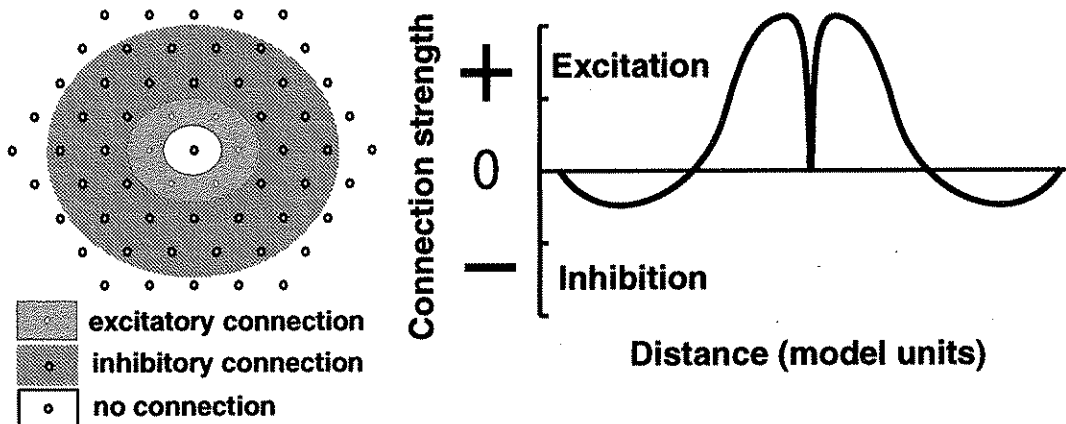
The basic computer model studied is based on the cortical maps of physical space found in retinal and visual cortex. A set of inputs represents this space while a processing layer represents the cortex. The organization of connections between and within layers is highly simplified.

The input layer (below) is a 2-dimensional map of space. This might be somatosensory or visual space. The cortex is represented by a 2-dimensional map above. (A vast simplification since neither skin nor retina projects directly to cortex.) A potentially very confusing point is that the input layer is alternately conceived of as a primary receptor array (for the purpose of mapping receptive fields) or as a thalamic or lower-level cortical area (for the purpose of assessing cellular interactions). Typically, single units of the input project to cortical units directly above them and diverge symmetrically to cortical units off to the side. In the basic model, the input layer has no internal connections.



Lateral Connectivity within cortex layer

The cortex layer has both excitatory and inhibitory lateral projections. Each white dot is the position of a model unit. Projections from the central unit are shown; unit does not project onto itself (zero connection strength). Nearby projections from a given cortical neuron are excitatory while more distant projections are inhibitory. Graphical view shows "Mexican hat."

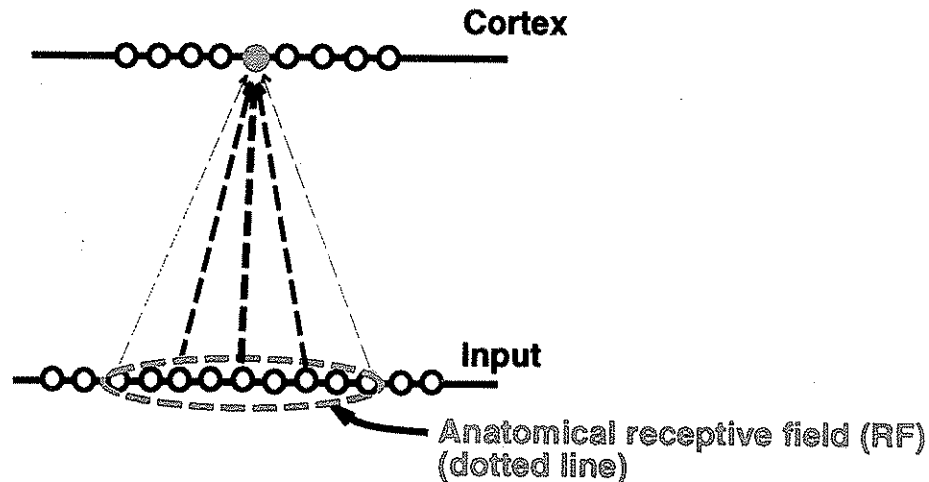


Generalization of the receptive field

The receptive field (RF) for an experimental animal, a patient, or a single neuron is the set of stimuli that can be perceived, or that can produce a measurable activation or change in behavior. Often such stimuli can be tested spatially: clinical visual field assessment or pin-prick assessment of dermatomal sensory fields for localizing peripheral nerve damage. These maps are not always spatial: e.g. the tonotopic map of an auditory neuron or orientation selectivity of a visual neuron.

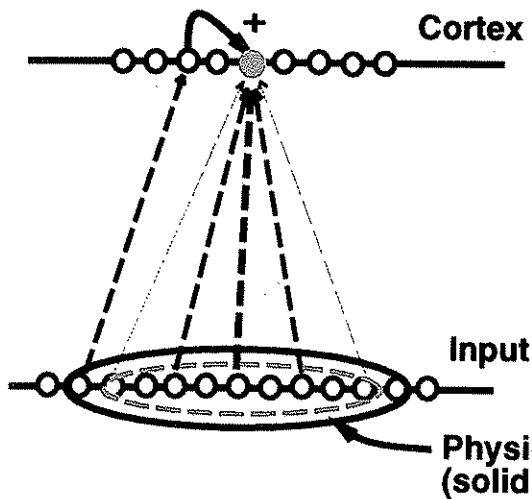
Anatomy proposes

The term receptive field is generally used behaviorally and physiologically, but not typically anatomically. However, an anatomical receptive field can be defined as the projecting neurons convergent onto a given neuron. The neurons circled in the input layer project onto the blue neuron in the cortex layer.

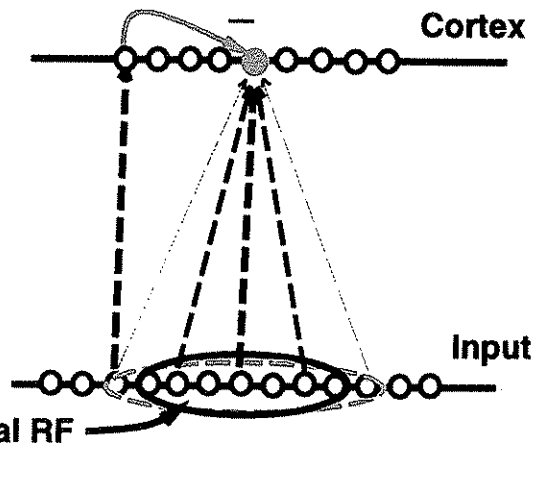


Physiology disposes

The physiological RF can be larger than the anatomical RF if lateral excitatory connections permit an outlying neuron to excite the cortical neuron.



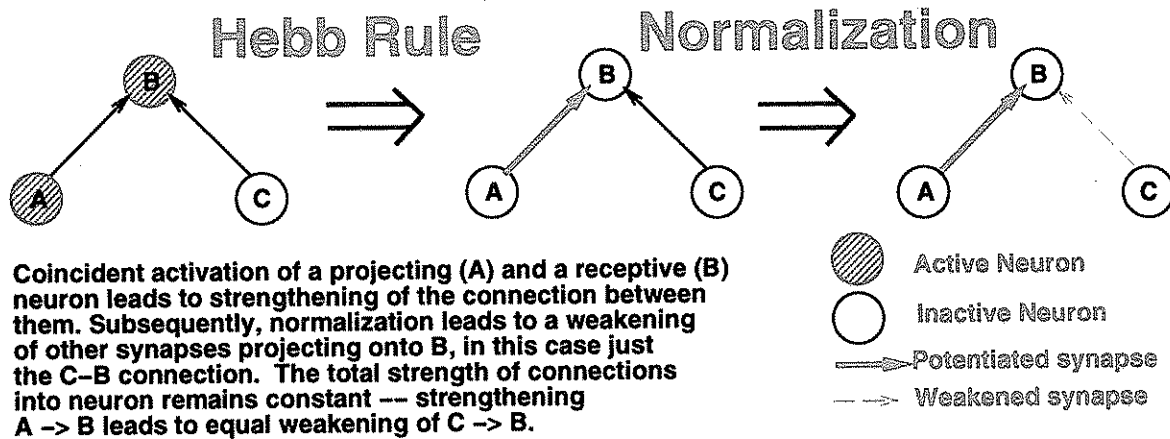
The physiological RF can be smaller than the anatomical RF if lateral inhibitory connections prevent an outlying neuron from exciting the cortical neuron.



Activity determines Plasticity

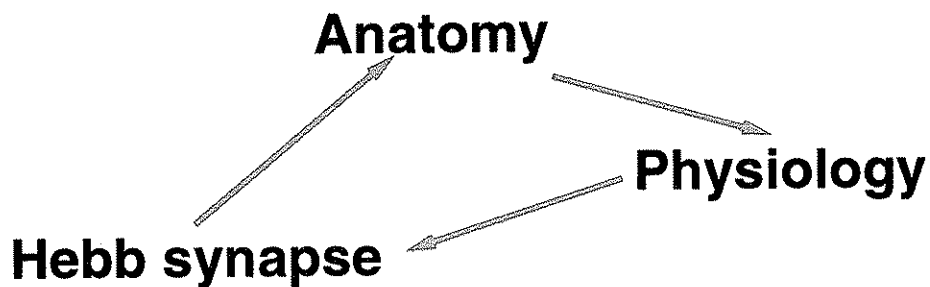
The Hebb synapse describes a mechanism for changes in synaptic strength in response to ongoing activity in the connected neurons.

Normalization is usually added to these models. This makes the Hebbian mechanism competitive, as one synapse gained in strength at the expense of another. Mathematically, this is done by maintaining the total strength of all synapses onto a particular cell at a constant normalized value.



Simultaneous Plasticity

Changes in activation dynamics (physiology) and in synaptic organization (Hebb synapses) are actually occurring simultaneously in a coupled dynamic. They can be treated separately because they occur at vastly different time scales (msec vs. hours).



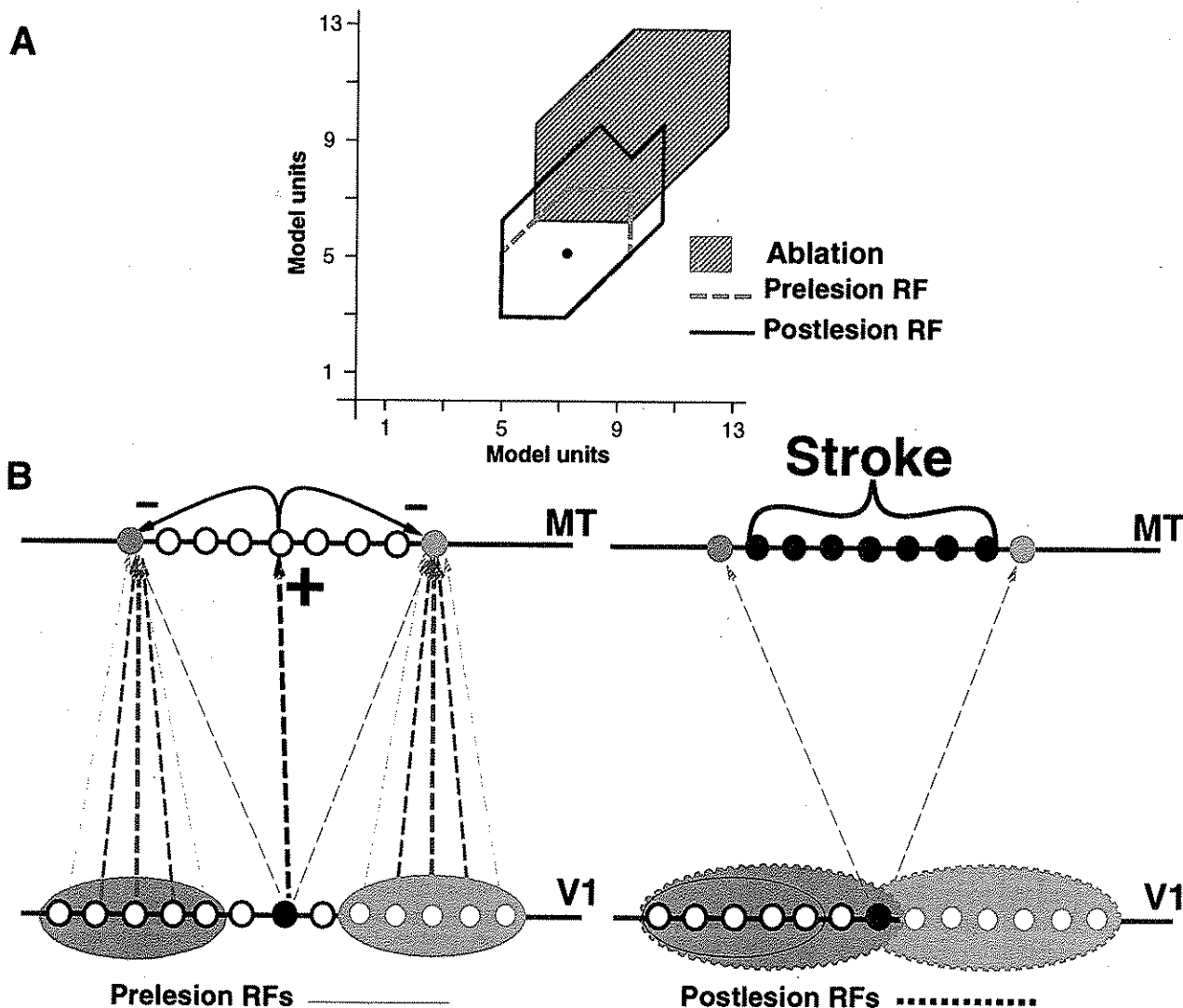


Fig. 2. A, Computer model shows expansion of a single receptive field (RF). Dot shows location of unit whose pre- and postlesion receptive fields are shown. Input layer and cortex layer are the same size and are therefore mapped on top of each other: ablation area (stipple) and unit are mapped in cortex space while pre- (dashed blue line) and postablation (solid line) RFs are mapped in input space. (Reprinted from Sober SJ, Stark JM, Yamasaki DS, Lytton WW, Receptive field changes following stroke-like cortical ablation: a role for activation dynamics, *J Neurophysiol* 1997;78:3438–3443, Copyright © 1997, with permission from the American Physiological Society.) B, RF expansion (unmasking) is caused by loss of lateral inhibition. Lack of lateral inhibition allows a unit to respond to even weak afferents; subsequently, that unit's RF expands. In prelesion state (left), receptive fields are relatively small. Units that project weakly to particular cortical units, such as the *black unit* in the input map that projects to the *blue* and *grey units* in cortex, are unable to activate the cortical units because of lateral inhibition (lateral arrows with negative signs). After the ablation (right), this lateral inhibition is no longer present, so the direct (albeit weak) excitation can activate these cortical units.

after experimental stroke in the middle temporal visual area of a macaque (Fig. 1A). The lesion produced a motion scotoma, an area where motion was poorly perceived. Even if motion was not perceived in this area, this scotoma was not a blind spot, because stationary objects could still be seen there.

Our model was able to replicate the observed expansion in receptive fields, with the characteristic asymmetry involving greater expansion toward the lesion site (Fig. 2A). Expansions were most pronounced in units at the lesion edge. The model provides a ready explanation of the pattern of receptive field expansion as a primary

effect of disinhibition (Fig. 2B). Model units near the lesion site expand because they no longer receive the lateral inhibition that came from the now ablated cells. The lack of inhibition allows the unit to respond to even weak afferents (unmasking). The degree of expansion is correlated with the amount of anatomical divergence from the input layer of the model (see Fig. 2C of Sober et al. [23]). The asymmetry of expansion can be understood by noting that the greatest disinhibition will be in areas nearer to the lesion, so that the tendency toward receptive field expansion will be greatest on that side. Inhibition from sites far from the lesion will be intact

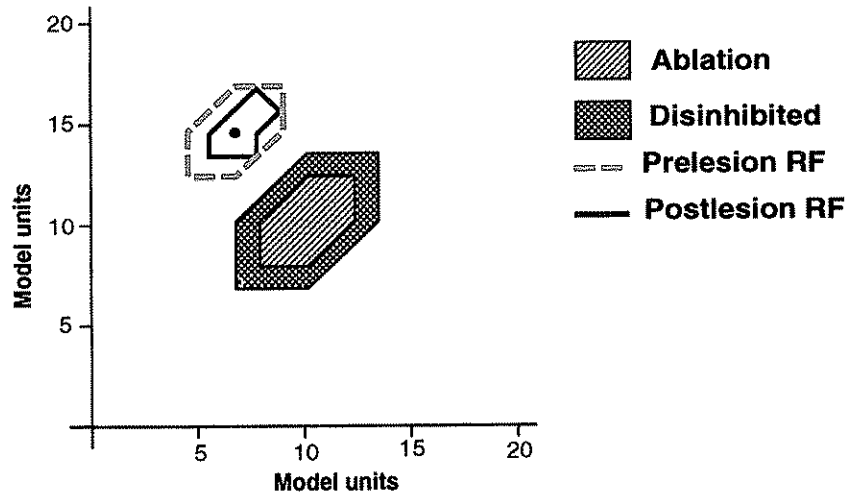
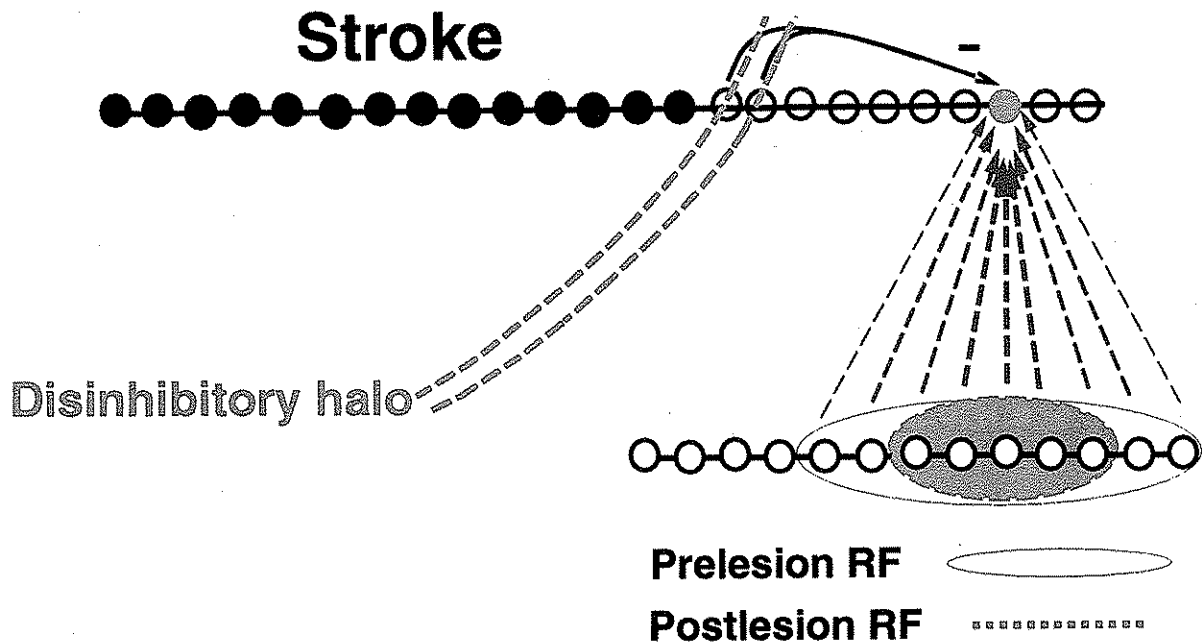
A**B**

Fig. 3. A, Computer model shows contraction of a single RF. Input layer and cortex layer are the same size and are therefore mapped on top of each other: unit (dot), ablation area (stipple) and disinhibitory halo (dark stipple) are mapped in cortex space, whereas pre- (dashed blue line) and postablation (solid line) RFs are mapped in input space. (Reprinted from Sober SJ, Stark JM, Yamasaki DS, Lytton WW, Receptive field changes following stroke-like cortical ablation: a role for activation dynamics, *J Neurophysiol* 1997;78:3438–3443, Copyright © 1997, with permission from the American Physiological Society.) B, RF contraction is a secondary effect of disinhibition. Model units distant from the disinhibitory halo contract because of the augmented lateral inhibition from the highly active units in the disinhibitory halo. These highly active units no longer receive substantial lateral inhibition themselves; rather, they produce high levels of inhibition on more distant cells, shrinking their RFs.

and will tend to maintain receptive field size on the other side, distal from the lesion.

Although the basic model readily replicated expansion, it did not easily produce the contractions that were seen physiologically. This prompted a re-evaluation of the assumptions of the model. Further analysis of the histology surrounding the lesion site revealed loss of protein markers that was suggestive of a loss or dysfunction of inhibitory cells in a halo around the lesion

site. Assuming that this cell loss might be an effect of the ablation itself, the model was modified to include a disinhibitory halo (Fig. 3).

The modified model produced larger receptive field expansions and also produced receptive field contractions. The larger expansions were a direct consequence of the increased disinhibition. The contractions were a secondary consequence of this, as these highly active cells produced a ring of increased inhibition in the zone

corresponding to the rim of the Mexican hat (negative values in the graph in Box 2). Neurons that no longer receive substantial lateral inhibition themselves (yet have intact inhibitory connections to other neurons) produce substantial inhibitory effects on these more distant units, contracting the distant units' receptive fields. This modeling result makes the prediction that contracted receptive fields will tend to be far from the ablation whereas expanded receptive fields are close to the ablation.

Phase 2: Activity-Induced Synaptic Reorganization

Stroke represents a structural brain change that is basically random with respect to the brain; instead, it is based on the superimposed vascular pattern. Some consequent structural changes may also be random. For example, it is unclear whether patterns of axonal sprouting will be related to activation of both pre- and postsynaptic cells or related to presynaptic activation alone. Other structural changes will occur because of the alterations in activity detailed above (42). Fifty years ago, Hebb (36) postulated that synaptic connections would be strengthened by coincident activation of pre- and postsynaptic neurons (Box 4). Long-term potentiation is a physiological mechanism that fits this description.

These models of synapse formation have been used to make fairly detailed predictions about the outcome of perinatal visual manipulations on development of visual cortex (35, 43–45). Subsequently, similar models were extended to reproduce the changes in cortical maps consequent to peripheral ablation, peripheral repetitive stimulation, or cortical stimulation (32, 33, 46, 47).

However, when it came to replicating the reorganization of cortex seen with stroke (24), this basic model was found to be inadequate. As pointed out by Sutton et al. (48), the process of reorganization after stroke is different from the process that takes place with a change in input pattern. Where the input pattern leads, synaptic strength will tend to follow, because the input pattern provides the consistent half of the pre- and postsynaptic coincidence that augments synaptic weights (49–52). Hence, if the input pattern remains the same, the synapses may not change much, even after a large alteration in cortical dynamics.

Modeling studies by Grajski and Merzenich (32, 46) found that the basic developmental model, although sufficient to explain most of their experimental findings of cortical reorganization with alterations of peripheral input, could not explain the synaptic reorganization that occurs after stroke. To reproduce stroke results in these studies, the authors completely rerandomized the synaptic connections, in essence starting over from scratch. After this, the system created a new mapping that efficiently used the remaining cortical space. Although their solution seems biologically implausible, it might none-

theless have some interest in developing new approaches to stroke rehabilitation, as described below.

The limitations of the basic developmental model led to the question of whether a different network organization would produce synaptic reorganization in response to stroke. Instead of using the standard inhibitory surround projection in the cortical layer (Box 2B), Reggia and colleagues postulated a system of "competitive activation," whereby the amount of activation available from each unit of the input layer was limited (53). This provided another level of normalization, which distributed activity rather than weight. Using this technique, they were able to produce some degree of reorganization in response to stroke (48).

Another model of synaptic reorganization after stroke was provided by Xing and Gerstein (54). They demonstrated reorganization with receptive field changes using a three-layer network (input, thalamus, cortex) and applied the Hebbian learning mechanism to the intracortical excitatory connections, rather than to the connections from input to cortex (Fig. 4). Their simulations showed that those cortical cells that were not excited by peripheral input in the control situation (cell 3 in Fig. 4) could become excitable immediately after the lesion and remain excitable after synaptic reorganization had occurred. Other cells showed dynamic receptive field expansion that persisted or increased slightly with retraining (Fig. 4, cells 1, 2). The authors found that when they augmented the model by adding Hebbian learning in the ascending projections to the Hebbian learning in the cortex, they could get still more dramatic receptive field expansions. With this combination of cortical and subcortical synaptic changes, receptive field expansions were large enough to fill quite large gaps in perception left by the stroke. One artifact of their model was that it tended to produce highly irregular and even discontinuous receptive fields, even in the normal control model. This peculiarity can be seen physiologically after recovery from peripheral ablation, but is not seen in control animals (24).

Negative results are compelling in computer modeling: they tell us that our assumptions are lacking, that we are missing the point. An initial assumption in modeling stroke recovery was that it could be completely explained by processes analogous to those of brain development. This turned out not to be the case, a negative result. This failure immediately suggests that additional mechanisms may be present that are not critical in development. As a corollary, the failure suggests that recovery from stroke may actually be hampered by the persistence of developmental mechanisms that are unsuited to this task.

Developing New Strategies for Stroke Rehabilitation

Physical and occupational therapy are currently the mainstays of treatment after stroke. There is growing

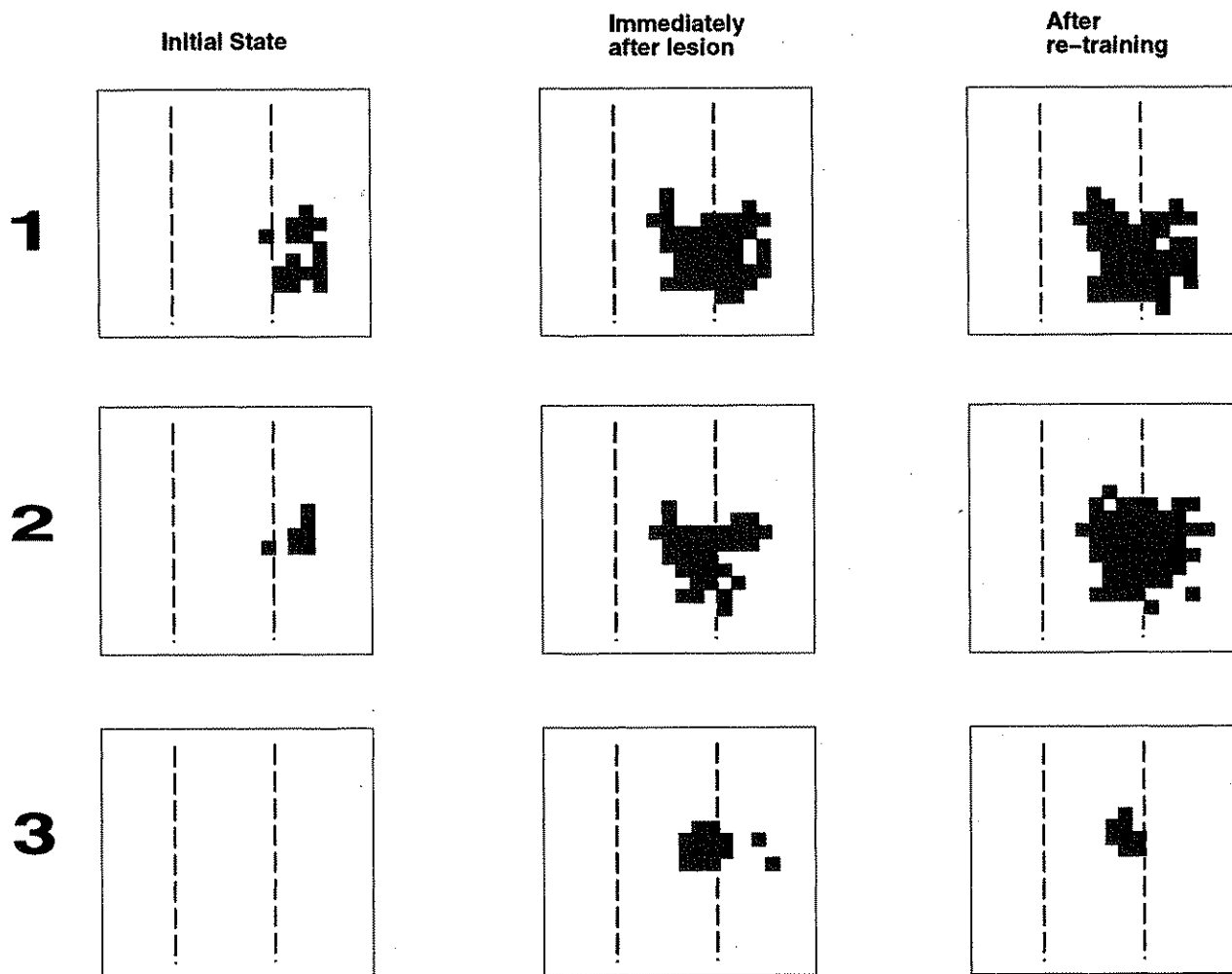


Fig. 4. Two stages of receptive field changes after cortical ablation in three neurons (1, 2, 3) of the Xing and Gerstein model. Ablated area is between the dashed lines. Receptive fields of neurons at the edge of the lesion tend to expand into the lesion immediately (*center*). They expand still further after cortical reorganization has taken place (*right*). (Modified and reproduced from Xing J, Gerstein GL, Networks with lateral connectivity, *J Neurophysiol* 1996;75:184–199, Copyright © 1996, with permission from The American Physiological Society.)

interest in augmenting this with pharmacological management as well. Although the results given above are still very preliminary, they do suggest ways in which greater understanding of activation dynamics and synaptic reorganization could lead to new therapeutic approaches.

To see how, let us summarize the two-phase process given above. A stroke happens. Suddenly, a bunch of neurons are gone. The activity in the remaining neurons changes. Some were receiving net activation from the lost cells. They will show decreased activation (diaschisis) and will be harder to stimulate from the periphery (decreased receptive field size). Others were receiving net inhibition from the lost cells. They will show increased activation and will be easier to stimulate from the periphery (unmasking—increased receptive field size). Reactions that follow are both 1) functionally non-specific reactions to cell injury, and 2) related by reor-

ganization to the changes in activity. The best-characterized of the latter reactions would be Hebbian synapse modifications, with increased cell activation in particular cells tending to produce strengthening of synapses in the presence of presynaptic cell activation. From this point, the different models make different assumptions: perhaps synapse strengthening takes place in a competitive environment so that other synapses are weakened concomitantly (synaptic weight normalization); perhaps there is only a limited amount of activation to go around, so selected neurons are activated more than neighbors (competitive activation theory); perhaps synaptic strength changes within the cortex, perhaps from thalamus to cortex, perhaps both.

Behavioral Implications

Although we can now begin to predict how neural activation changes after a stroke, it is still not possible to

say with any certainty how any given set of neural activities adds up to a perception or a movement (55). There is evidence that neural activity correlates with perception (56, 57) or with movement (58) and that altering neural activations can actually alter perception (59). It seems reasonable to expect that continued perception in the area previously covered by the lost neurons will require that some neighboring neurons show an expanded receptive field that includes this area. Immediate receptive field expansion (Figs. 2 and 4) might produce a "band-aid effect" that is important to both immediate preservation of function and to the eventual shift and spread of receptive fields to fill the gap after cortical reorganization (Fig. 4).

Physical Therapy's Effect on Recovery

The Hebb synapse immediately suggests how physical therapies might improve functional recovery. We have shown that stroke is likely to produce increased activation of a set of cortical neurons, which will then lead to increased synaptic strength with other neurons that are active. By purposefully activating specific pathways either by peripheral input or cortical stimulation, one could produce desired synaptic connectivity to compensate for lost pathways. Presumably, specific patterns of exercises currently used in physical therapy determine synaptic reorganization in the brain.

Pharmacotherapeutics of Rehabilitation

Classes of medication that might be useful in altering stroke recovery would include those that augment or prevent cell sprouting, prevent excitotoxicity, alter rates of synaptic potentiation, or change cell firing patterns. Specific models will permit us to predict the effects of various therapeutic strategies. A few examples:

1. Axonal sprouting may produce new connections unrelated to postsynaptic activity. Such a process might correspond to a rerandomization of synapses that would permit reformation of the cortical map, as described above.
2. It may be desirable to delay the onset of cortical reorganization to prevent formation of spurious connections caused by overexcited neurons of the ischemic penumbra. A term of pharmacological blockade of long term potentiation, the physiological Hebb synapse, might be used to allow cortical reorganization to occur during a period of intensive physical therapy to optimize useful connections.
3. Cholinergic or noradrenergic drugs can alter cell firing patterns between bursting and regular firing modes. Such firing alterations could serve to modulate long-term potentiation.

Lessons

Computer modeling has emerged as an important tool for understanding complex systems. Models are partic-

ularly valuable in brain research, where they permit conceptual links between levels of organization. The computer models used to simulate the processes of development and of synaptic reorganization assume two phases with vastly different time constants: a fast (millisecond) phase of "dynamic plasticity" based on neuron activation, followed by a slow (hour to day) phase of true plasticity based on synaptic reorganization. Computer model exploration of the first phase has shown that dynamic plasticity can explain neurophysiological observations. With regard to phase 2, however, mechanisms of synaptic reorganization that serve to explain development and cortical reorganization after peripheral deafferentation do not seem to explain fully the cortical reorganization seen after experimental stroke. Modifications of the basic model have been used to replicate the stroke results. Each of these models represents an implicit prediction of mechanisms that may be involved in stroke recovery. Extrapolation from these predictions suggests various ways in which physical and pharmaceutical interventions could modify the recovery process.

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