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SYNAPTOGENESIS, SELECTIVE STABILIZATION, AND FREE ASSOCIATION

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13. ABSTRACT *(Maximum 200 words)*

This report describes the material aspects of learning through the processes of synaptogenesis, transient redundancy, and selective stabilization. Synapses are potentiated during these processes and provide channels for incoming signal energy en route to nominate motor responses. They form codons that represent the activity of a large assemblage of neurons in various cortical regions. Codons are active during a state of dynamic instability in the neocortex when the thalamus blocks sensory input. They may also alter the gating cycle of the thalamus through interaction with the thalamic reticular nucleus. A computer simulation of these processes illustrates these concepts.

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TABLE OF CONTENTS

Tables

List of Illustrations

INTRODUCTION

It is common to view the neocortex as the key neural structure subserving higher brain functions, including human intellectual capabilities (ref 1). However, it can be considered an important extension of the thalamus, evolving as it enhances survival. The circuitry of the neocortex is exceedingly complex and may never be completely mapped out. It cannot be wholly gene-expression; the final structure, if there ever is a final structure, is developed through epigenetic experience.

The neocortex can be regarded as an electronic circuit through which signal energy flows. The circuit is highly unstable, with local positive feedback that is barely damped out. The signal energy comes in from the environment, external and internal, through sensory neurons, and flows out to the environment through the muscles. As the signal energy flows through the brain, it causes molecular rearrangements within the neocortex, some of which are relatively permanent. The formation and role of these molecular rearrangements within the neocortex are the subjects of this report.

BACKGROUND

Epigenesis

The brain of the human infant contains more neurons than the adult brain, yet weighs only one-fifth as much. Development continues several years after birth through the growth of axons, dendrites, the formation of new synapses, and the development of myelin sheaths around the axons. It is clear that genetic material alone cannot establish all of the estimated 10^{16} synaptic connections in the cerebral hemispheres. Genes determine reproducible patterns of cerebral organization by defining general rules for axonal growth cones. Neural growth is guided by this genetic envelope with the final distribution of synapses resulting from epigenetic experience (ref 2). As an example, topology is preserved as genes determine the geometric mapping from the retina to the lateral geniculate nucleus (LGN), then to the striate cortex. Yet it has been shown that connectivity within the striate cortex can be altered by changing the environment during postnatal development (ref 3).

Transient Redundancy

There is profuse axonal growth in the early years of postnatal development called transient redundancy (ref 2). Many connections are established that are not utilized and are eventually lost later in life. Simple rules govern the behavior of the expanding network. As the cerebral hemispheres develop, sensory input is channeled through the thalamus to specific regions of the cortex. This signal energy, coupled with inputs from other brain centers (hypothalamus, visceral), determines the final distribution of synapses within the constraints of the genetic envelope. Cortical connections are established reflecting the nature of the input and the resulting consequences. Connections are established that tend to maximize divergence among epigenetic events. Highly active neurons have a larger propensity for growth, and it is the environment that determines which cells are active. It is hypothesized that inactive cells secrete a trophic material that attracts the growth cone of growing axons. Consequently, inactive neurons are prone to new excitatory innervation. This pairing of hyperactive presynaptic cells with hypoactive target cells results in the environment evoking the maximum neural response from the postnatal brain (ref 4). The function of growth can be regarded as the environment fine-tuning the brain, rather than the genome matching the environment.

Selective Stabilization

Redundant connections are shed through selective stabilization of synapses as afferents compete for available postsynaptic sites. Selective stabilization is a combination of associative learning and synaptic shedding (ref 2). A popular position is that in the case of the estimated 85 percent of synapses that are excitatory, the efficiency of the synapse increases when both the presynaptic and postsynaptic cells are hyperactive (associative or Hebbian learning). Postsynaptic hyperactivity coupled with presynaptic inactivity results in a decrease in the efficiency of any common synapse. Therefore, those cells contributing the most to the hyperactivity of the postsynaptic cell activity acquire the most postsynaptic area (refs 5,6). The afferents with minimal influence on postsynaptic cell activity are pushed out. These synapses are the redundant connections that are eventually shed.

The efficacy of inhibitory synapses increases with presynaptic activity and postsynaptic inactivity. The propensity for inhibitory synaptogenesis increases with increasing cell activity, but receptor sites are generally hyperactive. General rules governing synaptogenesis and selective stabilization, without regard to cell structure and other contributing factors, are summarized in Tables 1 and 2.

Free Association

It is the signal energy from the environment, internal and external, flowing through the cortex that causes molecular rearrangements within the brain called codons. Codons represent the activity of a large number of neurons in the various cortical regions. Some of these codons return signals that are routed to the motor complex and result in a response to the stimulus. A codon has the static aspect of existing as potentiated synapses and a dynamic aspect of channeling signal energy.

At each "moment" there is an active codon in the neocortex. These moments come at about ten per second (10/sec) as marked off by the rhythmic activity of the thalamus (ref 7). The thalamus provides the channels through which the signal energy flows on its way to the premotor (areas 6 and 8) and motor (area 4) cortex. The ansa lenticularis and brachium conjunctivum carry motor signals from the basil ganglia and cerebellum respectively to the ventral anterior nucleus and ventral lateral nucleus (VA-VL complex). The thalamus relays these signals to the motor cortex (Figure 1). The neocortex furnishes the channel complexity that allows one set of signals to activate one motor pattern in the basal ganglia, and a slightly different set of signals to activate another. The neocortex is functionally an extension of the thalamus (ref 8).

The incoming signals are forwarded to the neocortex, and the energy flows back via massive reciprocal connections to either excite or inhibit the thalamic reticular nucleus (ref 5). The reticular nucleus is a structure that surrounds the thalamus and is traversed by all fibers connecting the cortex to the thalamus. It has inhibitory projections on the thalamus that are capable of altering the gating cycle of the thalamic nuclei (ref 9). An active thalamic reticular nucleus inhibits forwarding of a program to the motor cortex.

The energy continues to flow back from the neocortex until the thalamic reticular nucleus is inhibited, which allows the motor program to continue to the motor cortex. If a codon is excited that has excitatory synapses on the thalamic reticular nucleus, then the relay of signals to the motor cortex is inhibited. Sensory signals pass through to the primary cortex when a codon is excited that inhibits the inhibitor as motor signals pass through to the primary cortex. When sensory input is blocked for an extended period, the codon dies down as its store of molecules is depleted. Dynamic instability in the neocortex ensures that as one assemblage of neurons dies down, an associated set of neurons is excited.

SIMULATION

Our computer simulation is executed on a parallel processing system comprised of 30 transputers exercising a suite of homogeneous processing functions running under an Occam harness. The basic computational unit is the column. This is a generalized group of neurons with projections of both excitatory and inhibitory synapses. Columns are further grouped into slabs. Column activity is continuous and represents the average firing frequency of all neurons in any column at any point in time. The activity is bounded and is a function of the weighted sum of the activities of connected columns, group slab activity (Eq. (1a)), and previous activation values (Eq. (1b)). Firing frequency of columns is adjusted to achieve desired target average activation values for each slab. A refractory period follows any sustained period of hyperactivity.

$$x_i = \left(\frac{1}{2} + \frac{1}{\pi}\tan^{-1}\left(\sum_j w_{ij}x_i\right)\right)^P \cdot \frac{Tn}{\sum x_i} \qquad \text{(1a)}$$

x_i	=	column firing frequency
w_{ij}	=	synaptic weight from column j to column i (afferents)
T	=	target slab activity
n	=	number of neurons per slab
P	=	positive constant

$$A(x_i) = C_1 \int_0^{t_k} e^{\alpha(t-t_k)} x_i(t)dt \qquad \text{(1b)}$$
$$t = t_k$$

$A(x_i)$	=	average firing frequency of column x_i
C_1, α	=	positive constants

Growth is excitatory, nonrecurrent, and limited to columns on neighboring slabs. The propensity for growth is a function of average activity and the efferent area that must be supported (Eq. (2)). Highly active columns with few efferents to support have the largest propensity for axonal growth.

$$gpf_i = \frac{(A(x_i))^P}{C_2 + C_3 \cdot (\sum_k w_{ki})} \quad (2)$$

gpf_i	=	growth propensity factor of column i
w_{ki}	=	synaptic weight from column i to column k (efferents)
C_2, C_3, P	=	positive constants

Columns in the neocortex are highly inhibitory locally, and this is reflected in the simulation. Regions of mutual inhibition within each slab force the activity of all but the most active neurons to zero.

Synaptic acquisition is a function of cell activity and existing afferent synaptic area (Eq. (3)). Those columns with low activation values and few afferents are most receptive to new connections. Afferents compete for a maximum synaptic area and are shed based on the normalized weights of the afferent connections. Growth occurs from columns with the highest growth propensity factor to the columns with the lowest receptivity factor.

$$rf_i = C_4 \cdot (A(x_i))^P \cdot (\sum_j w_{ij}) \quad (3)$$

rf_i	=	receptivity factor of column i
w_{ij}	=	synaptic weight from column j to column i (afferents)
C_4, P	=	positive constants

Potentiation and depotentiation are functions of column activity (Eq. (4)). Potentiation of the synapse occurs when the activity of both presynaptic and postsynaptic cells exceeds a set threshold (hyperactive). Depotentiation occurs between hyperactive postsynaptic cells and hypoactive (< threshold) presynaptic cells (Eq. (4)). A synapse is shed when the magnitude of its weight falls below a minimum value (Eq. (5)).

$$\frac{dw_{ij}}{dt} = C_5 \cdot (A(x_j) - C_6) \cdot \lfloor A(x_i) - C_6 \rfloor^+ \quad (4)$$

C_5, C_6	=	positive constants

$$w_{ij} < \min \ , \ w_{ij} = 0 \qquad (5)$$

min = positive constant

Figures 2 through 4 demonstrate the simulation output for a network comprised of three slabs. The first row of slabs shows the activity of the individual columns and the second row displays the growth patterns. A bar graph provides a divergence measure between the activities of codons in the final (output) slab. For convenience, thalamic activity is displayed as an active divergence measure but is in no way related. The first slab is the input excitation pattern which provides a regular geometric mapping of excitatory connections to the second slab. There are no other connections except for the implied regional inhibition between neighboring columns. These columns can support many efferents and may have numerous afferents, so dynamic connections are displayed as single pixels randomly placed within a field defined by the locations of the columns.

Figure 2 shows two stages of synaptogenesis as neural stimulus results in growth from the hyperactive (dark) columns of the second slab to the hypoactive targets of the third slab. These columns are excited by two sets of patterns defining the regions that will evoke a neural response in the network. Any future stimulus outside these regions will have no affect on the network, unless growth is permitted to resume. There is no 'correct' result and thus no training. At this point in the simulation, the discrimination between outputs produced by unlike patterns is used as our measure of success or failure (ref 10).

Figure 3 shows the response of the network to two of five inputs that are presented as subsets of the original patterns. Selective stabilization prunes the network through potentiation of synapses between the columns of active codons and between the active codons and the inputs. Redundant connections are shed as inactive synapses are effectively pushed out by the changing synapses that define the codons.

Figure 4 shows an updated connectivity map and the response of the network to an active thalamus. Codon activity from the last innervation is maintained until the molecular store of its component columns is depleted and may not resume for a given refractory period. The network strives to maintain the slab's target activation value as those codons formed during selective stabilization cycle between those sharing common columns. Simulation parameters can be adjusted so the network cycles between codons in sequence or at random.

SUMMARY

We are investigating the mechanisms of learning using the reality of neural evolution as a guide. Although cerebral organization is largely genetically determined, irreproducible patterns are produced during genesis of the cortex. During the profuse axonal growth in the early years of postnatal development, epigenetic experience provides the signal energy that flows through the thalamus to specific regions on the cortex to define the structure of the cortical connections. As the neural growth cones of the axons aggressively seek out places to form new synapses, redundant connections are formed that are eventually lost through experience. The remaining synapses form codons that channel signal energy and define regions of cortical activity when sensory input is interrupted by the thalamus.

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Table 1. General Rules Governing Potentiation and Depotentiation of Synapses

	Presynaptic Active		Presynaptic Inactive	
	Postsynaptic Active	Postsynaptic Inactive	Postsynaptic Active	Postsynaptic Inactive
Excitatory	Increase	-	Decrease	-
Inhibitory	-	Increase	-	Decrease

Table 2. General Rules Governing Synaptogenesis

	Presynaptic Active		Presynaptic Inactive	
	Postsynaptic Active	Postsynaptic Inactive	Postsynaptic Active	Postsynaptic Inactive
Excitatory	-	Connect	-	-
Inhibitory	Connect	-	-	-

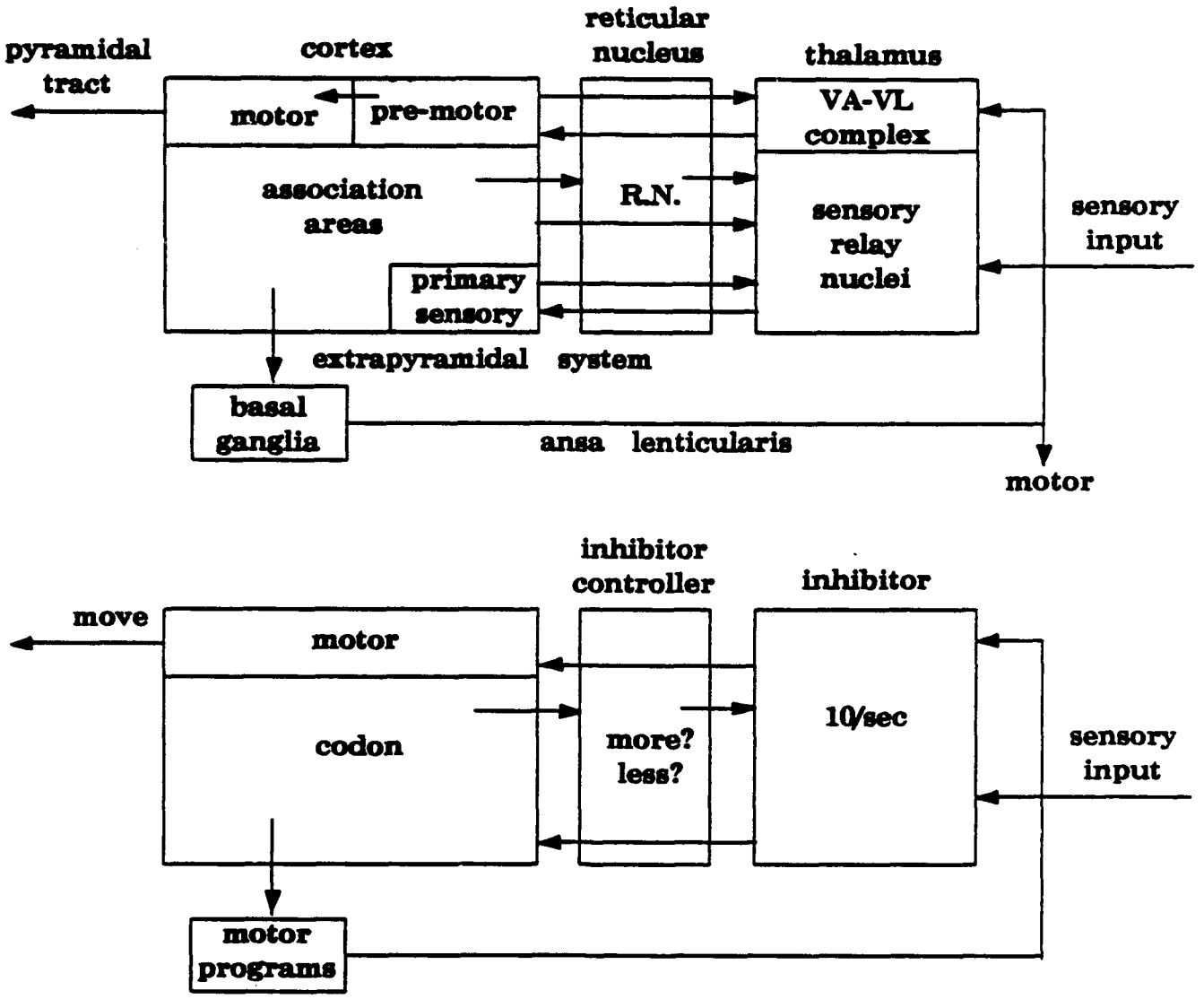

Figure 1. Gross structure of the flow of signal energy and simplified block diagram

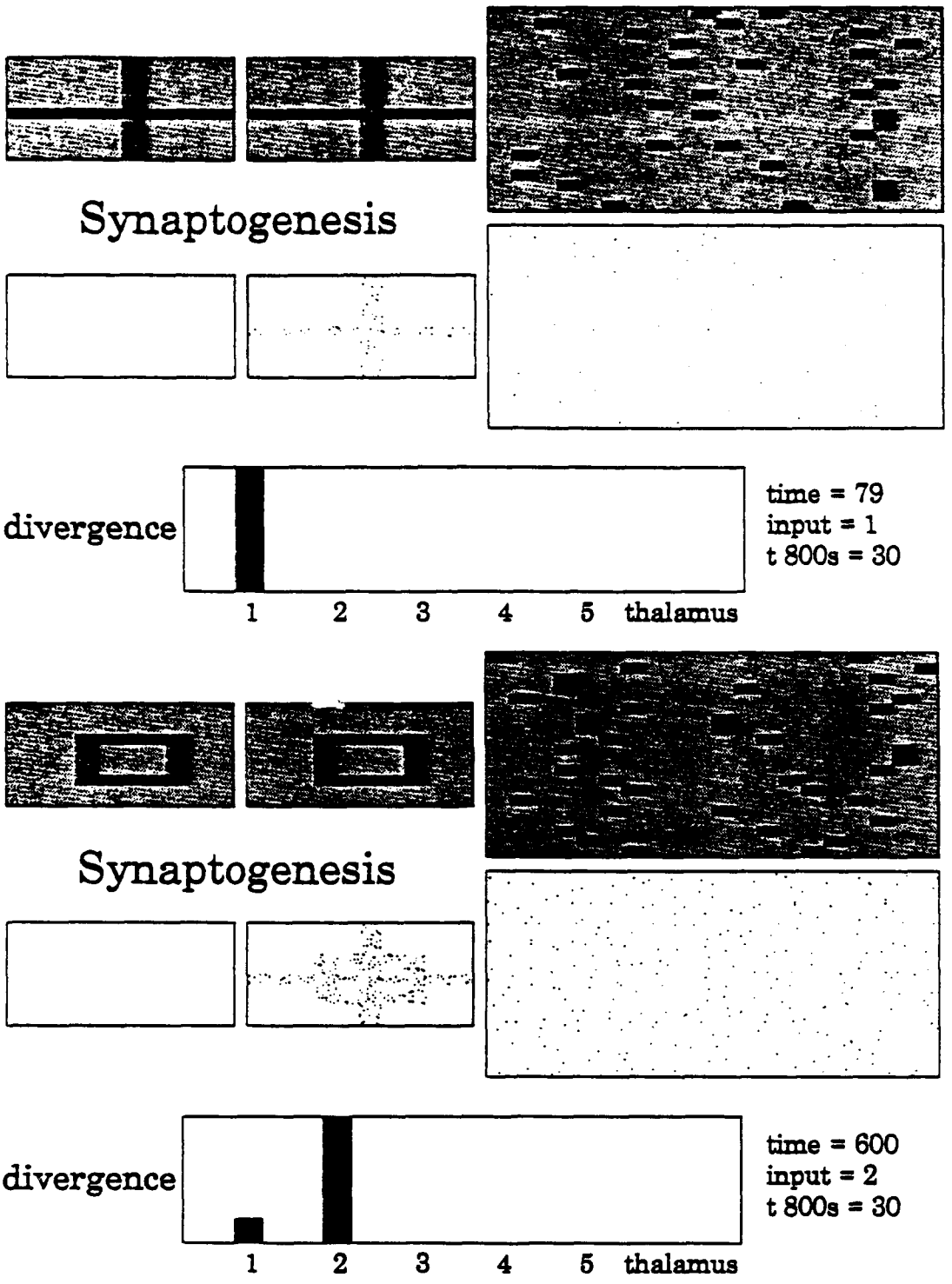

Figure 2. Output of simulation at two stages of synaptogenesis

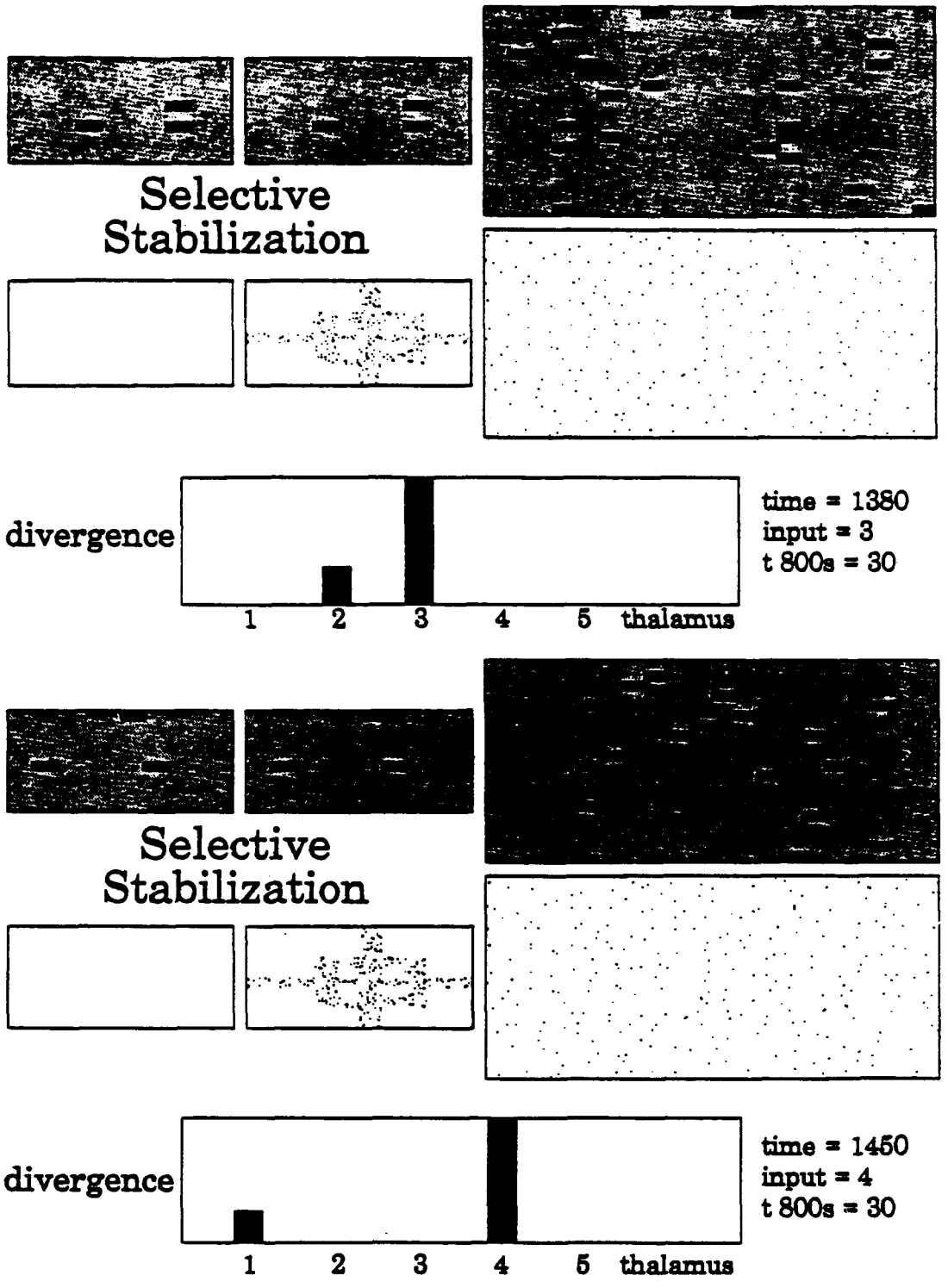

Figure 3. Response of network to two subsets of original patterns

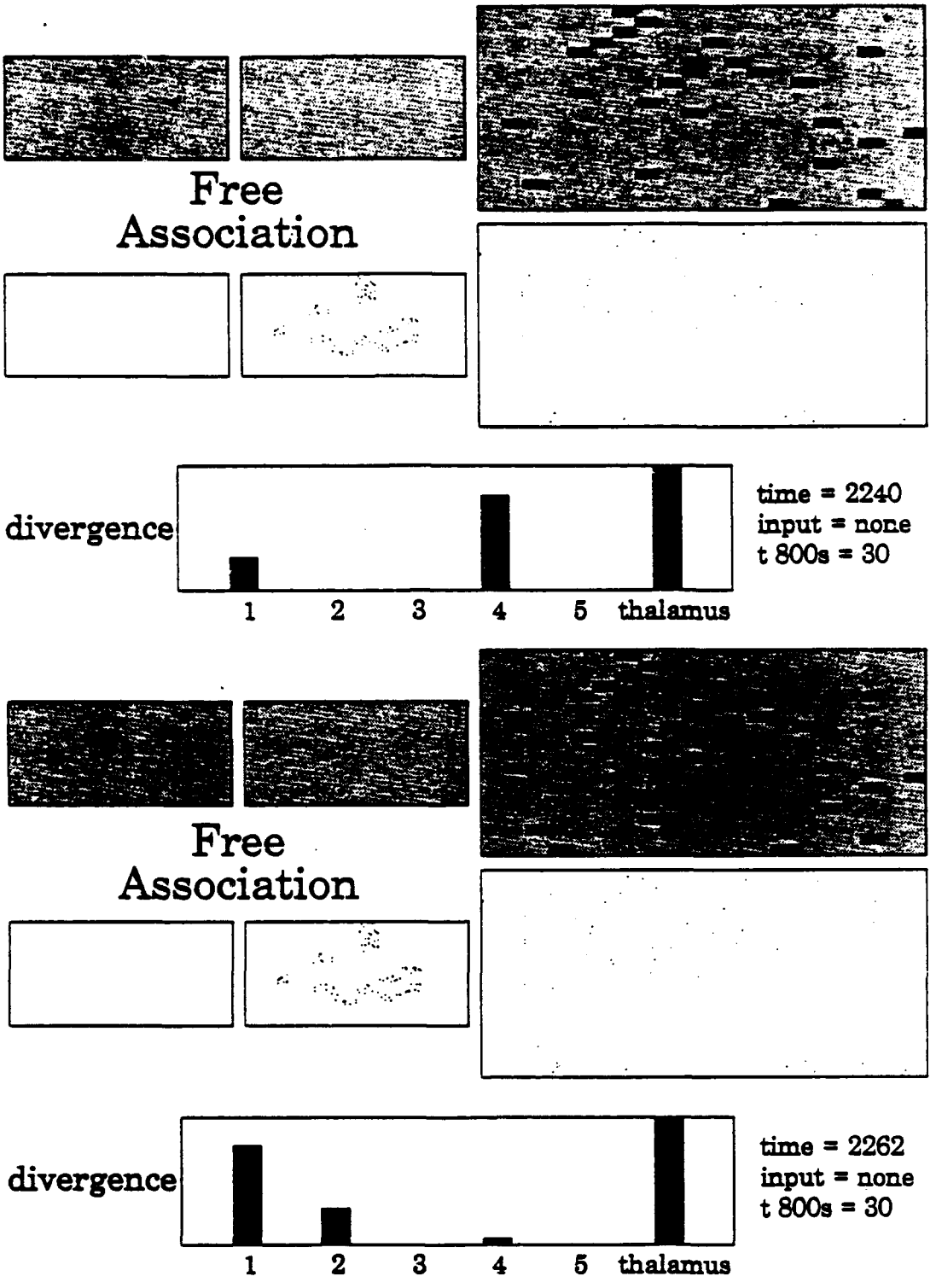

Figure 4. Codon activity resulting from an active thalamus

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