Concept of E-machine:
How does a ”dynamical” brain learn to process ”symbolic” information?
Part I *

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Abstract

The human brain has many remarkable information processing characteristics that deeply puzzle scientists and engineers. Among the most important and the most intriguing of these characteristics are the brain’s broad universality as a learning system and its mysterious ability to dynamically change (reconfigure) its behavior depending on a combinatorial number of different contexts.

This paper discusses a class of hypothetically brain-like dynamically reconfigurable associative learning systems that shed light on the possible nature of these brain’s properties. The systems are arranged on the general principle referred to as the concept of E-machine.

The paper addresses the following questions:

1. How can ”dynamical” neural networks function as universal programmable ”symbolic” machines?

2. What kind of a universal programmable symbolic machine can form arbitrarily complex software in the process of programming similar to the process of biological associative learning?

3. How can a universal learning machine dynamically reconfigure its software depending on a combinatorial number of possible contexts?

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The paper explains the concept of E-machine and outlines a broad range of its potential applications. These applications include: context-sensitive associative memory, context-dependent pattern classification, context-dependent motor control, imitation, simulation of complex "informal" environments and natural language.

0 Introduction

When observed "from the outside" the human brain seems to behave as a sequential symbolic machine. How else can one explain such "clearly symbolic" phenomena as mental computations and natural language? When observed "from the inside," however, the neural networks of the brain evoke an idea of a noisy dynamical system with distributed parameters rather than the image of a logic circuitry of a digital computer – gradually changing potentials, decaying residual excitation, high level of fluctuations. Neurons do produce spikes reminiscent of the pulses in a digital computer. It is widely believed, however, that it is the frequency of these pulses rather than their presence and absence that carry the important information.

1. How can "dynamical" neural networks function as universal programmable "symbolic" machines?

2. What kind of a universal programmable symbolic machine can form arbitrarily complex software in the process of programming similar to the process of biological associative learning?

3. How can a universal learning machine dynamically reconfigure its software depending on a combinatorial number of possible contexts?

The metaphor "the brain as an E-machine" (Eliashberg, 1967, 1979, 1981, 1989, 1990b) sheds light on these questions. The metaphor suggests that the brain is neither a traditional symbolic system, nor is it a traditional dynamical system. It is a "non-classical symbolic system" in which the probabilities of sequential discrete ("symbolic") processes are controlled by the massively parallel continuous ("dynamical") processes.

Note. The general idea that the brain employs a combination of symbolic and dynamical computational mechanisms was entertained in different forms by different researchers (Collins and Quillian, 1972; Anderson, 1976; and many others.) The concept of E-machine is an attempt to provide a neurobiologically consistent formalization of this general idea. The requirement of neurobiological consistency makes a big difference!
The paper is divided into two parts. Part I consists of the three main sections:

1. **The Whole Human Brain as a Universal Learning Computer.** This section takes a broader look at the problem of information processing in the whole human brain. It argues that there exists a relatively short formal representation of a universal learning computer similar to an untrained (unprogrammed) human brain.

2. **From Associative Neural Networks to E-machines.** This section establishes a link between associative neural networks and E-machines. It connects the effects of dynamic reconfiguration (neuromodulation) in neural networks with the hypothetical states of dynamical memory available in individual neurons. These states of "residual-excitation-like” memory are referred to as the E-states.

3. **Molecular Interpretation of E-states: Ensembles of Protein Nanomachines as Statistical Mixed-signal Computers.** This section addresses the problem of a neurobiological implementation of the E-states and the next E-state procedures. It describes a formalism that connects the dynamics of macroscopic E-states with the statistical conformational dynamics of ensembles of protein molecules (such as ion channels) embedded in neural membranes. A single protein molecule is treated as a probabilistic nanomachine, and the E-states are interpreted as the average numbers of such nanomachines in different states – the average occupation numbers. The formalism suggests that it is the statistical conformational dynamics of protein molecules in *individual* neurons rather than the *collective* statistical dynamics of neural networks that performs the main volume of the brain hardware computations. There is not enough neurons in the whole human brain to implement the required amount of computations in the networks built from "simple neurons.”

Part II includes the following main sections:

4. **Computing with E-states.** This section tackles the question as to how the massively parallel transformations of E-states allow a slow brain to efficiently process large arrays of symbolic data stored in its long-term memory (LTM) without moving this data into a read/write memory buffer.

5. **Hierarchical structure: sparse-recoding, data compression and statistical filtering.** This section explains how E-machines with hierarchical structure of associative memory can perform efficient data compression, context-dependent statistical filtering, and context-dependent generalization.
6. Discussion

1 The Whole Human Brain as a Universal Learning Computer

This section takes a broader look at the problem of information processing in the whole human brain. It argues that there exists a relatively short formal representation of a universal learning computer similar to an untrained (unprogrammed) human brain.

1.1 System (Man,World) as a composition of two ”machines”

Consider a cognitive system (W,D,B) schematically shown in Figure 1, where W is an external world, D is a set of human-like sensory and motor devices, and B is a hypothetical computing system simulating the work of the human nervous system. One can think of system (D,B) as a human-like robot. From the system-theoretical viewpoint, it is useful to divide system (W,D,B) into two subsystems: (W,D) and B, where (W,D) is the external world as it appears to the brain B via devices D. In this representation, both subsystems can be treated as abstract ”machines”, the inputs of B being the outputs of (W,D) and vice versa.

For the sake of simplicity, I refer to B as the brain. At this general level, the rest of the nervous system can be treated as a part of block D. Let B(t) denote the state of B at time t, where t=0 corresponds to the beginning of learning. I argue that the following general propositions are true:

![Figure 1: System (Robot,World) as a composition of two machines](image-url)
1. There exists a relatively short formal representation of $B(0)$. This representation is encoded in the human genome and can be small enough to fit into a single floppy disk.

2. No special mathematical formalism is needed to describe the work of $B(0)$. Given a powerful enough hardware, a relatively small $C$ or $C++$ program would be able to simulate the work of $B(0)$ with a time step of, say, $1\text{ msec}$. This program would be sufficient to adequately represent all important psychological characteristics of $B(0)$. A more complex, but still rather small $C$ or $C++$ program would be able to simulate the work of $B(0)$ with a time step of, say, $1\mu\text{sec}$. This program would be sufficient to adequately represent all important psychological characteristics of $B(0)$ and many of its neurobiological characteristics.

3. There exists a relatively short formal representation of the sensorimotor devices, $D$, since this representation is encoded in the human genome. The metaphorical floppy disk mentioned in item 1 has enough room for both $B(0)$ and $D$. We know that $B(0)$ can do well with different kinds of artificial devices, so the main secret is in $B(0)$ rather than in $D$.

4. In the general case, there exists no finite formal representation of system $(W,D)$ – this system can be infinitely complex. This doesn’t prevent one from simulating the behavior of system $(W,D,B)$, because the ”robot” $(D,B)$ has a finite formal representation, and the external world, $W$, is ”always there” to experiment with.

5. Any formal representation of $B(t)$ for a big $t$ (say, $t>10$ years) must be very long (terabytes?) – this representation must include in some form a representation of the brain’s individual experience which resulted from interaction with $(W,D)$. Whatever language is used for the representation of $B(t)$, the main part of this representation is the representation of the knowledge accumulated in the course of learning. Figuratively speaking, the human brain works as a ”complexity sucker” that gets most if its complexity from system $(W,D)$.

6. The knowledge is represented in $B(t)$ in a rather ”raw” form – the brain’s learning algorithm is close to ”memorizing raw sensory-motor-emotional experience.” No special data structures are needed. Instead of pre-processing data before putting it in memory, the brain uses a powerful massively parallel decision-making procedure capable of processing the ”raw” experience on the fly depending on context.

7. It is practically impossible to understand $B(t)$ without understanding $B(0)$ and studying the process of learning that changes $B(0)$ into $B(t)$. 
8. It is practically impossible to formally represent and simulate nontrivial parts of the behavior of system \((W,D,B(t))\) without having an adequate formal representation of \(B(t)\). That is, an adequate cognitive theory cannot be separated from the theory of the brain.

9. The main goal of brain modelling must be reverse engineering \(B(0)\). This is a clearly defined and practically achievable goal. (I refer to this reverse engineering project as the Brain Zero or the Brain 0 project. Visit www.brain0.com.) To advance toward this goal one should concentrate on the analysis of basic psychological and neurobiological observations rather than on the mimicking of the parts of the brain’s behavior. The latter strategy leads one into the "new-effect-new-model" pitfall and is cursed by the combinatorial explosion of the number of partial models needed to represent the whole behavior.

10. The role of \(B(0)\) in cognitive science can be meaningfully compared with the role of the Maxwell equations in the classical electrodynamics. The same Maxwell equations (a metaphorical counterpart of \(B(0)\)) coupled with an infinite variety of specific external constraints (a metaphorical counterpart of \((W,D)\)) allow one to simulate infinite variety of specific classical electromagnetic phenomena. Similarly, the same \(B(0)\) interacting with different external systems \((W,D)\) would allow one to simulate, in principle, infinite variety of arbitrarily complex cognitive phenomena.

1.2 The Maxwell equations metaphor: the pitfall of a ”pure phenomenology”

The example of physics warns us that one should not underestimate the power of simple basic mechanisms of Mother Nature. I argue that this warning is relevant to the problem of reverse engineering the "physical" system \(B(0)\). The brain is designed by Mother Nature – not by the human system engineers. This makes all the difference in the world.

We (humans) design artificial information processing systems to make them easier to understand, test and debug. This costs us extra resources. In contrast, Mother Nature tends to solve natural design problems with minimum resources. It makes Her designs look clever. It also makes them difficult to understand. In such minimum-resource designs different functions are necessarily strongly integrated and cannot be easily structured as independent blocks.

An integration of a set of simple physical principles can produce a ”critical mass” effect. The introduction of the so-called ”displacement current” in the Maxwell equations gives a classical example of this interesting phenomenon. All of a sudden, this simple addition to the set of known basic laws of electricity and
magnetism, allowed J.C. Maxwell to create his famous equations that cover the whole range of arbitrarily complex classical electromagnetic phenomena.

I argue that something similar had happened in the case of the human brain. Not too much was needed to transform the brains of simple animals into the human brain. A clever integration of a relatively small set of powerful "basic mechanisms" produced a "critical mass" effect.

To understand the pitfall of a "pure phenomenology" consider the following metaphor. Imagine a physicist who wants to simulate the behavior of electromagnetic field in a complex microwave device, e.g., the Stanford Linear Accelerator (SLAC). Assume that this physicist doesn’t know about the existence of the Maxwell equations and, even more importantly, doesn’t believe that the complex behavior he observes may have something to do with such simple equations. (In the AI jargon this physicist would be called "scruffy." If he believed in the existence of the basic equations he would be called "neat.")

So this "scruffy physicist" sets out to do a purely phenomenological computer simulation of the observed complex behavior per se. Anyone who was involved in the computer simulation of the behavior of electromagnetic field in a linear accelerator can easily predict the results of this gedanken experiment.

In the best case scenario, the above mentioned scruffy physicist comes up with a computer program (with a large number of empirical parameters) capable of simulating the behavior of electromagnetic field in a very narrow range. This computer program has no extrapolating power and is not accepted by the SLAC community as a theory of a linear accelerator.

Note that it would be impossible to reverse engineer the Maxwell equations (a metaphorical counterpart of B(0)) from the analysis of the behavior of electromagnetic field in such a complex "external world" as SLAC. I argue that, similarly, it is impossible to reverse engineer B(0) from the analysis of such complex cognitive phenomena in system (W,D,B(t)) as playing chess, solving complex mathematical problems, story telling, etc.

1.3 Basic observations

To formulate some "technical requirements" to an adequate model of B(0) consider the following basic observations:

**OBSERVATION 1.** A person with a sufficiently large external memory aid (for example, a sheet of paper divided into squares) can perform, in principle, any effective computational procedure. A formalization of this observation had lead famous English mathematician Alan Turing (1936) to the invention of his celebrated machine and to the corresponding formalization of the intuitive notion of an algorithm. (See Minsky, 1967, for a relevant discussion of Turing’s ideas.)

Now that the concept of an algorithm is defined, we can say that a model of
system (W,D,B), where W is an external memory aid, must be a *universal computing system*. (This is a necessary but, of course, not a sufficient, requirement.)

**OBSERVATION 2.** We are not born with the knowledge of all possible algorithms. We can learn, however, to perform, in principle, any given algorithm, say, by simulating the work of a Turing machine representing this algorithm.

This observation means that the above system (W,D,B) must be a *universal learning system*.

**OBSERVATION 3.** A person with a good visual memory performing computations with the use of an external memory aid learns to perform similar mental computations using the corresponding imaginary memory aid. A chess player learns to move chess pieces on an imaginary chess board. An abacus user learns to operate on an imaginary abacus (Baddeley, 1980). And so on. In principle, a person can learn to perform any mental computations by mentally simulating the process of writing symbols on a sheet of paper.

Ignoring some severe, but theoretically unimportant limitations on the size of the working space available via this mechanism of mental imagery, this observation suggests that the human brain, B, itself – not just a person with an external memory aid – must be treated by a system theorist as a universal learning system.

**Note.** An adequate model of B(0) *must* have the highest general level of computing power. Attempting to simulate the work of the human brain using a learning system with the general level of computing power lower than that of the brain can be compared with an attempt to design a Perpetual Motion machine in violation of the energy conservation law. No matter how sophisticated a learning process might be, no system can learn to do what it cannot do in principle. (An elephant learns to fly only in a Disney film.)

**OBSERVATION 4.** We (humans) can imagine new sensory events and synthesize new motor reactions. At the same time we can remember and recall the real sequence of events (reactions). For example, an experienced chess player can mentally play any chess party. At the same time he/she can recall the real parties he/she played. Similarly, we can generate a combinatorial number of new sentences. At the same time we can read by heart a specific text we’ve learned.

*What kind of learning algorithm can accommodate these different types of learning? Do we need different learning algorithms?*

**OBSERVATION 5.** We memorize new information with the references to the pieces of the information which we already have in our long-term memory (LTM). The more we know in a certain area the easier it is to remember new things related
to this area. For example, we can easily remember long sentences in the language
we know. It is next to impossible to remember long sentences in a language we
don’t know. It is also very difficult, for a second language speaker, to get rid of
the accent, because he/she tends to build the words of the second language from
the syllables of the first language.

How can this hierarchical referencing system be implemented in neural net-
works?

OBSERVATION 6. Our ability to retain information in our short-term memory
(STM) increases if similar information is present in our LTM. We can repeat a
sentence in the language we know. We cannot repeat a sentence in a language we
don’t know. We can imitate only those reactions of other people that we can do
ourselves. The same is true for perception. We have difficulties recognizing words
of a foreign language that we cannot pronounce ourselves.

What is STM? How does it interact with LTM? What is working memory?
What does motor control have to do with it?

OBSERVATION 7. To imagine different sensory events we need to do men-
tal motor reactions that would cause similar events. We need to mentally sing a
melody to imagine another person singing this melody. We need to mentally say
a sentence to imagine another person saying this sentence. Etc.

What is mental imagery? How does mental imagery interact with motor con-
trol?

OBSERVATION 8. We can see different sub-pictures in the same picture de-
pending on what we expect to see. The Necker cube is an example. We can hear
different tunes in the same sequence of sounds (e.g., the sounds produced by a
moving train) depending on what we expect (want) to hear.

What kind of mechanism available in neural networks can account for these
phenomena of mental set?

OBSERVATION 9. We can selectively tune our attention to a voice we want
to hear in a noisy room – the so called cocktail party phenomenon.

How can the brain temporarily increase sensitivity to signals with some not
easily definable characteristics?

OBSERVATION 10. Our short-term memory can retain only a limited number
(seven plus or minus two) of items: the "magical number" of Miller, 1956. How-
ever, due to the effect of "chunking" the size of a single item can be significantly
increased. We also can "see more than we can report" (Sperling, 1960). This
raises the same set of questions as the Observation 6.
OBSERVATION 11. The brain is a slow and noisy system. It cannot process symbolic information in a traditional (“classical”) way by moving symbols in a read/write memory buffer. Nevertheless, we can learn to mentally simulate different external systems (W,D) with the properties of a read/write memory. (For example, we can mentally move chess pieces on an imaginary chess board or mentally write and erase symbols on an imaginary sheet of paper.)

How can computational universality in Turing’s sense (Chomsky’s type 0) be achieved without moving symbols in a read/write memory? How can neural networks learn to simulate a symbolic read/write memory?

Note. The problem of how the brain can learn to simulate an external system (W,D) with the properties of a read/write memory must not be confused with the problem of how a neural network can implement a read/write memory. The latter problem is trivial. The former problem is nontrivial and critically important. Traditional neural network models cannot learn to simulate external systems with the properties of a read/write memory and, therefore, cannot serve as models of the brain’s systems responsible for mental imagery.

OBSERVATION 12. We can recognize that a certain object, A, is statistically strongly correlated with another object, B. We can also produce a reaction, R, statistically well correlated with a certain stimulus, S. Importantly, this statistical relationship depends on context. Two objects strongly correlated in one context may be not correlated at all in a different context. Our language has words usual, unusual, common, uncommon, etc., that reflect our ability to recognize statistical relationships.

How can a huge amount of computations required for context-dependent statistical processing be done “on the fly” by slow neural networks? (Note that it must be done “on the fly,” because context can change very rapidly. This statistics cannot be precalculated, because there is a combinatorial number of possible contexts!)

OBSERVATION 13. We can wait for a certain object, A. Once A appears we recognize that A is the object we were waiting for. If we expect a certain object, B, to appear and, instead, an unexpected object, C, appears we recognize that C is an unexpected object. We can answer the questions: “What are you waiting for? What do you expect?”

How does the brain temporarily mark an object as an object “being waited for” or as an object “being expected?”

OBSERVATION 14. Pattern recognition is a context-dependent activity. Con-
sider the question: "What is it?" In the context of this question a person behaves as a pattern classifier. He/she can answer, for example that this is a book. The person’s brain was able to distinguish a book from other objects, say, a box, a disk drive, etc. Now consider the instruction: "Take this." In this context it is no longer important that the object has the name book. What is important is the object’s size, weight, position, etc. The experience acquired while "taking a book" is applicable to "taking a box" and "taking a disk drive." That is, the same object is treated as a member of different classes depending on context.

*How can a context-dependent pattern classification be done "on the fly?"

**Observation 15.** We can recognize our emotional states. We remember our emotional experience. We use this experience to evaluate new events. Our concepts of good, bad, important, unimportant, etc. are formed in the process of learning.

*How do we learn to recognize our emotions? How does our emotional memory interact with other types of memory?*

**Observation 16.** We can recognize internal states and internal reactions of other people. We can say, for example, "I know how you feel." We know that another person is thinking, waiting, etc. When we learn by imitating another person, we are not imitating this person as a black box. This means that the problem of learning cannot be formalized as the automata theory problem of one machine deciphering the structure of another machine observed as a black box. (If this formalization were true, we wouldn’t be able to learn, in principle, a behavior of the Chomsky’s type 2 and higher.)

*How do we learn to control our internal reactions? How do we learn the names of our internal reactions (thinking, imagining, recalling, waiting, seeing, listening, etc.)? How do we recognize similar internal reactions in other people?*

*How does mental imagery interact with perception?*

**Observation 17.** Much of what we see we see from our memory. For example, when we are driving a car in a familiar environment we need only to glance at the scene to update the visual picture we expect. We can close our eyes and see the room we live in by mentally moving the eyes and mentally turning the head.

*How do the signals coming from external system (W,D) interact with the signals coming from memory? How is our mental imagery synchronized with the external system (W,D)? What does motor control have to do with it?*
1.4 Motor control and mental imagery

Let us expand the structure of system (W,D,B) of Figure 1 as shown in Figure 2. The brain B is divided into two blocks: AM and NM, where AM is an associative learning system that forms Sensory → Motor (SM → M) associations, and NM is a set of motor centers. The diagram also depicts the block TEACHER. In this case, the teacher acts as an idealized neurophysiologist, who can produce any desired output of centers NM, by "clamping" these centers. System AM receives sensory signals from system (W,D) and motor signals from the output of centers NM. This approach to teaching and learning is similar to the so-called supervised learning, except that, in our case, the learning system receives its sensory input from the external system (W,D) rather than from the teacher. This can be compared with the so-called instrumental conditioning. Let us make the further
expansion of the structure of system (W, D, B) as shown in Figure 3. The brain B is now divided into four blocks: AS, AM, NS and NM, where blocks AM and NM are the same as in Figure 2, NS are sensory centers, and AS is an associative learning system that forms Motor → Sensory (MS → S) associations.

The goal of system AM is to simulate the block TEACHER. The goal of system AS is to simulate the external system (W, D). It is easy to see that system (W, D) plays the same role for system AS as the block TEACHER does for AM. We will view systems AM and AS as the systems responsible for motor control and mental imagery, respectively. We will view the sets of (SM → M) and (MS → S) associations as the brain’s software associated with the above functions.

1.5 Mental computations (thinking) as an interaction between motor control and mental imagery

A specific example of system (W, D, B) shown in Figure 4 gives a simplified general explanation of the phenomenon of mental computations. The model was implemented as an educational program, called EROBOT, for the Microsoft Windows. (The program can be purchased from www.brain0.com.) An explicit description of this model was given in Eliashberg (2003). In Figure 4

- W is an external memory aid (the tape divided into squares).
- D is a set of devices including the eye, the hand and the speech organ.
- B is the brain divided into four blocks AM, AS, NM and NS that have the same general meaning as in Figure 3.

The robot’s devices, D, allow it to simulate the work of any Turing machine by performing the following elementary operations:

1. read a symbol from the single square scanned by the eye
2. write a symbol into the scanned square
3. move the eye and the hand simultaneously to the next square, the next square being the one to the left, the one to the right, or the same square
4. utter a symbol to be kept in mind for one cycle – this one-cycle memory is provided by the delayed feedback between the motor signal, utter symbol, to the speech organ and the proprioceptive signal, symbol uttered, from this organ.

An experiment with the model consists of two stages: training and examination. At the stage of training the teacher forces the robot (by acting on its motor
The following results of learning are achieved:

1. System AM learns to simulate the teacher, so the robot can perform the demonstrated algorithm with any input data without the help of the teacher.

2. In the case of a finite tape, and a sufficient number of training examples, system AS learns to simulate the external system (W,D). Accordingly, the robot learns to perform the demonstrated algorithm with the use of an imaginary memory aid. (The robot keeps writing symbols on the real tape to show what it calculates on the imaginary tape. The robot doesn’t see the real tape!)
1.6 The pitfall of a "smart" learning algorithm

The main part of today’s research in learning is devoted to the development and study of what can be referred to as "smart" learning algorithms. Such algorithms attempt to create "optimal" representations of the learner’s experience in the learner’s memory. I argue that this general approach (whatever interesting and important from the engineering and mathematical viewpoints) cannot be employed by a universal learning system similar to the human brain. The catch is that a smart learning algorithm aimed at a "single-context" optimization is not universal. While optimizing performance in a selected context, it throws away a lot of information needed in a variety of other contexts.

Consider, for example, Observation 14 from Section 1.3. This observation suggests that, in the case of the human brain, there is no such thing as an optimal context-independent classification. The main issue is not "how" to pre-process information in the course of learning (Hebbian learning, backpropagation, simulated annealing, etc.), and how to store this pre-processed information in memory (distributed, local, synaptic, optical, etc.), but "what" information to learn. The human concepts of "good", "bad", "important", and "unimportant" change with experience. Therefore, a "smart" learning algorithm with a fixed criterion of optimality – the criterion that is not affected by the contents of data – cannot serve as an adequate metaphor for human learning. What seems unimportant today may become important tomorrow when new information is acquired.

I argue that a really smart universal learning system – such as B(0) – must use a "dumb" but universal learning algorithm. Instead of doing much pre-processing of data before placing it in memory, such system must use an efficient decision-making (data interpretation) procedure to process "raw experience" dynamically (on the fly) depending on context. Theoretically, a powerful enough interpretation procedure can always make up for a "dumb" learning algorithm as long as this algorithm doesn’t lose data. In contrast, no decision making procedure can make up for a "smart" learning algorithm that throws away a lot of information. The loss of data is irremediable.

2 From Associative Neural Networks to E-machines

This section introduces the concept of a primitive E-machine (Eliashberg, 1979) as a natural information processing extension of the notion of a homogeneous associative neural network. A complex E-machine is a system built from several primitive E-machines. Complex E-machines will be discussed in Part II of this paper.
2.1 Simple example of associative neural network: Model ANN-0

Consider a neural network schematically shown in Figure 5. The functional model of this network described in this section will be referred to as Model ANN-0 (Associative Neural Network # 0).

In Figure 5 large circles with incoming and outgoing lines represent neurons with their dendrites and axons, respectively. Small white and black circles represent excitatory and inhibitory synapses, respectively. The network has three layers of neurons: input neurons N1, intermediate neurons N2, and output neurons N3. Neurons N2 have a global inhibitory feedback via neuron N4 and local excitatory feedbacks. It will be shown that in this network neurons N2 can compete via reciprocal inhibition in the winner–take–all fashion. A similar effect can be obtained in a network with lateral inhibitory feedbacks. Figure 5 uses the following notation:

- $Nk[j]$ is the $j$-th neuron from set $Nk$.
- $Smk[i,j]$ is the synapse between neuron $Nk[j]$ and neuron $Nm[i]$.
- $x_j$ is the output of neuron $N1[j]$.
- $g_{ij}^x$ is the gain of synapse $S21[i,j]$.

![Figure 5: Simple example of associative neural network](image_url)
• $s_i$ is the net synaptic current of synapses $S21[i, 1], \ldots S21[i, m]$ – $s_i$ represents a similarity between input vector $x$ and vector $g^x_i$ (expression 1).

• $r_i$ is the output of neuron $N2[i]$.

• $q$ is the output of neuron $N4$. This output is the sum of the feedback signal $\beta \sum r_i$ and an external signal $x_{inh}$.

• $\beta$ is the gain of synapse between any neuron from $N2$ and neuron $N4$.

• $\tau$ is the time constant of any neuron from $N2$.

• $\alpha$ is the gain of synapse providing local excitatory feedback for a neuron from $N2$.

• $g^y_{ki}$ is the gain of synapse between neuron $N2[i]$ and neuron $N3[k]$.

The following functional model of the network of Figure 5 was studied in Eliashberg (1967, 1979). In this model a neuron is treated as a linear threshold element with zero threshold and the time constant $\tau$. In spite of its simplicity, this model has a significant educational value because it allows one to explicitly bridge the gap between its neurobiological and psychological theories and to show what kind of mathematics is involved in this bridging. No learning algorithm is described, and it is assumed that the model is preprogrammed before the beginning of an experiment.

\[ s_i = \sum_{j=1}^{m} g^x_{ij} \cdot x_j \tag{1} \]

\[ \tau \frac{du_i}{dt} + u_i = s_i + \alpha \cdot r_i - q \tag{2} \]

\[ r_i = \begin{cases} u_i & \text{if } u_i > 0 \\ 0 & \text{otherwise} \end{cases} \tag{3} \]

\[ q = \beta \sum_{i=1}^{n} r_i + x_{inh} \tag{4} \]

\[ y_k = \sum_{i=1}^{n} g^y_{ki} \cdot r_i \tag{5} \]

Let all $x_j$ and $x_{inh}$ (and, therefore, all $s_i$) be step functions of time. Then, for all active neurons from layer $N2$ – the neurons for which $u_i > 0$ – the solution of
equations (2)–(4) can be represented in the following explicit form:

\[
    u_i = \frac{(s_i - s_{av})}{\alpha - 1} (e^{at} - 1) + (u_i^0 - u_{av}^0) e^{at} \\
       + \frac{(s_{av} - x_{inh})}{1 + \beta \cdot n_1 - \alpha} (1 - e^{-bt}) + u_{av}^0 \cdot e^{-bt}
\]

(6)

where

- \( n_1 \) is the number of active neurons from N2.
- \( u_i^0 \) \( (i = 1, \ldots n) \) are the values of \( u_i \) at \( t=0 \).
- \( s_{av} \) and \( u_{av}^0 \) are the average values of \( s_i \) and \( u_i^0 \) for all active neurons from N2.

\[
    s_{av} = \frac{1}{n_1} \sum_{i=1}^{n_1} s_i 
\]

(7)

\[
    u_{av}^0 = \frac{1}{n_1} \sum_{i=1}^{n_1} u_i^0 
\]

(8)

Parameters \( a \) and \( b \) in \( e^{at} \) and \( e^{-bt} \) are as follows:

\[
    a = (\alpha - 1)/\tau 
\]

(9)

\[
    b = (1 + \beta \cdot n_1 - \alpha)/\tau 
\]

(10)

Let \( 1 < \alpha < 1 + \beta \). Then \( a > 0 \). According to expression (6), neurons \( N2[i] \) with \( s_i > s_{av} \) increase their potentials \( u_i \). Neurons \( N2[i] \) with \( s_i < s_{av} \) decrease their potentials and switch off once \( u_i < 0 \). This reduces \( n_1 \) and increases \( s_{av} \) making \( s_i < s_{av} \) for some additional neurons from N2. Eventually, only neurons with \( s_i = \max(s_1, \ldots s_n) \) will have \( u_i > 0 \). It can be shown that this equilibrium is unstable if \( n_i > 1 \). Therefore, in the presence of noise, at the end of the transient response there will be only one winner randomly selected from the set of neurons with the maximum level of \( s_i \).

2.2 Model ANN-0 as a symbolic machine

Let us introduce a finite (“psychological”) time step \( \Delta t \gg \tau \), and let us assume that inputs change step-wise at moments \( t_\nu \) and \( t_\nu + \Delta t/2 \), where

\[
    t_\nu = \nu \cdot \Delta t \quad \nu = 0, 1, \ldots
\]

(11)
Let us introduce a periodic inhibition

\[ x_{inh} = \begin{cases} 
  x^0_{inh} & \text{if } t \in (t_\nu, t_\nu + \Delta t/2] \\
  0 & \text{otherwise} 
\end{cases} \]  

Let us sample outputs at the end of the first half of each cycle

\[ \bar{y}_k(\nu) = y_k(t_\nu + \Delta t/2) \]  

Let us assume that the states of ILTM and OLTM are specified at the beginning of an experiment with the model and don’t change during the experiment (the model is preprogrammed in advance and no learning takes place during the experiment). Let us also assume that the parameters of the model are the same for all experiments. To describe the “psychological” properties of Model ANN-0 we need the following system theoretical concepts.

**DEFINITIONS:**

- A (deterministic) **combinatorial machine** is a system \( M = (X, Y, f) \), where \( X \) and \( Y \) are finite sets of symbols, called the input and the output set (or alphabet) of \( M \), respectively; \( f : X \rightarrow Y \) is the output function of \( M \). Machine \( M \) works as follows: \( y_\nu = f(x_\nu) \), where \( x_\nu \in X \) and \( y_\nu \in Y \) are the input and the output symbols at the \( \nu \)-th cycle.

- A **probabilistic combinatorial machine** is a system \( M = (X, Y, \delta) \), where \( X \) and \( Y \) are the same as above; \( \delta : X \times Y \rightarrow [0, 1] \) is the function of output conditional probabilities of \( M \). Machine \( M \) works as follows:
  \[ P\{y_\nu = b \mid x_\nu = a\} = \delta(a, b) \], where \( x_\nu, a \in X \) and \( y_\nu, b \in Y \) and \( P\{B \mid A\} \) is the conditional probability of \( B \) given \( A \).

- Machine \( M_1 \) **simulates** (is equivalent to) machine \( M_2 \) if these two machines cannot be distinguished from each other by observing their inputs and outputs (observing them as black boxes).

The following properties of Model ANN-0 – with the inputs and outputs described by expressions 11, 12, 13, 14 – can be proved (Eliashberg, 1979):

1. Let \( X \) and \( Y \) be finite subsets of the sets of input an output vectors of the model, respectively. Let \( \bar{x}(\nu) \in X \) and \( \bar{y}(\nu) \in Y \). Let \( f^s : X \times X \rightarrow R \) be the similarity function from expression 11 – in this case \( f^s \) is the scalar
product. Let the pair \((X, f^*)\) satisfy the following correct decoding condition

\[
\forall x, x' \in X \quad (\text{if } x \neq x' \text{ then } f^*(x, x') < f^*(x, x))
\]

(15)

For any combinatorial machine \(M = (X, Y, f)\) there exists a state, \(g\), of the LTM of the model (and some fixed values of parameters of the model) such that the model in the state \(g\) simulates (is equivalent to) machine \(M\).

2. The previous result extends to any probabilistic combinatorial machine \((X, Y, \delta)\) with rational probabilities \(\delta\).

2.3 Model AF-0: A trivial primitive E-machine corresponding to Model ANN-0

The "psychological" properties of Model ANN-0 can be described in algorithmic terms. The description presented below gives an example of a trivial primitive E-machine – a primitive E-machine without E-states. This model will be referred to as Model AF-0 (Associative Field # 0).

Notation

In this paper I use a C-like notation mixed with scientific-like notation to represent models of E-machines aimed at humans. (I use C++ for computer simulation.) I use special notation for the following operations:

- A := \{a\} \select {a \text{ with } P(a)}
  - select the set of elements \(a\) with the property \(P(a)\). I use Pascal-like notation ":=" to emphasize the dynamic character of this operation.

- a ∈ A \select {a \text{ from } A \text{ at random with equal probability}}

DECODING: compare input vector with all vectors in Input LTM

\[
\text{for}(i = 1; i <= n; i++) \quad s[i] = \text{Similarity}(x[*], gx[*][i]);
\]  

(1)

CHOICE: select the set of locations with the maximum value of \(s[i]\)

\[
\text{MAXSET} := \{i \mid s[i] = \text{max}(s[1], \ldots s[n])\};
\]  

(2)

randomly select a winner (win) from MAXSET

\[
\text{win} \in \text{MAXSET};
\]  

(3)
ENCODING: read output vector from the selected location, \textit{win}, of Output LTM.

\[
\text{if}(s[\text{win}] > \text{xinh}) \quad y[\ast] = gy[\ast][\text{win}]; \quad \text{else} \quad y[\ast] = \text{NULL}; \quad (4)
\]

Comments:

1. As long as the \textit{Similarity()} function and the set of allowable inputs, \textit{X}, satisfy the correct decoding condition (expression \cite{15} with \(f^* = \text{Similarity}\)), Model AF-0 is a system universal with respect to the class of combinatorial machines.

2. The psychological Model AF-0 is much simpler than the neurobiological model ANN-0. Model AF-0 doesn’t have all the \textit{neural-implementation-parameters} of model ANN-0. It also doesn’t have the fast changing (neurobiological) state \(u\).

3. In the next sections Model AF-0 will be enhanced in several directions.
   
   (a) Adding a \textit{one-cycle delayed feedback} from \(y\) to \(x\). This will change model AF-0 into a system universal with respect to the class of state machines.
   
   (b) Adding a \textit{universal learning algorithm}. The new model will become a learning system universal with respect to the class of finite-state machines.
   
   (c) Introducing \textit{E-state arrays, a next E-state procedure}, and a \textit{Structural LTM (SLTM)}. This will transform Model AF-0 into a nontrivial primitive E-machine capable of producing some interesting effects of working memory and temporal context (mental set).
   
   (d) Introducing \textit{associative inputs and outputs}. This enhancement will allow us to get effects of sparse re-coding, data compression and context-dependent statistical filtering.

2.4 Delayed feedback and simulation of finite-state machines

\textbf{DEFINITION}

A (deterministic) finite–state machine is a system \(M = (X, Y, S, \alpha, \omega)\), where \(X\) and \(Y\) are finite sets of external symbols of \(M\) called the \textit{input and the output sets (alphabets)}, respectively, \(S\) is a finite set of internal symbols of \(M\) called the \textit{state set}, \(\omega : X \times S \rightarrow Y\) is a function called the \textit{output function} of \(M\), \(\alpha : X \times S \rightarrow S\) is a function called the \textit{next-state function} of \(M\). The work of machine \(M\) is described
Figure 6: Finite–state machine as a combinatorial machine with a one-cycle delayed feedback

by the following expressions: \( s_{\nu+1} = \alpha(x_{\nu}, s_{\nu}) \), and \( y_{\nu} = \omega(x_{\nu}, s_{\nu}) \), where \( x \in X \), \( y \in Y \), and \( s \in S \) are the values of input, output, and state variables at the moment \( \nu \), respectively.

Note. There are different equivalent formalizations of the concept of a finite–state machine. The formalization described above is known as a Mealy machine. Another popular formalization is a Moore machine. In a Moore machine the output is described as a function of the next–state. Practical electronic designers usually use the term state machine instead of the term finite–state machine. Any finite–state machine can be implemented as a combinatorial machine with a one cycle delayed feedback (see Figure 6). Using this trick, it is easy to show that Model AF-0 with a delayed feedback can simulate any finite–state machine.

2.5 Introducing a universal learning algorithm

Let us return to the system \((W,D,B)\) shown in Figure 4. Simple as it is, Model AF-0 has enough computing power to serve as the motor control system AM, because the one-cycle delayed feedback ”utter-symbol→symbol-uttered” transforms block AM into a system universal with respect to the class of finite machines (as explained in the previous section). This gives the system \((W,D,B)\) the power of a universal Turing machine. (A Turing machine is a finite–state machine coupled with an external tape through the I/O device called the head. The block \((W,D)\) provides the functionality of the tape and the head of this machine.)

What kind of learning algorithm does the Model AF-0 need to be able to learn to simulate any combinatorial machine?
It is easy to show that the simplest algorithm satisfying this requirement is "tape-recording" the X-sequence and the Y-sequence in the Input and Output LTM, respectively. In the case of a deterministic combinatorial machine, this algorithm can be improved by recording only new associations. In the case of a probabilistic combinatorial machine the same associations need to be recorded several times to accumulate statistics.

In phenomenological terms, the above tape recording algorithm can be described as follows:

```c
BOOL wen;  // write enable: auxiliary input variable
int wpoly;  // write pointer: auxiliary state variable

if (wen) {
  gx[∗][wpoly] = x[∗];
  gy[∗][wpoly] = y[∗];
  wpoly++;
}
```

It is interesting to mention that some famous psychiatrists were advocating this concept of tape-recording-learning. Here is a quotation from Meynert (1884): "Each new impression meets a new, still vacant cell. With the existence of such vast number of these vacant cells, impressions arriving in succession find carriers in which they will remain forever in the same close order".

As mentioned in 1.6, the concept of a "smart" learning algorithm creates a methodological pitfall. The catch is that the human concept of important information changes with experience, so no learning algorithm with a fixed criterion of optimality can be smart enough to know in advance which information is important to store and which is not. What seems unimportant today may become very important tomorrow where more information is acquired.

I argue that there is no special magic in how the knowledge is stored in the brain (distributed, local, analog, digital, etc.). The magic is in what knowledge is stored and how this knowledge is processed dynamically depending on context.

2.6 "Symbolic" or "nonsymbolic," that is the question

Starting with the neural network shown in Figure 5, one can proceed in two different directions:

1. When the neurons in layer N2 compete in a winner-take-all fashion ($1 < α < 1 + β$), the Model ANN-0 can be thought of as a neural counterpart of the Programmable Logic Array (PLA) shown in Figure 7. The input synaptic matrix (Input LTM) is similar to the programmable AND-array, and the output synaptic matrix (Output LTM) is similar to the programmable OR-array. If one goes in this direction one gets some "neural extras," such
as a generalization by similarity and the ability to simulate probabilistic combinatorial machines. Taking this path, eventually, brings one to the concept of a primitive E-machine.

2. If one reduces the competition of neurons in layer N2, one enters the realm of connectionist neural networks. Let us set $\alpha = \beta = 0$. Let us also replace the linear threshold output function by a sigmoid function. Model ANN-0 becomes a typical Parallel Distributed Processing (PDP) system. In the traditional connectionist graphical representation, this system looks like shown in Figure 8.
If one selects this "nonsymbolic" path, one is inspired to view neural networks as analog computational devices implementing multidimensional mappings \( f : \mathbb{R}^m \rightarrow \mathbb{R}^n \), where \( \mathbb{R} \) is the set of real numbers. It is seldom possible to find the weights, corresponding to nontrivial multidimensional mappings, analytically. Therefore the development and study of the learning algorithms, automatically adjusting the weights, becomes the main thrust of this research. (There is plenty of room in multidimensional real spaces, so one can spent one’s life searching for the "magical neural mappings.")

Which way to go? I argue that the first direction is the right way to go if one is interested in biological brain. The second approach has the following liabilities (each of which is sufficient to disqualify this approach as an adequate biological framework):

1. The learning algorithms used in PDP models (such as backpropagation, simulated annealing, etc.) are not universal. (See Rumelhart, McClelland, et al (1986) for the explanation of the PDP framework.)

2. Traditional PDP models don’t have a sufficient general level of computing power to adequately address such critically important "symbolic" problems as the problem of natural language. (See Pinker and Mehler (1988) for a discussion of this issue.)

3. PDP models provide no satisfactory explanation of the phenomena of working memory and mental set. They are largely inconsistent with Observations 1-17 from Section 1.5.

4. Biological neural networks don’t have the accuracy needed to implement traditional PDP algorithms.

5. Traditional PDP models have no room to accommodate the known complexity of biological neurons. The whole vision of the brain as a collective-distributed-dynamical system built from simple "atomic" neurons is inconsistent with the modern neurobiological data (Kandel and Spenser, 1968; Kandel, Jessel, and Schwartz, 2000; Nichols, Martin, Wallace, 1992, Byrne, 1987). A single neuron is a complex integrated computing element. The brain has many different types of neurons tailored for different tasks.

2.7 Introducing E-states: Model AF-1

The basic architecture of Model AF-1 is shown in Figure 9. As compared with Model AF-0, this model has two additional procedures: BIAS and NEXT E-STATE PROCEDURE. Both these procedures are included in the block EXCITATION.
DECODING: compare input vector with all vectors in Input LTM

\[\text{for}(i = 1; i \leq n; i++) \quad s[i] = \text{Similarity}(x[\ast], g_{x}[i]); \quad (1)\]

BIAS: calculate biased similarity. Coefficients \(a\) and \(b\) determine, respectively, the additive and the multiplicative biasing effect of the "residual excitation" \(e[i]\).

\[\text{for}(i = 1; i \leq n; i++) \quad s'[i] = s[i] + a \ast e[i] + b \ast s[i] \ast e[i]; \quad (2)\]

CHOICE: select the set of locations with the maximum value of \(s'[i]\)

\[\text{MAXSET} := \{i \mid s'[i] = \text{max}(s'[1], \ldots, s'[n])\}; \quad (3)\]

randomly select a winner (\(\text{win}\)) from MAXSET

\[\text{win} : \in \text{MAXSET}; \quad (4)\]

ENCODING: read output vector from the selected location, \(\text{win}\), of Output LTM

\[\text{if}(s[\text{win}] > \text{xinh}) \quad y[\ast] = g_{y}[\text{win}]; \quad \text{else} \quad y[\ast] = \text{NULL}; \quad (5)\]

NEXT E-STATE PROCEDURE: calculate next E-state

Figure 9: The general architecture of Model AF-1
For the sake of concreteness let us define the following similarity function:

\[ \text{float } \text{Similarity}(\text{int } * x, \text{int } * g) \]
\[ \{ \]
\[ \text{float } s; \]
\[ \text{int } j, k; \]
\[ s = 0; \quad k = 0; \]
\[ \text{for}(j = 1; j <= m; j ++) \]
\[ \{ \]
\[ \text{if}(x[j] == g[j] \&\& x[j] ! = 0) \quad s ++; \]
\[ \text{if}(k > 0) \quad s / = k; \quad \text{else } s = 0; \]
\[ \text{return } s; \}
\]

Note. The Similarity() is equal to the number of non-zero matches \((x[j] = g[j] \neq 0)\) divided by the number of non-zero components of input vector \((x[j] \neq 0)\).

Many other similarity functions, satisfying the correct decoding condition – Section 2.2, Expression (15) – would work as well.

2.8 Dynamic reconfiguration: ”many symbolic machines in one”

Model AF-1 uses a very simple mechanism of EXCITATION (expressions (2) and (6)). This simple mechanism is sufficient to illustrate some important effect associated with the introduction of E-states.

Terminology. The pair \((gx[*][*],gy[*][*])\) will be called the program or the table of associations of Model AF-1. The pair \((gx[*][i],gy[*][i])\) will be called \(i-th\) command (the \(i-th\) association) of the program (the table of associations). The number of commands in a program will be called the length of the program.
It is easy to prove the following result:

Let $C(X,Y)$ be a class of combinatorial machines with the input alphabet $X$ and the output alphabet $Y$. Model AF-1 with a fixed program of the length $|X| \cdot |Y|$ (or greater) can be changed (reconfigured) into any machine from class $C(X,Y)$ by changing its E-state, $e[*]$.

**Proof.** Let the program $(gx[*][*], gy[*][*])$ contain at least once each pair from $X \times Y$, and let $N(M)$ be the subset of locations containing all commands of a combinatorial machine $M$ from the above class. Let $\tau \gg 1$. Let $e[i] = 1$ if $i \in N(M)$, and $e[i] = 0$ otherwise. Model AF-1 with this program and this E-state will simulate machine $M$.

This result illustrates the importance of E-states. Model AF-0 with a program of the length $|X|$ can simulate a single combinatorial machine from $C(X,Y)$. To simulate a different machine, this model must be reprogrammed. Model AF-1 with a program of the length $|X| \cdot |Y|$ can simulate any machine from the above class without reprogramming.

**Example.** Let $C(X,Y)$ be the class of all logic functions with $m$ inputs and one output, that is, $X = \{0,1\}^m$ and $Y = \{0,1\}$. Model AF-1 with a fixed program of the length $2m$ can be reconfigured into any of the $2^N$ possible logic functions, where $N = 2^m$.

Why is it better to reconfigure than to reprogram? This critically important question will be discussed in Part II of this paper.

### 3 Molecular Interpretation of E-states: Ensembles of Protein Nanomachines as Statistical Mixed-signal Computers

What can be a meaningful neurobiological interpretation of the phenomenological E-states? How can nontrivial next E-state procedures be implemented in neural networks?

This section presents a formalism that offers an answer to these questions. The formalism can be viewed as a system theoretical extrapolation of the main idea of the Hodgkin and Huxley (1952) theory that the sodium and potassium ion channels, embedded in the axon membrane, work as stochastic switches with several internal states (conformations). The formalism was discussed in Eliashberg (1989, 1990a, and 2003).
3.1 Concept of protein molecule machine (PMM)

**DEFINITION.** A *Protein Molecule Machine* (PMM) is an abstract probabilistic computing system \((X, Y, S, \alpha, \omega)\), where

- \(X\) and \(Y\) are the sets of real input and output vectors, respectively
- \(S = \{s_0, \ldots, s_{n-1}\}\) is a finite set of states
- \(\alpha : X \times S \times S \rightarrow R'\) is a function describing the input-dependent conditional probability densities of state transitions, where \(\alpha(x, s_i, s_j)dt\) is the conditional probability of transfer from state \(s_j\) to state \(s_i\) during time interval \(dt\), where \(x \in X\) is the value of input, and \(R'\) is the set of non-negative real numbers. The components of \(x\) are called *generalized potentials*. They can be interpreted as membrane potential, and concentrations of different neurotransmitters.
- \(\omega : X \times S \rightarrow Y\) is a function describing output. The components of \(y \in Y\) are called *generalized currents*. They can be interpreted as ion currents, and the flows of second messengers.

Let \(x \in X\), \(y \in Y\), \(s \in S\) be, respectively, the values of input, output, and state at time \(t\), and let \(P_i\) be the probability that \(s = s_i\). The work of a PMM is described as follows:

\[
\frac{dP_i}{dt} = \sum_{j \neq i} \alpha(x, s_i, s_j)P_j - P_i \sum_{j \neq i} \alpha(x, s_j, s_i)
\]

at \(t = 0\)

\[
\sum_{i=0}^{n-1} P_i = 1
\]

\(y = \omega(x, s)\)

\[
\[dp_{ji} = \alpha(x, s_j, s_i)P_i dt
\]

\(\text{Current state } s = s_i\)

\(\text{Output } y = \omega(x, s)\)

![Figure 10: Protein molecule as a probabilistic nanomachine](image-url)
Summing the right and the left parts of (1) over $i = 0, \ldots, n - 1$ yields

$$\frac{d}{dt} \sum_{i=0}^{n-1} P_i^i = 0$$ (4)

so the condition (2) holds for any $t$.

The internal structure of a PMM is shown in Figure 10, where $dp_{ij}$ is the probability of transition from state $s_j$ to state $s_i$ during time interval $dt$. The output $y = \omega(x, s)$ is a function of input and the current state.

For the probability of transition from state $s_j$ to state $s_i$ we have

$$dp_{ij} = \alpha(x, s_i, s_j)P_j dt$$ (5)

It follows from (1) that

$$dP_i = \sum_{j \neq i} (dp_{ij} - dp_{ji})$$ (6)

### 3.2 Example: Voltage-Gated Ion Channel as a PMM

Ion channels are studied by many different disciplines: biophysics, protein chemistry, molecular genetics, cell biology and others (see Hille, 2001). I am concerned with the information processing (computational) possibilities of ion channels.

I postulate that, at the information processing level, ion channels (as well as some other membrane proteins) can be treated as PMMs. That is, at this level, the exact biophysical and biochemical mechanisms are not important. What is important are the properties of ion channels as abstract machines.

This situation can be meaningfully compared with the general relationship between statistical physics and thermodynamics. Only some properties of molecules of a gas (e.g., the number of degrees of freedom) are important at the level of thermodynamics. Similarly, only some properties of protein molecules are important at the level of statistical computations implemented by the ensembles of such molecules.

The general structure of a voltage-gated ion channel is shown schematically in Figure 11a. Figures 11b and 11c show how this channel can be represented as a PMM. In this example the PMM has five states $s \in \{0, 1, \ldots, 4\}$, a single input $x = V$ (the membrane potential) and a single output $y = I$ (the ion current).

Using the Goldman-Hodgkin-Katz (GHK) current equation we have the following expression for the output function $\omega(x, s)$.

$$I_j = \omega(V, j) = \frac{p_j z^2 F V' (C_{\text{in}} - C_{\text{out}} e^{-zV})}{1 - e^{-zV'}}$$ (7)

where
I
1
2
3
4
a
0
1
2
3
4

\( a_{ij} = \alpha(x,i,j) \)

\( y = \omega(x,s) \)

Figure 11: Ion channel as a PMM

- \( I_j \) is the ion current in state \( s = j \) with input \( x = V \)
- \( p_j \) [cm/sec] is the permeability of the channel in state \( s = j \)
- \( z \) is the valence of the ion (\( z = 1 \) for \( K^+ \) and \( Na^+ \), \( z = 2 \) for \( Ca^{++} \))
- \( F = 9.6484 \cdot 10^4 \) [C/mol] is the Faraday constant
- \( V' = \frac{V F}{RT} \) is the ratio of membrane potential to the thermodynamic potential, where \( T \) [K] is the absolute temperature, and \( R = 8.3144 \) [J/K·mol] is the gas constant
- \( C^{in} \) and \( C^{out} \) [mol] are the cytoplasmic and extracellular concentrations of the ion, respectively

One can make different assumptions about the function \( \alpha(x, s_j, s_i) \), describing the conditional probability densities of state transitions. It is convenient to represent this function as a matrix of voltage dependent coefficients \( a_{ij}(V) \).

\[
\alpha = \begin{pmatrix}
a_{00}(V) & \ldots & a_{0j}(V) & \ldots & a_{0m}(V) \\
a_{i0}(V) & \ldots & a_{ij}(V) & \ldots & a_{im}(V) \\
a_{m0}(V) & \ldots & a_{mj}(V) & \ldots & a_{mm}(V)
\end{pmatrix}
\] (8)

where \( m = n - 1 \). Note that the diagonal elements of this matrix are not used in equation (11).
In the model of spike generation discussed in Eliashberg (1990a) both sodium, \( Na^+ \), and potassium, \( K^+ \) channels were treated as PMMs with five states shown in Figure 11. Coefficients \( a_{10}, a_{21}, a_{32} \) were assumed to be sigmoid functions of membrane potential, and coefficients \( a_{43} \) and \( a_{04} \) - constant. In the case of the sodium channel, \( s = 3 \) was used as a high permeability state, and \( s = 4 \) was used as inactive state. In the case of potassium channel, \( s = 3 \) and \( s = 4 \) were assumed to be high permeability states.

### 3.3 Concept of an Ensemble of Protein Molecule Machines (EPMM)

**DEFINITION.** An *Ensemble of Protein Molecule Machines* (EPMM) is a set of identical independent PMMs with the same input vector, and the output vector equal to the sum of output vectors of individual PMMs. The structure of an EPMM is shown in Figure 12, where \( N \) is the total number of PMMs, \( y^k \) is the output vector of the \( k \)-th PMM, and \( y \) is the output vector of the EPMM. We have

\[
y = \sum_{k=1}^{N} y^k
\]  

(9)

Let \( N_i \) denote the number of PMMs in state \( s = i \) (the occupation number of

![Figure 12: The structure of EPMM](image)

32
state $i$). Instead of (9) we can write

$$y = \sum_{i=0}^{n-1} N_i \omega(x, s_i)$$  \hspace{1cm} (10)

$N_i$ ($i = 0, ...n - 1$) are random variables with the binomial probability distributions

$$P\{N_i = m\} = \binom{m}{N} P_i^m (1 - P_i)^{N-m}$$  \hspace{1cm} (11)

$N_i$ has the mean $\mu_i = NP_i$ and the variance $\sigma_i^2 = NP_i(1 - P_i)$.

Let us define the relative number of PMMs in state $s = i$ (the relative occupation number of state $i$) as

$$e_i = \frac{N_i}{N}$$  \hspace{1cm} (12)

The behavior of the average $\bar{e}_i$ is described by the equations similar to (1)

Figure 13: E-states as the numbers of PMM’s in different states
and (2).

\[
\frac{d\bar{e}_i}{dt} = \sum_{j \neq i} \alpha(x, s_i, s_j) \bar{e}_j - \bar{e}_i \sum_{j \neq i} \alpha(x, s_j, s_i)
\]  \hfill (13)

at \( t = 0 \)

\[
\sum_{i=0}^{n-1} \bar{e}_i = 1
\]  \hfill (14)

The average output \( \bar{y} \) is equal to the sum of average outputs for all states.

\[
\bar{y} = N \sum_{i=0}^{n-1} \omega(x, s_i) \bar{e}_i
\]  \hfill (15)

The standard deviation for \( e_k \) is equal to

\[
\sigma_k = \sqrt{P_k(1 - P_k)}/N
\]  \hfill (16)

Figure 13 illustrates the implementation of E-states as relative occupation numbers of the states of a PMM. The maximum number of independent E-state variables is equal to \( n - 1 \). The number is reduced by one because of the additional equation (14).

### 3.4 EPMM as a Robust Mixed-Signal Computer

An EPMM can serve as a robust analog computer with the input–controlled coefficient matrix shown in Figure 14. Because some coefficients in this matrix can

![Input–controlled coefficient matrix diagram](image-url)

Figure 14: EPMM as an analog computer with an input–controlled coefficient matrix
change sharply (almost step-wise) as functions of inputs (e.g., the membrane potential), an EPMM can be better characterized as a mixed-signal computer. The statistical molecular implementation of this computer is extremely robust, since all the characteristics of the whole computer are determined by the properties of a single PMM.

It is interesting to emphasize that the matrix of input dependent coefficients is implemented as the matrix of input dependent probabilities, so no external connections are needed. It would be very difficult (if at all possible) to reach this level of microminiaturization and this level of reliability using traditional VLSI techniques.

3.5 On conformational dynamics and chemical kinetics

When a neural modeler needs to simulate different effects of cellular STM, he/she usually assumes that these effects are associated with chemical kinetics and/or with the accumulation of different neurotransmitters and/or ions in different cellular compartments. This approach to cellular STM encounters serious problems:

1. It is difficult to justify sufficiently big time constants – chemical kinetics is quite fast, and cellular compartments are very small.

2. It is difficult to justify nontrivial nonlinearities. For example, it is difficult to get different time constants for increase (charge) and decrease (discharge) of an STM variable.

3. It is difficult (if not impossible) to get nontrivial timing effects, e.g., different results for different order of input events.

All these possibilities are readily available with the EPMM formalism that deals with sophisticated conformational dynamics rather than with a relatively simple chemical kinetics.

**IMPORTANT**! To avoid common misunderstanding, I want to emphasize that conformational dynamics has nothing to do with traditional chemical kinetics. Conformational dynamics is determined by the biophysical properties of protein molecules. No chemistry is involved, for example, in the case of voltage controlled channels. Even in the case of ligand controlled channels or enzymes it is inadequate to think about the interaction between a neurotransmitter molecule and a protein molecule as a chemical reaction. Protein molecules are very big (> 50,000 Dalton), whereas neurotransmitter molecules are tiny (< 100 Dalton). A tiny molecule changes the conformation of a big molecule, so the latter can temporarily open its pore (as in the case of an ion channel) or become a catalyst producing a second messenger. (See, for example, Changeux, 1993, and Hille, 2001.)
3.6 What can be computed with EPMM’s?

Very little is known about the properties of different membrane proteins to represent them as abstract probabilistic nanomachines. The best studied are the sodium and potassium channels used in the classical Hodgkin and Huxley (1952) model for the generation of nerve spike. It is believed that these protein molecules have close to five different states each. In this specific case, the EPPM formalism gives a good approximation of the available experimental data (Eliashberg, 1990a, 2003). Therefore, it seems reasonable to believe that this formalism should work well in many other less studied cases.

A single neuron can have several different EPMMs interacting via electrical messages (membrane potential) and chemical messages (different kinds of neurotransmitters). As mentioned in Section 3.2 the Hodgkin-Huxley (1952) model can be naturally expressed in terms of two EPMMs (corresponding to the sodium and potassium channels) interacting via common membrane potential (see Figure 15a). Figure 15b shows two EPMMs interacting via a second messenger. In this example, EPMM1 is the primary transmitter receptor and EPMM2 is the second messenger receptor.

Some examples illustrating nontrivial computational possibilities of the EPMM
formalism will be discussed in Part II of this paper.

3.7 The main statements

1. The whole human brain is a nonclassical symbolic system – an E-machine (Eliashberg, 1967, 1979).

2. The popular notion that the brain implements multidimensional real mapping is a fallacy. The whole concept of a learning algorithm that optimizes synaptic weights to create the above mappings is largely irrelevant to the problem of human learning.

3. The main data storage procedure of the human brain must be universal – close to “memorizing raw experience.” Instead of processing data before placing it in memory, the brain must process “raw” data dynamically (on the fly) depending on context. No context-dependent statistics can be pre-calculated in advance, in principle, because the number of possible contexts explodes combinatorially.

4. Biological neural networks have the right computational resources to implement the above dynamic approach. The main computational engine of the brain is the statistical mechanics of protein nanomachines rather than the ”statistical mechanics of neural networks.” The notion of a neuron as a simple atomic computing element, employed by the latter approach, is inconsistent with the available neurobiological data (Kandel and Spenser, 1968; Kandel, Jessel, and Schwartz, 2000; Nichols, Martin, Wallace, 1992, Byrne, 1987).

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