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TWO SIMPLE YET BIOLOGICALLY REALISTIC MODELS OF SYNAPSES TO BE USED IN NEURONAL NETWORKS

BY

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A dissertation submitted to the Graduate Faculty in Computer Science in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the City University of NewYork

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Abstract

TWO SIMPLE YET BIOLOGICALLY REALISTIC SYNAPSES TO BE USED IN NEURAL NETWORKS

BY

Michaelangelo Salcedo

Advisor: Prof. Thomas C. Wesselkamper

The connections between neurons where information is processed, transformed, and communicated is at the synapse. A common paradigm in Computer Science for the connection is a link between the two neurons, where the influence of the first neuron to the second is determined by an arbitrary weight, generally assigned by the implementor. A more biologically realistic paradigm is proposed and implemented. A single neuron may have thousands of synapses with other neurons, and several with another neuron. The connection is dynamic, based on the prior activity of the synapse, and the impact of the action potential invading the presynaptic terminal at the time. Two examples of synapses are studied, one at the giant synapse of the Loligo pealii, which is a neuromuscular junction, and the other is the Schaffer collateral/CA1 synapse of the Hippocampus, a central synapse, of a rodent. Experimental data is reviewed for these synapses, and the

basic primitives responsible for communication at the synapse, their functions and relationships, are identified from the research to build models that are easily implemented and computed, yet are biologically realistic, though not as detailed as those proposed by neuroscientists. State diagrams are given for both synapses, as well as the equations and relations necessary for their implementation.

The model of the Schaffer collateral/CA1 synapse is implemented in Qbasic, and data for a run of 5000 milliseconds is presented. The model demonstrated the feasibility of easy implementation. It is not as detailed as a model implemented by a neuroscientist, but maintains the primitive mechanisms responsible for dynamic communication and modulation over time at the synapse. The primitives and their relationships are listed and implemented in the Qbasic program. The data generated by the program is included and commented on . The data shows that the synapse responds according to the expected behavior : depletion and replenishment of available vesicular pool, failure of release, though invaded by action potential, multiquantal release, refractory periods, synaptic enhancement. This model offers a template that may serve to implement other types of central synapses that are based on the same kind of primitives, by adjusting the variables between the functions according to experimental data for a synapse under consideration. The next step in this research would be the expansion of synaptic enhancement to include PostTetanic Potentiation, and Long-Term Potentiation.

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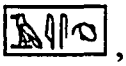
Chapter One

TOWARDS A MORE REALISTIC MODELING OF THE BRAIN

Figure 1.1 is the first record in recorded history where the hieroglyph for the *brain*,  , is used. The papyrus is dated seventeen-hundred years Before Christ. In 1943,

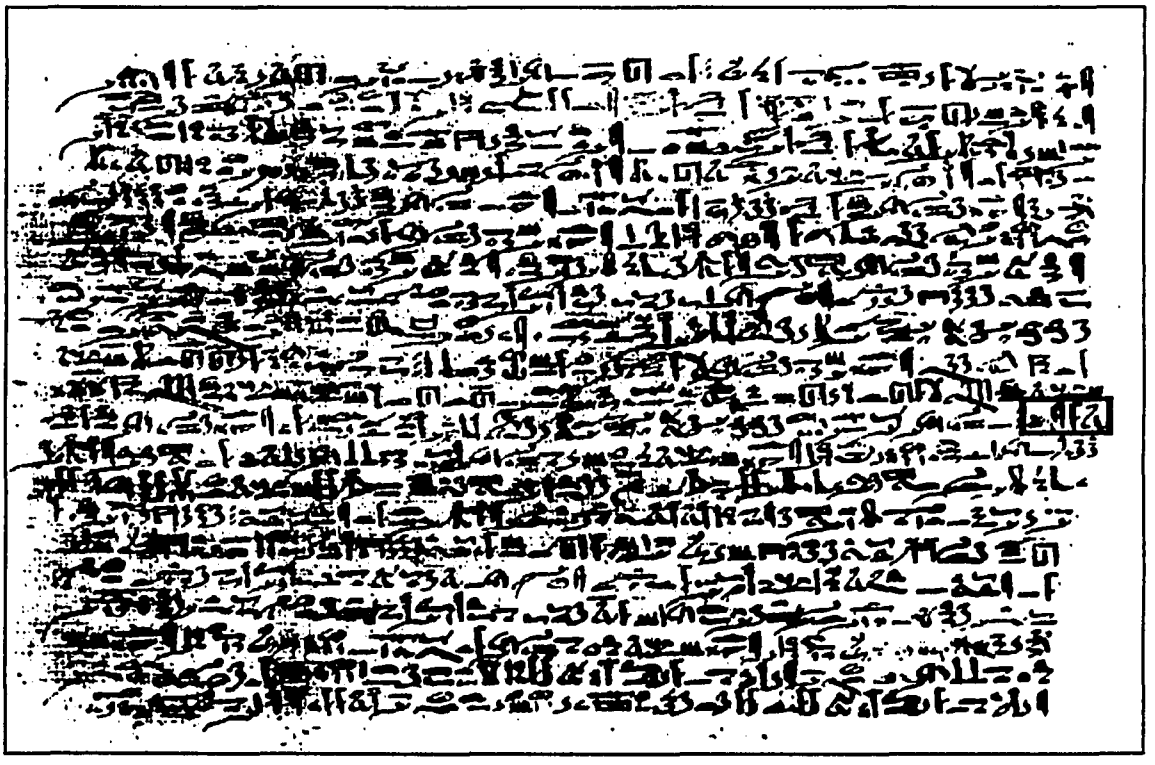


Figure 1.1 Edwin Smith Surgical Papyrus, 2 volumes. The University of Chicago Press, Chicago, 1930. Word for brain is in highlighted box.

thirty-six centuries after the writing of this papyrus, an article was published in *Mathematical Review*, *A Logical Calculus of the Ideas Immanent in Nervous Acitvity*, by Warren S. McCulloch and Walter Pitts, in which the first model of a *Neuronal Processing Unit* was introduced: "Because of the all-or-none character of nervous activity, neural

events and the relations among them can be treated by means of a prepositional logic."(McCulloch, et al, 1943).

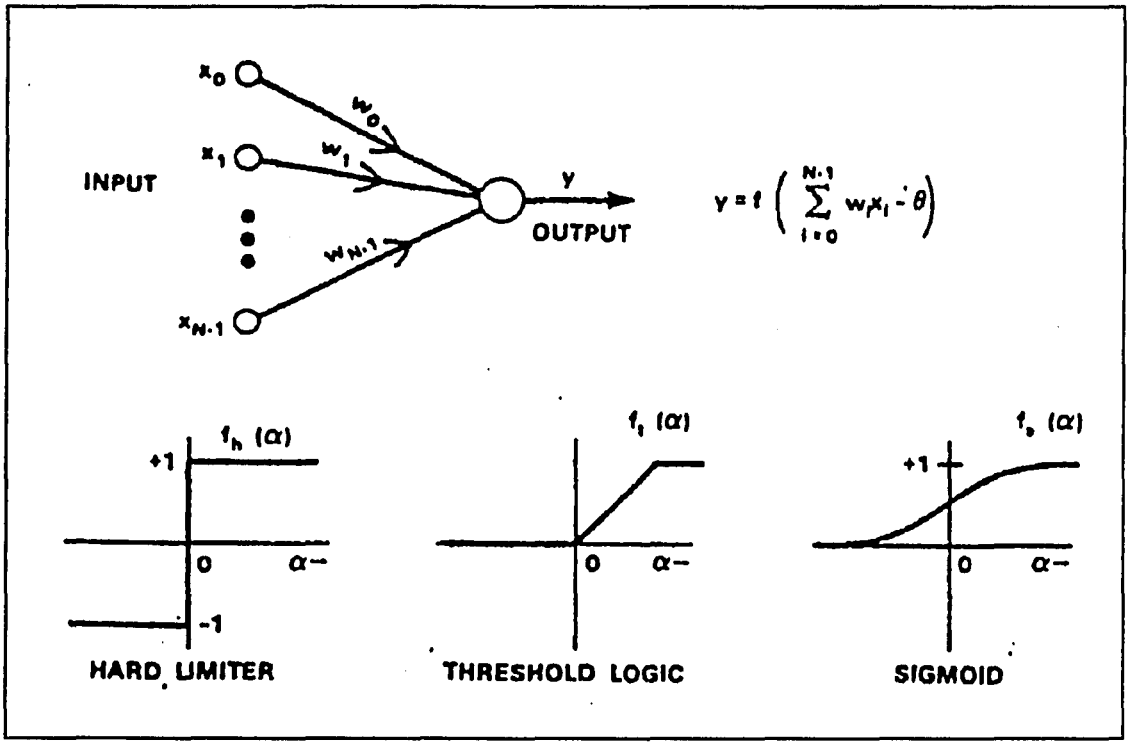


Figure 1.2 Computation element, or node, which forms a weighted sum of N inputs. The result is passed through a nonlinearity. Three representative nonlinearities are shown (V. Vermuri, 1988).

These conclusions were predicated on certain theoretical principles held in neurophysiology at that time:

1. The nervous system is a net of neurons, each having a soma and an axon.
2. The synapses are always between the axon of one neuron, and the soma of another.
3. At any instant a neuron has some threshold, which excitation must exceed to initiate an impulse.
4. From the point of excitation the impulse is propagated to all parts of the neuron.

On the basis of these established theoretical principles in neuroscience and their own research, they then proposed a calculus predicated on the following physical assumptions

1. The activity of the neuron is an "all-or-none" process.
2. A certain fixed number of synapses must be excited within a period of latent addition in order to excite a neuron at any time, and this number is independent of previous activity and position on the neuron.
3. The only significant delay within the nervous system is synaptic delay.
4. The activity of any inhibitory synapse absolutely prevents excitation of the neuron at that time.
5. The structure of the net does not change with time.

With the advent of computers and the commonly held metaphor of the brain as a computer, this McCulloch/Pitt abstracted model of a neuron (M-P *Neuron)* generated interest among researchers in Computer Science, Mathematics, Cognitive Sciences, and other related sciences. This abstracted model of the neuron was given a formal representation as a computational unit.

:

1. Finite number of excitatory (i.e., weight, $w_i = +1$) and inhibitory (i.e., weight, $w_i = -1$) inputs;
2. inputs, x_i, where i = 1,2 ,....,n;
3. a Threshold level, L;
4. an Output level, y;
5. the outputs and inputs can assume binary values (0 or I).
6. the Threshold can be any positive integer.

The output of the M-P neuron can be expressed mathematically

$$y = g(\sigma w_i x_i - L)$$

Equation 1-1 Output of M-P Neuron

1. where g(p) = O if p < 0
2. where g(p) = + 1 if p ≥ 0
3. this means that the M-P Neuron will ***fire*** if the total excitation ≥ threshold value, L.

For the first time, the most basic unit of the brain had been cast as a neural logic element and quickly picked up as a **digital device** that would lend itself to further extend the computer/brain metaphor. But, on the other hand, neurons take their synaptic inputs, do a spatial/temporal summation of these inputs, and then, if the threshold is reached, generate an output which is, generally, a continuous-valued firing frequency and represented as the time between discrete impulses: *action potentials* . Thus, the neuron may be viewed as an **analog device**. Quickly two camps sprang up one modeling the neuron as a digital device and the other as an analog device. Each camp looked upon its model as "a technological modeling unit" that would allow them to extract concepts learned about neuronal functioning, and use these extrapolations as new computational methodologies to serve as models inspired by brain functioning. These M-P Neurons were connected together to generate *Neural Networks and* given the name, *Artificial Neural Networks, (*ANNs), as a new "Computational Process" to be used in Computer Science and the Cognitive Sciences.

The computational process envisioned with an Artificial Neuronal Network (ANN) if a follows: An Artificial Neuron (AN) receives its inputs from a number of other ANs or from the external world. A weighted sum of these inputs constitutes the argument of an *activation function. This* activation function g is assumed to be nonlinear. Hard limiting (i.e., either the step or the signum function), threshold, and soft limiting (i.e., the sigmoidal) are the three most often used forms of nonlinearities. The resulting value of the activation function is the output of the AN. This output is distributed along weighted connections to other ANs. The notion of memory in a conventional computer is analogous to the concept of the weighted settings. As these weighted connections play an important role, these ANNs are also called the *connectionist* models of computation. It should be emphasized that models of this kind have only metaphorical resemblance to natural networks.(V. Vermuri, 1988).

More realistic models of the neuron were also proposed. One proposed the treatment of time as a continuous variable, where the **firing rate** *(viz.*, the number of spikes traversing the axon in the most recent 20 milliseconds) and the **membrane potential** *(viz.*, the total instantaneous input received by a neuron) are important parameters. The **state** of the neuron is defined as the **membrane potential (u)** of the neuron, where the time evolution of the membrane potential of the jth neuron can be described by:

$$\frac{du_j}{dt} = -u_j + \sum_{i=1}^{n} w_{ij} x_i - L_j$$

Equation 1-2

where the output, y_i, is related to the state, u_j, via the relation:

$$u_j = h(y_j)$$

Equation 1-3

If the inputs, x_i, are held stationary, or if the inputs vary slowly, we can set $du_j/dt \cong 0$, then we get:

$$y_j = h^{-1}\left(\sum_{i=1}^{n} w_{ij} x_i - L_j\right)$$

Equation 1-4

If h^{-1} is identified with g, or if the inputs vary slowly, this equation is analogous to the equation for a discrete neuron in Equation 1.1, Page 4.

This is an example of a continuous model for a AN where a collection of ANs are treated as a collection of continuous-state (e.g., analog) devices, that are modeled as a system of ordinary differential equations that simulate the graded, continuous outputs of ANs rather than the step-wise, two-state response curves of discrete models

The ANNs built from M-P *Neurons* have mushroomed in many disciplines (Computer Science, Cognitive Science, Biophysics, Neuroscience, Mathematics, etc.) and have created many interdisciplinary research projects. ANNs are being put to the test to see if they can perform they following cognitive functions:

- recognizing a familiar face,
- learning to understand a language,
- learning to speak a language,
- learning to read handwritten text,
- retrieving contextually appropriate information from memory
- maneuvering an environment,
- guiding a mechanical hand to grasp objects of different shapes/consistencies,
- learning, problem solving, thinking, and decision making,
- generally, all those tasks that are routinely performed by humans and animals in living our lives from day to day, which we often take for granted.

In Cognitive Science there has been great interest to develop models using ANNs that can perform certain brain functions, such as association, categorization,

generalization, classification, feature extraction, and optimization, which fall into three broad categories of searching, representation, and learning. These three categories reflect:

- the **Associative** property of the brain that allows one to recall an entire complex of information by using a small part of it as a key to search a process,
- the ***Self- Organizing*** capability of the brain, that allows one to acquire knowledge through a trial-and-error learning process involving organization/reorganization in response to external stimuli.

Groups of ANs can be interconnected in a variety of ways to form ANNs. Over the years, many topological configurations for these ANNs were proposed. Networks comprising only a single layer of ANs as well as many layers have been tried. Many layered networks comprise two or more rows of ANs. In *feed-forward* networks, the signal-flow from one layer to the next is unidirectional. In *feed--back* networks, both forward and backward connections exist. Among the feedback networks, another modification is to explicitly allow feedback paths within the same layer as well as from one layer to and "earlier" layer (V. Vermuri, 1988).

With the great wealth of knowledge that has been garnered since the original article of McMullough/Pitts in Neuroscience, some of the basic theoretical principals held in neurophysiology and some of their basic physical assumptions have been overturned: Synapses are *not* only between the "axon of one neuron, and the soma of another"; the structure of the net *does* change with time; the patterns of excitation/inhibition are quite complex, dendritic trees and terminal trees are abundant, extensive, complex, and should be taken into account in neuronal computing, homosynaptic plasticity is important, et cetera.

Emphasis now, due to wealth of research in the neurosciences, and the discovery that the most significant aspects of a neural model, are those which are based on the transmembrane electrical potential in neurons in terms of their respective ionic currents, the M-P Neuron is now considered not to be viable as a model to explain actually observed neurophysiological data, yet, it's "flavor" is still seen in many neural networks.

See Figure 1.3 on Page "8 for an illustration of a taxonomy of neural networks based on ANs.

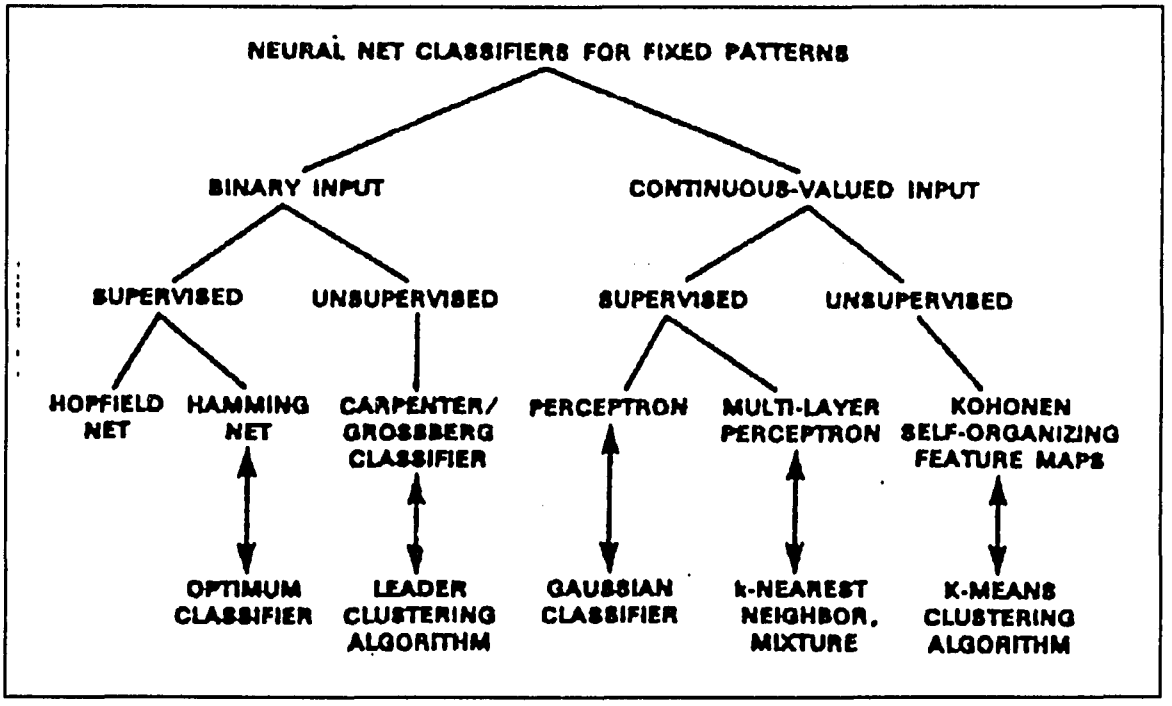


Figure 1.3 Neural network taxonomy. A taxonomy of six neural nets that may be used as classifiers. Classical algorithms which are most similar to the neural net models are listed along the bottom (V. Vermuri, 1988).

In 1949 a psychologist named D.O. Hebb (Hebb, 1949) proposed that the repeated activation of a monosynaptically connected postsynapse by an active presynapse increases its conductance: these two weakly connected synapses when activated *synchronously*, tend to organize themselves into a more strongly connected microcircuit. Therefore, the *connectivity* of the brain is continually changing as the organism "learns." Thus "cognitive" function is represented as based on a "membrane conductance modulation." Learning has as it's basis the strengthening of synapses.

With the explosion of research in the neurosciences and the increase in computational power and parallelism in Computer Science, many models have been proposed for the neuron that are neurobiologically more realistic. Some examples are:

• *Simplified Models of Single Neurons.* The model describes state variables:

1. One that describes the fundamental processes of accommodation and repetitive firing of trains of all-or-none action potentials.
2. One that describes the active calcium-related conductance including representation of active calcium spikes, complex spikes, and bursting activity.
3. One that describes the above model with an additional compartmentalized dendritic tree.

The integration step in this model is about 1 msec in model neuron time. The "point neurons" are then used repeatedly in larger hierarchical programs representing networks and systems of tens of thousands of single neurons (MacGregor, 1977).

• *The Hodgkin-Huxley Model.* This describes the transmembrane potential in the time course of a single-action potentials in terms of the underlying membrane conductance modulation of sodium and potassium currents. It embodies and describes quantitatively the causal mechanisms underlying the generation of action potentials (Hodgkin & Huxley, 1952).

• *The Equivalent Circuit.* A neuron has conductive, capacitive, and electromotive force components that can be represented as an equivalent circuit and serve as a great aid in the study of the cellular properties of neurons. (E.R. Kandel & J.H. Schwartz, 1985, Koch & Segev, 1989).

• *Compartmental Neuron Models.* This model is used to replace the analytical model of a set of continuous differential equations of the analytical model by a set of ordinary differential equations. The continuously distributed system is "divided" into sufficiently small compartments. Compartments may represent somatic, dendritic, or axonal membrane; they may be passive/excitable membrane, and may contain a variety of synaptic

inputs. It can also be designed to represent a neuron per compartment for use in a connectionist network model (C. Koch & I. Segev, 1989; Traub & Miles, 1988)

• *Analog VLSI* The development of microelectronic systems that are inspired by the analog computations performed by neurons (C. Mead, 1989).

• *Parallel Distributed Processing.* Many of these models are used to describe micro structures in Cognitive Psychology based on the concepts discovered in neuroscience There are eight major aspects of a parallel distributed model.

1. A set of processing units.
2. A state of activation.
3. An output function for each unit.
4. A pattern of connectivity among the units.
5. A propagation rule for propagating patterns of activities through the network.
6. An activation rule for combining the inputs impinging on a unit with the current state of that unit to produce a new level of activation for the unit.
7. A learning rule whereby patterns of connectivity are modified by experience.
8. An environment within which the system must operate. (Rumelhart, 1989)

In 1977 , MacGregor and Lewis (MacGregor, 1987) devised a table (Table 1.1, on Page "11) useful for mapping and considering various theoretical and modeling efforts in neuroscience. They also identified the central roots of engineering modeling methodology as relevant to neural and brain modeling (Table 1.2 on Page"12).

E., behavior, experience, consciousness	Direct Observations
D, theoretically inferred constructs	superego, id, drives, cognitive maps, cell assemblies, statistical configurations
C. electrical signals	field potentials ,spike trains, generator potentials
B. membrane, conductance modulations	synaptic conductances, active dendritic conductances, action potential conductances
A. molecular and chemical processes	chemical synaptic transmission, gating processes

Table 1-1 Stratification of variables (R.J. MacGregor, 1987)

In this stratification, the finest granularity of the model is in level A: Molecular and Chemical Processes, and the coarsest granularity is at level E. Behavior, Experience, Consciousness. Several principles concerning modeling are suggested by this stratification of *variables:*

1. Models which relate variables of adjacent strata are the most powerful; there is a sense in which the behavior of variables at the upper level is explained in terms of the variables at the lower level.
2. Models which skip a level are difficult to test and generally low in believability.
3. Models which interrelate variables at a single level are weak in predictive power.

4. Models which relate variables of several strata are the most broadly significant.

Linking levels D & E	Cognitive Science, Artificial Intelligence, and Psychology attempt to explain behavior of variables at level E in terms of variables at level D.
Linking levels C & D	Domain of Neural Networks
Linking levels B & C	Classical neurophysiology and the field of neural modeling (in a narrow sense) have been concerned with linking variables of level B with variables of level C.

Table 1-2 Linking levels. Relation of levels to respective discipline that are trying to integrate them. No mention is made of the disciplines that are trying to integrate levels A and B (MacGregor, 1987).

Fundamental quantitative techniques have been applied by theorists, researchers, and modelers in the quest to give a quantifiable expression to these variables. See Figure 6 for illustration of these variables. See Table 1.3 for illustration of these variables.

Various quantitative techniques: mathematics, engineering, and computation.	1. Differential equations (ordinary, partial), 2. Matrix algebra and tensor analysis, 3. Probability and statistics, 4. Set theory, 5. Fourier frequency analysis, 6. Digital and electronic simulation, 7. Discrete mathematics, Boolean algebra, et cetera
Physical theories:	8. Feedback control system theory,

engineering and physics	9. Classical mechanics and dynamical systems, 10. Continuum mechanics and conservation laws, 11. Nondimensional analysis and scaling, 12. Stochastic systems and information theory, 13. Statistical mechanics, General systems theory
Information processing paradigms: computer science and engineering.	14. Logic circuits, 15. sequential machines, 16. Organization of computing systems, 17. Artificial Intelligence

Table 1-3 Roots of Neural and Brain Modeling in Engineering (R.J. MacGregor, 1987)

From the basic assumptions introduced by the McCullough/Pitts neuron, it would seem that we are now in a position to take these models for neurons, connect them into assemblies, and be able to eventuate cognitive functions. However, there are more layers to be peeled from the onion:

Synapses	Neuronal interactions are mediated by the numerous junctions between neurons.
Microcircuits	The most local patterns of synaptic connection and interaction, involving small clusters of synapses.
Dendritic Trees	These microcircuits (measured in microns and fastest speed of operation measured in milliseconds) are grouped to form dendritic subunits within the dendritic trees of individual neurons.

Neuron	The whole neuron, containing its several dendritic subunits, is the next level of complexity.
Local Circuits	Interactions between neurons of similar or different properties. These perform the operations characteristic of a particular region of the brain.
Interregional Circuits	Interregional pathways, columns, laminae and topographical maps, involving multiple regions in different parts of the brain.
Behavioral Systems	Emergent types of behavior from multiple regions of different part of the brain.

Table 1-4 Some of the main levels of organization in the nervous system. Shepherd focuses on the levels from synapses to local circuits, as a basis for understanding the expression of molecules and ions in an integrative context, and for understanding the circuit basis of behavioral systems (Shepherd, 1990).

> It might seem that one could simply connect neurons together by means of synapses and make networks that mediate behavior, but this is *not* the way nature does it. A general principle of biology is that any given behavior of an organism depends on a hierarchy of levels of organization, with spatial and temporal scales spanning many orders of magnitude. This is nowhere more apparent that in the construction of the brain. As applied to synaptic circuits, it means that one needs to identify the main levels of organization in order to provide a framework for understanding the principles underlying their construction and function (The brain organization and its emergent functions described by Shepherd are at a finer granularity than the categorization of MacGregor) (Shepherd, 1990).

Shepherd emphasizes that the study of synaptic organization is very important in order to identify the types of circuits and the kind of functional operations they perform at each of these organizational levels because excitation and inhibition by single synapses usually have little behavioral significance. But it is the *patterns of connectivity* that emerge during development that produce significantly functional operations. It is estimated that in the cortical area of one hemisphere in the human, that measures approximately 100,000

mm^2, there most likely are 10 billion neurons and 60 x 10^{12}), or *60 trillion* synapses. The number of synapses amplifies the number of neurons by several orders of magnitude, making it possible to have a very rich substrate for the organization of microcircuits within the very compact structure of the brain.

He discusses different patterns used in neuronal connectivity:

- *Synaptic Divergence* Divergence of output from a single terminal: *fan-out.* A single action potential (ap) propagating to the presynaptic terminal can "simultaneously" cause excitatory postsynaptic potentials (EPSPs) in many postsynaptic dendrites. The benefits are many: the activity in the single terminal is amplified into acitvity in many postsynaptic neurons, and thus bestowing a high gain upon the system, where the activity is simultaneous, so that the timing of the output/input is maintained, and is of the same sign: excitation → presynaptic terminal → postsynaptic potentials.
- *Synaptic Convergence* Terminals make synapses onto a postsynaptic dendrite: "fan-in." Two or more terminals can synapse onto a postsynaptic dendrite (synchronously/asynchronously) and set up an EPSPs in the postsynaptic dendrite that can summate: "temporal summation" This process is essentially a nonlinear process. Fan-in can also involve summation of excitatory and inhibitory PostSynaptic Potentials (PSPs). This process in also nonlinear and complex. There also exists "spatial summation," where responses arising in different parts of a dendrite, or different parts of the dendritic tree, can be combined into one integrated postsynaptic response.

• *Presynaptic Inhibition* A presynaptic terminal is itself "postsynaptic" to another terminal, where the presynaptic action may involve a conventional type of Inhibitory PostSynaptic Potential (IPSP) produced by the pre-presynaptic terminal onto the presynaptic terminal (that is now acting as a postsynaptic terminal). Thus the effect of an input (presynaptic) to a cell can be reduced or abolished (pre-presynaptic) without there

being any direct action of the pre-presynaptic terminal on the synapse the presynaptic terminal was contacting. This form of presynaptic control may be exerted by either axon terminals or presynaptic dendrites.

• *Inhibitory Operations* He reviews configurations that produce operations that are building blocks for specific functions: "feedforward or afferent inhibition, feedback or recurrent inhibition, and lateral inhibition"

• *Dendritic Integration and Dendritic Subunits* Shepherd criticizes the model of the neuron where it is represented as a node with all inputs converging on this node because this is ***not*** the case when one studies the effects of dendritic morphology and synaptic architecture. The patterns of dendritic branching, impose geometrical constraints which separate the activity in different branches from each other and combined with the electrotonic properties to ensure that parts of dendritic trees can function semiindependently from one another. These dendrites are the substrate for generating a rich range of computation. It is thus evident that the single-node model ignores the contributions of the different levels of dendritic organization that are responsible for much of the computational complexity of the real nervous system. In exploring the properties of branching dendrites and dendritic spines, it is found that they are capable of powerful and precise (discreet) information processing such as OR, AND, AND-NOT logic operations that arise from specific synaptic configurations. Also, through the sequential activation of active sites in the dendritic tree, synaptic responses initialed at a distal part of the tree can exert a precise control over the generation of impulses in the cell body and initial axonal segment of the neuron.

• *Associative Learning* The possibility that long-term potentiation (LTP) may underlie learning and memory, which involves a long-term (hours to weeks) increase in synaptic efficacy in response to a presynaptic input volley.

• In closing he states that the vast majority of neural network simulations consider individual nerve cells to be single-node, linear integration devices and that this model neglects the powerful effect of dendritic, synaptic, and intrinsic membrane properties on the function of the individual cell.

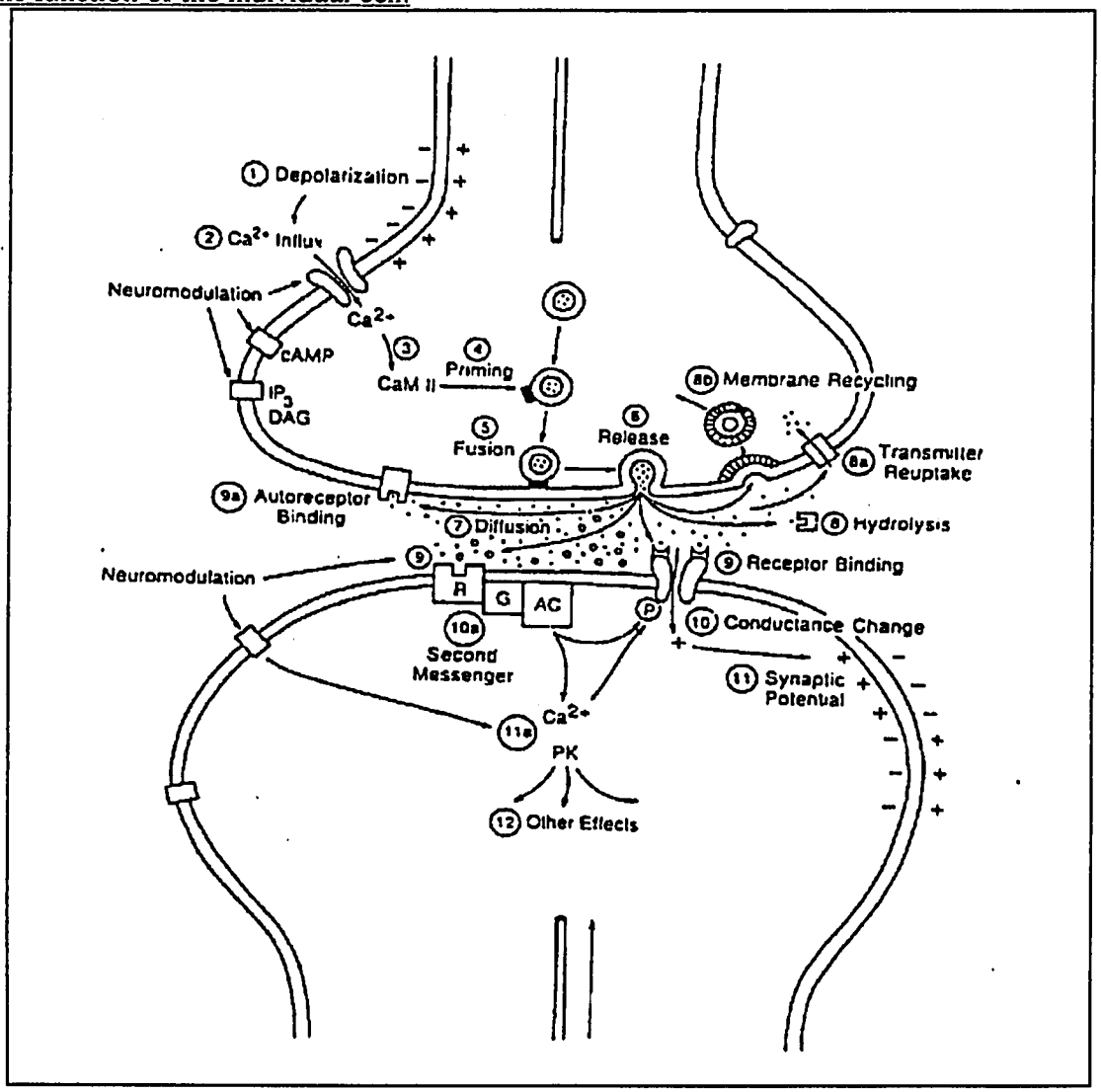


Figure 1.4 Summary of some of the mechanisms. Abbreviations: IP^3, inositol triphosphate; CaM II, Ca/Calmodulin-dependent protein Kinase II; DAG, diaclylglycerol; PK, protein Kinase; R, receptor; G, G-protein; AC, adenylate cyclase. (modified from Shepherd, 1988).

The *SYNAPSE* is the primitive structural and functional building block for the construction of neural circuits. By understanding synaptic transmission, we begin to

understand how the nervous system works. Behavior (perception, feelings, emotions, motorskills, learning, and memory) are based on these electrochemical interactions. Synaptic transmission can be either electrical or chemical. This paper focuses on the chemical giant synapse of the *Loligo Pealii*, and the Schaffer Collateral/CA1 synapse in the Hippocampus of the *Guinea Pig*.

Some basic principles underlying chemical synaptic transmission:

• On the basis of morphology, transmission occurs at the zone of apposition. For the chemical synapse, the zone of apposition is where the pre- and postsynaptic apposition is not contiguous, but there is a discrete synaptic cleft between the pre- and postsynaptic apposition (30-50nm) and is generally morphologically specialized, where the presynaptic terminals contain localized aggregates of synaptic vesicles, which release a chemical mediating agent.

• The chemical transmission may be divided into two mechanistic processes: the PRESYNAPTIC transmitting process (which determines the release of the chemical messenger) and the POSTSYNAPTIC receptive process (which determines the interaction between the chemical transmitter and the receptor molecules on the postsynaptic apposition, which leads, in turn, to the gating of specific ion channels that give rise to currents that produce the various synaptic potentials in the postsynaptic receptive process).

• The active zone forms a punctate junction that has about 1 μm or less of contact synaptic width, is oriented from the "pre" to the postsynaptic process, and converts a presynaptic electrical signal into a chemical mediating agent that acts on the postsynaptic process, which, in turn, converts the signal back into a postsynaptic electrical signal: a nonreciprocal two-port in the language of electrical engineers.

See Figure 1.4, page "17 for illustration of the current view of a synapse.

Steps for the action of a synapse:

- 1. Depolarization of the presynaptic membrane
- 2. Influx of Ca ions into the presynaptic terminal
- 3-5. Fusion of a synaptic vesicle with the plasma membrane
- 6. Release of a packet (quanta) of transmitter molecules
- 7. Diffusion of the transmitter molecules across the narrow synaptic cleft separating the pre- and postsynaptic processes.
- 8. Hydrolysis reuptake of transmitter, and membrane recycling.
- 9. Action of the transmitter molecules on receptor molecules in the postsynaptic membrane.
- 10. Which can lead to direct gating of a membrane conductance.
- 11. Which, in turn, causes a change in the membrane potential and, thus, in the excitability of the postsynaptic process.
- The receptor (9) may activate a second messenger system (10a), which indirectly gates a membrane conductance, as well as having other metabolic effects (11a, 12). The transmitter may also act on autoreceptors on the presynaptic process (9a) to activate systems that influence the subsequent release of transmitter. These steps are concerned primarily with rapid (2 - 20 msec) and relatively rapid (20 msec -2 sec) transmissions. There are slower cellular mechanisms that impinge on synaptic transmissions over longer periods of time:
    1. axonal and dendritic transport,
    2. storage of transmitters and peptides,
    3. corelease of peptides and direct modulation of transmitter response (neuromodulation),
    4. these effects are slow (sec - min) or slower (min - hours).

We begin to see that the synapse is a **primitive** for the building of circuits, and is a basic modulator in the brain, offering great flexibility of function by the following mechanisms involved:

1. different transmitters
2. different modulators
3. different types of receptors
4. different second-messenger systems linked to different kinds of machinery in the cell: electrical/mechanical/genetic.
5. different mechanisms with different time courses can exist in the same synapse conferring on the synapse the ability to coordinate rapid activity with the slower changes that maintain the behavioral stability of the organism over time. This engenders tremendous potential for functional diversity at the very basic unit of information processing and computation of the brain.

Chapter Two

A MODEL OF A GRAMMAR FOR A SYNAPSE

> The signaling is by coded information of uniformly sized impulses. Intensity is signaled by frequency.. .1 like discussing this problem of impulse coding because in recent years my research has been based on the firing patterns of signal nerve cells that have this coded language in all their responses to controlled sensory inputs. In this way we learn to understand the mode of operation of some parts of the brain. In fact, nerve impulses are the only language that is used in the brain for communication at a distance.. ..The frequency of firing may not be the same size, but the impulse is always the same size. It is the universal currency of the nervous system. It is the only currency that the nervous system knows for any actions at a distance. All signals from one nerve cell to another are conveyed by impulses. A nerve cell not firing impulses is mute. It is not communicating. (John C. Eccles, 1973)

An *action potential* occurs when the membrane potential of the cell is sufficiently depolarized to reach the action potential threshold for that particular cell (about -50 to -60 mV). The "all-or-nothing" event at threshold of the action potential generates the transfer of information down the axon to cause the release of neurotransmitters at chemical synapses. If the threshold is not reached the depolarization may still serve to modify the probability that other postsynaptic potentials in the cell do so. In the soma and the dendrites, voltage-gated Ca^2 + currents are also involved. Also, complicated arrays of K+ currents are involved in the repolarization of the neuron. As a matter of fact, the membrane of the neuron is always in constant flux due to the presence of a remarkable variety of ionic currents (Figure 9 on page 1 8) These currents are classified according to time course, sensitivity to membrane potential, sensitivity to neurotransmitters, and other chemical agents, and most are activated by depolarization.

Sodium (Na) currents: widely distributed throughout neurons in many different parts of the nervous system. Depolarizing in nature and the main depolarizing current in the activation of the action potential.

Calcium (Ca) currents: Have been found to act as modulators of neuronal firing patterns and as intermediaries in nonelectrical cellular processes such as neurotransmitter release, enzyme activation, metabolism, and possibly gene expression.

Potassium (K) currents: Are hyperpolarizing in nature and form a diversified group. They are responsible for the probability of the generation of the action potential at any given point in time.

Currents activated by hyperpolarization: Are carried by both Na+/K+ ions and are relatively slow in time course. They are activated by hyperpolarization and they bring the membrane back to more positive values - towards rest. They have been named "queer", hyperpolarization-activated', and "funny" currents. Their exact functions are not yet known.

Depending on the currents active or not active at the time of depolarization and the currents that become active or inactive after depolarization and into hyperpolarization, the action potential reflects all their interplay. The interplay of these currents generate the unique language of the neuron. Each class of neuron is brilliantly "calibrated" to do its particular task in the nervous system by the precise modulation of these currents by neuroactive substances. Neurons release a large number of these neurotransmitters in order to modulate the electrophysiological properties of **other** neurons. A single neurotransmitter may cause more than one postsynaptic response, which are mediated by pharmacologically distinct receptor molecules on the postsynaptic process. And different neurotransmitters can modulate the same ionic current.

These are the components for the language of a neuron communicating with another neuron via the action potential (there has been spatial and temporal summation of postsynaptic potentials to the point that the summation/integration has reached the threshold of the neuron). But the neuron has to first be depolarized beyond its intrinsic threshold, and then, once the neuron is depolarized and generates the action potential, the spike is carried down the axon into the terminals where it most likely will be **modulated** (presynaptic-to-postsynaptic). What we have is: Summation/Integration of PostSynaptic Input → Threshold reached in Soma → Action Potential down Axon → Presynaptic Modulation at Terminals, and this cycle cascades again in another neuron.

The currency of the nervous system for communication at a distance is this coded language of the impulse. But we must also consider what kind of language is being generated when there is the spatial/temporal postsynaptic input that can depolarize the soma of the neuron to the threshold limit, and the language that is being generated when the terminal (presynapse) is being invaded by the action potential and the presynapse is activated to communicate this impulse, via its synaptic mechanisms, to the postsynapse of the other neuron in line. I feel there is a pre-postsynaptic language that may be more rudimentary than the language of the action potential. In order to know how a neuron codes, transforms, and transfers information, we must know the language of the **Input/Threshold-Action Potential/Output** of a neuron.

I will used an extensive example from a paper written by David A McCormick in the book, *The Synaptic Organization of the Brain* (1990, Pages 64-66), to illustrate, on a very simplistic level, how the intrinsic and synaptic currents come together for synaptic computation and modulation of a representative neuron: the cerebral cortical pyramidal cell, which is similar in structure to the pyramidal cells that constitute the Schaffer Collateral/CA1 synapse. See Figure 2.1 on page"24 for the illustration of the example.

'The neuron receives excitatory, inhibitory, and modulatory inputs from a variety of sources. Putative *glutamergic* synapses (Schaffer Collateral/CA1 synapse is a glutamergic synapse), which have typical fast excitatory actions, are found on the spines of apical and basilar dendrites. *GABA ergic* inhibitory synapses are found on the soma, proximal and distal dendrites, and initial segment of the axon. putative *neuromodulatory* substances make their synaptic contacts on the dendrites."

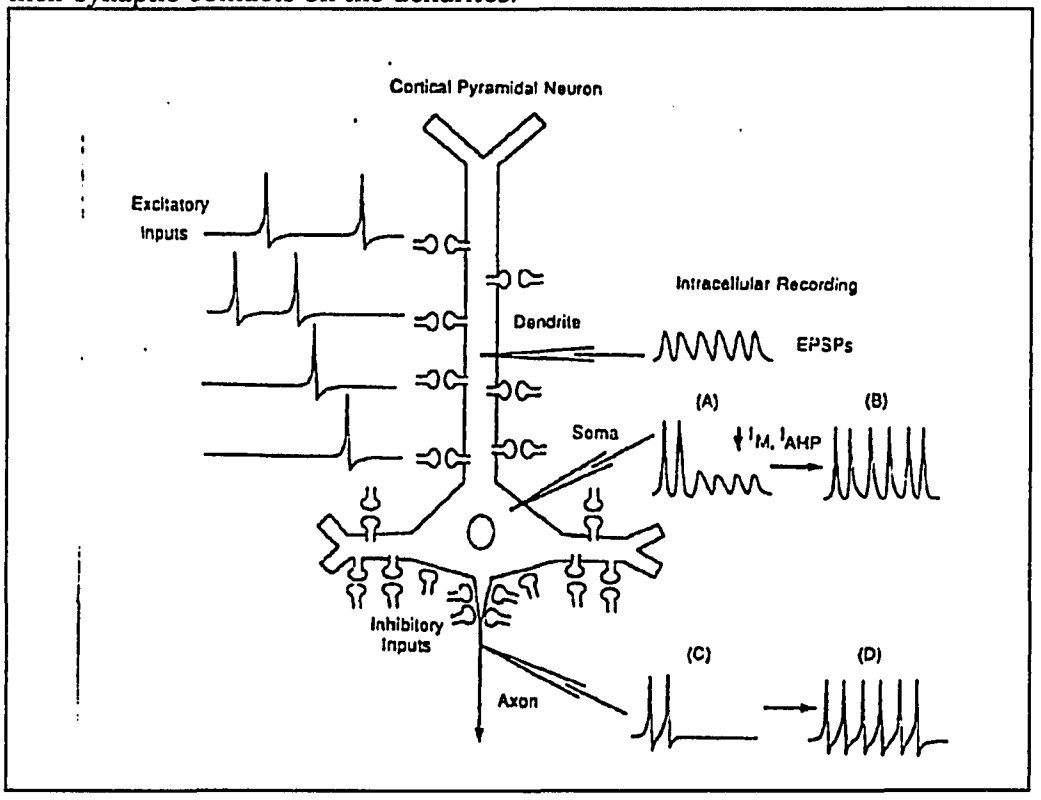


Figure 2.1 Effect of activation of excitatory inputs to a cortical pyramidal cell. A train of action potentials arriving at different synaptic endings on a apical dendrite of the pyramidal cell results in a generation of a train of EPSPs. The first two EPSPs generate action potentials in the somatic region, whereas the last four fail, owing to activation of the Im and Iahp currents (A). This is further reflected in the axonal output of the neuron.(C). Blocking of these two currents reduces spike frequency adaptation and allows all six EPSPs to generate action potential (B and D), (Shepherd, 1989).

"Assume that the cortical pyramidal cell is in the visual cortex and that, although the animal is awake and attentive (This example begins at the level of behavior, and traverses

the entire range of brain organization to the impact of the behavior on the synapse as proposed by Shepherd in Table 1.4), the cell is not yet receiving any specific visual input. The resting potential of our *hypothetical* cell will probably be somewhere around -65 mV, depending upon the state of input from the slowly acting neurotransmitters especially those (e.g., acetylcholine) that can alter the level of the resting potassium conductance. This resting potential is about 10 mV below (more hyperpolarized than) the threshold of around -55 mV for the generation of action potentials by cortical pyramidal neurons.

"Now let us stimulate the visual receptive field of our cell with an adequately adjusted light stimulus to the retina (e.g., a moving bar of light). This input will first cause excitation of thalamic relay neurons. Because the animal is awake and attentive, the thalamic neurons respond to the input in a one-spike-out/one-spike-in fashion and in turn five rise to a train of action potentials that reach some of the presynaptic terminals onto our cell. Each action potential causes an increase in the calcium concentration in the presynaptic terminal, which in turn causes the release of an excitatory transmitter from a variable number of synaptic vesicles. The transmitter diffuses across the synaptic cleft and binds to specific receptor molecules on the postsynaptic spine, increasing the probability that certain ionic channels (sodium and potassium) will be in the open and conducting state. In this manner, each presynaptic spike will cause an EPSP in the postsynaptic dendrite. The exact amplitude and time course of each EPSP depends upon a large number of factors, including the amount of transmitter released, the density of postsynaptic receptor molecules, the sensitivity of the of the postsynaptic element, and finally the amplitude and distribution of active currents that the postsynaptic element possesses. Indeed, the "efficacy" of each synaptic connection is not a static number, since it is probably modified during the acquisition of new information, as well as by new strategies

to analyze that information, perhaps through a process similar to Long Term Potentiation (LTP).

"In order for the barrage of EPSPs generated by the train of inputs from the thalamus to cause our cell to fire, it must cause the output decision point of the cell (the cell body and axon hillock in this case) to rise above firing threshold (e.g., -55mV). To do this, the EPSPs must spread from their points of generation in the dendrites, through the cell body, to the axon hillock. What happens to these EPSPs as they make this trip is determined by the intrinsic properties of our cell and the actions of other neuroactive substances impinging upon it. The dendritic EPSPs will probably be large enough to activate, sodium current, or a Ca^{2+} currents and thereby receive an extra "boost" from these depolarizing currents. This enhancement is needed to help overcome the fact that cell membranes are not perfect insulators and some of the current will leak out, thereby reducing the size of the EPSP as it spreads toward the cell body (electronic conduction). If the train of EPSPs comes at a high enough frequency, they will exhibit temporal summation, whereas EPSPs that arise from more than one point in the cell will exhibit, in addition, spatial summation. If the summated EPSP is large enough, it may be capable of causing the generation of a dendritic Ca^{2+}-mediated action potential which will, of course, greatly enhance and transform the response of the cell to the synaptic input. However, for simplicity, assume that the threshold for the generation of a dendritic Ca^{2} + spike in not reached."

"Now consider the situation in which many of the EPSPs in the train are large enough to cause the generation of an action potential in the cell body and axon hillock. In this circumstance, the initial EPSPs in the train will be more likely to cause the generation of spikes than the later ones, owing to the progressive activation of hyperpolarizing, and sodium current, both of which contribute to spike frequency adaptation. Thus, although

the cell may fire in response to the initial few EPSPs, the later ones will not reach firing threshold, and the cell's firing will cease. This is where modulatory transmitters come into play. If we were to arouse our animal such that there were an increase in the release of, for example, norepinephrine and acetylcholine, then the hyperpolarizing current, muscarinic, and potassium current would be reduced. Reduction of these potassium currents would enhance the response of the neuron by reducing spike frequency adaptation as well as by moving the cell's membrane potential closer to the firing threshold."

"As the visual stimulus moves out of the cell's excitatory receptive field and into those of neighboring cortical neurons, our pyramidal cell may now be actively inhibited through the connections on intrinsic GABAergic neurons. These barrages of IPSPs will meet with many of the constraints as did the previous EPSPs, although they may occur in a portion of the membrane potential where other conductances are not activated (i.e., between -65 and -75 mV). The fast GABAergic IPSPs will be important in terminating the residual excitation from the previous barrage of EPSPs by causing an increase in *CL*-conductance. The influential position of the IPSPs on or near the soma and initial portion of the axon hillock make them particularly effective."

"Many of the properties outlined for our hypothetical cortical pyramidal neuron can be generalized to neurons in all regions of the nervous system. However, each type of neuron is an individual, and generalizations **must** be used with caution so as not to neglect the important features of each neuronal type that allow it to perform its own unique brand of cellular processing and thereby make its specific contributions to the synaptic circuits of which it is a part

."But what if the question (the person is listening to a radiocast in a foreign language and asked to interpret what s(he) is being said) were put to a person who understood no English? He would be

> able to say that some human being was speaking, but he would not be able to identify the speech as anything but a continuous stream of acoustic signals or noise. For, in a very real and important sense, what comes out of the radio is nothing but noise. The question to be answered is: What does the hearer need to do in order to understand the message carried by the noise - to know, in other words, that the noise he hears is, in fact, a newscast? He must do this: He must somehow connect this continuous stream of noise with a meaning. He must somehow relate the sound to meaning Thus the general problem of understanding a language is finding a meaning in sound (R.A. Jacobs, P.S. Rosenbaum, 1968).

As humans, when we understand a language, it suggests that we are equipped with some fashion of a "neural interpreter" which processes this noise that invades the ears, and converts these sensations into coherent meaning. We must also be able to generate a continuous stream of noise which has meaning in our language. To study our language we must establish a framework within which a set of questions regarding our human intellectual capacity and the knowledge involved in speaking a language are currently described by a set of universal principles, called linguistic principles. These principles allow us to describe what we know about our language intuitively. They are essential to obtain a correct description of our language. But before we can describe what we know, we must know *how* to describe it. In other words, we must know how to classify the facts we observe.

> These linguistic facts cannot be classified by any random method; they must be classified so they represent all that we know about our language and only that information. After investigating some of these facts you will be able to appreciate that it is no simple matter to discover a classification scheme which meets this requirement. If such a classification scheme, in the form of a set of principles, existed right now, the description of our language would not be the enormously difficult task that it is at present. Unfortunately, only the barest outline of this set of principles is visible. This means that we can acquire at the moment only the most general understanding of our own competence to speak and comprehend the sentences of English. Not only will our understanding necessarily be incomplete; it will often, when we overextend our speculations and make unjustified assumption about how to organized the facts, be incorrect. (R.A. Jacobs, P.S. Rosenbaum, 1968)

In a human language, linguistic universals and the construction of a correct description of a speaker's linguistic knowledge **must** coincide. Unfortunately, I do not

know of any neurons who speak Neuronese, and are able to share with us a description of their linguistic knowledge. We know that neurons code, transform, and transfer information. We know that all that we think, sense, and feel is housed in the Central Nervous System (CNS), but how? I propose that we start simply. Since we have no neuron that can tell us its understanding of its linguistic knowledge, why not take the data that we have at the most basic component of information coding/transformation/transfer: *The Synapse*, and begin to view it as a generator of a constituent of a language. I am not inferring that the synapse generates a language. As in the English language a *morpheme* is considered a unit containing no smaller meaningful parts, whether a free form word or a bound form part of a word (e.g. '-s' to indicate plural), I will consider the synapse as a generator of a neural morpheme of modulation. As the synapses are integrated into the functioning of the neuron, then neuronal functioning might be analogical to words being formed. As the neurons are connected into networks, this might be analogous to sentences, and so up to line of greater neuronal interconnectedness and complexity. Though the syntax at the synaptic level might be considered trivial; put in perspective, they are the building blocks of microcircuits, which, in turn are the building blocks of dendritic trees ➡ neurons ➡ local circuits ➡ Interregional circuits ➡ behavioral systems. And considering that for 12 billion neurons there are approximately *70 trillion* synapses, this investigation into a grammar for a specific synapse is warranted.

Presently, we look upon the synapse as an electrochemical process. Within the synapse there are mechanism that execute functions in time and space, and these are the basis of synaptic communication. It is through the study and investigation of natural phenomena that are taken for granted that the most puzzling scientific mysteries are uncovered. What if these mechanisms, their functions, and the interrelations of these functions are the basis of a language among synapses that may be deciphered and

represented as a *formal grammar;* that by analysis of the data collected we discover a set of production rules that can describe the process of communication between the presynaptic and postsynaptic entities of a synapse of a specific kind, in a specific part of a structure in the brain. The syntax may not be at all similar to that of a human language, or maybe not even similar to a set of grammars that are used in computer science. But by analysis of the data in the context of a grammar, we might be able to discover a set of rules that describe the communication between a pre/postsynapse.

The syntax might be quite rudimentary when compared to human language and only capable of a limited range of coding/transformation/transfer of information. But when the syntax is understood for all the synapses of a particular neuron, and then combined with the model we have for the temporal and spatial summation and integration of neuronal input and the generation and propagation of the action potential for that specific neuron, a new more complex *grammar* might emerge for the neuron, and subsequently, when the neuron is combined into a network, more of the language of the brain might begin to be discernible and understood. Initially, the language might be very superficial, but will serve the purpose of starting us on the road to a deeper understanding of the language of the brain.

Neuronal models range from the fairly simple where a neuron is represented as a node with an axon (that is assigned a weight representing the influence it has on the neuron it impinges on), and these neurons are interconnected into networks, to compartmentalized models of a neuron which are computationally heavy (and neural networks of these models are computationally almost unmanageable). I am interested in a model of a neuron that captures the biology of the organism (soma, axon, dendrites, synapses), and is easy to computationally simple: a set of linear equations. Detailed data exists about neuronal functioning, and I intend to use it to model snapshots of the process

of the synapse at different times, instead of running a continuous model in time (having to differentiate and update multiple variables at each time step). I think this approach will not be as detailed as neurophysiological model of a synapse, but will capture the basic primitive functions and their interrelationship, and yet be computationally manageable for very large networks that would have thousands of synapses..

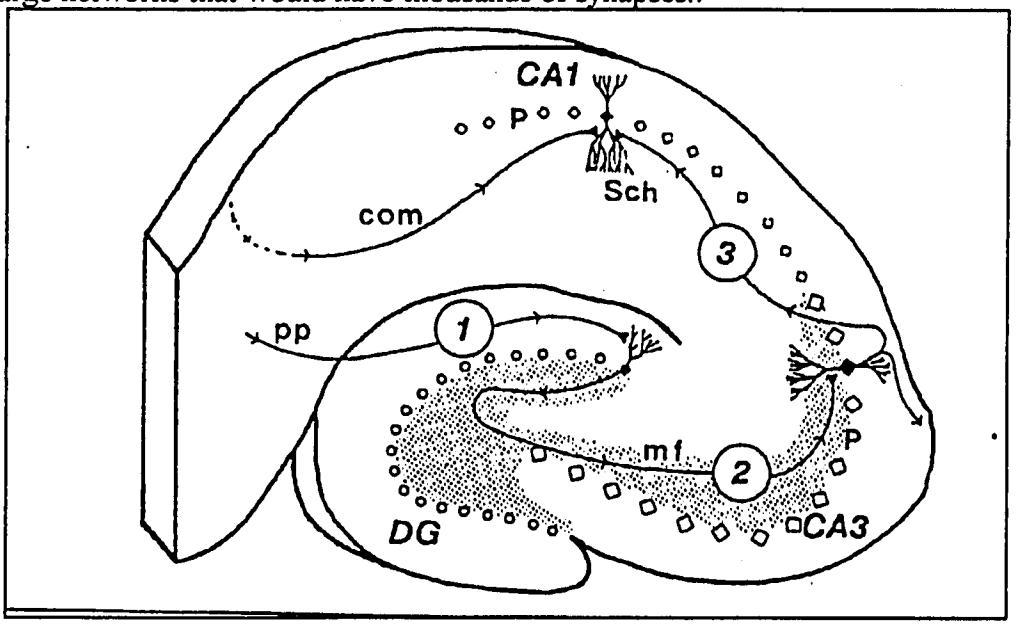


Figure 2.2 Circuitry of the transverse hippocampal slice. Schematic diagram of trisynaptic circuit showing (1) perforant path (pp) input to granule cell in the dentate gyrus (dg); (2) mossy fiber (mf) input to a pyramidal cell (P) in the CA3 region; and Schaffer collateral (Sch) input to a pyramidal cell in the CA1 region. This is a very simplistic circuit of the Hippocampus suitable for the illustration of the basis circuit in the Hippocampus. (Shepherd, 1990)

One possibility is the interpretation of synaptic functioning in terms of a *formal grammar* used in computer science. A good candidate for modeling would be the Schaffer collateral synapses because they are among the most extensively studied in the mammalian brain. The Schaffer collateral axons of the CA3 pyramidal neurons are partially myelinated, and have nodes of Ranvier at about 60-70 μm intervals. One to three unmyelinated axons emerge from each node and then bend to course parallel to the parent fiber, where each branch has numerous swellings ≅ 7μm apart), and makes contact with

one or two dendritic spines. The action of the Schaffer collateral synapse is **excitatory**. The Schaffer collateral synapses are of the type 1 variety: they have asymmetrical membrane thickenings and round vesicles and the synapses are generally made on slender dendritic spines, which are typically unbranched in the CAl region. A characteristic feature of the synapses is the "spinule" that protrudes into the presynaptic terminal. See Figure 2-3 on page "35 for an illustration of a Schaffer collateral/ CAl pyramidal cell synapse.

Following are a few of the features that have been observed at this synapse:

- Observations of endogenously generated synaptic responses have been observed by the use of a transverse hippocampal brain slice as a neurophysiological preparation. With this preparation it is "routinely" possible to observe and analyze in detail their biophysical properties Intracellular recording reveal an incessant barrage of synaptic activity. At the normal resting potential all of the spontaneous activity is depolarizing.
- Some of the synaptic activity represents (1) evoked impulse-dependent (resulting in release of neurotransmitter); (2) nerve impulse-independent (spontaneous release of single quantal packets of neurotransmitter - miniature excitatory postsynaptic potentials (MEPSPs)); (3) the "giant synaptic potentials" associated with interictal epiliptiform activity which is a field potential that results from a synchronous bursting of a large population of neurons. Its *intracellular* correlate is a burst discharge called the *paroxysmal depolarizing shift* (PDS). In the CA3 region, the burst appears as a train of action potentials superimposed upon a sudden 20 - 50 mV depolarization that lasts about 90 - 150 msec. The PDS is considered a *network-driven* burst discharge.

- Another aspect of this synapse that has had serious investigation is Long Term Potentiation (LTP): a persistent increase in synaptic efficacy that can be rapidly induced. Seconds or less of the appropriate activity cause a synaptic strengthening that can last hours, days, or longer. For a variety of reasons, LTP is a leading candidate for a synaptic mechanism of rapid learning in mammals. This fascinating form of synaptic *plasticity* has been most thoroughly studied in the mossyfiber synaptic input to region CA3 and the Schaffer collateral synaptic input to region CAl. There appear to be differences in the LTP mechanisms in these two systems (G.M. Shepherd, Synaptic Organization of the Brain, 1990).

As discussed earlier, a Hebbian synapse is one that is strengthened when there is a co-occurence of pre/postsynaptic activity. This Hebbian nature of LTP induction in the Schaffer collateral synapses has been clearly demonstrated. It appears that the induction steps appear to be controlled by the NMDA subtype of a glutamate receptor. It is proposed that the voltage - and neurotransmitter-dependent gating of Ca^{2+} influx through the NMDA receptor-gated channels is an attractive explanation for the Hebbian interactive mechanism.

The NMDA receptor ionophore complex must receive two signals simultaneously to become highly permeable to Ca^{2+}: An agonist (such as glutamate or NMDA) must be bound to the NMDA receptor, and the membrane must be sufficiently depolarized to relieve the Mg^{2+} block of the channel that occurs at voltages close to the normal resting potential. The common working hypothesis is that Ca^{2+} influx through the NMDA receptor-gated channel and the resultant increase in the intracellular Ca^{2+} - concentration are partly responsible for triggering the induction of LTP. Research on LTP has suggested a more general lesson regarding synaptic diversity. It is now clear that different

classes of hippocampal synapses may be quite different in terms of their physiological and pharmacological properties, even when they use the same neurotransmitter To understand the computations that occur within the circuitry of the hippocampus, it will be necessary to determine the functional properties of each class of synapses (G.M. Shepherd Synaptic Organization of the Brain, 1990).

See Figure 2-3 on page "35 for illustration of the possible mechanisms of LTP at the Schaffer collaterals onto CAl pyramidal cells.

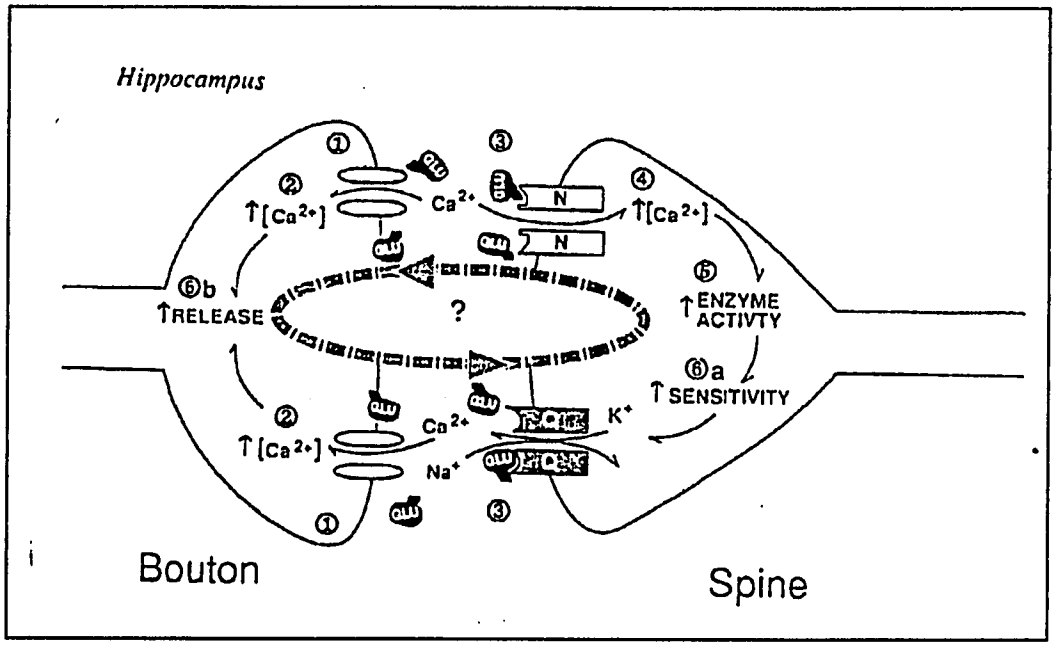


Figure 2.3 Possible mechanisms of LTP. Depolarization (1) of the presynaptic bouton causes an influx of calcium through voltage-dependent calcium channels in the presynaptic terminal. The subsequent increase of presynaptic calcium (2) leads to release of glutamate (GLU), which binds (3) to two subtypes of postsynaptic receptors, the NMDA (N) and the kainate-quisqualate (Q) receptors. Postsynaptic depolarization coupled with binding of glutamate relieves the magnesium block of the NMDA receptor-associated channel and permits entry of calcium , leading to an increase in the concentration of postsynaptic calcium (4) that is the critical step in the induction of LTP. This increase is thought to trigger a series of biochemical changes that ultimately lead to the expression of LTP. The expression of LTP is thought to be mediated by the postsynaptic increase in sensitivity (6a), a presynaptic increase in neurotransmitter release (6b), or both. (Shepherd, 1989)

There are varied and different parts of the puzzle that will have to be put together to try to get as detailed a picture as possible of the Schaffer collateral/CAl pyramidal cell synapse. A partial list of the mechanisms to be included are:

1. Synaptic Potentials
2. Synaptic Currents
3. Calcium/Calmodulin-dependent protein kinases
4. Neurotransmitters (exocytosis and quantal release)
5. receptor-sites

6. time
7. space
8. Reuptake of Neurotransmitter
9. Hydrolysis of Neurotransmitter
10. Autoinhibition of presynapse
11. Long term potentiation
12. Homosynaptic plasticity (facilitation, potentiation, and depression)
13. Retrograde communication
14. intracellular stores

Once I have a fairly detailed representation of the Schaffer collateral/CAl pyramidal cell synapse, I will then begin to study the data and model to:

1. Identify the mechanisms of the synapse. list each mechanism , and give a description of it and the formalism used to describe it (i.e., electrical, chemical, it cetera.)
2. Identify the function of the mechanism and determine if this is the smallest entity which may be represented as a primitive within the context of the synapse as a model of information coding/transformation/transfer.
3. Establish a set of steps from invasion of the presynapse by action potential to output response of the postsynapse based on the primitives and their respective analyzed functions.
4. Establish if previous activity of the pre/postsynapse is important to the present step: *homosynaptic plasticity*.
5. Establish if processes represented by steps are digital/analog, and if the analog steps may be represented as discrete steps.

6. Then begins the process of identifying a *formal grammar* for the synapse. Where a formal grammar is defined as a (possibly infinite) set of strings of finite length formed from a finite vocabulary (A. Barr, it al, 1981). The grammar of a formal language is specified in terms of the following:

- *The syntactic categories* They are referred to as *nonterminal symbols, or variables* and are often enclosed in angle brackets: "<", ">".
- *The terminal symbols of the language* They are to be concatenated into strings called *sentences* (if the terminals are words). A language would be the subset of the set of all the strings that may be formed by combining the terminal symbols in all possible ways. Exactly which subset is permitted in the language is specified by the *rewrite rules.*
- *The rewrite rules, or the production rules* They specify the relations between certain strings of terminal and nonterminal symbols, such that the production on the left-hand side may be "rewritten into the symbols on the right-hand side; be they nonterminals or terminals.
- *The start symbol* One nonterminal is distinguished as the *start* symbol, and by applying a sequence of productions a set of strings of terminals are derived: the language generated by the grammar.

So a *grammar G* is defined by a quadruple (VN,VT,P,S) representing the nonterminals, the terminals, the productions, and the start symbol. The symbol V for *vocabulary* represents the union of the sets VN and VT, which are assumed to have no elements in common. Each production in P is of the form "X -> Y" where X and Y are strings of the elements in V, and X is not the empty string.

7. Once a set of *syntactic categories*, a set of *terminals*, and the set of *production rules* are established, then we will have a formal way of capturing and expressing the information coding/transformation/transfer happening at the synapse.
8. Compare the generation of a string in the grammar with the data for the output of a CAl pyramidal cell to see if the string generated from a start state (input to Schaffer collateral synapse) captures and represents the data used to derive the formal grammar.
9. Progressively refine the grammar, making it more detailed.
10. The grammar may have to reflect components of time and space, be sequential and/or parallel in its production rules, and possibly context sensitive.

S	→	< ACTION POTENTIAL>
<ACTION POTENTIAL>	→	<DEPOLARIZE PRESYNAPSE> ^
		<T-EFFECT POSTSYNAPSE>
<DEPOLARIZE PRESYNAPSE>	→	<INT-CAL-CON> X
		<TRANS-QUANTUM RELEASE> X
		<TRANS-DIF/HYD/REUP> X
		<AUTORECEPTOR EFFECT>
<T-EEFFECT POSTSYNAPSE>	→	<TRANS-ACTION ON RECEPTORS> X
		<GATINGMEMBRANE CONDUCTANCE> X
		<2ND MESSENGER SYSTEM>
<GATING MEMBRANE CONDUCTANCE>	→	<POSTSYNAPTIC EXCITABILITY>

<2ND-MESSENGER SYSTEM>	→	<GATING MEMBRANE CONDUCTANCE>
<CALCIUM INFLUX>	→	ci
<TRANS-QUANTUM RELEASE>	→	tdlir
<TRANS-DIF/HYD/REUP>	→	tqr
<AUTORECEPTOR-EFFECT>	→	ae
<POSTSYNAPTIC EXCITABILITY>	→	pe
<TRANS-ACTION OF RECEPTORS>	→	tar
<METABOLISM>	→	m

I will give a simple example to convert the synapse to a computer grammar previously defined, and give an idea of the procedure involved. Please refer to Figure 1.4 for the model of the synapse I will use. I have generated a simple basic grammar for the synapse based on its description. Please refer to the grammar above, as it will be used in the example

From the grammar generated from the example of the synapse, I will use the following production rule for my example:

<DEPOLARIZE PRESYNAPSE> → <INT-CAL-CON>
<TRANS-QUANTUM RELEASE>
<TRANS-DIF/HYD/REUP>
<AUTORECEPTOR EFFECT>

In the above example, the syntactic categories are *depolarize presynapse, calcium influx, trans-quantum release, trans-dif/hyd/reup, and autoreceptor effect.* In examining a production rule, it states that the syntactic category on the left-hand of the arrow can be resolved into the syntactic categories on the right-hand side of the arrow.

From the grammar, it can be seen that the syntactic categories on the right-hand side can be further resolved into other syntactic categories and/or terminals.

For further evaluation, I will choose the syntactic category *INT-CAL-CON.* It represents the concentration of free calcium in the presyantic terminal (intracellular calcium concentration), $[Ca^{2+}]_i$, that is comprised of the calcium influx through calcium channels, and the intracellular calcium stores (There are also calcium channels in the axon that are involved in the generation of the action potential and hyperpolarization of the neuron, but these will not be considered here, since I am only interested in the effect of the intracellular calcium concentration in the presynaptic area as dictated by the production rule) Calcium is very important in the functioning of the neuron; some of the functions calcium plays in the functioning of the neuron follow:

1. Calcium ions contribute to the generation of the action potential
2. Calcium ions contribute to the modulation of the beating/bursting activity (and other aspects of electrical activity) of the neuron.
3. triggering of secretions
4. muscle contractions
5. activation of protein kinases, other enzymes and calcium-dependent ion channels

It has been suggested that calcium channels are clustered near the transmitter release sites in the presynaptic terminal because recorded calcium currents are much greater in these sites than in the regions of the axon leading to the presynaptic terminals (calcium is also involved in the postsynaptic terminal, but, again, I am following the production rule that dictates that I am only to consider INT-CAL-CON in the presynaptic terminal).

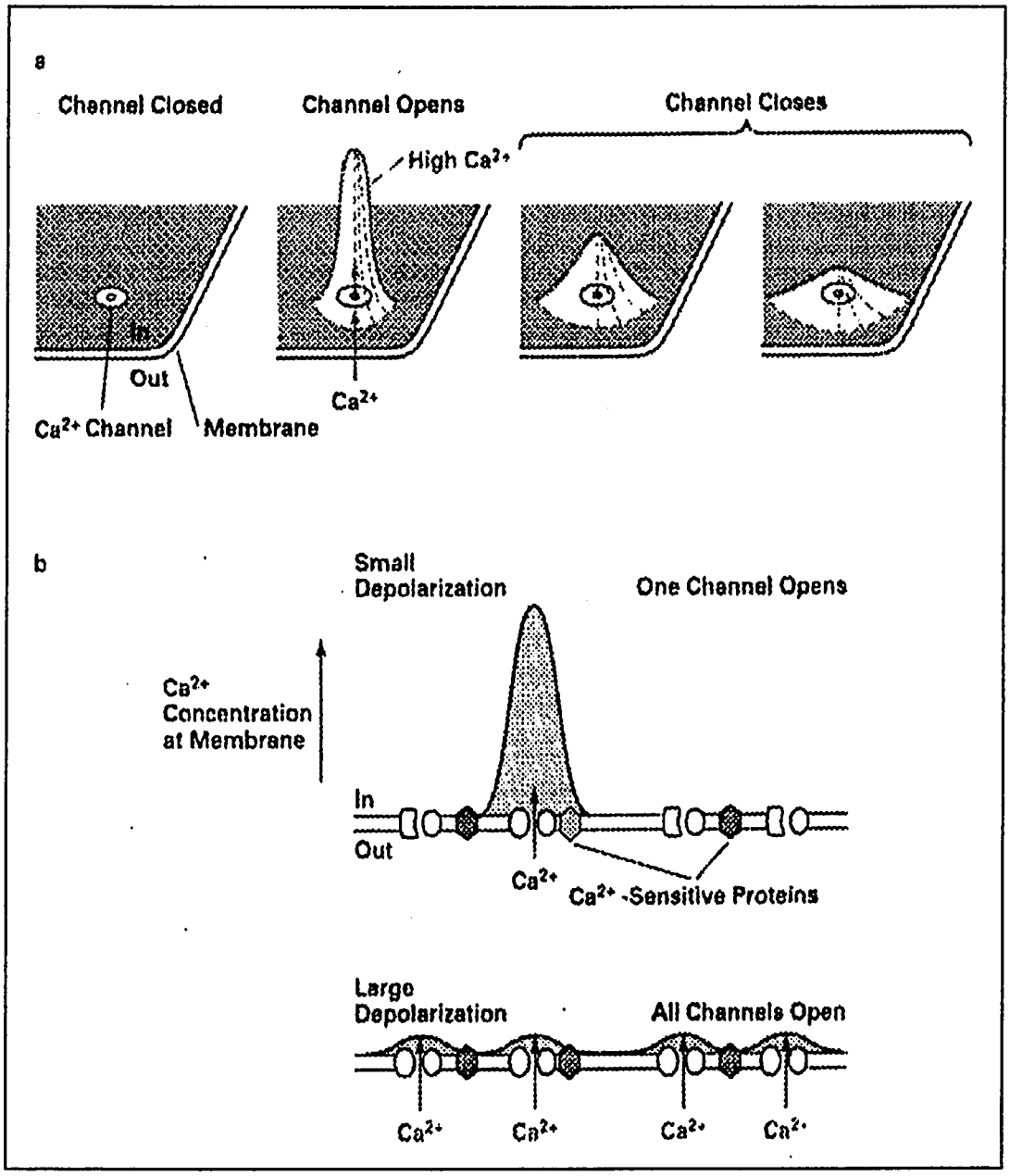


Figure 2.4 Calcium concentration in terminal. High levels of calcium occur at the mouth of calcium channels. (a) Volcanoes of calcium forming inside a cell near the mouth of an open channel; (b) Comparison of the spatial profiles of intracellular calcium expected with small and large depolarization. (Levitan, 1991)

Electrical and intracellular calcium measurements have provided important conclusions concerning the mechanisms of transmitter release:

1. transmitter release depends on the high power of the calcium concentration.
2. transmitter release is more sensitive to calcium ions than to other divalent cations.
3. release of transmitter occurs very rapidly following calcium entry. Calcium diffuses a short distance a acts within 0.2 msec to achieve transmitter release.
4. We see that calcium entry through voltage-dependent calcium channels results in the transduction of an *electrical signal- a* change in voltage - into a *chemical signal-* transmitter release.

When the presynaptic terminal is *depolarized* to allow calcium channels to open, the calcium levels are much higher directly under the membrane where the calcium channels are located. Please refer to Figure 2-4 on page "41 for an illustration of the distribution of calcium at a presynaptic terminal. The profile of the calcium concentration takes on the form of a "volcano" emerging from the mouth of the calcium channel, where the concentration of calcium may reach as high as 100 *mircoM* from a resting level usually at 0. l microM. Neurotransmitter release sites located close to the mouth of the channels may be exposed to these higher concentrations of calcium. As calcium diffuses from the channel, the calcium concentration around it drops. The illustration also shows that a small depolarization and a large depolarization will have a different effect on the amount of calcium concentration around the mouth of the channel. The *net* INT-CAL-CON into the terminal is the same but the effect is different. In the large depolarization nearly all the channels are opened, but the driving force for calcium is low because of the very positive

potential, so the flux through each channel is greatly reduced. Therefore, levels at any one site may **not** reach the critical level needed for triggering the key calcium-activated processes (one being transmitter release. I am making the assumption that only **one** vesicle is released at each terminal depolarization, and reaching the **key critical** level is necessary). The small depolarization allows only a few calcium channels to open, but since the driving force on the calcium ions is high because of the large driving force, a relatively high concentration of calcium is achieved at the mouths of these few opened channels, and the key calcium-activated processes are activated - one being transmitter release.

So, in this example I will assume that there has been a small depolarization at the terminal from the resting membrane potential to about -25 mV and that a *100 microM* calcium concentration has been reached at the few calcium channels that have been opened, and, therefore, the appropriate critical level has been reached for the key calcium-activated processes to happen: one being transmitter release. Based on the model presented in Figure 2-4 on page "41, I would modify the grammar to reflect the difference in a small/large depolarization.

In considering the effect that the large depolarization has on the release of neurotransmitter- from the vesicle stores by the process of *exocytosis*, which is that the calcium-activated process would not take place, I would introduce the production rule: "<INT-CAL-CON> -> no". This would indicate that the calcium influx has *not* reached the critical level to initiate the key calcium-activated process which leads to transmitter release. I would introduce the production rule: "<INT-CAL-CON -> yes". This would indicate that the key calcium-activated process has been initiated because INT-CAL-CON has reached the critical level. I would delete "INT-CAL-CON -> ci" from the grammar, as it has been replace by production rules with more definition.

I represent <INT-CAL-CON> in table 2-1 page "44 for clarity:

Mechanism	Opening of voltage-gated calcium channels that allow the influx of calcium into the terminal (presynapse) of the neuron, thereby, causing an inward calcium current in the terminal.
Function	The inward calcium current raises the intracellular level of calcium in the terminal, specifically in the proximity of the transmitter release sites, and when a critical calcium concentration level is reached, key calcium-activated processes may be activated which lead to transmitter release.
Formalism	$I_c - n \times \gamma \times (V_m - E_c)$, where (n) is the number of channels, (γ) is the conductance of each channel, and $(V_m - E_c)$ is the driving force that acts on the ions.

Table 2-1 Table of descriptive formalism for calcium influx into presynapse.

Quantal transmission has been demonstrated at all chemical synapses so far examined. However, at the vast majority of synapses each action potential releases not 200 quanta, as it does at the nerve-muscle synapse, but a much smaller number ranging typically between 1 and 10. Thus, the excitatory synapses made onto the motor neurons by the afferent fibers from a single sensory neuron,

which we considered in the last chapter, release on the average only 1 quantum per presynaptic action potential. (Eric R. Kandel, 1985)

Based on this statement, I will assume that the quantal release will be one vesicle, and will rewrite the production rule to be: "<TRANS-QUANTUM RELEASE> -> one". The transmitter is released as a uniform packet of transmitter molecules - each packet containing the same amount - which is in the vicinity of several thousand molecules of transmitter (from approximately 2,000 to 10,000 molecules per packet). Once the packet is released into the synaptic cleft by the process of *exocytosis* then there is the process of diffusion of the transmitter molecules across the narrow synaptic cleft. Not all of the transmitter acts on receptor molecules on the postsynaptic terminal. Some of the transmitter is lost to the receptors because of diffusion, hydrolysis, autoreceptor binding, and transmitter uptake. I have not found a figure that represents the loss, but I will assume that the loss in small (12.5%), and will not hamper the opening of **all** the receptors on the postsynaptic process.

to <TRANS.DIF/HYD/REUP> ➞ thdr, I assign <TRANS-DIF/HYD/REUP> ➞ 12.5%

to <AUTORECEPTOR-EFFECT> ➞ re, I assign <AUTORECEPTOR-EFFECT> ➞ 12.5%

So, now, the string generated to this point in the grammar is:

S ➞ (yes) (one) (12.5%) (12.5%)<T-EFFECT POSTSYNAPSE>.

This states that a -25mV depolarization has invaded the presynaptic terminal, and that this has caused the release of 100% of a quantum of transmitter (approximately anywhere from 2,000 to 10,000 molecules of the transmitter) to

be released into the narrow synaptic cleft, but only 75% will be available for the postsynaptic receptors because of the loss through diffusion, hydrolysis, reuptake.

For the resolution of the production rule , "<T-EFFECT POSTSYNAPSE>", I will use a model described by R. D. Traub in, 'Neuronal Networks of the Hippocampus'. He states that a quantum of transmitter corresponds to the contents of a single presynaptic vesicle, and has a postsynaptic action of q, which can be quantified in units of potential, conductance, or change transfer. There is attached a probability, p to the release of the quantum at a single release sight after an action potential. Since a synapse may receive input from one or more terminal, *n* is the number of terminals. If *n* sites release *transmitter* independently, then the number of quanta released follows a binomial distribution, and the mean amplitude of the *postsynaptic* event is *npq* The values for n, p, and q are extracted by statistical methods from the fluctuations in amplitude of synaptic events. In our example I have ONE release site, therefore, n = 1. I will use his data that the number of receptor channels opened by a single quantum of transmitter may represent a fundamental unit (these values may be obtained by analysis of PostSynaptic Potential (PSP) fluctuations, or by measurements of miniature synaptic events), and for an excitatory postsynaptic potential, less than 100 quisqualate-kainate channels may open. And let us assume that each channel opening changes the membrane potential by 0.22 mV, then I will assume that q = 90 times 0.22 mV = a 19.8 mV depolarization of the postsynaptic terminal large enough to cause an action potential in the cell Please refer to Figure 2-5 on page "49 for a pictorial representation of the processing at the synapse. I have chosen the probability that the transmitter will be release to be p = 50%, and, therefore, the transmission failure will be (1 - 0.50) = 50%.

The preceding model for EPSP amplitude fluctuations at an excitatory synapse would be translated into the production rule:

<T-EFFECT POSTSYNAPSE> ➞ <TRANS-ACTION ON RECEPTORS> ^
<GATINGMEMBRANE CONDUCTANCE
^ <2ND MESSENGER SYSTEM>

I would equate "<TRANS-ACTION ON RECEPTORS> = *np*", and "<GATING MEMBRANE CONDUCTANCE> -> <POSTSYNAPTIC EXCITABILITY>" I would equate with *q*, which equals 19.8 mV. In this example, "<2ND MESSENGER SYSTEM>" is not applicable since there are no 2nd messenger systems that would be responsible for the depolarization of the postsynapse. So, now, the string generated from the grammar would look as follows:

S ➞ (yes) (one) (1%) (1%) (n=1) (p=50%) (q=19.8 mV)

This states that a small depolarization (-25mV in the model of the hypothetical synapse) would release one quantum of transmitter, with a 50% chance of being released, (of which 75% would be available to the postsynaptic receptors) and would cause the opening of transmitter gated channels, and, therefore, and influx of *Na* ions into the postsynapse; causing depolarization of 19.8 mV. An input of 45mV (from -70 mV, resting membrane potential, to -25mV in the presynapse) has caused a 19.8 depolarization in the postsynapse. We now have an input/output relationship, but also have kept in the grammar the modulatory/mediating mechanisms responsible for this coding/transforming/transfer of information.

Revisiting our model synapse, and its respective mechanisms that contribute to the depolarization in the postsynapse, I can "clean-up" the grammar. With one quanta of transmitter released, the response from the postsynapse is the depolarization, I may drop the syntactic categories "<TRANS-DIF/HYD/REUP>" and "<AUTORECEPTOR EFFECT>", without affecting the *output.* I may also drop "<2ND MESSENGER SYSTEM>" since it is not involved in the generation of the depolarization in the postsynaptic membrane. I can replace "<GATING MEMBRANE CONDUCTANCE>", with "<POSTSYNAPTIC EXCITABILITY>" since they are equivalent syntactic categories. The updated grammar would look as follows

S	→	<ACTION POTENTIAL>
<ACTION POTENTIAL>	→	<DEPOLARIZE PRESYNAPSE> ^ <T-EFFSCTPOSTSYNAPSE>
<DEPOLARIZE PRESYNAPSE>	→	<INT-CAL-CON> ^ <TRANS-QUANTUM RELEASE>
<T-EFFECT POSTSYNAPSE>	→	<TRANS-ACTION ON RECEPTORS> ^ <POSTSYNAPTIC EXCITABILITY>
<INT-CAL-CON>	→	yes, no
<TRANS-QUANTUM RELEASE>	→	one
<POSTSYNAPTIC EXCITABILITY>	→	19.0 mV
<TRANS-ACTION OF RECEPTORS>	→	np = (1) (50%)

And the string generated from the grammar would look as follows:

S ➞ (yes) (one) (n=1) (p=50%) (q=19.8mV)

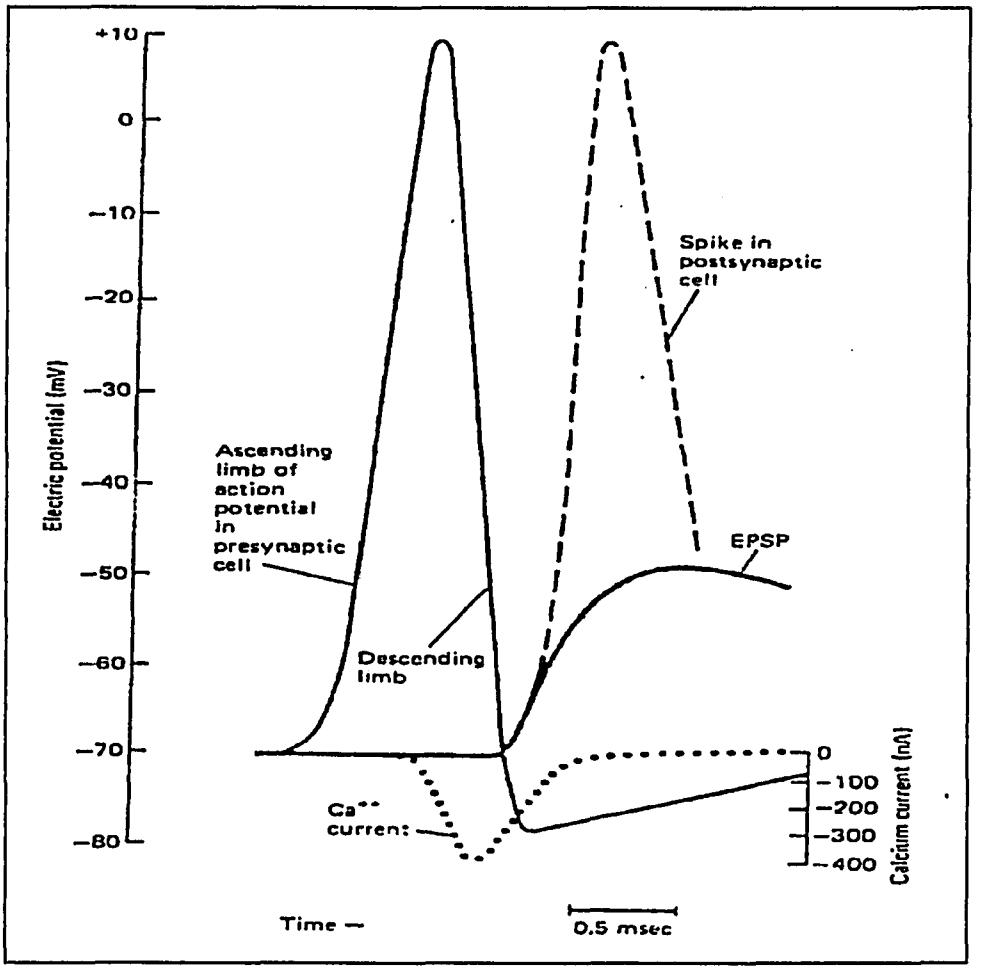


Figure 2.5 Timecourse of 4 events related to synaptic transmission. (1) the presynaptic action potential, (2) the Calcium current in the presynaptic neuron, (3) the synaptic potential (EPSP) in the postsynaptic cell, and (4) the action potential (spike) in the postsynaptic cell. An action potential in the presynaptic cell leads to the release of transmitter from the terminal by causing calcium current to flow into the terminal. The calcium current is turned on late during the presynaptic potential during the falling phase. The postsynaptic response to the transmitter begins soon afterwards and, if sufficiently large, will trigger an action potential in the postsynaptic cell (Llinas, 1982)

In a simple example as the one just presented for this model neuron there are just two inputs: the small or the large action potential. In a more realistic example, the

inputs would be small, or large action potentials, tetanic stimulation, spontaneous burst, spontaneous transmitter release at presynapse; and these inputs would be influenced by homosynaptic plasticity, Long Term Potentiation (LTP), and other possible and probable inputs. If a grammar could be formulated that could capture fairly realistically these inputs and their output relations, generated by the grammar, then we would have a syntax for that synapse that would capture allot of the neurophysiological data relevant to synaptic communication, and would also relate the mechanisms and their functions to this data. It is interesting to me that from the neurons perspective, all it knows is on the basis of its synaptic connections, not the action potential, which seem to be the emphasis for researchers. Action potentials are transparent to the communicating neurons.

With the McCullough-Pitts model of the neuron, even today, in neural networks, when a neuron is represented communicating with another neuron, it is shown as:

<NEURON ONE> ➔ <NEURON TWO>

All synaptic connections that might have different spatial/temporal dimensions are clustered into one neuronal input from <1> to <2>. They average out the impact that <1> will have on <2>, and model that as a weight assigned to the input vector that may be modified. I would like to give more detail to this model and offer a way of representing individual synapses in a way that would capture more of the realism of the morphology, and a formal grammar that would more realistically reflect the known data today. It is not that I intend to model the synapses with the same biophysiological detail of neuroscientists, but that I will look at the input to the presynapse and the output of the postsynapse, and in between them (in a black box), I will describe its function in terms of a set of functions and their interrelationships. In *NO WAY* do I suggest that this procedure,

in its final development, will capture the complexity, or magnificence of the brain. It would be extremely presumptuous, and naive, to think that a somewhat detailed, though simplified, model of the brain developed by this process, or any other current methods used to model brain functioning, would be able to duplicate the functions that have taken over of million years to develop in the unfathomable crucible of Nature.

In defining a set of *primitives* (in my example, I consider *INT-CAL-CON* a primitive, whereas *depolarized presynapse* is not, since it may be resolved into several syntactic nonterminals) for the grammar, I would like to examine some considerations put forth by Dr.Yorick Wilks in his discussion of *semantic primitives* (Wilks, 1977) He defines certain properties desirable for the set of primitives: Though his primitives are semantic, these considerations seem effective for syntax.

1. *Finitude* The number of primitives should be finite and should be smaller than the number of words whose meanings the representation scheme is to encode.
2. *Comprehensiveness* The set should be adequate to express and distinguish among the senses of the word set whose meanings it is to encode.
3. *Independence* No primitive should be definable in terms of other primitives.
4. *Noncircularity* No two primitives should be definable in terms of each other.
5. *Primitiveness* No subset of the primitives should be replaceable by a smaller set.

Presently, this is a very general outline of the process. With further collection of data and analysis, the process will become more detailed. I think this kind of approach will

make the understanding of the synapse easier to comprehend and grasp. as this grammar will introduce a shorthand for the process of information coding/transformation/transfer for the model of the synapse.

Chapter Three

MODEL AND DISCUSSION OF SYNAPSE IN LOLIGO PEALII AND CA3/CA1 SYNAPSE IN HIPPOCAMPUS

Model for the Giant Synapse in the Squid *Loligo Pealii*

Dr. Rudolfo Llinas (Llinas, 1982) studied the role of calcium in synaptic transmission (specifically, the aspect called depolarization-release coupling) in the giant synapse between the second-order axon and the largest third-order axon in the squid Loligo Pealii. The question asked in his paper is, "How does the depolarization of the membrane lead to the release of neurotransmitter, so that the neuron can act on the next cell in the neuronal chain?"

It is known that when an action potential invades the membrane of the presynaptic terminal it causes the presynaptic terminal to release (secretion of a biologically active substance by the mechanism of exocytosis) neurotransmitter into the synaptic cleft. The postynaptic membrane, which makes the synaptic cleft with the presynaptic terminal, has embedded receptor molecules that react with the arriving molecules of neurotransmitter to cause a postsynaptic potential. The sequence of events are: **Presynaptic Depolarization** (electrical) → **Neurotransmitter Release** (chemical) → **Postsynaptic Depolarization** (electrical), after a delay of about one millisecond (ms). The degree of postynaptic depolarization increases with the **amplitude** and **duration** of the presynaptic action potential up to a point: The response decreases if the presynaptic depolarization is greater

than 60 millivolts (mV) with respect to its resting potential of - 70 millivolts. If the presynaptic depolarization goes beyond +100 mV, the postsynaptic response could actually disappear; but a brief synaptic transmission is detected as the presynaptic potential returns to its resting value.

Earlier researchers discovered that signal transmission across the synapse did not require invasion of the presynaptic terminal by an action potential (Chappell et al, 1972). The passing of an electric current through a microelectrode that impaled it, caused the terminal to release neurotransmitter. This experiment is significant because it separated the mechanism of electrical excitability responsible for the action potential from the mechanism responsible for the release of neurotransmitter out of the presynaptic terminal, the inward calcium current.

From voltage-clamp experiments and mathematical models, Llinas and colleagues developed a kinetic model for the relationship of presynaptic clamped potential to the presynaptic calcium current, and a model for the presynaptic calcium current to the postsynaptic potential. Artificial action potential produced by a voltage-clamp circuitry is shown on the giant synapse identical with those of a natural action potential (Llinas, 1982).From his research, Llinas contends that the time course from the time an action potential invades the presynaptic terminal to a postsynpatic response is about **one millisecond**. This includes the time for the calcium channels to open when the presynaptic membrane is depolarized. On the other hand, at a voltage step of 130 mV, the calcium current and the postsynaptic response are suppressed until the end of the voltage step. At that time a "tail current" of calcium flows (at this time the calcium channels are open), and in **0.2 msec** a postsynaptic response is recorded. He concludes from this observation that the actual time of the subsequent events in synaptic transmission, once calcium ions have entered the presynaptic terminal during the falling phase of a voltage spike (from the time

the calcium channels are opened), must be quite fast, possibly in the 0.2 msec range. And that a large part of the synaptic delay (approximately 1 msec) is due to the time the calcium channels require to open when the membrane is initially depolarized.

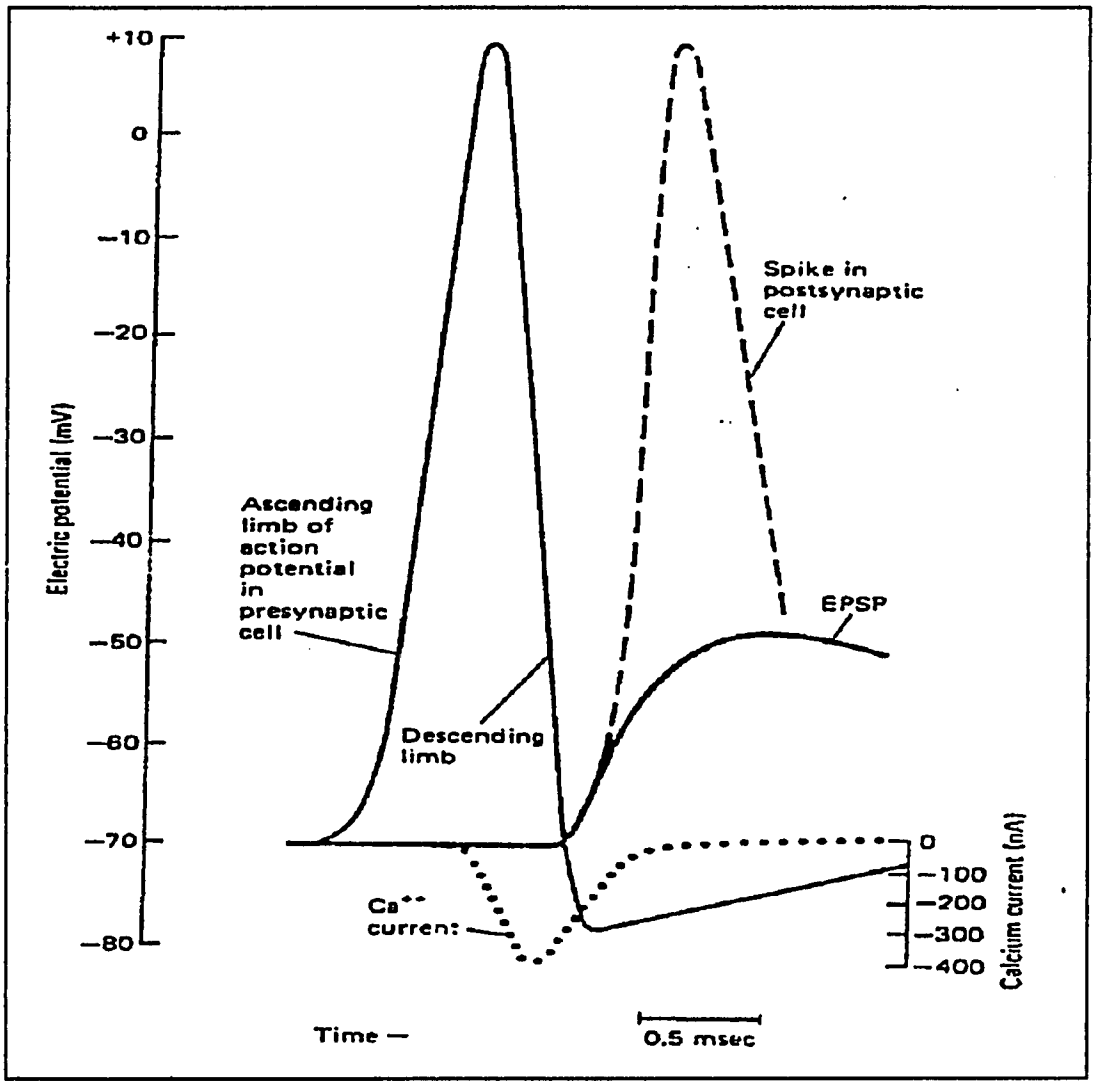


Figure 3.1 Artificial Action Potential (Ilinas, 1982).

Figure 3.1 is an artificial action potential produced by the voltage-clamp circuitry . Dr. Llinas describes the diagram, "First, a natural action potential (a) is recorded by a microelectrode positioned in the presynaptic terminal. Normally, it produces a postsynaptic action potential (b). Now, however, the postsynaptic terminal is voltage-clamped at its resting potential. Under this circumstance the transmitter molecules arriving at the postsynaptic terminal open channels in the

membrane and ions flow through them, but the clamp circuitry injects currents in precisely the right amount to keep the net current zero, and the voltage unaltered. The amount of current the clamp injects (c) is therefore equal in time course and magnitude to the "synaptic current" through the postsynaptic membrane. Next, the membrane channels on both sides of the synapse that open in response to a change in voltage (as opposed to the arrival of transmitter) are incapacitated by drugs, so that they no longer pass sodium and potassium ions, the basis of a natural action potential. If the presynaptic voltage-clamp circuitry delivers the voltage pattern of the action potential recorded earlier, the resulting synaptic current (d) has the same latency, amplitude and time course as the one caused by natural events. If the postsynaptic terminal is then unclamped but the drugs remain, the postynaptic terminal respond to the artificial action potential by showing a prolonged change in voltage (e). The change represents the passage of ions through transmitter-dependent channels. Ordinarily, the postsynaptic change in voltage serves to open the voltage-dependent channels in the membrane, so that a postsynaptic action potential is generated.

Relating the sequence of events of Figure 3.1 to synaptic transmission, we have:

Action Potential (a) → Calcium Current (c, d) → Postsynaptic Response (b, e)

- Action Potential : Mechanism that depolarizes presynaptic membrane, and activates the voltage-gated calcium channels.
- **INT-CAL-CON** : The mechanism that triggers the release of neurotransmitter in the presynaptic terminal.
- **Postsynaptic Response** : Once the neurotransmitter is released by the process of exocytosis into the synaptic cleft, it opens the channels in the postsynaptic membrane, ionic currents flow through , and in to the membrane, depolarizing it

Three events are investigated in describing the effects of Depolarization-Release Coupling: Presynaptic Potential, **INT-CAL-CON**, and Postsynaptic Response. These I will refer to as the Primitives of my model. They are related in specific relationships to each other : Prestsynaptic Potential virsus Presynaptic Current, and Presynaptic Current virsus Postsynaptic Response, by the research of Dr. Llinas and his colleagues. The relationship between Presynaptic Potential and Presynaptic Calcium Current is treated in a paper written by Llinas, Steinberg, and Walton, and the *Presynaptic Calcium currents in the Squid Giant Synapse*, (1981a). The thrust of this paper presents a quantitative analysis of the relationship of the presynaptic potential presynaptic calcium current.

Assumptions are made about the existence and characteristics of the sequential steps between the presynaptic potential, and the presynaptic current:

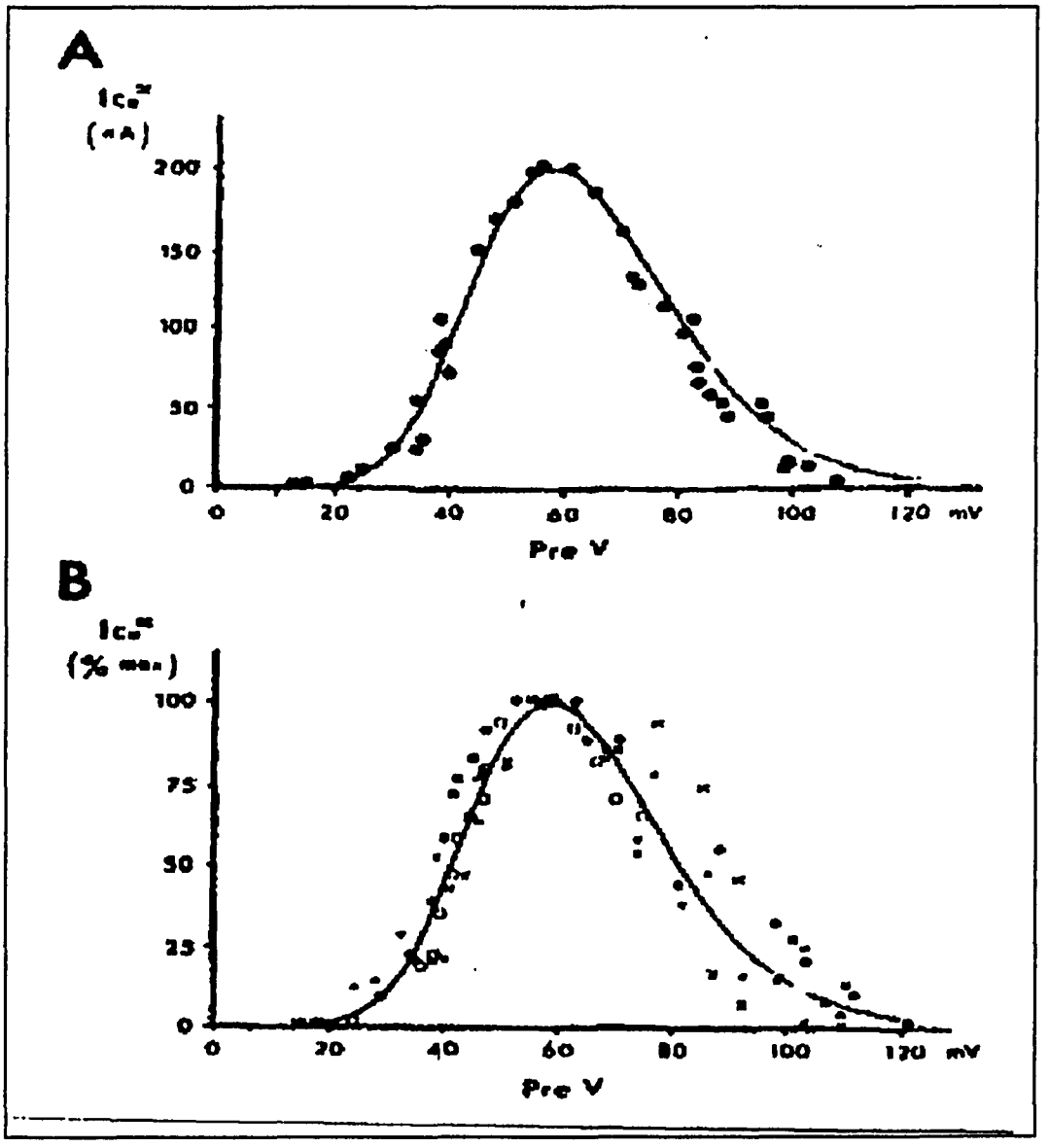


Figure 3.2 Plot of peak calcium current (I_{Ca}) against a presynaptic voltage.. Peak voltage at approx. 60 mV depolarization. Solid line indicates numerical solution for I+ca+ of Equation 17 in paper. (Ilinas et al., 1981a)

- calcium channels are composed of n subunits,
- each subunit may be in S or S' state,

- channel gate is in open state when all subunits are in S' state,
- the number of open channels,
- the contribution of the membrane potential to the opening of channels,
- the time-moment of interest,
- the flow of calcium ions per unit of time, through a single channel,
- the number of channels open from the total amount of channels.

Between the presynaptic potential, and the presynaptic calcium current, these characteristics and intermediary steps are subsumed and represented in the kinetic model of Llinas 1981a), and are, by extension, represented in the primitives I will use in my model. In a table devised by MacGregor and Lewis, Figure 4, Chapter 1, (MacGregor, 1977), he classifies the different stratification of theoretical and modeling efforts in neuroscience. He states that models which relate variables of adjacent strata are the most powerful in that the variables of the upper level are explained in terms of the variables of the lower level. In the kinetic model of Llinas et al. (1981a), the variables in level B (Membrane Conductance Modulations) are explained in terms of the variables in level A (Molecular and Chemical Processes). Equation 3.1 is an example from the kinetic model where the calcium current is expressed in terms of the intermediary steps.

This kinetic model is constructed based on the data gathered from voltage-clamp experiments, and the assumption that the mechanism for the initiation of the inward calcium currents is similar to that suggested for sodium and potassium currents in the squid nerve: i.e., a voltage gating of ion-specific transmembrane channels.

The plot of Figure 3.2-A shows the relationship between the **amplitude** of the Presynaptic Potential and the **amplitude** of the inward steady-state of the calcium current for one synapse. The maximum current reached by each synapse varied; therefore, in 3.2-B, the currents were normalized, and the maximum current for each synapse set to 100

percent. That the currents varied is not surprising given the differences in presynaptic terminal morphology - probably digit size. In a table presented in the paper, for a set of 18 synapses, the maximum peak of the steady-state calcium current, (I_{ca}), ranged from 110 - 370 nanoAmperes (nA). The solid line in both plots is the solution to Equation 17 in the kinetic model for the inward calcium current presented in their paper (equation 3.1):

Equation 3.1 is the steady-state calcium current I_{ca} in terms of the relative contribution of calcium current flowing through an open channel (j), (equation 3.2), and

$$I_{ca}^{\infty} = [G]_0 \left(k_1 / k_1 + k_2 \right)^5 \cdot \frac{\beta_1 K [C_0 \exp(-80V) - C_1)}{1 + K C_0 \exp(-80V)}$$

Equation 3-2 Equation 17 from kinetic model. (Llinas et al, 1981a) I(ca is the steady-state calcium current, Ica , k1 and 2 are the forward and backward rate constants for the conversion of an nth subunit of a calcium channel from an S to an S' state. When all units are in the S' state, the channel is open, G. G0 = Total number of channels (open or closed). (1 is a proportionality constant, and K is the equilibrium constant.

$$j = \frac{\beta_1 K [C_0 \exp(-80V) - C_1)}{1 + K C_0 \exp(-80V)}$$

Equation 3-1 Plot of peak Calcium current I_{ca} against a presynaptic voltage. Peak voltage occurs at (60 mV depolarization. Solid line indicates numerical solution for I_{ca} of Equation 17 in paper. (Llinas et al, 1981a)

$$\left(k_1 / k_1 + k_2 \right)^5$$

Equation 3-3 The number of open channels from total, G_0.

the number of channels that are open, (equation 3.3). As may be seen from Figure 2.2, (the solid line being the solution to equation 3-1 from the kinetic model developed by Dr. Llinas and his colleagues), the calcium current in the presynaptic terminal is the

consequence of the voltage gating of ion-specific transmembrane channels in the presynaptic terminal in the *Loligo Pealii*. Examining the close overlap of the data from the voltage-clamp experiments to the model, it is obvious that the kinetic model is a good fit to the data, and has a predictive functionality.

My intention is to develop a model that is not as detailed as the model presented by Llinas et al (1981a), maintaining the basic relationships between the primitives mentioned, and easy to compute. I have represented the bell-shaped curve of Figure 3.2-B by five linear equations presented in table 3.1. In Figure 3.2-B, the voltage dependence of I_{ca} for eight synapses fits well the solid line that represents the kinetic model. The data is normalized for each synapse, such that the maximum current equals 100 percent. Considering that the general synaptic amplitude is the same for the synapses in Figure 3.2-B, I will use it as my representative presynaptic terminal.

Segment	Equation
(15,0),(29,9)	z = 0.643x -9.643
(30,10),(53,99)	z = 3.870x -106.087
(54,100),(61,100)	z = 100-0x
(62,99),(94,23)	z = 246.250-2.375x
(95,22),(120,0)	z = 105.600-0.880x

Table 3-1 Equations for Figure 3.2.

The relation between the presynaptic calcium current and the postsynaptic potential in Loligo Pealii is the next part of the model. In *Relationship Between Presynaptic Calcium Current and Postsynaptic Potential in Squid Giant Synapse* (Llinas et al., 1981b), the authors present the caveat, "While the postsynaptic

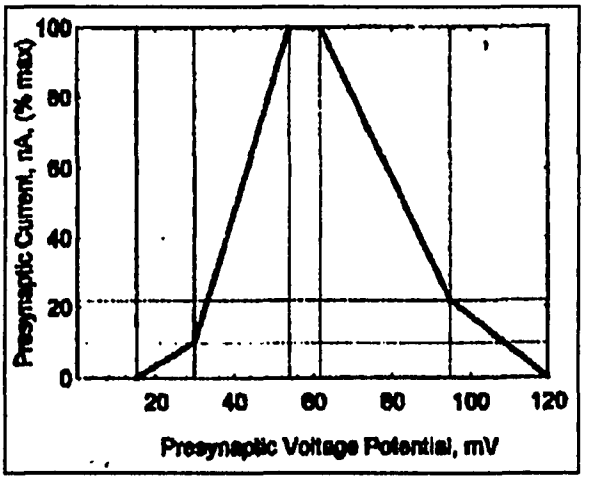


Figure 3.3 Linear representation of Figure 3.2.

response itself is not a completely accurate indicator of transmitter release, it is possible, using this measurement, to approximate the time course and amount of transmitter release by a given presynaptic. I_{ca}" Considering the complexity of the relationships, the authors have made some assumptions regarding the existence of several sequential steps, and their characteristics, in the relationship between the presynaptic calcium current and the postsynaptic response. These considerations form the basic constructs for the kinetic model presented in their paper:

- diffusion of calcium in the presynaptic terminal,
- activation of a fusion promoting factor (fpf),
- inactivation of fpf,
- vesicle fusion and depletion,
- general properties of the postsynaptic conductance gates,
- passive membrane properties of the postsynaptic fiber

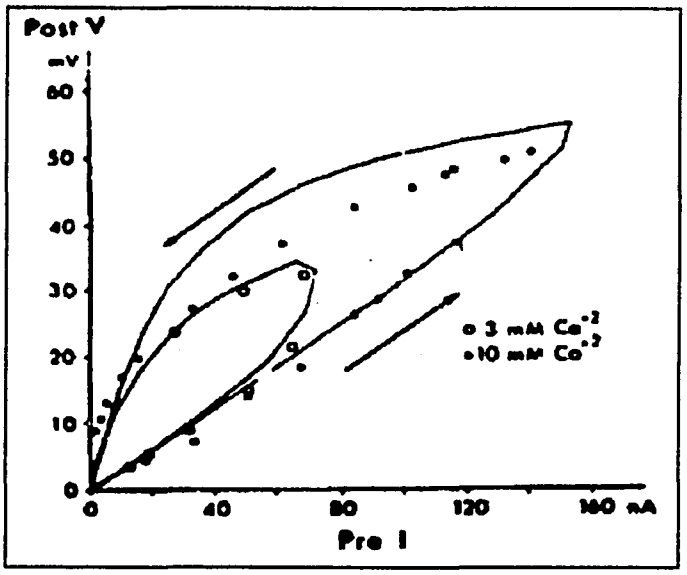


Figure 3.4 Relationship between presynaptic calcium current and postynaptic response at two extracellular calcium concentrations. Arrow pointing up corresponds to voltage clamp pulses up to 60 mV, and arrow pointing down to voltage clamp pulses above 60 mV (Llinas et al, 1981).

They plotted the relation between the presynaptic current and the postsynaptic potential, and discovered that the relationship is not simple (Figure 3.4). As the presynaptic potential increases, the plot shows hysteresis in the I_{ca} - EPSP relationship. As indicated by the researchers, "The hysteresis of the Ica - EPSP curve demonstrates that for a given I_{ca}, different values can be obtained for the postsynaptic response depending on the level of depolarization of the presynaptic membrane.....This indicates that parameters other than the $[Ca^{2+}]_i$ can modulate calcium-dependent transmitter release...The potential across the presynaptic membrane seems to regulate the effectiveness of calcium-mediated vesicle fusion and, thus, the amount of transmitter released by a given presynaptic depolarization (Llinas et al., 1981b)." For my model, I will accept the assumption that presynaptic depolarization, which causes the potential across the membrane, can modulate the depolarization-release coupling, and will use the plot of Figure 3.4 to generate a set of linear equations to represent the hysteresis loop for a 10 mM extracellular calcium concentration. Dr. Llinas et al are interested in the direct dependence of the EPSP on I_{ca} , and in the subsequent analysis of the paper they only consider the rising phase (arrow going up and right) of the relationship in their kinetic

model which is constructed from experimental data and results derived only from this portion of the linear relationship, and its intermediary steps.

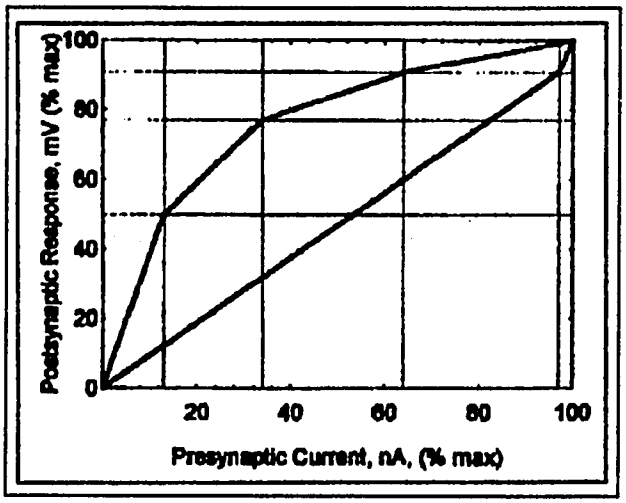


Figure 3.5 Linear representation of Figure 3.4.

As previously stated, the relationship of the primitives selected for the model are: **Presynaptic Action Potential → Presynaptic Calcium Current → Postsynaptic Response.** The relationship **Presynaptic Action Potential → Presynaptic Calcium Current** is represented by the linear equation: $z = a + bx$ from Table 3.1; the relationship **Presynaptic Calcium Current → Postsynaptic Response** by $y = c + dz$ from Table 3.2. Illustration 3.1 is a state diagram the invasion of the presynaptic terminal by an action potential to the postsynaptic response.. Given an input of a postsynaptic potential in millivolts, one would easily be able to calculate a postsynaptic response as a percentage of the maximum of the postsynaptic response. Suppose a presynaptic terminal was invaded by a 50 millivolt depolarization. Following Illustration 3.1, input = x = 50.

segment	equation
(0,0)-(97,91)	y = 0.938z
(98,92)-(100,100)	y = 4z - 300
(100,99)-(65,92)	y = 79 + 2z
(64,91)-(35 ,78)	y = 62.310 + 0.448z
(34,77) -(14,51)	y = 32.800 - 1.300z
(13,50)-(0,0)	y = 3.846z

Table 3-2 Linear equations for Figure 3.5.

On the other hand, in a table presented by Llinas (1981b), values for the peak presynaptic current (PC), and peak postsynaptic voltage (PV) for several synapses at different extracellular calcium concentrations are listed. Below is a list of the synapses at a 10 mM extracelluar concentration from their table.

Peak presynaptic current and peak postsynaptic voltage for several giant synapses of the Loligo Pealii at a 10 mM extracellular concentration.

It is obvious that there seems to be allot a variability between the synapses. Some of the variability may be attributed to the state of the synapse in the preparation, the preparation, or the morphology of the digit. In any case, one could either take the Mean of the values for z and y, normalize them to 100 % , and, following the state diagram, calculate the range of values for z and y at different presynaptic potentials. Or, one could use the values for individual synapses, arguing that these values reflect the different morphology of the synapse, and, hence, synapses will vary in their processing, and output from a given postsynaptic potential. Whichever method is used for calculation, using the linear equations presented, will be easy, and maintain the relations of Figures 3.2 and Figure 3.4.

Synapse No.	Peak PC, nA	Peak PV, mV
S273	14	550
S274	14	400
S714-0	35	210
S714-2	50	140
S714-3	48	320
S714-4	15	125
S717-1	64	216
D717-2	65	236
S719	50	200
S725	44	392
S725	48	440
S725	32	400
S818	36	370
S827	53	289
S874	51	250
S875	53	289
S878	48	250
Mean ± SD	41.9 ± 16.3	298.6 ± 110

Table 3-3 Peak presynaptic current and peak postsynaptic voltage for several giant synapses of the Loligo Pealii at a 10 mM extracellular concentration.

Some interesting points brought out by the research in the three papers used in this section are listed below, as they elucidate the process of depolarization-release coupling and some of the intermediary steps:

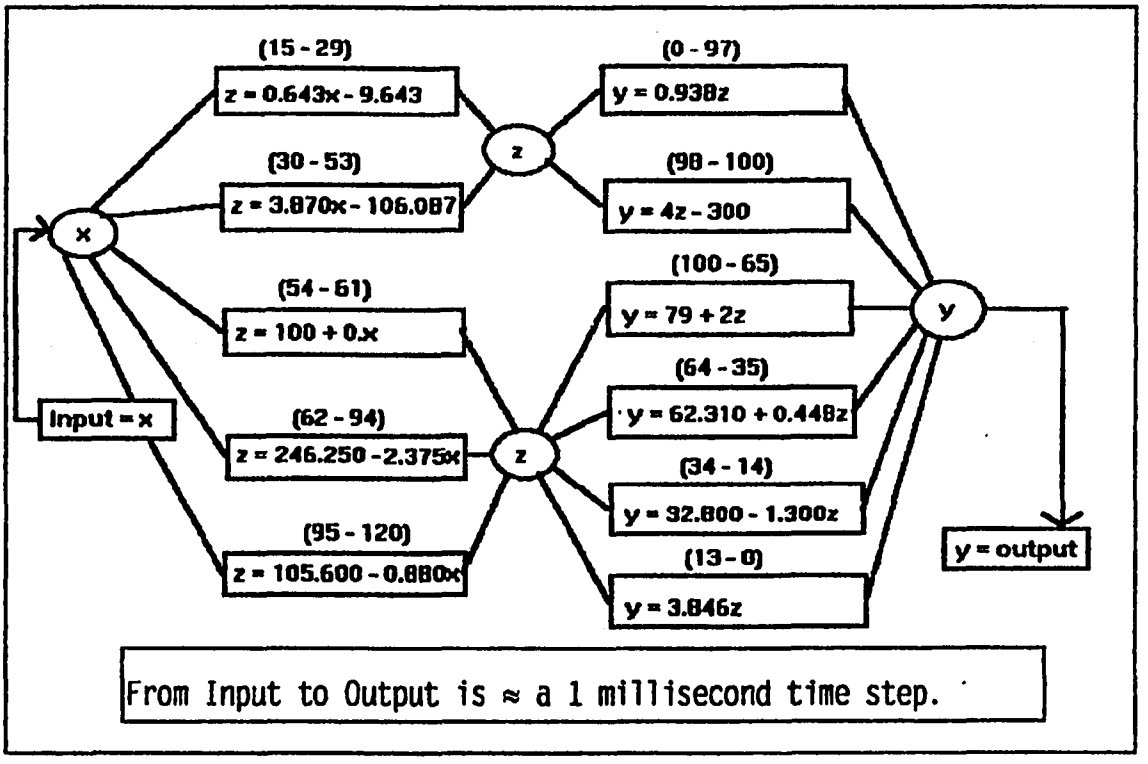


Illustration 3-1 State diagram of the model from Presynaptic Action Potential (input = x) to Postsynaptic Response (output = y). Input would be in millivolts, output would be in percentage from maximum of 100 percent.

- Transmitter release is triggered by an increase in intracellular calcium concentration in the presynaptic terminal, by an inward calcium-ion current.
- The maximum for the steady-state calcium current was found to be near a 60 mV depolarization from the resting state (-70 mV) for the presynaptic terminal.
- The time course of the calcium current is dependent on the transmembrane depolarization at the presynaptic terminal, not on the extracellular calcium concentration (in the model presented in this section, I used results based on a 10mM extracellular concentration).
- The amplitude of the calcium current is dependent on the extracellular calcium concentration.

- The time between the activation of the calcium current, and the postsynaptic response might be approximately 0.2 milliseconds.
- The time course from the peak of a presynaptic action potential to the peak of a postysnaptic action potential is approximately one millisecond, hence, the presynaptic action potential is less than one millisecond. If the presynaptic voltage-clamp pulses are increased (0.4 - 4.7 ms) for the same depolarization amplitude, a steady rate of rise in the postsynaptic potential is observed for pulses > 1.5 ms, and slower rate of rise for amplitudes < 1.5 milliseconds. The extended duration of the presynaptic pulse, and the postsynaptic response, is a good model for the degree of transmitter depletion in the presynaptic terminal. There does not exist an infinite store of transmitter; it is depleted during a prolonged depolarization pulse.

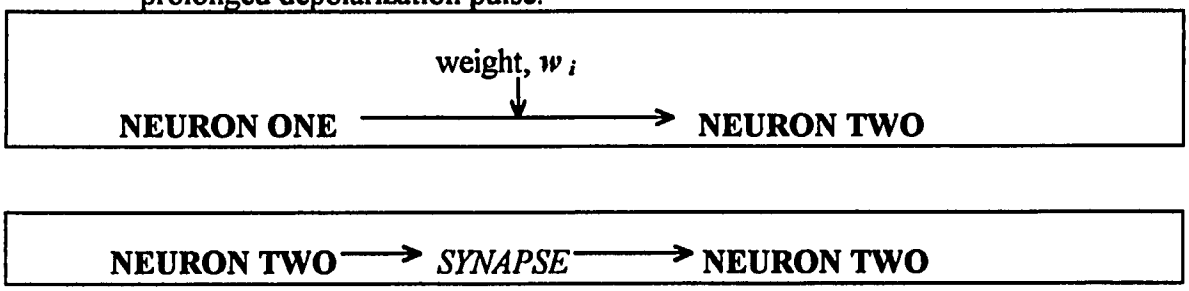


Illustration 3-2 Comparison of model of M-P Neuron to model proposed in this section for the Loligo Pealii. This synapse would be implemented from the linear equations derived from the relationships of the primitives.

As discussed earlier, from the McCullogh/Pitt (1943) abstraction of a neuron **(M-P Neuron),** neuron **one** connects to neuron **two** through an arbitrary weight input: The weight could be *one* to indicate that neuron one is active, or an arbitrary weight assigned by the implementor:

By implementing the **SYNAPSE**, the **M-P** Neuron is biologically more realistic. Consequently, M-P Neuron would not be a generic neuron, but one that could be used to develop a neural network that would be based on the functionality of the giant synapse in the Loligo Pealii. The computation would be a little more complex than a weight, but much less complicated than the kinetic model proposed by Dr. Llinas et al - though not as detailed. Typically, the weight assigned to the connection between neuron one and neuron two may either be static (every impulse from neuron one projects the same weight to neuron two), or dynamic (may be changed dynamically by a training algorithm, or implementor). The **SYNAPSE** will be self-modulating based on the relationship between the primitives, and generate a wider range of responses, dependent on the value of the presynaptic potential.. The research of Dr. Llinas and his colleagues in the three papers used to create the model of the synapse did not consider Facilitation or Postsynaptic Potentiation, which take into account the effect on the synapse of a train of action potentials of different durations, intensities, and the effect on the synapse of prior synaptic activity.

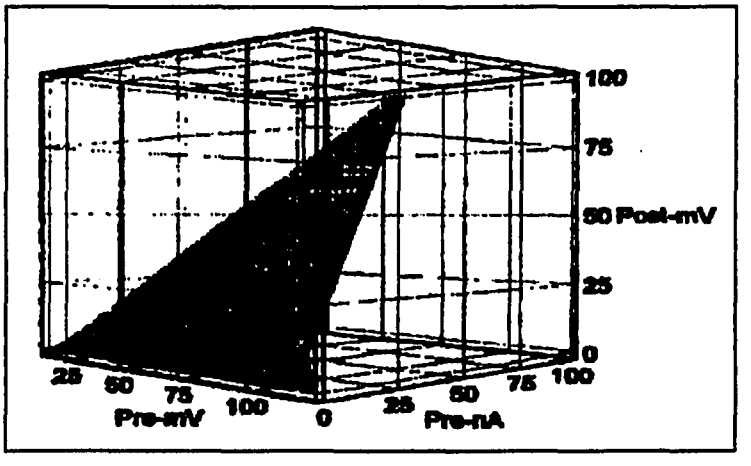


Figure 3.6 Plot of presynaptic potential (Pre-mV) X presynaptic current (Pre-nA) X[postsynaptic response (Post-mV) to give a visual sense of the dynamic of the primitives, and the range of modulation of the synapse.

Model for Intracellular Calcium Concentration in the Presynaptic Terminal of the Giant Synapse in the *Loligo Pealii*

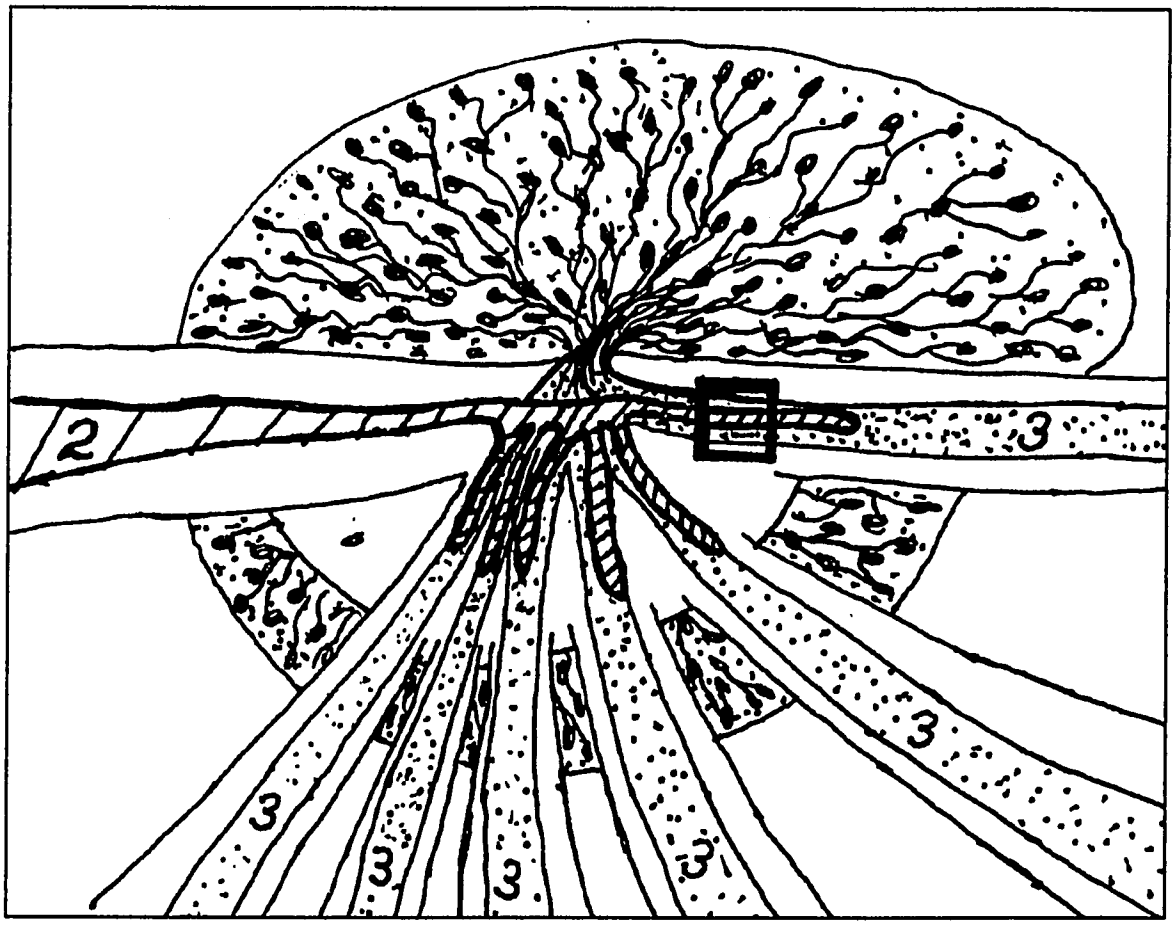


Figure 3.7 This is a drawing of the Stellate Ganglion in the Loligo Pealii. The second-order axon (number 2 with cross-lines drawn through it for identification) branches into a series of fingerlike extensions onto the third-order axon (number 3 with dots throughout), which arises from the fusion of the axons emitted by several hundred neurons in the ganglion. The finger-like extensions of number 2 are the presynaptic terminals. The postsynaptic terminals are formed by number 3. The little rectangle in the upper right hand corner is enlarged in Figure 3. 8 (Llinas, 1982).

In 1985, Sanford Simon and Rodolfo Llinas published an article, *Compartmentalization of the submembrane Calcium Activity during Calcium Influx and its Significance in Transmitter Release*, that addressed the issue of detailed spatial and temporal information of local cytosolic calcium bulk, $[Ca^{2+}]_i$, and its relationship to the

biological or biochemical mechanisms in transmitter release (Simon and Llinas, 1985). Present experimental techniques are not available at present to resolve changes of $[Ca^{2+}]_i$ at submicron and submicrosecond levels, the authors have developed mathematical models to address this issue. They feel that their model of depolarization-release coupling not only gives a quantitative explanation for the role of calcium in transmitter release, but will help clarify the physiological significance of localized [Ca2+]i in other systems:

> **"Our model examines the microscopic distribution of [Ca2+]i during calcium influx and the relationship between changes of $[Ca^{2+}]_i$ and transmitter release. This approach to modeling ionic gradients differs from previous models in two respects: (a) It is formulated in the microscopic domain and examines the calcium concentration within hundreds of Angstroms of the membrane, (b) It is based on the well-documented view that calcium entry occurs through distinct channels that are independently gated as a probabilistic function of voltage."**

Their modeling equations predict (I will quote directly from their paper):

1. The opening of calcium channels results in spatially restricted large peaks of calcium concentration.
2. Steady state concentration of the peaks is achieved very rapidly relative to the open time of the channels.
3. A complex relationship exists between the magnitude of the membrane depolarization and the [Ca2+]i change, the greatest local concentration changes occurring for the smallest depolarizations from the resting potential.

The results obtained from the model predict:

1. Calcium entry is primarily restricted to within the radius of an average synaptic vesicle.
2. The nonlinear properties of transmitter depletion may be explained by the effects of trandmembrane voltage on the distribution of calcium influx.
3. Modeling transmitter release as a nonlinear function of submembrane $[Ca^{2+}]_i$ can result in predictions that are not consistent with experimental findings.

4. Nonlinearities between calcium influx and the rate of transmitter release can be adequately modeled by either (i) the effect of transmembrane voltage on synaptic transmitter depletion or, (ii) by assuming that two or more channels adjacent to a vesicle must be simultaneously open to effectuate vesicular release.

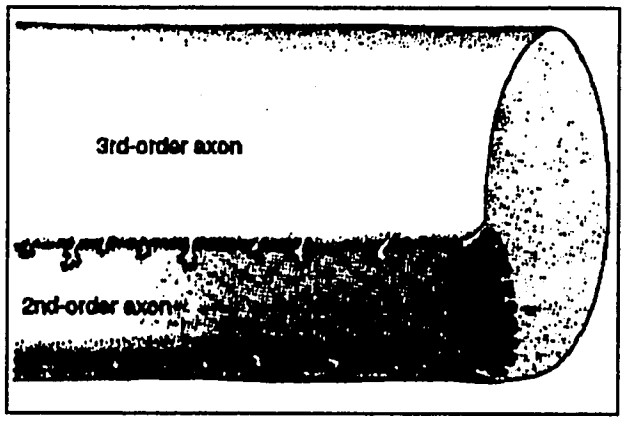


Figure 3.8 The giant synapse is made up of two apposed membranes (2 and 3 from Figure 3.7). The postsynaptic membrane of the third-order axon has some 5,000 spiny extensions, that face the presynaptic membrane (Llinas, 82).

They end their introduction by stating that their model is in good correlation with the physiological consequences of calcium entry at the squid synapse, and when investigating calcium as a mechanism for transmitter release, knowing the precise location of its entry may be as important as its magnitude. They note that their research into the nonlinearities between the total transmembrane calcium fluxes, I_{Ca}, and cytosolic calcium bulk, $[Ca^{2+}]_i$, must be analyzed in the process of synaptic transmission, when the functional role of calcium conductance in all cell types is more than just as an ionic charge carrier.

At the presentation of this article, the density or distribution of calcium channels was not known. But from freeze-fracture replicas of presynaptic membrane approximately 1.5 million membrane-bound particles of larger than average size per terminal were revealed in the active zone of the terminal. These particles are aggregated into one micrometer^2 patches with a 380 Angstrom separation between particles. It has been proposed that these represent the calcium channels. Figure 3.9 illustrates the calcium flux through such an open calcium channel. After the opening of the channel pore, the transient rise of $[Ca^{2+}]_i$ falls close to the steady state $[Ca^{2+}]_i$ in less than one microsecond, and, after

channel closing, the peaks of $[Ca^{2+}]_i$ also disappear in less than one microsecond over the first few hundred angstroms from the channel pore. On the other hand, the submicromolar calcium shifts dissipate only after seconds.

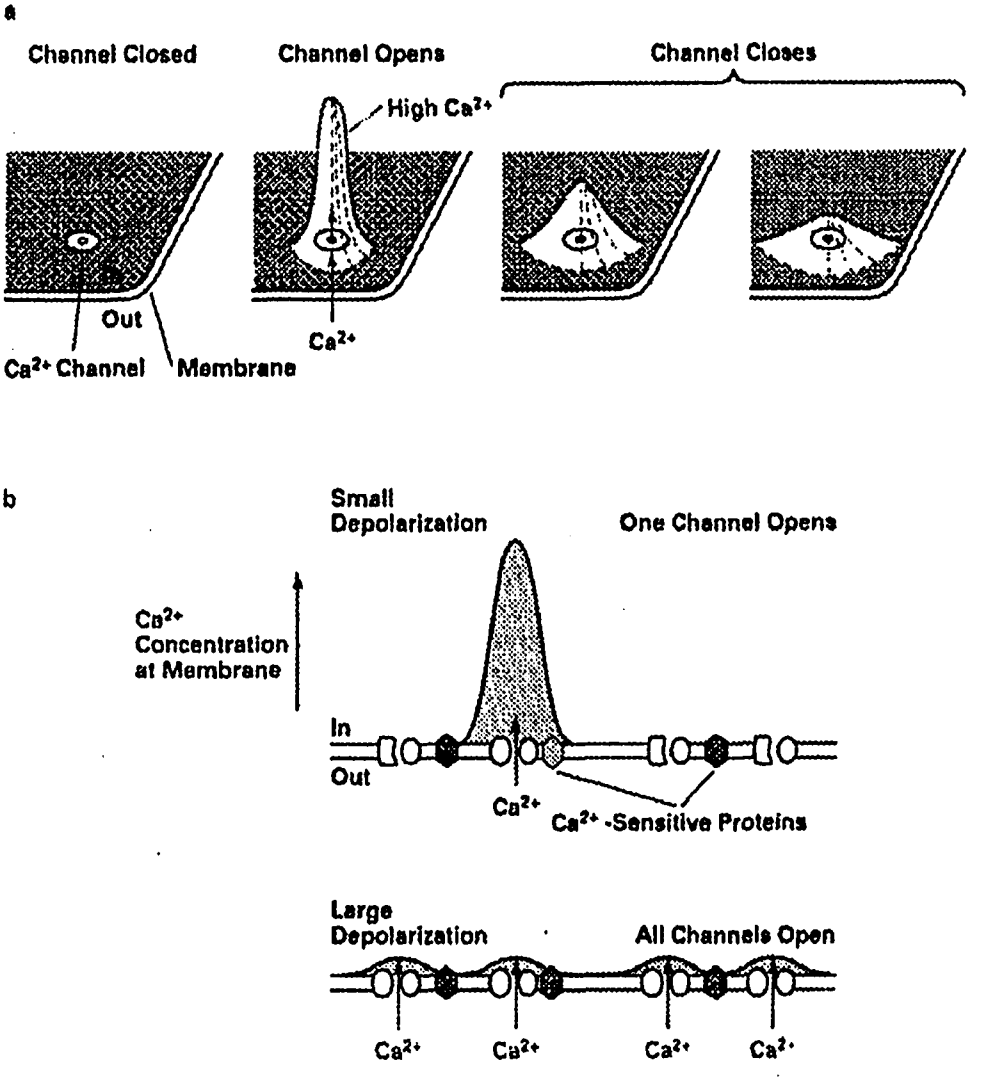


Figure 3.9 High levels of calcium occur at the mouth of calcium channels. a: "Volcanoes" of calcium forming inside a cell near the mouth of an open channel. b: Comparison of the spatial profiles of intracellular calcium expected with small and large depolarization (I. B. Levitan and L. K. Kaczmarek. The Neuron, Oxford University Press, (1991), Page 159.

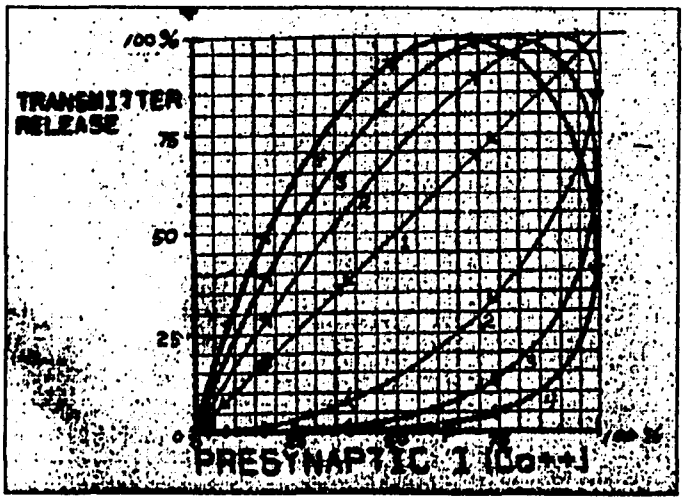


Figure 3.10 Effects of varying stoichiometry of cytosolic calcium ions (one, two, three, and four needed for the release of a transmitter vesicle) for the release of transmitter as a function of I_{ca}. Arrows indicate direction of the plot. (Sanford, 1985)

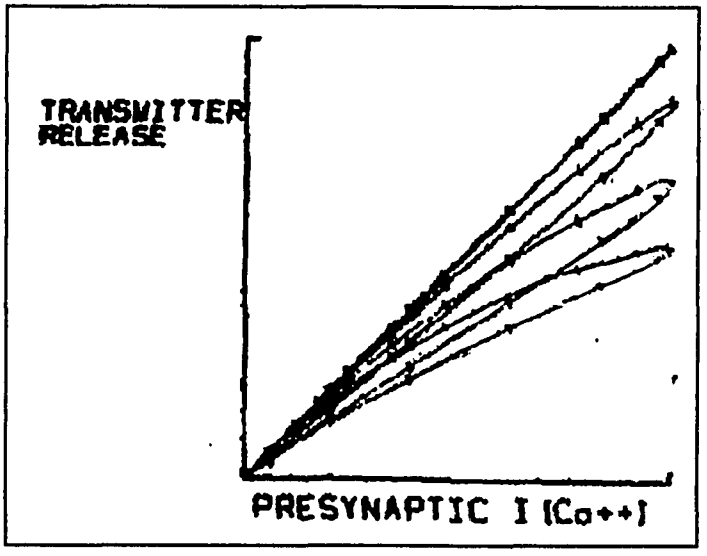


Figure 3.11 The predicted transmitter release is plotted as a function of the presynaptic I_{ca} for different vesicle replacement times. With increasing depolarization. cooperativity between I_{ca} and transmitter release is apparent. (Sanford, 1985)

An important point that is made in this paper is that I_{ca} is determined by *J*, the calcium flux through a single channel, and the number of **open** channels; whereas, $[Ca^{2+}]_i$ in the vacinity of the channel pore is primarily determined by *J*, as illustrated by Figure 3.9. Increasing the depolarization of the presynaptic terminal **increases** the I_{ca} , but **decreases** the $[Ca^{2+}]_i$ under each open channel - as the membrane is depolarized, more calcium channels open, but, also, there is a dramatic **decrease** in the **driving force** for calcium entry. This points to an **inverse** relationship between depolarization and peak local $[Ca^{2+}]_i$. As may be seen from Figure 3.9, the largest influx of calcium per open channel, and resulting local $[Ca^{2+}]_i$ peak, was due to small depolarizations. Very few channels open, the

distance between open channels is quite large, and the changes of $[Ca^{2+}]_i$ are restricted to a few sites. At larger membrane depolarizations more calcium channels open and are distributed over more of the inner membrane surface, but the calcium influx per channel is reduced, as is the resulting local $[Ca^{2+}]_i$ peak., **minimizing** the overlap of calcium entering from adjacent channels.

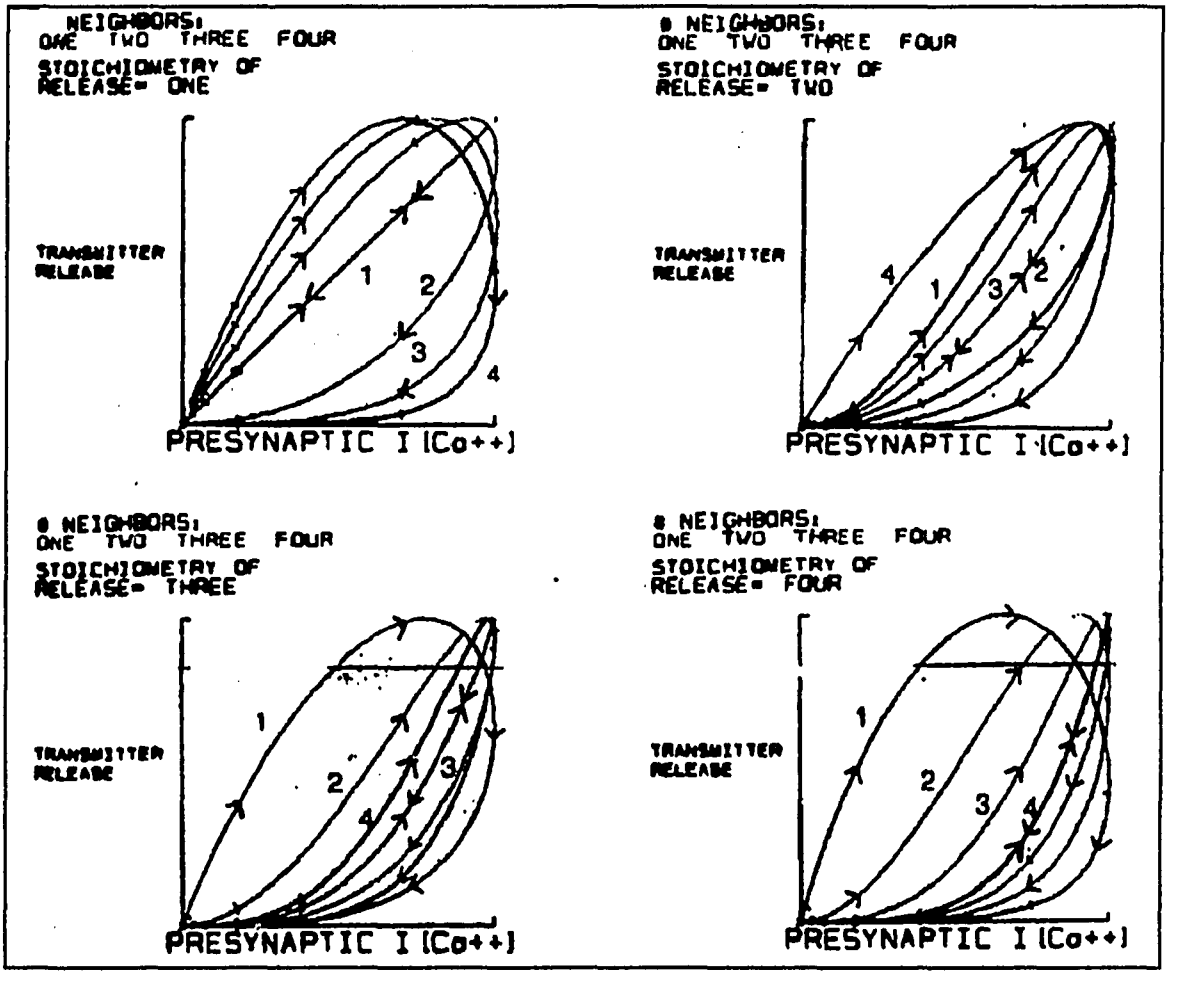


Figure 3.12 The effect on predicted transmitter release assuming that the vesicle must sense the calcium entering from one, two, three, or four channels that are open simultaneously. The release is plotted as a function of the presynaptic I_{Ca} assuming that there is a linear (one), second -(two), third-(three), fourth-(four)-order stoichiometry for calcium in transmitter release. The amplitude of both the transmitter release and the I_{Ca} have been normalized to their largest values. (stanford, 1985)

The results of their model is most consistent with experimental data when a linear relationship is assumed between $[Ca^{2+}]_i$ and the rate of transmitter release. Figure 3.10 illustrates the negative voltage modulation of the relationship between I_{ca} and transmitter release dictated by the inverse relationship between depolarization and local $[Ca^{2+}]_i$. The stoichiometry for $[Ca^{2+}]_i$ in transmitter release is given for one, two, three, and four calcium ions needed for the release of one vesicle. When a stoichiometry of one is assumed, an increase in I_{ca} is accompanied by a linear increase in transmitter release. Figure 3.2 shows that as the presynaptic terminal is depolarized, I_{ca} rises and then falls. Figure 3.10 illustrates that as I_{ca} rises and falls due to depolarization of the presynaptic terminal, transmitter release follows in a linear fashion. This relationship does not reflect the functional effects of vesicular replacement time. There is a local refractory period for transmitter release as a function of the time for replacing a vesicle that has been released. Since vesicles are 300 - 500 Angstrom in diameter, a calcium channel will have only one vesicle within the range of its calcium flux. Once the vesicle in its vicinity is released, further calcium flux will have to wait until another vesicle moves into the vacated position before it can again effect vesicle release. This time period for vesicle replacement could be an important variable in the transmitter release process. Since vesicle replacement times have not as yet been determined, the researchers established a range for replacement time, 10^{-5} to 10^{-1} seconds, that is incorporated into their model. They comment of their results

"The effects of this replacing time are particularly significant during small depolarizations, where Ica flows through few channels. Indeed, if all calcium entry were to occur through one channel, then after the vesicle near that channel was released, further release could not occur, regardless of the increases in $[C^{2+}]_i$, until the vesicle was replaced. On the other hand, if the same magnitude Ica were to enter through many channels, then calcium could have access to many more vesicles and thus greater transmitter release would ensue. For large depolarizations where many more calcium channels are open there are more vesicles available for release and the effects of the local refractory period are less noticeable. Thus, increasing the duration of vesicular replacement results in a voltage modulation of transmitter release." (Sanford, 1985, page 493)

Figure 3.11 shows the effect of varying the vesicle replacement time on transmitter release as a function of I_{ca}. Evidently, varying the replacement time would affect the

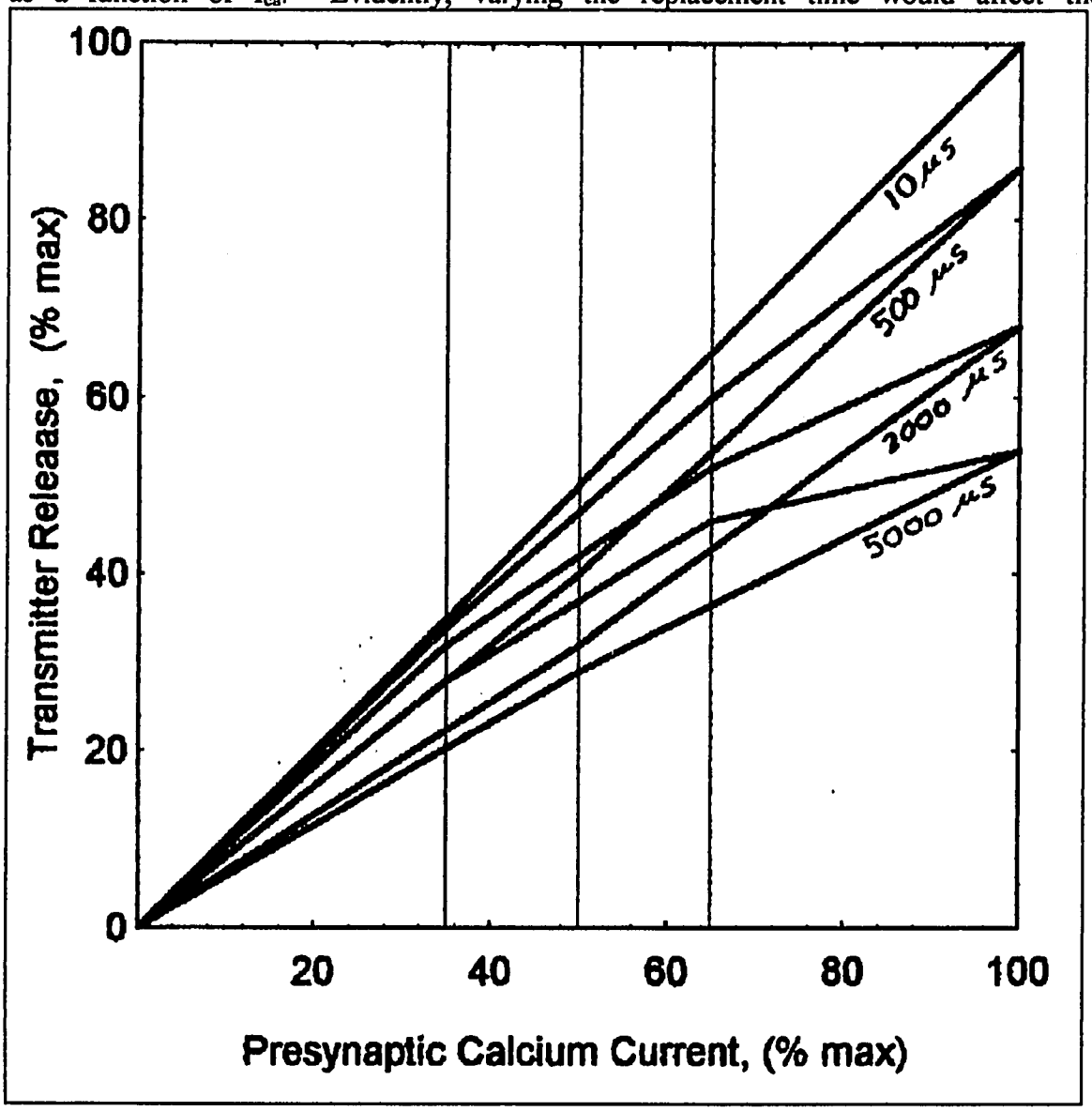


Figure 3.13 Linear representation of the time plots for 10, 500,2000,5000 microsec in Fig. 3.11.

postsynaptic response, and should be accounted for in a model.

Vesicles are larger (500() than the assumed distance between calcium channels (380(), and, therefore, a vesicle could be affected by the calcium influx from more than

one calcium channel (Fig. 3.12). If this is the case, as the membrane is depolarized, the probability that two or more channels open under a given vesicle, and more vesicles are subsequently released **increases**. The ratio of transmitter release to calcium entry **increases** with **increasing** depolarizations, and there is a **positive** voltage modulation between I_{ca} and transmitter release.

In Section One, I stated that the sequence of events to synaptic transmission is:

Action Potential → Calcium Current → Postsynaptic Response.

From the conclusions of this article I revise this sequence to now be:

Action Potential → Calcium Current → Transmitter Release → Postsynaptic Response.

10 microsec	1.0 slope
500 microsec	0.84 slope
2000 microsec	0.64 slope
5000 microsec	0.58 slope

Table 3-4 Slope for each line of increasing I_{ca} from 0 to 50 on x-axis.

The models for all of the above primitives have been given in Section One, except **Transmitter Release**. I will use the data presented in this paper (Sanford, 85) to derive the relationship **transmitter release** to **Calcium Current** and **Postsynaptic Response**.

Figure 3.10 illustrates the predicted transmitter release as a function of I_{ca}. I will accept the researcher's claim that the stoichiometry of $[Ca^{2+}]_i$ in transmitter release is one, and, therefore, will use this in developing this part of my model. Figure 3.11 represents the effect vesicle replacement time will have on the amount of transmitter that will be released by a depolarization of the presynaptic terminal. As mentioned earlier vesicular replenishment plays an important role in the modulation of the synaptic response to depolarization. In order to incorporate the effect of vesicle replacement time into my model, I simplified the plots by giving a linear representation to each tome-plot. Figure 3.13 illustrates this simplification. I could simply have draw a

straight line for each plot from the origin to it's maximum point, but that would have left unaccounted quite a large region. For the increasing I_{ca}, I cut the horizontal plane at 50 on the x-axis to allow for some curvature. For the decreasing I_{ca}, I cut the horizontal plane at 35 and 65 on the x-axis to account for greater concavity of the individual plots. Each plot, except at 10 microseconds, has five linear segments. Table 3.5 gives the coordinates for each plot. From these coordinates, linear equations may be derived, and given the time for vesicle replacement, and the Ica, one may calculate the transmitter release for 10, 500, 2000, and 5000 microseconds.

10 msec	(0,0),(50,50), (100,100)
500 msec	(0,0),(50,20), (100,54),(65,46), (35,28),(0,0)
2000 msec	(0,0),(50,32), (100,68),(65,52), (35,32),(0,0)
5000 msec	(0,0),(50,40), (100,87),(65,60), (35,34),(0,0)

Table 3-5 Linear coordinates for each of the time plots in Figure 3.11.

On the other hand, one could examine the different horizontal segments. I will consider the **increasing** I_{ca} from 0 to 50 on the x-axis. From the coordinates, I was able to calculate a linear equation for each time. Evidently, the slope of each line was different:

From 10 msec to 5000 msec, the slopes for this segment are decreasing. If I could fit an equation that could represent this change in slope, then I may be able to predict the transmitter release for any time period between 10 msec and 5000 msec for **increasing** I_{ca}, in the range from 0 to 50 on the x-axis.

We would then have to calculate an equation for the slopes in each of the remaining four ranges. With the five equations evaluated, the entire range of vesicle replacement

time from 10 to 5000 microseconds, for the entire range of increasing and decreasing Ica would be covered. But if having to calculate an exponential function every time a synapse is depolarized seems computationally expensive, then, I offer another alternative: For the same slopes I used an exponential linear fit which gave me the **Primary** equation: ***0.875441 - 0.0000665623t***. With this equation the time periods 10, 500, 2000, 5000 microsec gave the respective outputs for their slopes: ***0.874775, 0.84216, 0.742316, 0.542629***. These fall short of the respective slopes: ***1.0, 0.8, 0.64, 0.58***. This may be compensated for by calculating an Add-On linear function that would add the necessary increment to bring the slopes to their expected values. I have done this for the range from 10 to 500 microseconds with this proposed linear equation: ***0.0841982 - 0.000335634t***.

Below are the equations that were derived using the least-square fit method to the data obtained from the linearization of the time plots in Figure 3.10. Mathematica is the tool used:

Exponential: $_{E}$ $0.155334 - 0.0849633t^{\frac{1}{4}}$	for Figure 3.14
Linear: $0.875441 - 0.0000665623t$	for Figure 3.15a
Linear: $0.0841982 - 0.000335634t$	for Figure 3.15b

Illus. 3.3 Update of Illustration 3.1; introducing the primitive, Transmitter Release, and time variation for vesicle replacement.

With the introduction of the primitive, Transmitter Release, and the variable of vesicle time replacement, Illustration 3.1 is revised in Illustration 3.3. I Suppose a presynaptic terminal is invaded by an action potential that depolarizes the terminal by 40 millivolts from its resting membrane potential of -70 millivolts, what will be the postsynaptic response? I take this as an example, and follow it through Illustrations 3.1

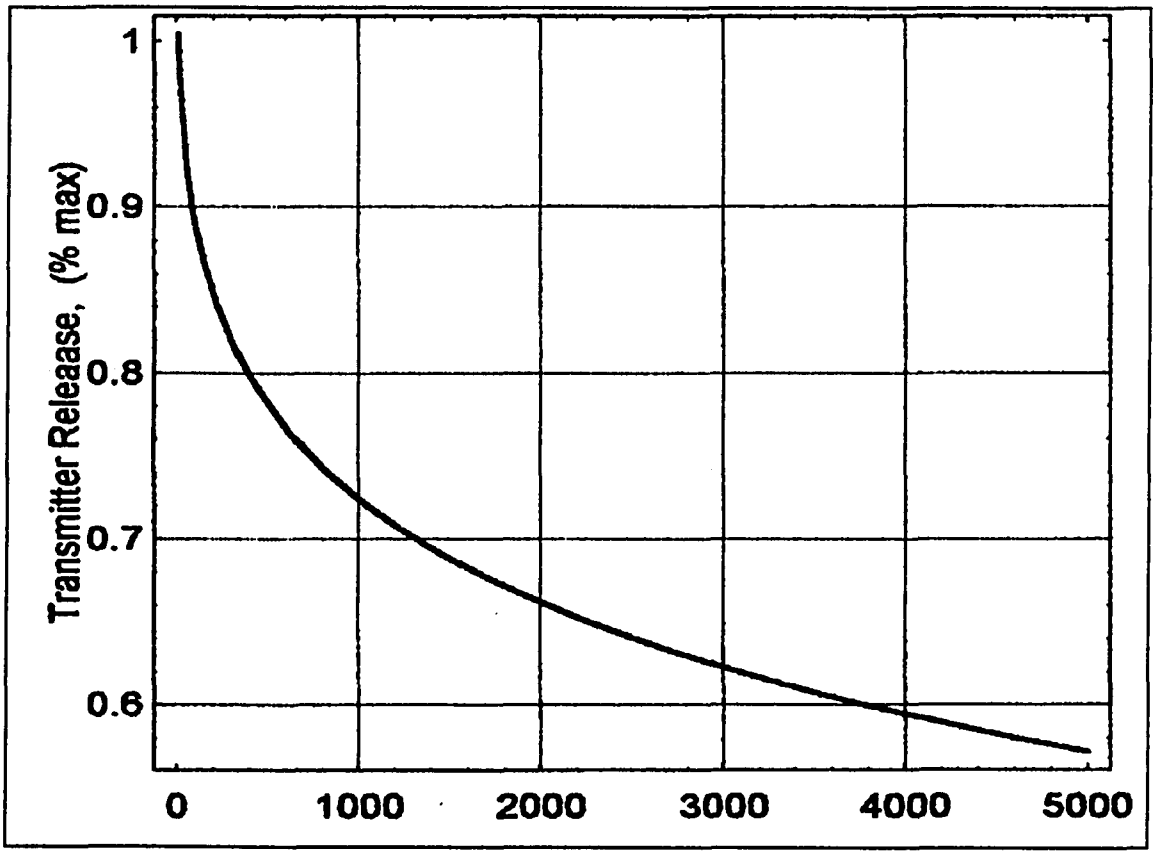


Figure 3.14 Decreasing exponential function that fits the slopes for the increasing calcium current in the range from 0 to 50 on x-axis.

and 3.3. Figure 3.3 graphs the relationship between Presynaptic Voltage Potential, (mV), and Presynaptic Calcium Current (%, max.). x is the value of the depolarization: 40 millivolts, $x = 40$. As x goes through its range from 0 to 120, the Presynaptic Current traverses its range from 0 to 100% of its maximum value, and, then, back to 0% of its maximum value. The Postsynaptic Voltage Response has an increasing Presynaptic Current range, (0 - 53), , and a decreasing Presynaptic Current, (54 - 120). We follow the increasing range, and from Illustration 3.1 use equation $z = 3.870x - 106.087$ for range 30 to 53 millivolts. Evaluating the expression gives $z = 48.713\%$ of the maximum Presynaptic Calcium Current. In Illustration 3.1, with z evaluated, we would now evaluate x. But

with the introduction of the primitive, Transmitter Release, and the implementor chosen variable, t (refractory time for vesicle replacement), *z* now goes to *w*, Transmitter Release.

Time	Primary	Add-On	Total	Exponential
10	0.874775	0.0808418	1.0	1.0
50	0.872113	0.0674164	0.9	0.9
150	0.865457	0.33853	0.9	0.9
300	0.855472	-0.0164922	0.8	0.8
500	0.84216	-0.0836191	0.8	0.8

Table 3-6 Table 3-6 Comparison of the slope value for the Exponential equation representing the plot for 10, 50, 150, 300, and 500 microseconds to the slope attained by adding the Primary + Add-On = Total. The values are very close. The values at 50, 150, and 300 microseconds have been interpolated from the exponential equation. Total and ExpFunc are rounded up to the nearest tenth.

Figure 3.11 is a graph of the plots of the different refractory times for vesicle replacement, and the effect it would have on transmitter release, according to the model of the researchers. Figure 3.13 is a linearization of Figure 3.11. The x-axis has been segmented into five regions: (0 - 50, 51 - 100) for the increasing presynaptic calcium current, and (100 - 66, 65 - 36, 35 - 0) for the decreasing presynaptic calcium current. For each segment the slope for each time plot has been calculated. The slopes have been plotted against their times, and for each segment an equation that represents the change in the slope (where a change in the slope represents a change in the percentage of transmitter released) of the refractory time has been derived using the least-square fit method. Figure 3.14 is a plot of the exponential equation of the rate of transmitter release (%, max.) for the range of 0 to 50 percent. In my example, the presynaptic calcium current, *z*, is at ***48.713*** percent of its possible maximum value. By this point, a value for t would have to have been chosen by the implementor. With the derivation of the

exponential equation, the implementor may choose a time that is anywhere in the range from 10 to 5000 microseconds.

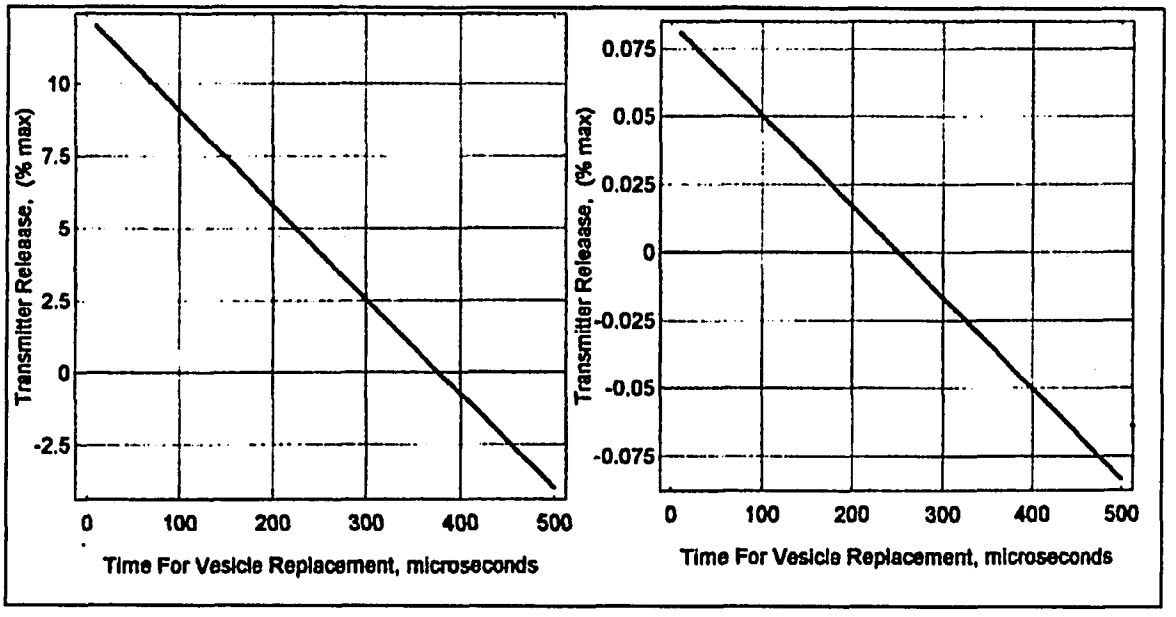


Figure 3.15 Plot of the Primary and Add-On linear equations. Primary is for the INCREASING range for I_{ca} from 10 to 5000 microseconds. Add-On is from 10 to 500 microseconds. An Add-On equation would have to been evaluated from 500 - 2000, and 2000 to 5000 to cover range of Primary equation.

For our example. let us assume that a value of 300 microseconds had been chosen. From Table 3-6, the ExpFunc has a value of 0.8, which means 80% of the maximum of transmitter is released; therefore, w = 80%. If, instead of using the exponential function, we wanted to calculate w using linear functions, then we may use the Primary and Add-On linear equations from Table 3.6. The Primary equation extends the range from 10 - 5000 microseconds, but the Add-On equation has to be derived for ranges (10-500, 500-2000, 2000-5000) microseconds, or three Add-On equations for every Primary equation in each segment.. This would be implemented as a look-up table, and will be fast at execution time. Figure 3.10 shows the different stoichiometry for cytosolic calcium. The researcher believes that the stoiciometry for calcium for release of transmitter is one ion for the

release of a transmitter vesicle. But once the vesicle is released, the refractory period has a modulatory effect on the release process: The calcium channel may be open, and calcium flowing through the channel to the active zone where the vesicles are located, but if a vesicle has not replaced the one that was released, the calcium has no affect on transmitter release. This is another mechanism for synaptic plasticity or modulation. It has to wait until a vesicle comes into place before it may activate its release. In our example z = *48.713%.*

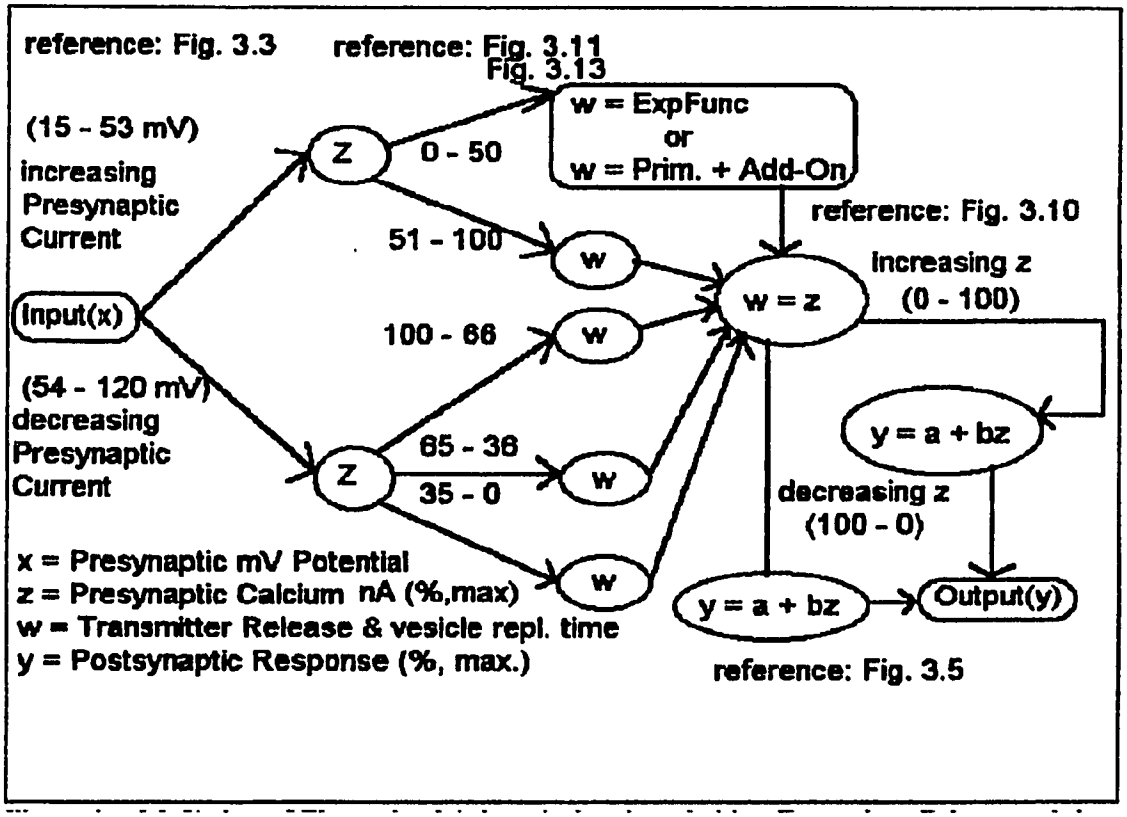


Illustration 3-3 Update of Illustration 3.1. Introducing the primitive, Transmitter Release, and refractory periods for vesicle replacement.

Figure 3.10 shows that for the stoichiometry of **one**, the relationship between Presynaptic Calcium Current and the amount of Transmitter Release is a slope of **one**. With z = *48.713%,* transmitter release would also be *48.713%* of its maximum release

potential. But $w = 80\%$ means that with a refractory period of 300 microseconds, only 80% of z, or wz (38.97% of transmitter would be released): $wz = z'$. Again, we are on the increasing edge of Presynaptic Calcium Current. Illustration 3.1 shows that for the range 0 to 97, ($z = 48.713$ falls in this range), the equation is $y = 0.938z$ or $y = 0.938z'$ in Illustration 3.3. $y = 45.693\%$ **of 100 maximum of a Postsynaptic response**. This example may seem a little complicated, but it is not. The algorithm would be set up as simple look-up ***if ,then, else*** statements, and the equations to solve to get from x to y are:

x to $z \rightarrow a + bz$.

$w \rightarrow e^{c-dx}$ *or* $(a - bt) + (c - dt)$, t chosen by implementor.

$z' \rightarrow wz$

$y \rightarrow a + bz'$

The calculation is simple, and , yet, this model of the synapse offers the primitives responsible for the information processing and transfer at the synapse, and their relationships. The synaptic modulation offered by this model is based on these respective primitives, and their relationships. The model stays close to biological processes, yet is calculated by a set of simple linear equations.

The Presynaptic Calcium Current, Transmitter Release, and Postsynaptic Response were calculated as a percentage of a 100% maximum. Table 3.3 gives a list of peak presynaptic current, and peak postsynaptic response. The implementor may use these individual values or the mean of these values to generate output that reflects the data for different synapse preparations simply by multiplying the value of the Presynaptic Calcium Current by the percentage, z', or the Postsynaptic Response by the percentage, y.

Model for the Schaffer Collateral/CA1 Synapse in Pyramidal cells in the Guinea Pig Hippocampus

Pyramidal cells in the CA3 region of the hippocampus send ***at least one*** axonal branch (***Schaffer Collateral***) into the stratum radiatum of area CA1 (Tamamaki et al., 1984), where they make excitatory synaptic connections with the apical dendrites of CA1 pyramidal cells There are three articles that deal specifically with the single cell-to-cell connection of the CA3-CA1 projection, its structure, and its basic structural and functional elements. From each article I will garner data and conclusions relevant to the model of the CA3-CA1 synapse.

Amplitude Fluctuations in Small EPSPs Recorded from CA1 Pyramidal Cell in the Guinea Pig Hippocampal Slice, (R.J. Sayer, S.J. Redman, P.Andersen, 1989).

Simultaneous intracellular recordings from individual CA3 and CA1 pyramidal cell pairs were made. One hundred and ninety CA3-CA1 pairs were tested in 36 hippocampal slices. Five pairs revealed EPSPs in the CA1 neuron after averaging 100 responses, and are presented in Table 3-7.

Cell Pair Number	**1**	**2**	**3**	**4**	**5**
Number of Records	1280	847	980	800	1127
Mean Amplitude of EPSPs	96	113	275	85	90

Table 3-7 Mean Amplitude of EPSPs Deconvolution results for the 10 EPSPs accepted for fluctuation analysis. Amplitude in microVolts (Sayer et al., 89).

Results from statistical analysis suggest that some CA3-CA1 EPSPs have intrinsic amplitude variations from trial-to-trial, when the CA3 neuron is reliably discharged on

each trial. And this variability is due, in part, to the variations in the number of quanta released on each trial. In order to ascertain fluctuation analysis of EPSPs, with minimization of noise interference from electrode resistance and spontaneous neuronal activity, microstimulation of the stratum radiatum, combined with microsurgery was attempted. These large samples of EPSPs with average peak amplitudes of about the same magnitude as unitary EPSPs were then statistically analyzed, and subjected to deconvolution analysis, in an attempt to determine the size of quantal EPSPs.

Cell no.	Stimulation	Number of Records	Mean Amplitude	Quantal Size
1	prox	1718	170	224
1	dist	1818	164	179
2	prox	1789	322	194
2	dist	2191	294	213
3	prox	2398	395	115
3	dist	2396	203	85
4	prox	3838	94	141
4	dist	4817	131	120
5	prox	1795	282	193
5	dist	2298	227	126

Table 3-8 Deconvolution results for the 10 EPSPs accepted for fluctuation analysis. Mean amplitude and quantal size in microVolts (Sayer et al., 1989).

From the experiments performed for this paper, and the data analyzed, some basic indicators associated with EPSPs generated at synapses formed by the collaterals of a single CA3 pyramidal neuron with a CA1 pyramidal neuron have been realized:

1. Mean Amplitude of EPSP at synapse.
2. Quantal Size, as reflected in EPSP.
3. Release Probability associated with EPSP.

A little Morphology: Extensive collateralization of Schaffer collaterals in the rat hippocampus have been reported (Tamamaki et al., 1984), with as many as eight major collaterals into the CA1 region from one CA3 neuron. The collaterals extended for more than 1.7mm in the transverse plane, and more than 600 micrometers in the longitudinal plane. In order to bring a CA1 neuron to discharge (in vitro 10mV for distal and 14mV for proximal apical dendritic synapses) to initiate an impulse in a CA1 neuron (Anderson et al., 1987), and in Table 3.7 the CA3-CA1 EPSPs ranged from 85 to 275 microvolts.) many Schaffer collaterals must be simultaneously conducting impulses. If linear summation is assumed for the EPSPs (Langomoin and Andersen, 1983), then , for example, cell number one in Table 3.8 at 170 mV (proximal), it would take about 94 proximal synapses to bring the CA1 cell to discharge, and, at 164 mV (distal), it would take about 61 distal synapses to bring the CA1 cell to discharge. The number of boutons on a CA1 cell which may be activated by a **single** impulse from a donor CA3 cell may be two per single axon contact. In CA3 cells, up to five axonal branches have been seen. Hence, in a CA3-CA1 cell contact, anywhere from two to 10 boutons may be activated by a single impulse from a CA3 neuron (Andersen, 1986).

From the deconvolution analysis for the cells in Table 3.9, only two deconvolution results were considered reliable, and the increments between adjacent peak amplitudes represent the quantal EPSP (it is assume by analogy to other systems studied) that results from transmitter release at one release site.

Cell no.	stimulation	Amp./Prob	Amp./Prob .	Amp./Prob .	Amp./Prob .	Amp/Prob.
1	prox	16/0.44	240/0.44	463/0.10		
1	dist	28/0.34	196/0.54	386/0.13		
2	prox	25/0.08	206/0.42	395/0.34	608/0.16	
2	dist	24/0.16	232/0.51	480/0.27	663/0.07	
3	prox	179/0.11	273/0.19	382/0.31	512/0.23	640/0.11
3	dist	46/0.15	142/0.23	171/0.17	259/0.34	386/0.07
4	prox	-4/0.43	131/0.42	277/0.15		
4	dist	-17/0.18	75/0.35	196	0.37	343/0.10
5	prox	5/0.17	184/0.36	381/0.29	585/0.13	
5	dist	22/0.09	100/0.22	206/0.40	356/0.21	526/0.06

Table 3-9 Decovolution Results: discrete amplitudes and probabilities for each EPSP component. Cell no 1 (prox) and Cell no. 5 (prox) have been accepted as reliable by deconvolution analysis. Amplitude in microVolts (Sayer et al., 1989).

In the discussion section of their paper Sayer et al. give interpretations for the data for Cell no. 1 (prox), and Cell no. 5 (prox):

Cell no. 1 (prox):

1. One single axon is reliably excited on all trials:

- of trials, it fails to release transmitter
- of trials, it releases transmitter at 1 release sites..
- of trials, it releases transmitter at 2 release sites.

2. One single axon is activated intermittently, and when excited:

- failure to release.

- release at one site.
- release at two sites

3. Two axons are involved, each with only one release site with CA1 neuron:

- when both excited, transmission occurs at each site at 12% of time.
- failure occurs at one, both, none, and no transmission occurs.
- the 240 microV/0.44% occurs when either (1) both axons are excited but only transmitter release occurs at one of the two release sites, or (2) only one axon is excited.

Cell no.3 (prox) would most likely involve **three** axons with a 193 microV increments between adjacent peaks: **Quantal EPSP**. The researchers suggest that values of 224 and 193 microV represent the upper limits of the quantal size, and that the EPSP generated at each release site will have similar amplitude and time course at the soma.

The Time Course and Amplitude of EPSPs Evoked at Synapses Between Pairs of CA3/CA1 Neurons in the Hippocampal Slice, (Sayer, Friedlander, and Redman, 1990)

In this paper unitary EPSPs were evoked in CAl neurons by the activation of a single CA3 pyramidal neuron. For 71 of the unitary EPSPs, the amplitude ranged from 30μV to 665μV, with an overall mean of l33μV. Whereas, in the previous paper, the EPSPs were estimated by stimulating CA3 axons in the stratum radiatum, and obtaining large samples of EPSPs with average peak amplitudes of about the same magnitude as unitary EPSPs. The material and methods were the same as Sayer (1989). Of 12 EPSPs for which sufficient records were obtained, only one gave reliable deconvolution results, most likely because the quantal value was large, and detectable. Number three in Table 3-10 is the acceptable unitary EPSP:

No.	Quantal step	Amp/Prob	Amp/Prob	Amp/Prob	Amp/Prob	Paper
1	224μV	16/.44	240/.44	463/.12		Sayer, 1989
2	193μV	5/.17	184/.36	382/.29	585/.13	Sayer, 1989
3	278μV	17/.19	267/.38	523/.30	850/.10	Sayer, 1990

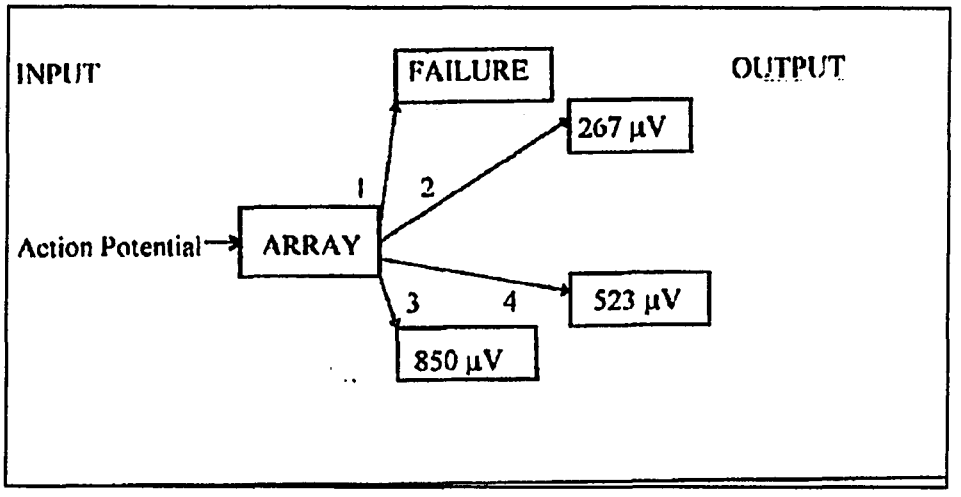
Table 3-10 Quantal increments for three acceptable EPSPs. One and Two obtained by stimulation of the stratum radiatum, and Three by direct stimulation of CA3/CA1 pair. Amplitude in microVolts.

The recordings of the EPSPs were made at the CAl soma. The synaptic current had to spread from the synapse to the soma. It is proposed that the electrical spread from

the synapse to the soma for an EPSP is passive, and that the passive membrane properties of the dendrites are unlikely to determine the amplitude and time course of the unitary EPSPs. The EPSPs produce a shape indices the is used to locate is position relative to the soma: The 10-90% rise time (3.9 ± 1.8 msec) is used to determine proximal synapses, and the half-width time (95 ± 8 msec) used to determine the distal synapses to the soma Again, the values for the EPSPs in this study are from the soma of the CAl neuron. The possibility that the signal is attenuated by the time it reaches the soma is not addressed. In a model study to predict the attenuation of peak synaptic current (Major, 1992; Major et al., 1993) under somatic voltage clamp, constructed a passive electrical model with zero resistance, it was found that the peak current recorded at the soma is about 80% of its value at the synaptic site for the proximal location, and 15% of its value for a mid-oblique location (distal to soma). For my model I make the assumption that the value recorded at the soma is the value for the EPSPs , and do not factor in attenuation

From the two Sayer papers, a simple model may be implemented for an EPSP at the Schaffer collateral/CAl synapse. Entry number three in Table 3-10, as it is the only accepted quantal increment. There are four amplitudes given, each with a corresponding probability. The amplitude of 17 μV would be considered a failure, since it is way below a quantal increment. The other two are approximate multiples of the 274μV quantal increment. The connection between the Schaffer collateral bouton and the CAl dendrite is considered monosynaptic, but the Schaffer collateral may contact the CAl neuron at more than one junction, and, hence, the values of 523μV (two quanta) and 850μV (three quanta). Another possibility is that one Schaffer collateral/CAI synapse has two or three active zones that release, at times, synchronously. To date, the exact morphology is not settled; and, therefore I just implement the data , and leave interpretation open. As an action potential invades the presynaptic terminal, one of four responses will occur with a

given probability. I will implement an array of 100 to signify 100 percent probability. To each probability I will assign a number: 1 to 19%, 2 to 38%, 3 to 30%, and 4 to 10%. I then insert, in a random fashion 19 ones, 38 twos, 30 threes, and 10 fours into the array. Illustration 3.4 on page 39 shows the implementation;



- **Illustration 3-4 Simple model for Schaffer collateral/CA1 synapse**

The model works as follows: The Sayer papers talk of a depolarization of the Schaffer collateral. I assign a value of ONE for depolarization, and ZERO for no depolarization of the presynaptic terminal. If the input is a zero no calculation is made: output is failure. If the input is a one, then the value of the pointer into the array (1,2,3,4), that represents the percentages, is chosen. If Input = 1, then failure; if 2, a 267 μV depolarization; if 3 a 523μV depolarization; if 4 a 850 μV depolarization is the output. Every time an action potential invades the presynaptic terminal, the pointer is updated to point to the next value in the array. When the end of the array is reached, the array counter is set to one, and it starts again; implementing a simple random function for percentages of the outputs. This simple model for the synapse will implement the experimental data from neurophysiological studies, offering the function

of modulation to the incoming action potential. in the neural network But is this enough?

It is mentioned several times that the EPSPs vary. This must reflect in the release behavior at the CA3/CA1 synapse. In a study of male Wistar rats (Andersen et al, 1994), it is found that, **on average**, only slightly more than on branch from a Schaffer collateral bush will be found within the borders of the dendritic tree of a given CA1 target cell The bouton of the Schaffer collateral will contact the spine of the CA I dendrite. From the study, it is concluded that most likely there is **one (or very few)** release sites per afferent fibers

Another possibility for the variability of synaptic currents may be that these synapses have undergone activity-dependent plasticity (Murphy et al. 1994). Murphy's results suggest a model in which each synapse has a characteristic rate of quantal synaptic transmission, and they state that current electrophysiological studies indicate that release probability may vary widely among central synapses innervating a single neuron.

Can this variability be a model for learning and memory? The excitatory synapses onto CA I pyramidal cells (Schaffer collateral/CA1. as an example) have become a model system for understanding the activity-dependent changes in synapses that underlie learning and memory (Lisman and Harris, 1993). Lisman proposes the question, "Do the mechanisms involve structural growth or modulation of existing structures? Is the modification presynaptic, postsynaptic, or both ?" The paper goes on to point out correlations between quantal analysis and synaptic anatomy:

1. have greater efficacy. This points to postsynaptic heterogeneity. and that the spine size is likely to be one of the factors that determines postsynaptic efficacy.

2. Synapses onto the same CAl cell differ in their postsynaptic responsiveness to transmitter
3. The size of the particle aggregates at the CAl PostSynaptic Density (PSD), some of which are likely to be glutamate-gated channels, vary from spine to spine by more than an order of magnitude. Since larger spines have larger synaptic regions, they probably have more synaptic channels. and are therefore likely to While there is enormous variability from synapse to synapse, the size of the postsynaptic structure in any one synapse is closely related to the size of its respective postsynaptic structure The volume of the presynaptic bouton and the total number of vesicles it contains correlate closely with the size of the postsynaptic structures.
4. A specialization called the synaptic grid is seen at the presynaptic active zone. From the grid emerge "dense projections' that may be involved in vesicle docking and release. The lateral dimensions of the presynaptic grid are very close to that of the postsynaptic density and the ends of the two structures are in register This is one indication that there is a coordinated process that governs the growth of pre- and post synaptic structures.
5. Structural changes are involved in plasticity, but, also, processes involving modulation of existing structures.
6. The postsynaptic response to a single action potential involves the linear summation of multiple quanta. At some excitatory synapses, the response to stimulating a single axon is due to multiple synapses, each of which releases a vesicle with a probability less than one. This implies that elicited responses are due to the summation of single-quanta generated at multiple boutons rather than

multiple quanta at a single bouton. In the CA3 area, there is now evidence that a single axonal branch can make multiple synapses with its target pyramidal cells.

7. The postsynaptic density may become segmented into different regions. A single vesicle can release enough transmitter to saturate a postsynaptic receptor locally, but not if the PSD is segmented.

Lisman and Harris make an interesting observation: "An intriguing possibility is that the heterogeneity in size and efficacy are the anatomists' and physiologists' views of the animal's stored memories.

There is recent research that examines the different variables responsible for the variability found in the function and anatomy at synapses using statistical analysis. The following is recent research addressing these issues:

- A study of the analysis of synaptic currents evoked in the CAl pyramidal neuron by minimal stimulation of the stratum radiatum (Stricker et al., 1994),. uses statistic analysis (an Expectation-Maximization algorithm) to interpret results. Their conclusion is that the statistical differences between fits to the data when no quantal separation and no quantal variance are imposed, compared with models where quantal separation, with and without quantal variance. is assumed, are not significant This model requires that EPSPs arising at different active sites to have similar amplitudes at the soma, such that differences in electrotonic locations of these sites with the soma would have to be adjusted to compensate for synaptic location. That the stochastic nature of channel opening must contribute negligible variability to the synaptic current from each site (if channel opening probability is not close to 1.0, and saturating concentrations of glutamate are not present at the receptors in the synaptic cleft), the quantal variance model may not be appropriate when transmission occurs at a small number of active sites distributed to different regions of a dendritic tree (as is possible in the Schaffer

collateral/CAl synapse). When considering release probabilities, they state that recent research for synapses formed between cultured hippocampal neurons has demonstrated a non-uniform release probability. From calculations made from research of quantal current, they state that a measurement of 2. l2±06 p5 as a synaptic current recorded at the soma, may actually be approximately 40 pS as a quantal current

- It has been generally accepted that following an impulse, an active zone releases the contents of only one synaptic vesicle, with probability, p But this leaves some mechanistic questions still unanswered. But what about the possibility of multivesicular release? The question asked in this paper is whether one or several vesicles are released by a given active zone following an impulse, since the amount of transmitter packaged in a vesicle is not known for central synapses (Korn, et al.,' 1994). Results of experiments on the M-Cell dendrite of the Zebra Fish larvae suggests that each terminal can release synchronously as many vesicles as the number of active zones it contains. They conclude by saying that even if synchronocity dominates, it most likely is not the rule, and may even wax and wane. Regardless, it is difficult to predict if impulse-triggered exocytosis events are independent or synchronized. They feel all evidence is in favor of the one-vesicle hypothesis, but confirmation will come when the amount contained in a single quantal packet is known, and with imaging of vesicles during release.
- In a study of the quanta analysis of excitation in a CAl neuron (Jack et al., 1994) a histogram for three peaks showed discrete separations of 280 μV (274 μV in Sayer, I990) They speak of the possibility of quantal variance: Type 1 - occurring at a **single site** from trial-to-trial, and Type II - which represents the

variability in effects produced by **different sites** (on average), at a recording electrode. For a Type I at a CAl excitatory synapse (a given value of $p = 0.67$ open probability of a receptor channel on the postsynaptic density, where 100 channels are opened with an average sized quantum.), the quantal coefficient of variation would be about 6% For a TYPE 11. It is argued that the more common organization for quantal release may be that many single axons supply multiple boutons, some with more than one release site, to a single postsynaptic cell. If there are multiple release sites, which could be more or less electrotonically remote from the recording electrode, it is very likely that quanta evoked at one release site will have an average amplitude different from those at another site because of different degrees of electrotonic attenuation. Furthermore, there is no a priori reason why the number of postsynaptic receptor channels should be exactly the same at two separate release site. Both of these factors contribute to **Type II** quantal variance. From their research they conclude that Type II variance is greater than **Type I** variance. In a study by Jonas et al., (1993), they found that the sum of the two quantal variances was **22%.** It has been found that postsynaptic densities at different release sites **of the same fiber , on the came cell,** differed on average by 35%, whereas the **same fiber** could innervate post synaptic densities on **different postsynaptic** cell that differed on average by 00%. They conclude by stating that:

√ At a single release site, approximately 100 channels open, and all avaiable postsynaptic receptors are occupied by the released transmitter. The major **factor** contributing to variability from trial to trial is the probabilitstic opening of the channels ($p = 0.67$) . The coefficient of variation for the form of quantal variance **(Type 1)** is about **6%.**

√ A single presynaptic fiber can make several synaptic connections with a postsynaptic cell. There exists significant variability in the number of postsynaptic channels at each release site, and this vaiability contributes to Type II quantal variance. Differing degrees of electrotonic attenuation in the propagation of the synapitc event to the recording electrode can also contribute to the total **Type II** variance.

√ **Type II** variance may be greater than **Type I** variance.

√ Spontaneous synaptic events are expected, and is natural in synaptic functioning; and they may be multiquantal

- Their is also the hypothesis that at individual synapses, the quanta released vary widely in size (the number of molecules per packet), (Bekkers and Stevens, 1994), and that the Katz theory (Katz, 1969) for central synaptic transmission, usually in the Poisson limit, provides an accurate description of transmission, but only if the quantal variability is taken into account.
- The differences in active zone structure (different spatial distributions of vesicles) as a reason for the mixtures of quantal versus multiquantal spontaneous release is considered (Bennett , Gibson and Robinson, 1995). Their present model indicates that multiquantal spontaneous release may occur more frequently at varicosities and **boutons,** than at active zones of motor nerve terminals. For their model, they assumed the power relationship between intracellular calcium and transmitter releases has been taken as $n = 4$, not until four calcium ions are bound onto the vesicle will it be released. Their model predicts that about **29%** of the releases are multiquantal for a synaptic bouton. It is not known if these are from single or multiple active zones on a single bouton. That is to be determined. Their present stochastic model tends to give

predictions for higher multiquantal spontaneous release than those recorded (even given the caveat that it is not known whether the recordings are from single active or multiple zones). This may point to the possibility of a **refractory system** within single active zones that restricts the level of multiquantal spontaneous release.

- In a study of the relationship between presynaptic calcium levels and postsynaptic potentials by recording a presynaptic calcium transient from a population of CA3/CA1 synapses ,and the corresponding field EPSP evoked by a single stimulus given to the Schaffer collateral-commissural (SCC) pathway (Wu and Saggau, 1994) during synaptic transmission, to measure paired-pulse facilitation (PPF), and long-term potentiation (LTP), interesting results were found:

√ The relationship between a normalized amplitude of calcium influx (Z) and the presynaptic calcium transient (Y) may be well approximated by $Z = Y$.

√ The relationship between the slope of the field EPSP (X) and the amplitude of the presynaptic calcium transient (X) may be well approximated by the equation $Y=X^n$, where the mean of n is **3~6±O.5.**

√ The slope of the field EPSP is also related to the amplitude of the calcium influx by a similar relationship: $V = Z^m$ where $m = 3.7 \pm 0.4$.

√ In a paired-pulse stimulation, it takes about 300 msec after the first calcium transient for the second calcium transient to recover, and return to the amplitude of the first one, but the fEPSP increased as the interstimulus intervals were shortened and closer to the first calcium transient.

√ After induction of Long-Term Potentiation (LTP), neither the presynaptic calcium transient nor calcium influx was significantly increased. Neither was

there a significant increase in sustained residual calcium, which accumulated between successive depolarizations of the presynaptic terminal. A possibility for LTP maintenance is the concurrent pre-and post synaptic modification as judged by an increase of quantal content and quantal amplitude

√ There is an approximately linear relationship between PPF and residual calcium.

√ Very high levels of calcium concentrations, $[Ca^{2+}]$ (estimated to be > than 100 nM) are formed at the mouths of the calcium channels during and immediately after action potential invade the presynaptic terminal, which produces the process of exocytosis responsible for the release of transmitter into the synaptic cleft. Dissipation of these transients by diffusion and buffering adds a small calcium load to the longer-lasting, spatially uniform $[Ca^{2+}]i$ - termed the **residual free calcium concentration** of the terminal. In the *crayfish* terminal each action potential adds increases the $[Ca^{2+}]$ volume by about I 0 nM, and the removal of this residual calcium concentration is approximately exponential, with a time constant about 6 sec . This is a model for $[Ca^{2+}]$ mediated enhancement, where increased residual calcium produces a large enhancement of action potential-evoked release without causing a continuously high rate of spontaneous release (Zucker, 1989; Hamlya and Zucker, 1994; Delaney and Tank, 1995). In a study on the *crayfish* claw opener neuromuscular junction, it was observed that there exits a close correspondence between $[Ca^{2+}]$ recovery and the duration of synaptic enhancement during the period associated with augmentation. The time enhancement trajectory occurs with a very similar time course: a linear relationship (Delaney and Tank, 1995). A scheme has been proposed (Magleby, 1987) to separate facilatory processed that act **independently** and **multiplicatively** to produce the total accumulated synaptic

enhancement during and after trains of stimuli. In the *crayfish* preparation, the recovery of synaptic enhancement after high-frequency trains, as well as its buildup during trains, is kinetically complex, requiring up to five time constants for a complete description. In the *Crayfish* each action potential increases the $[Ca^{2+}]$ in the volume of the terminal by about 10 nM (1 μM is necessary and sufficient to cause enhanced transmitter release during augmentation), and removal of this residual calcium is approximately exponential with a time constant of 6 seconds. With moderate frequency trains, synaptic enhancement and residual $[Ca^{2+}]i$ normally build up and plateau within 15 seconds. The total synaptic enhancement brought about by the residual calcium buildup is accounted for in the previously suggested model of Magleby (1987): ***Release*** = $R_0\, t(1 + F)\, *(1 + A)\, *(1 + P)$, where R_0 = release in the absence of synaptic enhancement, F = effect of short-term facilitation F_1 and F_2, A= Augmentation, and P = Post Tetanic Potentiation. Because of the moderate and brief trains of stimulation, P is not used in this paper. From their experiments they found that enhancement one to two seconds **after** the onset of the train was approximately $3.5(1 + F)$, suggesting $F = 2.1$. In their modeling, Delaney and Tank used *2.1*. *It* is believed that the slowly changing, low-concentration residual $[Ca^{2+}]$ certainly acts as a second messenger at a site physically distinct from that mediated by fusion, or facilitation to enhance release during augmentation. The model suggests that augmentation increases the **availability of vesicles** for release while facilitation increases the **probability of releasing an available vesicle.** The **total** increased probability of vesicles is then determined by the product of these two independent processes.

- The exocytosis of vesicles from the presynaptic terminal is the chemical messenger across the synaptic cleft that produces the postsynaptic response. In two studies (Stevens and Tsujimoto, 1995; Liu and Tsien, 1991995) evaluation of the readily releasable stores and their replenishment have been realized in hippocampal synapses in culture. Stevens et al. have determined that with sustained stimulation, the initial release rate is about 20 quanta per second per synapse (rate declines exponentially with a time constant of 1.2 seconds, and the replenished with a time constant of about 10 seconds. Liu et al., maintain that there is a vesicular pool capable of generating about 90 EPSPs without recycling, and a recovery rate with a time constant of 40 seconds. which may be used in the model of the Schaffer collateral/CA1 synapse. Though the synapse modeled in Illustration 3.4 replicates the data of Sayer et al., it does not incorporate these variables, that give the synapses a greater degrees of modulation.
- <u>Considerations for the model</u>:

⇒ The data of Sayer et al. is of unitary EPSPs. The quandary is whether there is more than ones synapse involved. It is not known, it may be one active zones at one synapses, mores than one active zone at ones synapse, or more than one synapse. I will make the assumption the a monosynaptic connection may be more than one active zone - either at one synapse or more than one synapse. This means that there may be non-uniform, independent, synchronous, release probabilities

⇒ For **Type I** and **Type II** variation, I will implement **Type I** as a percentage of the calcium channels opening in the presynaptic terminal at the times of an action potential. It is possible that when an action potential invades the postsynaptic

terminal, all the calcium channels do not open and in the area of the vesicle, and if *4* calcium ions are necessary for the release of the vesicle, and only two open, that vesicle might not be released. At the next action potential, all may open, possibly by the influence of residual calcium by way of facilitation, and the vesicles will release. I will make the assumption that 100% of the time, not all calcium channels open for release. For Type II variance, I will assume that from *50%* to *67 %* of the postsynaptic receptors open to bind to the transmitter during an action potential.

⇒ Since spontaneous releases is part of synaptic functionality, the synapse will keep a counter of time. Each time slice will be **one millisecond,** approximately the time from the peak of the invading action potential, to the peak of the postsynaptic response. Every 20 to 30 msec, when their is a lull in presynaptic depolarization, the active zone(s) will releases a vesicle

⇒ Paired-pulse facilitation and augmentation are considered as independent in synaptic enhancement. I will not distinguish them, but have employed the data of Delaney et a!. to derive a simple linear equations to calculate enhancement during a train, and after a train. The result of the equations will be multiplied as a percentage in an enhancement equation in the model. For enhancement during a train of stimulus: $1 + 0.004x$, after a train: $3 + 0.01.4x$. The value for x is calculated from the value of the residual calcium in the presynaptic terminal, in the range from 0 to 1000 nM.

⇒ I will use the model suggested by Liu et al., and Stevens et al. to calculates the available vesicles pool, and its depletion, but will also uses the data generated by Stevens et al. in Liu's formula

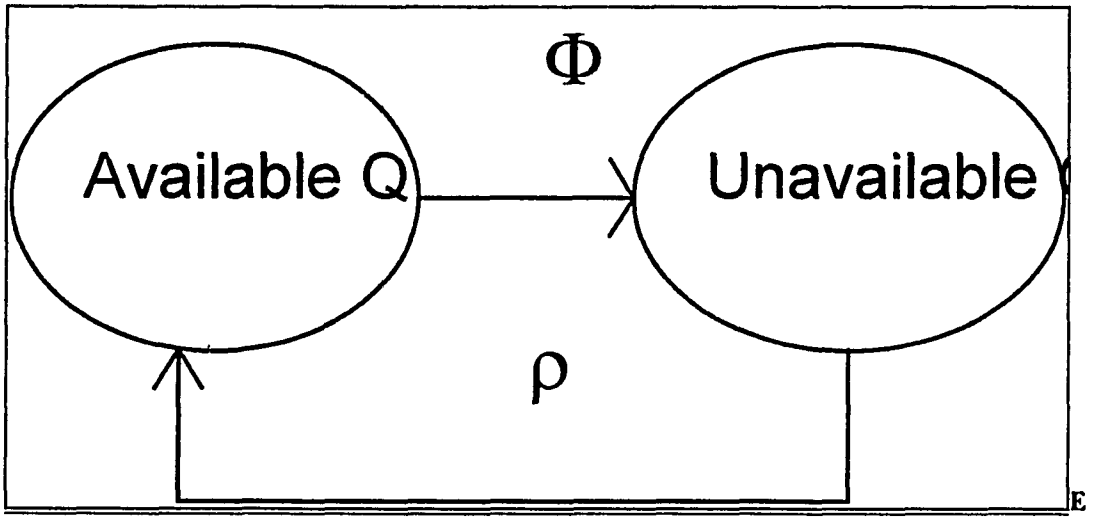


Illustration 3-5 Simple model which generates theoretical curves for recovery and release of vesicular pool (Liu et al., 1995)

- **Variables:**
- Φ: **0.375** per trial - Vesicles docking and other steps up to and including transmitter release. Stevens : **0.72**
- ρ: **0.017** for interstimulus interval - represents endocytosis and repriming. Steven's:; **0.11**
- $V_0 = N_a \Phi$
- N_a: **66** - initial (maximal) value of N after a long period of rest. Stevens: *22*
- N: number of events than may be generated by the available vesicular pool in the absence of endocytotic retrieval.
- $V\infty: N_a \Phi\rho / \Phi + \rho$
- τ_d: $1/(\Phi + \rho)$
-

Formula: $v = (v_{(t)} - v\infty)e^{-t/\tau d} + v_{\infty}$

Illustration 3-6 Kinetics of recovery of responsiveness, following a varying rest interval, t (liu, 1995)

At each time step (one millisecond) Liu's formula will be calculated to assess if there is a vesicle for release. if yes, then **one**; if no, then **zero.** This will be one of the components in the equation used in the model. Liu's *p* is based on one second stimulus, then a one to four second rest period. Stevens' *p* is based on a five second continuous stimulus, in which over 75% of the quanta are released. Stevens releasable vesicles pool ranges from *2-24* releasable quanta, Liu's from *42 -162* releasable quanta. Their is a great sources of variability in the model. A synapse may be implemented within these ranges to have greater modulation and variability amongst presynaptic active zones stimulated by the same axon.

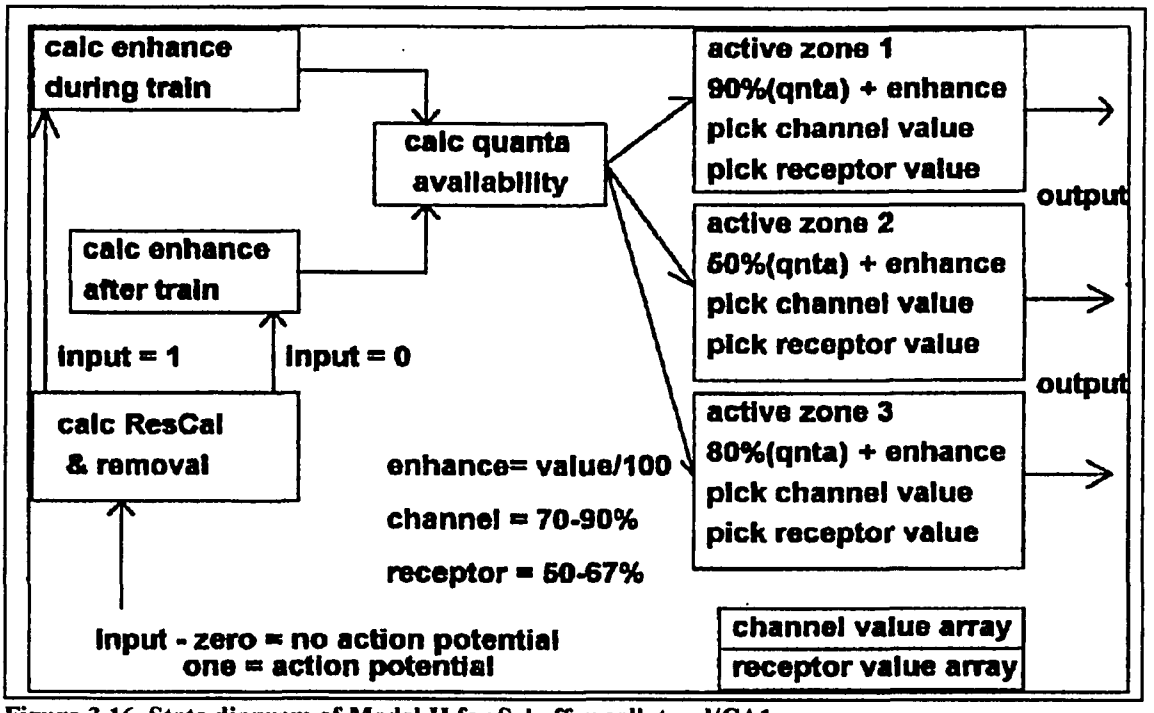


Figure 3.16 State diagram of Model II for Schaffer collateral/CA1 synapse

A guided tour through model II:

1. **Input:** The input to the model will be a simulation of input from a depolarizing CA3 neuron. In the literature reviewed little is said about the amplitude of the depolarizing action potential. What is the measure for the action potential is it's frequency in Hertz. The pyramidal cell fires not only single action potential, but also intrinsic bursts of up to eight spikes at intervals of 5-10 milliseconds. A burst consists of a series of action potentials, riding on a depolarizing wave. It lasts from 30 to 50 milliseconds (Traub, 1992; Schormair, 1993).The depolarization of the presynaptic terminal will be modeled as a **one** for depolarization, and a **zero** for quiescence. The approximate time between the peak of the action potential at the presynaptic terminal, and the peak of the postsynaptic response is about I msec; therefore, since the processing time of the synapse is about 1 msec, that will be the time-slice for the model. two counters, **Yes** and **No**, will be implemented to keep a running count of trains of action potential, and quiescent time. Spontaneous synaptic events (Jack et al., 1994) are part of synaptic functioning. When an input is processed, one is added to a time counter. If the **input** = 1, one is added to the **Yes** counter; if **input** = 0, one is added to the **No** counter. If a certain period has passed without a synaptic discharge (20-50 msec), and the **input** = **0** , then the model will convert the input to 1, **input** = **1,** and set the **No** counter to zero. The model will then behave as if it received an **input** = **1**, and will effect synaptic transmission. When **input** = **1**, one is added to the counter, and then control is passed to **calc ResCal & removal**.

2. **Calc ResCal & removal:** When an action potential invades the presynaptic terminal, the calcium concentration under the calcium channels increases dramatically, and almost just as dramatically, it diffuses into the volume of the terminal. The process of calcium removal, and the time for calcium to return to it's base level of calcium concentration takes time, and is slower than diffusion at the mouth of the channel. Every action potential leaves a little residual calcium. It builds up about 10 nM per action potential to a maximum in about 15 seconds, and plateaus at approximately 1000 nM. As calcium is building up, the process of removal is happening simultaneously, described by an exponentially decreasing function with a time constant of 6 seconds: e^{6t}. If **input = 1**, and residual is less than 1000 nM, then the model adds 10 nM to residual calcium. In the next processing step, the amount of calcium decay for a 1 msec time step is subtracted from the residual calcium. Since the time step of the model is 1 msec, the removal equation is calculated once, when the model is initialized at implementation, and that amount is just subtracted every time step as long as there is residual calcium. This simulate the parallel process of buildup and decay in a simple way: residual calcium is incremented (if appropriate), and decay is subtracted. Once **calc ResCal & removal** is calculated, if **input = 0** , control is given over to **calc enhance after train**; if **input = 1**, then control is turned over to **cal enhance during train.** To keep the running balance of calcium, a variable is set up, **Calcium**. If **input = 1** , and **Calcium < 1000,** then 10 is added to **Calcium.** The value for calcium diffusion is kept in constant, **Diffusion.**
3. **cal enhance during train, calc enhance after train:** Synaptic enhancement is based on residual calcium concentration, and their relationship is linear (Delaney, , 1994; Wu, 1994). The slope of the enhancement (magnitude of enhancement) is different during and after action potential trains. During the train, the equation is: $y = (1 +$

0.004x)/100; after the train the equation is: $y = (3 + 0.014x)/100$. The value of x is the value of the calcium concentration from 1-1000 (1-1000 nM). I divide the equation by 100 to use the result as a percentage. Facilitation most likely enhances the vesicle release process, possibly by enhancing the opening of the calcium channels, and augmentation by increasing the availability of vesicles. I will use the value of y as a percentage of enhancement of the total number of available vesicles for release. if **input = 1,** then **calc enhance during train** is evaluated; if **input = 0,** then **calc enhance after** train is calculated. Once y is evaluated, control is then turned over to **calc quanta availability.**

4. I have presented the models of Stevens and Liu for vesicle availability and depletion. In the model, I would like to use a simpler mechanism, but one that maintains the integrity of the mechanism. I call it supply and demand. I initialize the available releasable vesicular pool to the value of N_a , and initialize a counter, N_a. This establishes the pool size and availability. But the pool is depleted, and there has to be a way of replenishing it. Llinas (1985) states that the exact time required to replace a vesicle once it is released is not known, so he gave a feasible range for the refractory period as 10-5000μsec, based of his experiments. I will use the range from 1 msec to 1000 msec as the time to add a vesicle to the available pool. A counter, **Add Vesicle** will be initialized, and set to zero. At every time slice, one is added to **Add Vesicle** and it's value is checked. If the value equals the value picked by the implementor to add a vesicle, and the pool is less than N_a , one is added to the available vesicular pool, and the counter, **Add Vesicle** , is set to zero. If **input = 1** , (if a vesicle has to be added, it is added), and a vesicle is available for release, control is given over to the active zone to determine if release will occur. If **input = 0** , **Add Vesicle** is checked to see if vesicle is added to available pool. If vesicle is added, **Add Vesicle** is set to

zero, and control is given over to the active zones. This model of vesicular availability and depletion will only require simple addition and subtraction.

5. **(90% + enhance)*(qnta):** The pool of available vesicles is not the same for every synapse (Liu, 1995; Stevens, 1995). I assume that the demand and supply mechanism is the same for the active zones, what is different is the available pool. To differentiate on active zone from another, I assign a percentage of the N_a to each active zone. As an example, I have assigned active zones different percentages: 90%, 50%, and 80%. When it is determined that there are available vesicles from **calc quanta availability** each active zones calculates it percentage of the pool available to itself. It adds the value of its percentage of the available pool plus the percentage of the enhance value, y , and multiplies it by N_a. If the value is greater than one, it has a vesicle it may release, and it continues towards the release process. If the value is less than one, it does not fire. Transmission is failure. Once it is determined that a vesicle is available for release, the active zone determines if the necessary number of channels will open for release, and if enough receptors will open to effectuate the postsynaptic response. Control is not turned over to **pick channel value, pick receptor value.**
6. **pick channel value, pick receptor value:** It is known that during an action potential, not all calcium channels open, nor all receptors open. A value for the receptors at the CA1 neuron is give as $=.67$ (Jack, 1994). I make the assumption that the calcium channels open in the range 70-90 % of the time, and receptors 50-67 % of the time. For transmission to happen, enough calcium channels must open to release a vesicle, and enough receptors to create the postsynaptic response. Their probabilities a multiplicative. To implement the values assigned for channel and receptor availability, I implement two arrays. **Channel array** will be 126 in size. There are 21 values between 70-90. Each one will be represented 6 times in the array. The values are

randomly put into the array. **Receptor array** will be 108 in size, since there are 18 values between 50-67, and each one is put 6 times into the array. When an active zone has a vesicle ready for release, it goes to the arrays, picks out the value pointed to by the arrays, and multiplies then. If the value is less than **0.50** , not enough channels and receptors have opened, and there is no release of the vesicle. Transmission is failure. If the value is equal to, or greater than 50, release is effectuated, and the vesicle sends out it's quanta of 278 μV. The values picked by the active zones from the arrays, **Channel array** , **Receptor array** , as the pointer to the array advances, reaches the end, and starts again. The values available to the active zones will vary, but will be within the acceptable ranges. This offers greater dynamism and modulation to the synapse, with very little computing overhead.

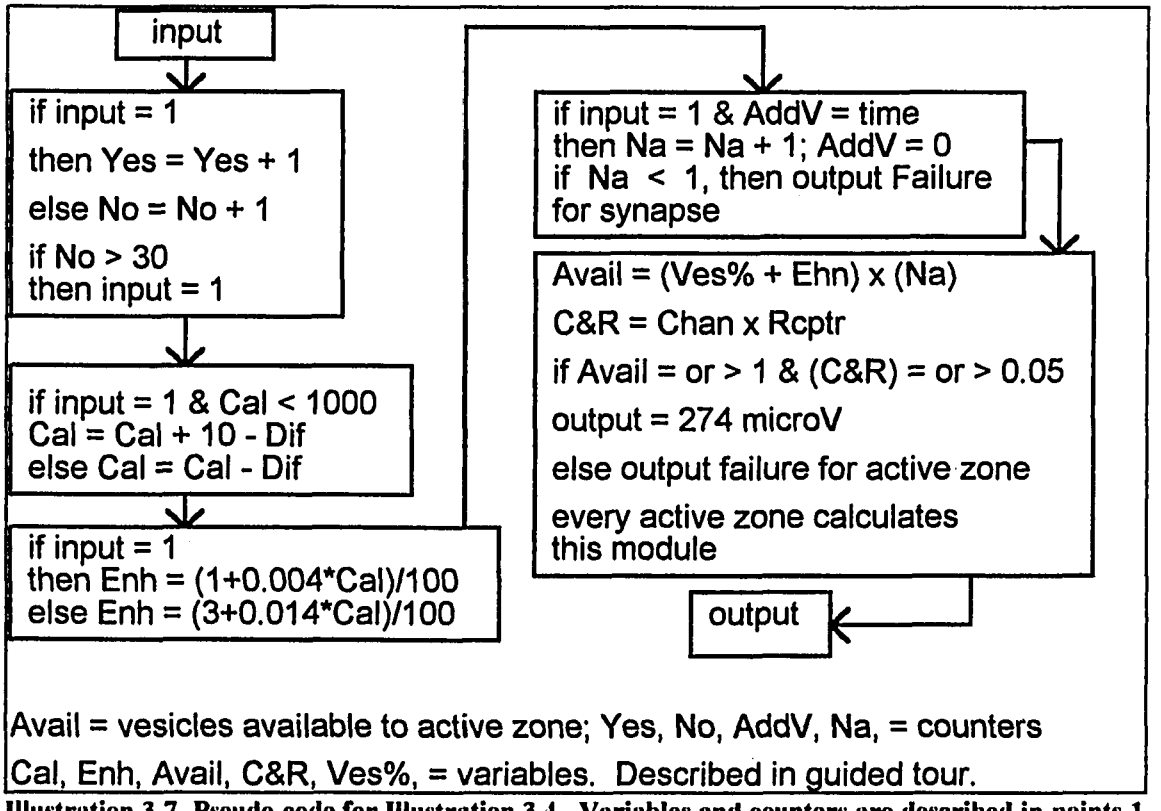


Illustration 3-7 Pseudo-code for Illustration 3.4. Variables and counters are described in points 1 - 6 above in guided tour of model II.

Implementation: Below is an implementation of Illustration 3.7 in Qbasic. I have also included a run of the program for 1000 iterations; each iteration is a 5 msec time step, for a total of 5 seconds. Bursts are 8-10 spikes, and last 30-50 msec, with 5-10 msec intervals. Dividing 10 spikes into 50 msec, gives approximately 1 msec for the spike, and 4 msec until the next spike of the burst; therefore, I chose the 5 msec time step to cover each spike of the burst, and intervals between burst (5-10 msec). Calcium residual, synaptic enhancements, decay of calcium, vesicle depletion and replacement are calculated once every 5 msec. The depletion of the vesicular pool during a train and during no action potential were modeled by linear functions: ***1.05 + .08*Na*** during **no** action potential, and ***0.008*Na*** during action potentials. During an action potential the synapse experiences some synaptic enhancement, and that is modeled by the ENH function, and the equation for vesicular replacement. During implementation and generating runs of the program, it became evident to me that the basic primitives set forth: residual calcium, synaptic enhancement (EHN), percentage of channels and receptors open, depletion and replenishment of vesicles, can all be easily modulated, to structure the behavior of the synapse. With this flexibility, an implementor could use the data, and relationships of these primitives as a template, to structure a synapse that reflects the collected experimental data. I did not do extensive modeling with other data, but with the limited modeling I did, I feel this could be a primitive model of a synapse that may be implemented as. different synapses by adjusting the parameters of ENH, CRI, NA, and vesicle depletion and replenishment.

Synapse Program in Qbasic

This is the initialization of variables, constants, counters, and arrays.

```
1 CAL% = 0      'keeps running total of residual calcium
```

```
2 ENH# = 0      'keeps total of synaptic enhancement
3 CR1# = 0          'percentage of receptors & channels open for active zone one
4 CR2# = 0          'percentage of receptors & channels open for active zone two
5 CR3# = 0          'percentage of receptors & channels open for active zone three
11 AVAIL1# = 0    'available vesicle pool for active zone one
12 AVAIL2# = 0    'available vesicle pool for active zone two
20 AVAIL3# = 0    'available vesicle pool for active zone three
21 SINPUT% = 0      'action potential input
22 TOUTPUT% = 0   'total output for synapse
30 OUTPUT1% = 0   'output from active zone one
40 OUTPUT2% = 0   'output from active zone two
50 OUTPUT3% = 0   'output from active zone three
70 k% = 0           'counter for input to synapse in 5 msec intervals
80 I% = 0           'counter for receptor & channel input from array C & R
90 ADDV% = 0        'counter for when to add a vesicle
100 DIF% = 5        'decay of residual calcium per 5 msec
120 DIM C(100)      'array for percentage of channels open
130 DIM R(100)      'array for percentage of receptors open
```

Arrays are set up with values for probabilities of channel and receptor opening, and the action potential simulation data:

```
140 OPEN "I", #1, "e:\WNMATH22\CHANNEL.DAT"  'insert channel values
150 I = 0
160 FOR I = 0 TO 100
161 IF EOF(1) THEN 190
170 INPUT #1, C(I)
```

```
180 NEXT I
190 OPEN "I", #2, "e:\WNMATH22\RECEPTOR.DAT"  'insert receptor values
200 I = 0
201 FOR I = 0 TO 100
210 IF EOF(1) THEN 230
211 INPUT #2, R(I)
220 NEXT I
230 DIM A(1000)
240 OPEN "I", #3, "E:\WNMATH22\IMPULSE.DAT"  'input data  (1s & 0s)
250 k = 0
251 FOR k = 0 TO 1000
260 IF EOF(1) THEN 290
261 INPUT #3, A(k)
280 NEXT k
290 I = 0   ' REINITIALIZE COUNTER FOR PROGRAM RUN
291 k = 0   ' REINITIALIZE COUNTER FOR PROGRAM RUN
      'OPEN FILE FOR PROGRAM OUTPUT
293 OPEN "C:\DOS\SYNAPSE.OUT" FOR OUTPUT AS #4
294 NA = 24  'INITIAL VALUE OF VESICULAR POOL FOR SYNAPSE
```

The actual program begins here and iterates 1000 times, or 5000 msec = 5 seconds

```
295 FOR k = 0 TO 1000   'PROGRAM STARTS HERE, RUN FOR 1000 TIME
STEPS.  EVERY STEP = 5 MILLISECONDS
296 SINPUT = A(k)
      CALCULATE RESIDUAL CALCIUM DURING ACTION POTENTIAL = 1
AND  QUIESCENCE = 0
```

```
310 IF SINPUT = 1 AND CAL < 1000 THEN CAL = CAL + 10 - DIF ELSE CAL =
CAL - DIF 'CALCULATE RESIDUAL CALCIUM)
320 IF SINPUT = 1 THEN ENH = (1 + (.004 * CAL)) / 100 ELSE ENH = (3 + (.014 *
CAL)) / 100
 'CALCULATE SYNAPTIC ENHANCEMENT WHEN SINPUT = 1, SINPUT = 0
325 IF SINPUT = 0 THEN NA = NA + (1.05 + .08 * NA)
326 IF SINPUT = 1 THEN NA = NA + (.0008 * NA)
      'SET VESICLE TO ZERO IF VESICLE LESS THAN ONE
330 IF NA < 1 THEN NA = 0
'PERCENTAGE OF VESICULAR POOL AVAILABLE  TO EACH ACTIVE
ZONE
 340 AVAIL1 = NA
345 AVAIL2 = .9 * NA
350 AVAIL3 = .8 * NA
'REINITIALIZE COUNTERS FOR RECEPTOR & CHANNEL ARRAY
      355 IF I = 99 THEN I = 0
      MULTIPLY PROBABILITY OF CHANNELS OPEN * RECEPTORS OPEN +
VALUE OF ENHANCEMENT FOR EACH ACTIVE ZONE
365 CR1 = ENH + 1.5 * ((C(I) * R(I)))
370 I = I + 1
380 CR2 = ENH + 1.5 * ((C(I) * R(I)))
385 I = I + 1
395 CR3 = ENH + 1.3 * ((C(I) * R(I)))
400 I = I + 1
IF NA = 0 THEN THERE ARE NO AVAILABLE VESICLES IN POOL
```

```
419 IF NA = 0 THEN AVAIL1 = AVAIL2 = AVAIL3 = 0
IF TOTAL OF AVAIL *CR1 THEN VESICLE IS NOT RELEASED FOR EACH
ACTIVE ZONE
425 IF AVAIL1 >= 1 AND CR1 >= .5 THEN OUTPUT1 = 1 ELSE OUTPUT1 = 0
430 IF AVAIL2 >= 1 AND CR2 >= .5 THEN OUTPUT2 = 1 ELSE OUTPUT2 = 0
435 IF AVAIL3 >= 1 AND CR3 >= .5 THEN OUTPUT3 = 1 ELSE OUTPUT3 = 0
IF INPUT IS 1, AND THERE IS AN AVAILABLE VESICLE, AND THE TOTAL
OUTPUT IS GREATER THAN ONE, THEN A VESICLE WILL BE RELEASED AND
IT IS SUBTRACTED FROM THE SYNAPTIC POOL
436 IF (((OUTPUT1 + OUTPUT2 + OUTPUT3) >= 1) AND (SINPUT= 1)) AND (NA
>= 1) THEN NA = NA - 1
IF INPUT =0, AND TOTAL OUTPUT < 1, THEN ALL ACTIVE ZONES FAIL TO
FIRE.  TOTAL OUTPUT = 0
437 IF SINPUT = 0 THEN TOUTPUT = 0 ELSE TOUTPUT = (OUTPUT1 +
OUTPUT2 + OUTPUT3)
PRINT OUT TABLES OF OUTPUT:  TIME, SYNAPTIC VESICULAR POOL,
INPUT, TOTAL OUTPUT FOR ALL THREE ACTIVE ZONES
PRINT #4, K; NA;  SINPUT; TOUTPUT
451 NEXT k
453 END
```

Below are the tables for 1000 iterations of the program. The first column is for the time steps, where one time step equals 5 msec. Column two is the running count of the synaptic available vesicular pool. Each active zone has a percentage of this pool. This distributes a range in available vesicle pools, more in keeping with research. Notice how the pool is depleted, and replenishes; cycling between both points. This accounts for the

fatigue, or refractory period seen at the synapse. Columns **I** and **O** are for input and total output for all three active zones. I wanted to show the number of vesicles that are released by each action potential, so instead of an output in mV, the output is in the number of vesicles per synapse.. For 1000 iterations, and when **INPUT = 1** , there were 316 Failures, 424 ones, 215 twos, and 46 threes. By manipulating the functions for the variables, these values may be changed, giving the implementor the ability to develop a neural network with synapses that are structurally the same, but, by choosing the parameters, synapses that are different in their response to input - yet within the range of experimental data. This gives more realism to the network.

The next step would be to implement Long-Term Potentiation for this synapse from data from experimental data. Once implemented, the synapse would then serve as a template for the modeling of the other synaptic connections in the hippocampus. Below are the basic connections :

- EPSP from dentate granules cell to CA3 cell (mossy fiber)
- Recurrent EPSP from CA3 pyramidal cell to CA3 pyramidal cell
- EPSP from pyramidal cell to inhibitory cell (CA1 and CA3)
- IPSP from CA1 inhibitory cell (stratum pyramidal) to CA1 pyramidal cell
- IPSP from CA1 inhibitory cell (stratum lacunoscum/moleculare) to CA1 pyramidal cell
- IPSP from CA3 inhibitory cell (stratum pyramidale) to CA3 pyramidal cell
- Electrotonic interactions between CA3 cell and between dentate cells

Points of information on run:

When the run begins, the synapse vesicular pool starts out with 24 vesicles available to the synapse (23.0192 + 1 released as output). Each active zone has a percentage of the pool available to more closely model real synapses. I could have implemented a vesicular pool for each active zone, but that would have meant more code; whereas, by assigning a

percentage of the available pool to each active zone, what happens to the synaptic pool happens to the virtual available pool. The mechanisms of depletion and replenishment would be the same if implemented as one synaptic pool, each active zone with it's virtual pool, or three separate active pools. In this implementation, active pool one has the same amount as the synaptic pool, active zone two has 90% of the synaptic pool, and active zone three has 80% of the synaptic pool. What could happen during a run is that the synaptic pool could be down to one, and active zone one would be able to release a vesicle, but active zones two and three would be depleted. In this case, total output could only be one. This is what happens at time-step 75. There is what might be happening at time-step 76 (I say "might be" because the output might be due to unavailable vesicle, ***or*** not enough channels and receptors were open to effect release at one of the active zones). The available vesicles are .21796 + 1 released. For active zone three with 80% of synaptic pool, at time-step 76, it would have less than a vesicle, and could not release: total output = 2.

There could be an input of one, vesicles available for release, and yet there is failure of release. Time-step 120 shows this possibility. Though there is a total of 2.186696 vesicles available for release, and the input is one, there is failure of release low numbers of open channels and receptors.

There is also the situation where the synaptic pool is exhausted, and there is a burst. The total output then is failure. This is an absolute refractory period. Time has to be given until the active zones can replenish their stores. This may be seen in many parts of the run when bursts fatigue the synapse.

When there is an input of one, not all active zones release every time. Every active zone calculates for itself the probability of channel opening and receptor opening. Since these are independent events, their probabilities are multiplied. If they are less that 0.5, the

active zone will not release: failure. By manipulating this variable, you may have more stringent or more lenient regulation for vesicular release. With the present values for the variables, this run gave 316 failures, 424 ones, 215 twos, and 46 threes out of 1000 inputs.With the manipulation of the variables, these could be adjusted by the implementor to fit experimental data.

Tables for 1000 iterations of synpase model

T = timestep, QNTA = available vesicle pool at synapse, I = input, O = output

T	QNTA	I	O
0	23.0192	1	1
1	22.03761	1	1
2	21.05524	1	2
3	20.07209	1	2
4	19.08815	1	2
5	18.10342	1	1
6	18.1179	1	0
7	17.13239	1	2
8	16.1461	1	1
9	15.15902	1	1
10	14.17114	1	2
11	16.35483	0	0
12	18.71322	0	0
13	17.72819	1	1
14	20.19645	0	0

15	22.86216	0	0
16	21.88045	1	2
17	20.89796	1	3
18	19.91467	1	1
19	18.93061	1	2
20	17.94575	1	2
21	17.96011	1	0
22	16.97448	1	3
23	15.98806	1	2
24	18.3171	0	0
25	20.83247	0	0
26	19.84913	1	1
27	18.86501	1	2
28	17.88011	1	2
29	16.89441	1	2
30	15.90792	1	1
31	14.92065	1	1

32	13.93259	1	2
33	12.94373	1	1
34	15.02923	0	0
35	17.28157	0	0
36	16.2954	1	2
37	15.30843	1	2
38	14.32068	1	1
39	14.33214	1	0
40	13.3436	1	2
41	12.35428	1	1
42	11.36416	1	1
43	10.37325	1	2
44	9.381552	1	2
45	8.389057	1	2
46	10.11018	0	0
47	11.969	0	0
48	10.97857	1	2

49	9.987353	1	2
50	8.995343	1	3
51	8.00254	1	1
52	7.008942	1	2
53	6.014549	1	2
54	6.019361	1	0
55	5.024176	1	3
56	4.028195	1	2
57	3.031418	1	1
58	2.033843	1	3
59	1.03547	1	1
60	1.036298	1	0
61	1.037127	1	0
62	2.170098	0	0
63	3.393705	0	0
64	4.715202	0	0
65	6.142418	0	0
66	5.147332	1	1
67	6.609118	0	0
68	8.187847	0	0
69	7.194397	1	2
70	6.200152	1	2
71	5.205112	1	1
72	4.209277	1	1
73	3.212644	1	2

74	2.215214	1	1
75	1.216986	1	1
76	.21796	1	2
77	1.285397	0	0
78	2.438228	0	0
79	3.683287	0	0
80	2.686233	1	2
81	3.951132	0	0
82	2.954293	1	2
83	1.956656	1	3
84	.9582216	1	1
85	0	1	0
86	0	1	0
87	0	1	0
88	0	1	0
89	0	1	0
90	0	1	0
91	0	1	0
92	0	1	0
93	0	1	0
94	0	1	0
95	1.05	0	0
96	2.184	0	0
97	3.40872	0	0
98	2.411447	1	2

99	1.413376	1	1
100	.4145068	1	1
101	0	1	0
102	0	1	0
103	0	1	0
104	0	1	0
105	0	1	0
106	0	1	0
107	1.05	0	0
108	2.184	0	0
109	1.185747	1	3
110	.1866957	1	1
111	0	1	0
112	0	1	0
113	0	1	0
114	0	1	0
115	0	1	0
116	0	1	0
117	1.05	0	0
118	2.184	0	0
119	1.185747	1	2
120	1.186696	1	0
121	.1876451	1	2
122	0	1	0
123	0	1	0

124	0	1	0
125	0	1	0
126	0	1	0
127	0	1	0
128	1.05	0	0
129	2.184	0	0
130	1.185747	1	1
131	.1866957	1	2
132	0	1	0
133	0	1	0
134	0	1	0
135	0	1	0
136	0	1	0
137	0	1	0
138	1.05	0	0
139	2.184	0	0
140	3.40872	0	0
141	2.411447	1	1
142	1.413376	1	3
143	.4145068	1	2
144	0	1	0
145	0	1	0
146	0	1	0
147	0	1	0
148	0	1	0

149	1.05	0	0
150	2.184	0	0
151	1.185747	1	2
152	.1866957	1	1
153	0	1	0
154	0	1	0
155	0	1	0
156	0	1	0
157	0	1	0
158	0	1	0
159	0	1	0
160	1.05	0	0
161	2.184	0	0
162	3.40872	0	0
163	4.731418	0	0
164	6.159931	0	0
165	7.702725	0	0
166	6.708888	1	2
167	8.295599	0	0
168	10.00925	0	0
169	9.017254	1	2
170	8.024467	1	1
171	7.030887	1	1
172	6.036511	1	2
173	5.041341	1	1

174	4.045374	1	1
175	3.04861	1	3
176	2.051049	1	2
177	1.05269	1	2
178	1.053532	1	0
179	5.43E-02	1	1
180	0	1	0
181	0	1	0
182	0	1	0
183	0	1	0
184	0	1	0
185	0	1	0
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187	0	1	0
188	1.05	0	0
189	2.184	0	0
190	3.40872	0	0
191	4.731418	0	0
192	6.159931	0	0
193	7.702725	0	0
194	9.368943	0	0
195	11.16846	0	0
196	13.11194	0	0
197	12.12243	1	2
198	11.13212	1	2

199	10.14103	1	2
200	9.149141	1	2
201	8.156461	1	2
202	7.162986	1	2
203	6.168716	1	1
204	5.173651	1	1
205	6.637543	0	0
206	8.218546	0	0
207	7.225121	1	1
208	8.85313	0	0
209	10.61138	0	0
210	9.619869	1	2
211	8.627565	1	1
212	10.36777	0	0
213	12.24719	0	0
214	11.25699	1	2
215	10.266	1	3
216	9.274208	1	1
217	8.281628	1	2
218	7.288253	1	2
219	7.294084	1	0
220	6.299919	1	3
221	5.304959	1	2
222	6.779356	0	0
223	8.371704	0	0

224	7.378402	1	2
225	6.384305	1	2
226	5.389412	1	2
227	4.393723	1	2
228	3.397238	1	2
229	2.399956	1	1
230	1.401876	1	2
231	.4029975	1	2
232	1.485237	0	0
233	2.654056	0	0
234	1.656179	1	2
235	.6575043	1	2
236	0	1	0
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238	0	1	0
239	0	1	0
240	0	1	0
241	0	1	0
242	0	1	0
243	0	1	0
244	1.05	0	0
245	2.184	0	0
246	3.40872	0	0
247	2.411447	1	2
248	3.654363	0	0

249	4.996712	0	0
250	4.000709	1	2
251	3.00391	1	2
252	3.006313	1	0
253	4.296818	0	0
254	3.300255	1	2
255	2.302896	1	1
256	1.304738	1	3
257	.3057816	1	2
258	0	1	0
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262	.0508399	1	1
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269	0	1	0
270	1.05	0	0
271	2.184	0	0
272	1.185747	1	1
273	.1866957	1	1

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276	0	1	0
277	0	1	0
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279	0	1	0
280	1.05	0	0
281	2.184	0	0
282	3.40872	0	0
283	4.731418	0	0
284	6.159931	0	0
285	6.164859	1	0
286	7.708048	0	0
287	9.374692	0	0
288	11.17467	0	0
289	10.18361	1	3
290	9.191754	1	2
291	8.199108	1	2
292	7.205667	1	2
293	6.211432	1	2
294	5.216401	1	2
295	4.220574	1	1
296	3.223951	1	2
297	4.531867	0	0
298	5.944417	0	0

299	4.949172	1	2
300	6.395106	0	0
301	7.956714	0	0
302	6.963079	1	1
303	5.96865	1	1
304	4.973425	1	2
305	3.977404	1	1
306	2.980586	1	1
307	1.98297	1	3
308	.9845563	1	2
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310	1.05	0	0
311	.0508399	1	1
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313	0	1	0
314	0	1	0
315	0	1	0
316	0	1	0
317	0	1	0
318	0	1	0
319	1.05	0	0
320	2.184	0	0
321	1.185747	1	1
322	2.330607	0	0
323	3.567055	0	0

324	2.569909	1	2
325	1.571965	1	2
326	.5732225	1	2
327	0	1	0
328	0	1	0
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330	0	1	0
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332	0	1	0
333	0	1	0
334	1.05	0	0
335	2.184	0	0
336	1.185747	1	1
337	.1866957	1	1
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344	1.05	0	0
345	2.184	0	0
346	1.185747	1	2
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357	2.184	0	0
358	1.185747	1	2
359	.1866957	1	2
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364	0	1	0
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366	1.05	0	0
367	.0508399	1	1
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369	2.243299	0	0
370	1.245094	1	2
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372	3.636277	0	0
373	2.639186	1	3

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375	5.262347	0	0
376	4.266557	1	1
377	3.26997	1	2
378	2.272586	1	2
379	1.274404	1	2
380	.2754235	1	3
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383	0	1	0
384	1.05	0	0
385	2.184	0	0
386	1.185747	1	2
387	.1866957	1	1
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389	0	1	0
390	0	1	0
391	0	1	0
392	0	1	0
393	1.05	0	0
394	.0508399	1	1
395	1.104907	0	0
396	2.243299	0	0
397	3.472763	0	0
398	4.800584	0	0

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400	2.807468	1	2
401	1.809714	1	1
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405	0	1	0
406	0	1	0
407	0	1	0
408	1.05	0	0
409	1.05084	1	0
410	5.16E-02	1	1
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413	0	1	0
414	0	1	0
415	0	1	0
416	0	1	0
417	1.05	0	0
418	.0508399	1	1
419	1.104907	0	0
420	1.105791	1	0
421	.1066756	1	1
422	1.16521	0	0
423	.1661419	1	1

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429	0	1	0
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431	0	1	0
432	0	1	0
433	1.05	0	0
434	1.05084	1	0
435	1.051681	1	0
436	1.052522	1	0
437	1.053364	1	0
438	1.054207	1	0
439	5.50E-02	1	1
440	0	1	0
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442	0	1	0
443	0	1	0
444	1.05	0	0
445	.0508399	1	1
446	1.104907	0	0
447	2.243299	0	0
448	3.472763	0	0

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451	5.239619	1	3
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453	8.295491	0	0
454	7 .302128	1	3
455	8 .936298	0	0
456	10.7012	0	0
457	9.709764	1	2
458	11.53654	0	0
459	10.54577	1	2
460	12.43944	0	0
461	14.48459	0	0
462	13.49618	1	2
463	12.50698	1	2
464	11.51698	1	2
465	10.52619	1	2
466	9.534616	1	2
467	8.542243	1	1
468	7.549077	1	1
469	6.555116	1	2
470	5.56036	1	1
471	4.564809	1	1
472	5.979993	0	0
473	4.984777	1	2

474	3.988765	1	2
475	2.991956	1	1
476	1.99435	1	2
477	.9959452	1	2
478	0	1	0
479	1.05	0	0
480	1.05084	1	0
481	5.16E-02	1	1
482	0	1	0
483	0	1	0
484	1.05	0	0
485	2.184	0	0
486	3.40872	0	0
487	2.411447	1	3
488	3.654363	0	0
489	4.996712	0	0
490	4.000709	1	2
491	5.370766	0	0
492	6.850427	0	0
493	5.855907	1	1
494	7.37438	0	0
495	6.380279	1	2
496	7.940701	0	0
497	9.625957	0	0
498	11.44603	0	0

499	13.41172	0	0
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501	17.82743	0	0
502	20.30362	0	0
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505	21.01389	1	3
506	20.0307	1	2
507	19.04673	1	2
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510	16.09007	1	2
511	15.10295	1	2
512	14.11503	1	3
513	13.12632	1	1
514	12.13682	1	2
515	14.15777	0	0
516	16.34039	0	0
517	15.3535	1	3
518	17.63174	0	0
519	20.09228	0	0
520	19.10835	1	3
521	18.12364	1	2
522	17.13814	1	2
523	16.15185	1	2
524	15.16477	1	2
525	14.1769	1	2
526	13.18824	1	1
527	12.19879	1	2
528	14.2247	0	0
529	16.41267	0	0
530	15.4258	1	2
531	14.43814	1	2
532	13.44969	1	2
533	12.46045	1	1
534	11.47042	1	1
535	10.4796	1	2
536	9.487982	1	1
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538	7.502369	1	3
539	6.508371	1	2
540	5.513577	1	2
541	4.517988	1	1
542	5.929427	0	0
543	7.453781	0	0
544	9.100083	0	0
545	10.87809	0	0
546	9.886792	1	1
547	11.72774	0	0
548	13.71595	0	0
549	13.72693	1	0
550	12.73791	1	3
551	11.7481	1	2
552	10.7575	1	1
553	9.766103	1	3
554	8.773915	1	2
555	7.780934	1	2
556	6.787159	1	2
557	8.380132	0	0
558	10.10054	0	0
559	11.95859	0	0
560	10.96815	1	2
561	12.89561	0	0
562	11.90592	1	2
563	10.91545	1	2
564	9.924179	1	2
565	8.932118	1	2
566	7.939264	1	1
567	6.945616	1	1
568	5.951172	1	2
569	4.955933	1	1
570	3.959898	1	1
571	2.963066	1	3
572	1.965436	1	2
573	.9670086	1	2

574	0	1	0
575	1.05	0	0
576	2.184	0	0
577	3.40872	0	0
578	2.411447	1	3
579	1.413376	1	1
580	.4145068	1	2
581	0	1	0
582	0	1	0
583	0	1	0
584	0	1	0
585	0	1	0
586	0	1	0
587	1.05	0	0
588	2.184	0	0
589	1.185747	1	2
590	.1866957	1	2
591	0	1	0
592	1.05	0	0
593	.0508399	1	1
594	0	1	0
595	0	1	0
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597	0	1	0
598	1.05	0	0

599	2.184	0	0
600	1.185747	1	1
601	.1866957	1	1
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607	0	1	0
608	0	1	0
609	1.05	0	0
610	2.184	0	0
611	1.185747	1	3
612	.1866957	1	1
613	0	1	0
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615	0	1	0
616	0	1	0
617	0	1	0
618	0	1	0
619	1.05	0	0
620	2.184	0	0
621	1.185747	1	2
622	.1866957	1	1
623	0	1	0

624	0	1	0
625	0	1	0
626	0	1	0
627	0	1	0
628	0	1	0
629	1.05	0	0
630	2.184	0	0
631	1.185747	1	2
632	.1866957	1	1
633	0	1	0
634	0	1	0
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636	0	1	0
637	0	1	0
638	0	1	0
639	0	1	0
640	1.05	0	0
641	2.184	0	0
642	3.40872	0	0
643	4.731418	0	0
644	6.159931	0	0
645	7.702725	0	0
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654	4.045374	1	2
655	3.04861	1	2
656	2.051049	1	2
657	1.05269	1	2
658	5.9E-02	1	1
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665	0	1	0
666	0	1	0
667	0	1	0
668	1.05	0	0
669	2.184	0	0
670	3.40872	0	0
671	4.731418	0	0
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674	9.368943	0	0
675	11.16846	0	0
676	13.11194	0	0
677	12.12243	1	3
678	11.13212	1	1
679	10.14103	1	2
680	9.149141	1	2
681	9.156461	1	0
682	8.163786	1	3
683	7.170317	1	2
684	6.176053	1	1
685	7.720137	0	0
686	9.387748	0	0
687	8.395258	1	2
688	10.11688	0	0
689	11.97623	0	0
690	10.98581	1	2
691	9.994598	1	1
692	11.84417	0	0
693	13.8417	0	0
694	12.85277	1	2
695	11.86305	1	2
696	10.87254	1	2
697	9.881243	1	2
698	8.889148	1	1

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701	5.908099	1	1
702	7.430747	0	0
703	9.075206	0	0
704	8.082466	1	2
705	9.779063	0	0
706	8.786886	1	1
707	7.793916	1	2
708	6.800151	1	2
709	5.805591	1	2
710	4.810236	1	3
711	3.814084	1	1
712	2.817135	1	2
713	4.092505	0	0
714	5.469906	0	0
715	4.474282	1	3
716	3.477861	1	2
717	2.480644	1	1
718	1.482628	1	3
719	.4838145	1	2
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722	0	1	0
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725	1.05	0	0
726	2.184	0	0
727	3.40872	0	0
728	2.411447	1	2
729	3.654363	0	0
730	4.996712	0	0
731	4.000709	1	1
732	3.00391	1	1
733	2.006313	1	2
734	1.007918	1	1
735	1.008724	1	0
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740	0	1	0
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742	.0508399	1	1
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751	2.184	0	0
752	1.185747	1	2
753	.1866957	1	1
754	0	1	0
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757	0	1	0
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759	0	1	0
760	1.05	0	0
761	2.184	0	0
762	3.40872	0	0
763	4.731418	0	0
764	6.159931	0	0
765	5.564859	1	1
766	6.628048	0	0
767	8.208292	0	0
768	9.914955	0	0
769	8.922887	1	3
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771	6.936369	1	2
772	5.941918	1	1
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775	2.953789	1	2
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786	1.247463	1	2
787	.248461	1	1
788	0	1	0
789	0	1	0
790	1.05	0	0
791	.0508399	1	1
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797	0	1	0
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800	2.184	0	0
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803	3.567055	0	0
804	2.569909	1	2
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819	.2526326	1	2
820	0	1	0
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825	1.05	0	0
826	2.184	0	0
827	1.185747	1	2
828	.1866957	1	1
829	0	1	0
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833	0	1	0
834	0	1	0
835	0	1	0
836	0	1	0
837	1.05	0	0
838	2.184	0	0
839	1.185747	1	2
840	.1866957	1	1
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847	0	1	0
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853	2.569909	1	2
854	3.825502	0	0
855	5.181542	0	0
856	4.185687	1	1
857	3.189035	1	2
858	2.191587	1	2
859	1.19334	1	2
860	.1942947	1	2
861	0	1	0
862	0	1	0
863	0	1	0
864	1.05	0	0
865	2.184	0	0
866	1.185747	1	1
867	.1866957	1	1
868	0	1	0
869	0	1	0
870	0	1	0
871	0	1	0
872	0	1	0
873	1.05	0	0

874	.0508399	1	1
875	1.104907	0	0
876	2.243299	0	0
877	3.472763	0	0
878	4.800584	0	0
879	4.804425	1	0
880	3.808268	1	3
881	2.811315	1	2
882	1.813564	1	1
883	.8150145	1	3
884	0	1	0
885	0	1	0
886	0	1	0
887	0	1	0
888	1.05	0	0
889	.0508399	1	1
890	0	1	0
891	0	1	0
892	0	1	0
893	0	1	0
894	0	1	0
895	0	1	0
896	0	1	0
897	1.05	0	0
898	1.05084	1	0

899	2.184907	0	0
900	1.186655	1	1
901	.1876042	1	2
902	1.252612	0	0
903	.2536145	1	2
904	0	1	0
905	0	1	0
906	0	1	0
907	0	1	0
908	0	1	0
909	0	1	0
910	0	1	0
911	0	1	0
912	0	1	0
913	1.05	0	0
914	1.05084	1	0
915	1.051681	1	0
916	5.25E-02	1	1
917	0	1	0
918	0	1	0
919	0	1	0
920	0	1	0
921	0	1	0
922	0	1	0
923	0	1	0

924	1.05	0	0
925	.0508399	1	1
926	1.104907	0	0
927	2.243299	0	0
928	3.472763	0	0
929	4.800584	0	0
930	6.234631	0	0
931	7.783401	0	0
932	6.789628	1	1
933	8.382798	0	0
934	10.10342	0	0
935	9.111505	1	2
936	10.89042	0	0
937	12.81166	0	0
938	11.82191	1	2
939	13.81766	0	0
940	12.82871	1	2
941	14.90501	0	0
942	17.14741	0	0
943	16.16113	1	2
944	15.17406	1	2
945	15.1862	1	0
946	14.19835	1	3
947	13.2097	1	2
948	12.22027	1	1

949	11.23005	1	3
950	10.23903	1	2
951	9.247222	1	2
952	8.25462	1	2
953	9.964989	0	0
954	8.97296	1	2
955	7.980139	1	1
956	6.986523	1	2
957	5.992112	1	2
958	4.996905	1	2
959	4.000903	1	2
960	3.004103	1	2
961	2.006506	1	2
962	1.008112	1	1
963	1.008918	1	0
964	2.139632	0	0
965	3.360802	0	0
966	4.679666	0	0

967	3.68341	1	3
968	5.028082	0	0
969	6.480329	0	0
970	5.485513	1	1
971	6.974354	0	0
972	8.582302	0	0
973	7.589168	1	2
974	9.246301	0	0
975	8.253697	1	1
976	9.963993	0	0
977	11.81111	0	0
978	13.806	0	0
979	15.96048	0	0
980	18.28732	0	0
981	20.8003	0	0
982	23.51433	0	0
983	26.44547	0	0
984	25.46663	1	2

985	24.487	1	2
986	23.50659	1	2
987	22.5254	1	2
988	21.54342	1	1
989	20.56065	1	2
990	19.5771	1	2
991	18.59276	1	2
992	17.60764	1	2
993	16.62172	1	2
994	19.00146	0	0
995	21.57158	0	0
996	20.58883	1	1
997	19.60531	1	2
998	18.62099	1	1
999	17.63589	1	1
1000	16.65	1	3

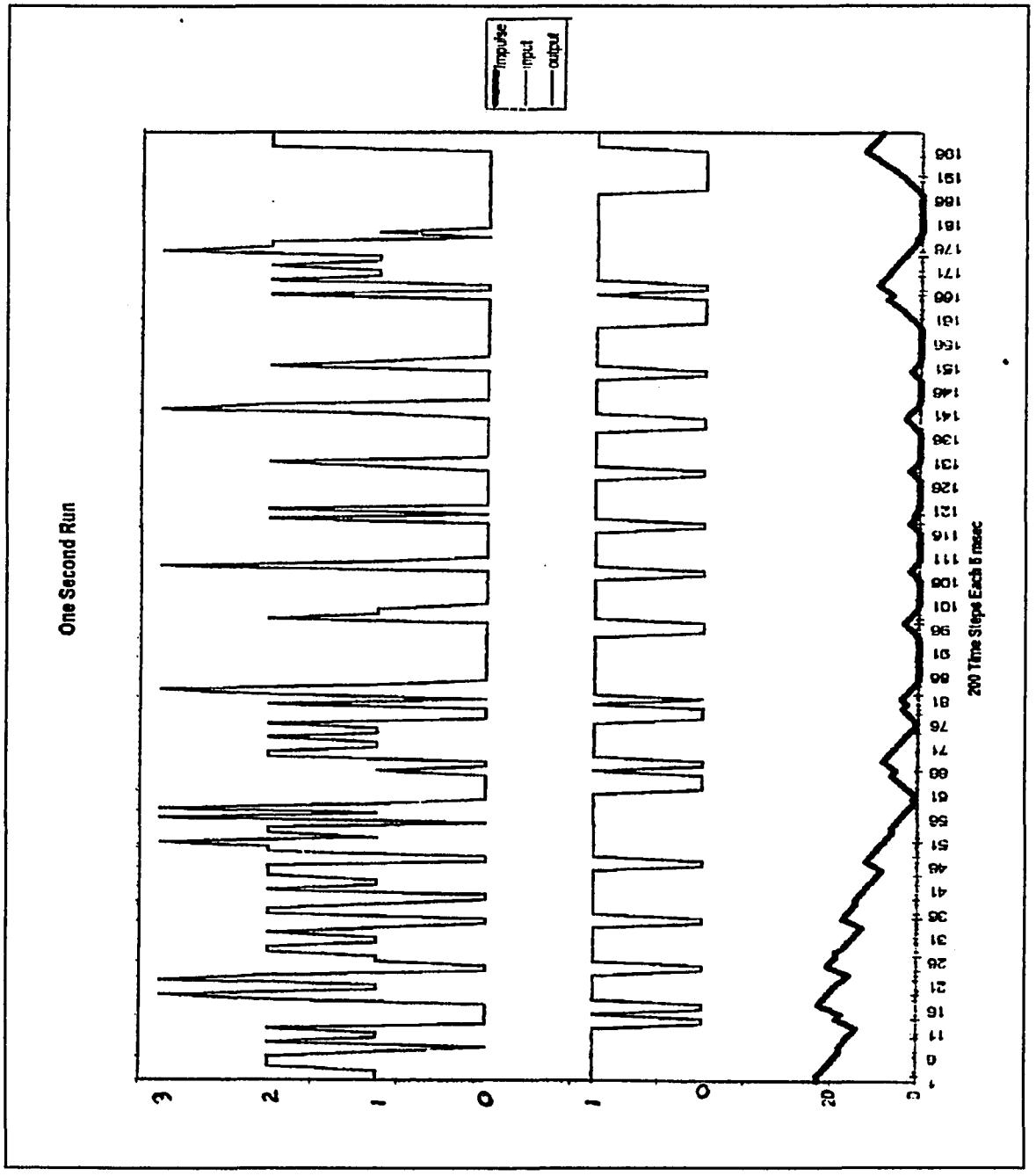


Illustration 3-8 Graph of first 200 time-step run from tables of run of synapse model

Chapter Four

CONCLUSION AND FUTURE DIRECTIONS

Since the seminal work of McCullough-Pitts (1943), when the neuron was described as an "all-or-none" character of nervous activity, and that relations among them be treated by means of a prepositional logic, researchers in Neuroscience, Cognitive Science, Computer Science have forged ahead with a myriad of implementations mainly in two camps: the biologically realistic, and the abstract model. The biologically realistic is generally computationally very elaborate and requires a tremendous amount of computing power for a substantial implementation. The abstract model, though computationally more feasible, greatly simplifies the neuron to some basic abstracted concepts.

What I have attempted to do is to take the best of both worlds. The **M-P** neuron established a link, with a weighted value, between two neurons. The weight is arbitrary. That is not how neurons are connected. The synapse is the juncture where neurons communicate. If we are going to establish links between neurons, why not model them as synapses? Synapses that are biologically realistic, yet easy to compute. I believe that by reviewing the great cornucopia of research in the different fields of Neuroscience on the synapse, one may distill the basic mechanisms, their function(s), and their interrelationships to other mechanisms, to obtain a synthesis that is more representative of the synapse than the "weighted link". The first point is that the synapses that connect neurons are **not** the same in structure, and functionality. Different parts of the brain are associated with different functions, and the synapses are structured according to the type of connection needed to perform these functions. To construct a neural network that

might perform a specific cognitive function, why not design the representative neurons, and their connections, as they are morphologically? Attempts to do this have been done by neuroscientists and collaborators, but they are massive, and computationally almost prohibitive. I seek a model of a synapse that is representative of the brain area it represents, demonstrating the basic mechanisms necessary to perform its function of synaptic transmission, yet is easily implemented and calculated.

To this end, I have modeled two synapses: The giant synapse of the *Loligo pealii, a neuromuscular synapse,* and the *Schaffer collateral/CA3* synapse, a central synapse, in the *Guinea Pig* hippocampus. The goal was not the implementation of these models, but the discovering of the primitives of the system in question, and if they would lend themselves to a simpler representation than attempted by neuroscientists.

The primitives involved in synaptic transmission at the giant synapse of the *Loligo Pealii* (Section 3.1) are Presynaptic Depolarization, Calcium Current, and PostSynaptic Response. These are at the membrane conductance modulation level, but they subsume molecular and chemical processes. It makes the model more robust, and far reaching in capturing the variables of one domain in another. The papers reviewed for this model had both experimental data from preparations, and models proposed and executed from the data. From their conclusions, the results of their models, and their graphs, I was able to create my model. The relationship between presynaptic potential and presynaptic calcium current was a continuous curve, which I was able to section in to linear equations. The same was true with the presynaptic calcium current relationship to the postsynaptic response. I reduced the two sets of relationships to a small set of linear equations, yet maintained the mechanisms, their functions , and their interrelationships. This established the set of primitives for this model as: **Presynaptic potential ➡ Presynaptic Calcium Current ➡ Postsynaptic Response.**

Further study revealed that the release of neurotransmitter is modulated by the availability of releasable vesicles. It is possible to have an action potential and no release. One salient reason is vesicle depletion. That was also addressed, and models with different refractory periods were given. I was able to linearize their graphs, and represent the modulation of vesicular (time to replace a vesicle anywhere between 10 -5000 μseconds) depletion in two linear equations. I added the modulator, Transmitter Release, as a primitive: **PostSynaptic Depolarization ➡ Calcium Current ➡ Transmitter Release ➡ PostSynaptic Response**. In Illustration 3.3, I graph the transition diagram for the model, and run an example through it. The realism it kept, and the computation is simple. The model succeeded. This model, as a link between two neurons, offers much greater modulation than a static link. The output of the neuron is modulated at the synapse based on the 1) **amplitude of the depolarization**, and the 2) **refractory period of vesicular depletion**. Because of this, the synapse is self-modulating. The model is only for the response to one action potential, and then it loses its memory when another action potential invades the presynaptic terminal, as the researchers did not address facilitation and augmentation. The emphasis of this model is on the relationship of the amplitude of the presynaptic depolarization to the postsynaptic response.

The second model is more complicated, as it deals with amplitude and frequency. In the research dealing with the Schaffer collateral/CA1 synapse, the emphasis was not on the amplitude of the action potential, but the frequency with which it was generated, in Hertz. The studies were designed to find unitary EPSPs , and on the histograms generated, extracts the quantal value of the vesicle of transmitter released into the synaptic cleft. They wanted to estimate the quantal size, and the probability of its release during an action potential. From the data generated from their research a very simple model is implemented (Illustration 3.4), that allows reproduction of the quantal size estimated, and

at their respective probabilities. But this would not offer modulation based on the primitive mechanisms responsible. Further study revealed a lot of variability, and hypothesis to explain them. Researchers have their areas of specialization. It is incredible how many components are found in one synapse, and every aspect has researchers. The task was to read papers in the different disciplines, and synthesize these different areas of study, presenting a coherent whole that offers amplitude, frequency, and greater modulation. But. most importantly, a model that is based on the mechanisms, their functions, and their interrelationships. And it is simple to implement and calculate. We start with the four primitives; Presynaptic Depolarization, Calcium Current, Transmitter Release, PostSynaptic Response. But the calcium current has a spin-off. After each action potential, a little residual calcium remains in the internal volume of the terminal, and it accumulates during a train. This acts as a second messenger in the terminal, and gives rise to synaptic enhancement in the form of facilitation and augmentation. This work was done in the *crayfish* for augmentation (Delaney et al., 1994), and in cultured neuron from the hippocampus of rodents. Facilitation aids in the release process (Wu et al., 1994; Liu et al., 1995), and augmentation in the availability of vesicles for release. Therefore, the calcium current has two functions, and two places for modulation: the calcium channels for immediate release, and residual calcium as a second messenger affecting synaptic enhancement. From the research presented, synaptic enhancement has been modeled simply, yet biologically realistically by a linear equation. From papers on vesicular release, and vesicular depletion, I propose a model of supply and demand, that, again, is biologically realistic, and very easy to implement. The synaptic enhancement has been interpreted (according to the papers reviewed) as having an effect presynaptically on the number of vesicles available for release. These are implemented as percentages of avaiable quanta, and easy to implement. Caveat: The model has implemented what I call the

primitives of synaptic functioning that demonstrate a trajectory in the synpase from input to output. This is not to say that all the factors responsible for the functioning of the synapse are implemented. Arachidonic acid and nitric oxide, which are termed retrograde messengers, and are considered important in LongTerm Potentiation and pre/postsynaptic communication, have not been implemented in this model, but would have to be considered when the model is extended to cover LTP. Glial cells, which are 10 to 50 more in number than neurons in the vertebrate nervous system, and are grouped into 6 distinctive functions (one is the removal of chemical transmitter released by neurons), are not implemented in the diffusion of neurotransmitter in the synaptic cleft during synaptic tranmsission. In considering the componenets of the model, I had to be parsimonious, and choose only those primitives that I thought were the most essential for basic synaptic functioning, and that would demonstrate the general bahavior of the synapse.

Data shows that not all calcium channels open during an action potential, nor do all receptors open at the postsynaptic density. They again have been given probabilities, and at this juncture in the process of synaptic transmission it is their multiplication (since they are independent) that determines if a vesicle will be released.

Primitives of implemented model:

- Presynaptic depolarization: These are implemented in the model as **input = 1, input = 0.** The measure is not the amplitude, but the frequency in hertz.
- Residual Calcium: determines synaptic enhancement. During action potential accumulates at 10 nM per action potential, and decays exponentially, with a time constant of 6 seconds.
- Synaptic enhancement: Has a linear relationship to residual calcium. Has one slope during action potential, and another during quiescence.

- Available vesicular pool depletion and replenishment: Both implemented as linear relationships to the available vesicular pool.
- Probability of calcium channel opening: Not all channels open at each action potential, and this affects the release of neurotransmitter. Values chosen from array of 100 random numbers in probability range.
- Probability of receptors open: Not all receptors open at each action potential, this affects the postsynaptic response.. Values chosen from and array of 100 random numbers in probability range.
- Postsynaptic response: In the research this is expressed in voltage or current, but in my implementation, for clarity, and to serve more as a template, I implemented it as the number of vesicles that are released at each action potential.

These primitives may serve as a template for a large portion of synapses that are governed by these same mechanisms. What would have to be changed are the values of the variables that interrelate them. These values may be ascertained from experimental data that is plentiful.

This model offers a much greater array of modulation, is simple to implement, and is constructed from the building blocks of the synapse. It offers synaptic enhancement over time, has memory of prior synaptic activity, and is self-modulatory. It is designed to be modular, and easily manipulated for calibration. Again, it is not the implementation that is important in this work, but that from the research available today in the neurosciences, a synthesis from the many areas of study may be distilled to discover basic mechanisms, their functions, and interrelations to construct models that are more in keeping with their biology, and yet are simple to implement. If we want to model cognitive and motor functions of natural systems, then it is only fitting that we create a model that has a sense of vertical integration, starting with the finer granularity of the organism.

The model has both amplitude and frequency. From the data presented from the run of the implemented synapse, it may be seen that over time (the run is for 5 seconds) the synapse has characteristics that are in keeping with the predicted functioning of a synapse: The vesicular available pool ebbs and wanes with use, according to the trains of action potentials, suffers from fatigue and has refractory periods, experiences synaptic failure even though an action potential invades the presynaptic terminal, and demonstrates variable multiquantal release. And this is done in a simple implementation that may be serve as a template. In an implemented program, this could be the synapse module that gets passed the arguments (variables) for different synaptic connections. Once template module would serve for many synapses.

These two models show that finding the best of both worlds in the implementation of neural networks is possible. The challenge it to now expand this model to include Post Tetanic Potentiation, and Long-Term Potentiation. Considering the plethora of research

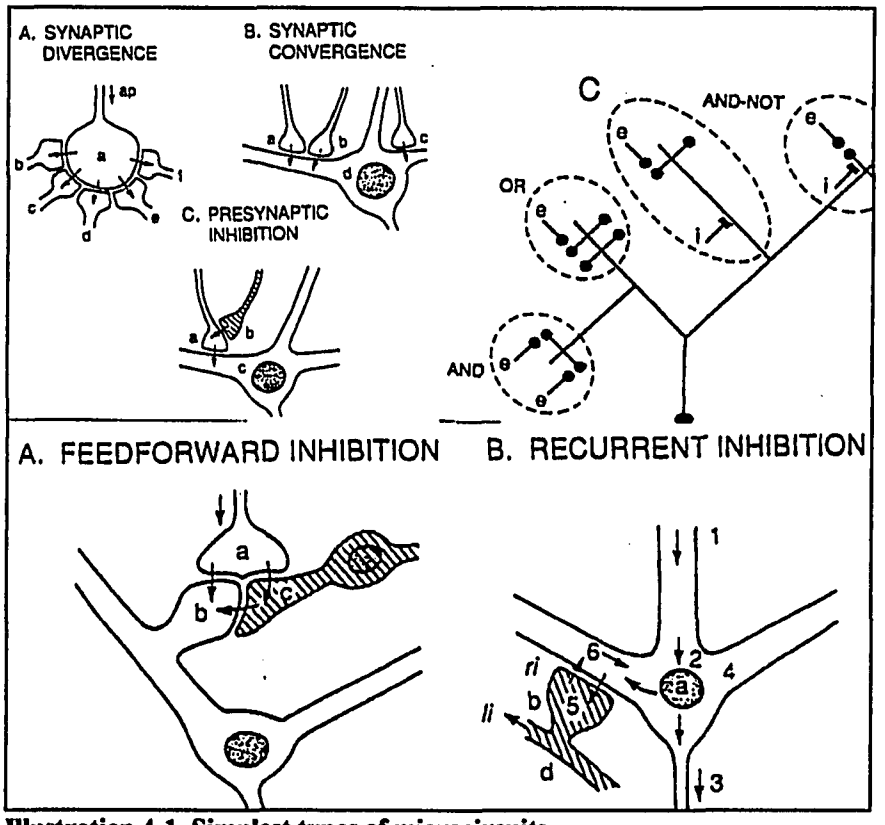


Illustration 4-1 Simplest types of microcircuits

on LTP, I fee this is very realizable. Once the full range of synaptic functioning over time caused by different forms of stimuli is modeled, then the next step would be the development of the microcircuits discussed by Shepherd as the computing building blocks of the brain. Significance is found in the ***patterns of connectivity*** of these synapses. The process of implementing neural networks that hold to the biology of the cognitive function the hope to implement are forthcoming. They may be from the camp of the neuroscientists, and much more detailed than the one presented here, but they will be bigger, and more complex.

Illustration 4.1 shows some of the basic and simple microcircuits that are known. Top left: (A) Synaptic divergence, from a single large axonal terminal (a) onto multiple postsynaptic dendrites (b-f); (B) Synaptic Convergence, of several axons (a-c) onto a single postsynaptic neuron (d).; (c) Presynaptic to axon (c). Top right: Possible arrangements for subserving logic-operations. (C) Branching dendritic tree with excitatory synapses on spines, and inhibitory synapses on spine necks or on dendritic branches. These perform different logic operations in the synaptic connections. These are taken from Shepherd (1990).

Chapter Five APPENDIX A

From the data presented in Chapter Three for the giant synapse of the *Loligo Pealii*, I have implemented the synapse in a very simple manner as look-up tables. Figure 3.2, Page 57 is a plot of the relationship between the Presynaptic Voltage in mV and the Presynaptic Current. The presynaptic voltage is presented as the value of the depolarization, whereas the presynaptic current as a percentage of the maximum calcium current. I have followed their format in the program presented. By simply creating a table of values, where each value from 0 to 120 mV, incremented by one, is given the corresponding value on the graph for the presynaptic current value. Once this table was constructed, a similar look-up table was constructed for the Presynaptic Current to the Postsynaptic Response in Figure 3.4, Page 62. In this case two tables had to be fashioned: one for the increasing presynaptic calcium current , and one for the decreasing calcium current. Once the look-up tables were constructed, given a value for the presynaptic depolarization, the program looks up the corresponding value for the presynaptic current in the look-up table for the pressynaptic voltage X presynaptic current relationship. If the value is less than 60 mV, then the program looks up the value in the increasing presynaptic X postsynaptic response look-up table, and gets the value, which is in a percent of the maximum value of a postsynaptic reponse for this synapse model (in this example, I chose a value of 200 mV as a maximum value for this synapse) . If the value is more than 60 mV, then the program looks up the value in the decreasing presynaptic current X postsynaptic response look-up table. The values retrieved from these tables are in percent values; therefore, the value is multiplied by the PEAK value to attain the final value of the

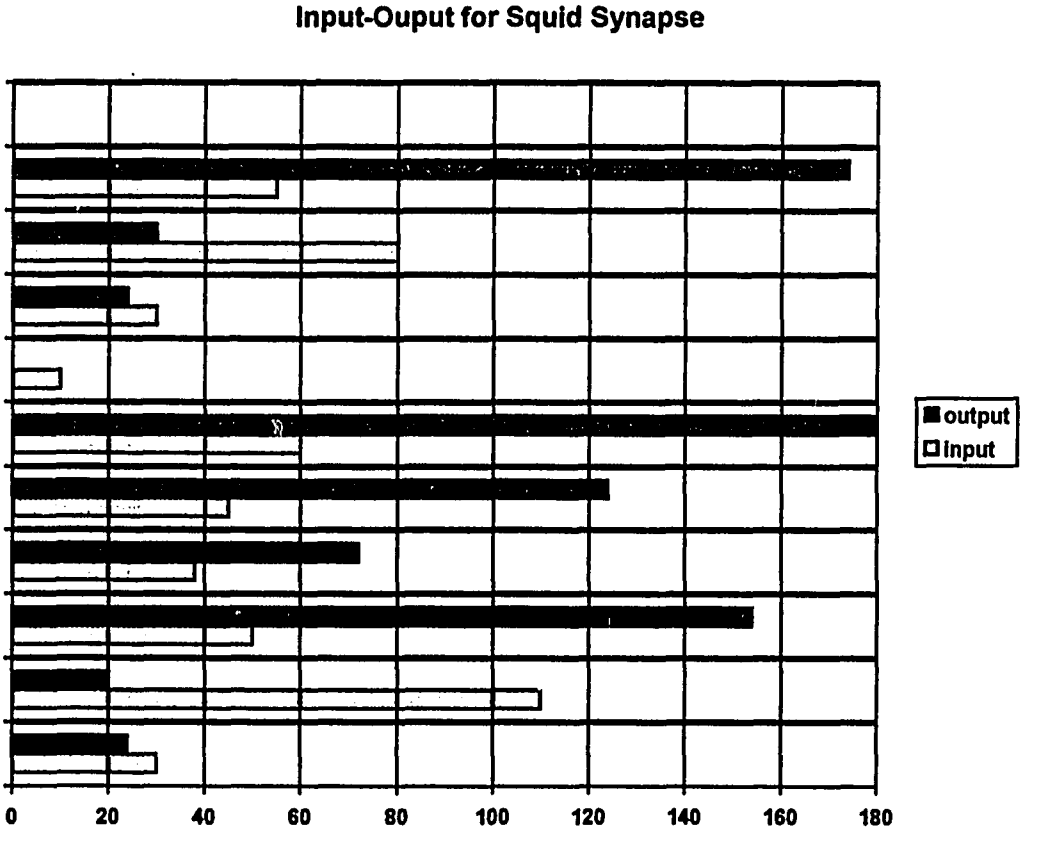
postsynaptic response. This procedure is very easy to implement, and the value are very close to the graphs presented. Below is the program, and a graph of ten inputs to the program, and the corresponding ten outputs:

Initialization of variables

```
10 DIM A(120)          Array for values of Presynaptic Depolarization
11 DIM B(100)          Array for values of  Presynaptic Calcium Current
12 DIM C(100)          Array for values of Postsynaptic Response
13 DIM D(10)           Array for 10 inputs of different values
14 I% = 0              counters
15 J% = 100
16 K% = 0
17 L% = 0
18 M% = 0
19 PEAK = 200          For this synapse, peak postsynaptic response is 200 mV
20 SINPUT# = 0
30 SOUTPUT# = 0
40 OPEN "I", #1, "PRE-VXA.DAT"   Open corresponding Prsynaptic Current to
Presynaptic Potential look-up table
50 FOR I = 0 TO 120
60 IF EOF(1) THEN 90
70 INPUT #1, A(I)
80 NEXT I
90 OPEN "I", #2, "POST-V-I.DAT"   Open corresponding Increasing Presynaptic
Current to Postsynaptic Response in look-up table
```

```
100 FOR J = 1 TO 100
110 IF EOF(1) THEN 140
120 INPUT #2, B(J)
130 NEXT J
140 OPEN "I", #3, "POST-V-D.DAT" Open corresponding Decreasing Presynaptic
Current to Postsynaptic Response in look-up table
150 FOR K = 0 TO 100
160 IF EOF(1) THEN 181
170 INPUT #3, C(K)
180 NEXT K
181 OPEN "I", #4, "IMPULSE.DAT" Open Input file of 10 values
182 FOR M = 0 TO 10
183 IF EOF(1) THEN 190
184 INPUT #4, D(M)
185 NEXT M
190 I = J = K = 0
200 OPEN "IMPULSE.OUT" FOR OUTPUT AS #5 Output file
210 FOR M = 0 TO 10          Program starts here
211 SOUTPUT = 0
220 I = D(M)    Get value of input
If input is less than 60 then get increasing presynaptic current value and calculate
postsynaptic respone.  If less than 60, then get decreasing presynaptic value and calculate
postsynaptic reponse.
230 IF I < 60 THEN SOUTPUT = PEAK * B(A(I)) ELSE SOUTPUT = PEAK *
C(A(I))
```

```
240 PRINT #5, D(M), SOUTPUT
250 NEXT M
260 END
```



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