ESANN'2000 proceedings - European Symposium on Artificial Neural Networks
Bruges (Belgium), 26-28 April 2000, D-Facto public., ISBN 2-930307-00-5, pp. 425-430

NONSYNAPTICALLY CONNECTED NEURAL NETS

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Abstract. Neural nets are generally considered to be connected synaptically. However, the majority of information transfer in the brain may not be by synapses. Nonsynaptic diffusion neurotransmission (NDN) may be a major mechanism for information transfer in the brain. In this paper, a model of a diffusive-only neural net, based on a ligand-receptor dynamics, is presented. A mechanism of active release of neurotransmitters as a response to binding, along with one of depletion of free ligands, make the net capable of spontaneous activity. States of thermodyamical equilibrium, and trajectory of the system in the phase space have been numerically determined. The results indicate the possibility of chaotic behavior. The relevance of the theoretical model to the study of some brain mass-sustained functions is discussed.

Introduction

Information in the brain appears to be transmitted both by synaptic connectivity and by nonsynaptic diffusion neurotransmission (NDN). NDN includes the diffusion through the extracellular fluid of neurotransmitters released at points that may be remote from the target cells, with the resulting activation of extrasynaptic receptors, as well as intrasynaptic receptors reached by diffusion into the synaptic cleft. NDN also includes the diffusion of substances such as nitric oxide (NO) and carbon monoxide (CO) through both the extracellular fluid and cellular membranes.

As we have noted elsewhere (1), early studies on regional distribution of enkephalin in the brain pointed out discrepancies, or "mismatches", between opiate peptide distributions and opiate receptors (2). Although these were initially considered to be exceptional instances, Herkenham concluded that, in the brain, mismatches are the rule rather than the exception (3).

Non synaptic receptor sites can be demonstrated on cell bodies: Basbaum and associates have demonstrated mismatches in the substance P receptors and sites of release, where only 15% synaptic opposition was noted, while 70% of the cell surface was found to be covered by substance P receptors. Those findings support their conclusion that "much of the surface of substance P receptor-expressing neurons can be targeted by substance P that diffuses a considerable distance from its site of release" (4).

Studies in Routtenberg's laboratory in the late 1960s demonstrated that transmitters could readily move in the extracellular space (c.f., 5), and microdialysis studies indicate that virtually all the neurotransmitters are found in the extracellular fluid (6, 7), which confirms that the conditions exist for NDN.

Estimates of space requirements (8) and energy consumptions (Aiello and Bach-y-Rita, submitted) in synaptic and nonsynaptic neurotransmission suggest that it is very unlikely that synapses could be the exclusive means of information transmission

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in the brain. NDN may be the primary information transmission mechanism in certain mass-sustained functions, such as sleep, vigilance, hunger, brain tone and mood (9), as well as several abnormal functions, such as mood disorders, spinal shock, spasticity, and drug addiction (10).

Many brain functions appear to be controlled by cell-assemblies of varying numbers and populations of neurons. Tononi and Edelman (11) predicted that during cognitive activities involving consciousness, there should be evidence for a large but distinct set of distributed neuronal groups that interact much more strongly among themselves than with the rest of the brain. They cited evidence that, in working memory tasks, sustained neural activity is found in the prefrontal cortex. We suggest that NDN may play an important role in these mass- sustained functions, which may involve those brain areas that are highly developed in humans.

Cell-assembly architecture for mass-sustained functions is likely to consist of varying combinations of synaptic and NDN connectivity, depending on the specificity of the function. The unrealistic figures resulting from hardwired connectivity calculations (8), and the space and energy saving functional roles of the extracellular space in NDN (12), support Tononi and Edelman's (11) considerations.

2. NDN neural network

For cell-assemblies controlling mass-sustained functions, such as "mood" and "hunger", the exchange of information along "private lines" appears less mandatory than for selective, fast functions, such as the finger movements of a piano player. It is likely that densely populated neuronal arrays handle information *mainly* through synchronization of the activity of the *whole* array. Mass-sustained functions would then be "ensemble" functions, ruled by statistics rather than by mechanistic determinism. An hypothetical "wireless" cell-assembly would be capable of handling this kind of information at a relatively small metabolic cost.

The approach to neuronal modules as thermodynamic systems provides a theoretical framework in which modern computational algorithms can be successfully imported. Thus, a neuronal module would have "degrees of freedom", a "position" in the phase-space, an "energy", and other measurable, "collective" (*thermodynamic*) properties. It also would have "equations of motion", and "states" to which to tend, or from which to depart in its wandering in the phase-space. Information would be stored in such states.

Formally, a NDN-network is an assembly of N identical "neurons", uniformly distributed in a volume V, and n particles of "neurotransmitters" of different species, which diffuse passively in the extracellular space. Neurotransmitters are released and uptaken according to a ligand-receptor dynamics (13). The average molar concentrations of neurotransmitters (*ligands*) are taken as the *generalized coordinates* of the net. Thus, in a 3-ligand model, the generalized coordinates will be L_1, L_2 and L_3. Binding sites are assumed ligand-specific, i.e., the affinity for a ligand depends whether or not a *different* ligand is already bound to the cell. In other words, the neurons behave like "multivalent" receptors (13). The cell responds to the binding of a ligand with the release of more neurotransmitters. Injection of ligands from outside (*phoretic* injection) represents an external stimulus. Neurotransmitters are re-uptaken

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(*endocytosis*), mopped off, and degraded by specific agents (*enzymes*) in the extracellular environment. A stochiometric equilibrium is reached for suitable concentrations of free and bound ligands. Seven stochiometric constants result, corresponding to the reactions listed in Table I.

Table I – Stochiometric equilibrium

Binding reaction	*Stochiom. const.*
$R+L_1 \Leftrightarrow RL_1$	K_1
$R+L_2 \Leftrightarrow RL_2$	K_2
$R+L_3 \Leftrightarrow RL_3$	K_3
$RL_2+L_1 \Leftrightarrow RL_{1,2}$	K_{12}
$RL_3+L_1 \Leftrightarrow RL_{1,3}$	K_{13}
$RL_3+L_2 \Leftrightarrow RL_{2,3}$	K_{23}
$RL_{1,2}+ L_3 \Leftrightarrow RL_{1,2,3}$	K_{123}

R represents the neuron with all binding sites empty, RL_{123} the neuron with all sites occupied (bound). Likewise, RL_1 is the neuron with L_1 bound, RL_{12} when both L_1 and L_2 are bound, and so on. The extent of binding is measured by:

$$B_j = \frac{K_{jeq} L_j}{1 + K_{jeq} L_j} \quad (j=1,2,3) \tag{1}$$

where L_j is the molar concentration of ligand "j". The equivalent stochiometric constant K_{jeq} is a non–linear function of the concentrations of the *other two* ligands.

In general, when the ligand concentrations are perturbed by small injections δL_1, δL_2, δL_3, some of the excess is sequestered by the receptors, so that the variations *at equilibrium* are: $dL_1=\delta L_1–NdB_1$, $dL_2=\delta L_2–NdB_2$, $dL_3=\delta L_3–NdB_3$, with NdB_1, NdB_2, NdB_3 the amounts of ligand of each species sequestered by the neurons. Since each binding fraction is a non-trivial function of all three ligands, its differential is a sum of three terms. As a consequence, the general equation $dL_j+NdB_j=\delta L_j$ yields the following system of (linear) algebraic equations:

$$\begin{aligned}
&\left(1+N\frac{\partial B_1}{\partial L_1}\right) dL_1 + N\frac{\partial B_1}{\partial L_2} dL_2 + N\frac{\partial B_1}{\partial L_3} dL_3 = \delta L_1 \\
&N\frac{\partial B_2}{\partial L_1} dL_1 + \left(1+N\frac{\partial B_2}{\partial L_2}\right) dL_2 + N\frac{\partial B_2}{\partial L_3} dL_3 = \delta L_2 \\
&N\frac{\partial B_3}{\partial L_1} dL_1 + N\frac{\partial B_3}{\partial L_2} dL_2 + \left(1+N\frac{\partial B_3}{\partial L_3}\right) dL_3 = \delta L_3
\end{aligned} \tag{2}$$

The sources δL_1, δL_2, δL_3 may be *internal*, e.g., the *active* release of neurotransmitters by the cells themselves as a response to a molecular stimulus (i. e.,

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the binding of a ligand). In this case, each cell is thought as having a "hidden pool" of neurotransmitters, maintained by metabolic processes. This is a realistic assumption. As for the mechanism of active release, we make the hypothesis that neurons release in order to saturate all their binding sites. A further assumption is that neurons would actively release *provided* there are enough sites to fill. Thus, a low extent of binding would favor active release. In operative terms, a measure of the available sites for ligand L_j is $1-B_j$ (i.e., the *complement* $\bar{B}_j$ of the binding fraction). With η_j a *threshold* value, active release (*firing*) of L_j would occur if $(1-B_j)\geq\eta_j$.

Depletion of free ligands may also turn the net on. In fact, depletion induces passive release of bound ligands, which might lower the binding fractions below the critical value. The mechanism of ligands *depletion* is here assumed in the form: $\mu_j=-\Delta L_j/L_j$, with μ_i a *constant*. In presence of depletion, an injection δL_j would be reported in eq.s (2) as $\delta L_j-\mu_j L_j$. Fig. 1 shows the spontaneous response of the net under all the above assumptions.

4. Discussion

In this model of neural net, hard links among neurons are replaced by probabilistic interactions. Any topological driving structure, typical of classical ANN, disappears, as our "neurons" interact *with the microenvironment*, rather than with each other. The microenvironment, in turn, changes its properties in response to the interactions. Repetitive features, like "reverberations", are visualized in the phase space as closed lines connecting states of *thermodynamical* equilibrium.

As a consequence of the thermodynamic approach, "time" is never considered explicitely. We refer to the time-interval between successive states of equilibrium as to a "clock pulse", a *constant* independent of the actual distance between states. The states of our system are not stable in a strict sense. Even in absence of active release, depletion would cause the system to drift in space. Our states of equilibrium are "stable" only for the duration of a clock pulse.

Our interest is entirely focussed on the *geometric* features of the trajectory. All efforts are aimed to gain control upon these features. For each parameter settings we try to analyze the system tendency to "spiral", we count the number of "turns", or check whether the system sets on a periodic orbit, or ends into a stable point. In other words, we look for the presence of *chaotic* features.

Chaos dynamics has an impressive similarity to the *modus operandi* of brain mass-sustained functions, like "moods". One can stay in a mood for a long time, not forever though: a mood change sooner or later *will* occur, often suddenly. Typical trajectories, with their apparently endless winding around a "basin of attraction", and their sudden jumping from a basin of attraction to another (*bifurcations*), closely mimic this brain behavior. In Chaos theory, states of equilibrium belong to the so called "non-wandering" set (17). Finding out the topology of this set, and how it is affected by a change in the parameters of the net (e.g.,distance between cells, tortuosity, initial concentrations of free ligands, etc.), would help modeling brain behavior. Behavioral changes induced by drugs may be interpreted in terms of

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"bifurcations" induced by phoretic injections, thus providing a theoretical basis to investigate pharmacodynamics as well.

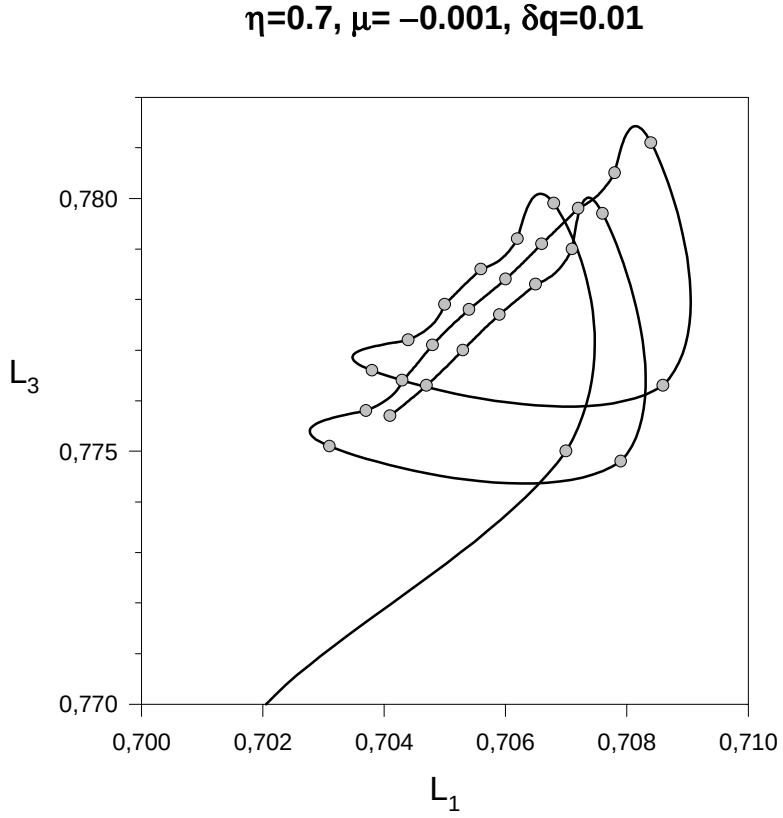

Fig. 1 – Profile of the trajectory of the system in the L_1,L_3 plane, after 20 clock pulses. Some "winding" appears. The trajectory does not actually intersect, as the coordinates L_2 *differ* at the points of intersection. (*Data*: $K_1=K_2=K_3$, $K_{12}=0.7\ K_1$, $K_{13}=0.2\ K_1$, $K_{23}=0.5\ K_1$, $K_{123}=0.1\ K_1$).

Our results are quite preliminary. Chaotic features of a NDN net are still to be sought. Three loops, as shown in Fig. 1, are too few to indicate a tendency of the system to loop around a basin of attraction. Consequently, it is hazardous to claim that a "mode" - to which some sort of "information" may be associated - has been found. Actually, after the third loop, the behavior (not shown) changes abruptly, resembling

a Brownian motion. We do not know whether a more “regular” behavior will be resumed in the long range. It is not even clear whether this sudden change is a computer artifact, or an intrinsic feature of the model. Questions like these are common in the study of chaotic systems. Our future work is devoted to providing reliable answers to these questions.

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