SIMULATING A NETWORK OF CORTICAL AREAS USING ANATOMICAL CONNECTION DATA IN THE CAT

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Abstract:
To what extent does corticocortical connectivity alone provide an explanation of the macro-scopical flow of activity recorded in the cerebral cortex of anesthetized cats?
Different models of connectivity between cortical areas have been incorporated into a simple cortex model with binary activity states. We compare simple connection schemes (nearest-neighbor and nearest-neighbor-or-next-door-but-one) with a connectivity model based on a database collated from anatomical tracer studies. The agreement with functional neuronographic experiments produced by systematic connections is considered in relation to random connectivity constrained by equal connection distributions. All connectivity models reproduce the experimentally observed activity patterns in the cerebral cortex of the cat significantly better than random connections (mean error percentage 20 % versus 40 %). However, real anatomical connections exhibit the most significant performance difference of systematic versus random connectivity. In addition, they reproduce typical topographic features of electrophysiologically demonstrated activity spread in the cerebral cortex of the cat.

1. INDRODUCTION

Systematic application of tracer techniques in neuroanatomical research has revealed a wealth of association fibres connecting distinct areas in the cerebral cortex of mice, rats, cats, and macaques. The complexity of these association fibres calls for higher order analysis tools that can unravel general principles of organization and function of these networks.

Previous investigations concentrated on the structural organization of association fibre networks. Analysis of laminar patterns of fibre termination provided evidence that all major cortical sensory systems show hierarchical arrangements of cortical areas and that some systems can be divided further into several “streams of processing“ \cite{AN:Youngetal94, AN:FellemanVanEssen91}. Optimization analysis of the topological organization of cortical areas indicates prominent connectivity between cortical motor and somatosensory systems, while frontal and allocortical areas form the most central network of interconnected processing units \cite{AN:Youngetal94, AN:Youngetal95}.
Association fibres provide the most massive and direct route of information transfer between cortical areas. Therefore, it is likely that the structural organization of these fibre networks reflects functional interactions between cortical areas. In order to substantiate this notion, it is necessary to correlate the structural organization of association fibre networks with functional maps of the cerebral cortex. It is seldom remembered that extensive functional maps of cortical connectivity patterns were recorded between the 1920s and 1950s using a method called strychnine neuronography \cite{AN:DusserDeBarenneMcCulloch38}. Local application of strychnine to very small portions of cortex in vivo results in the appearance at the stimulation site of rapid potential fluctuations (``strychnine spikes") that can be measured in the electrocorticogram. Application of strychnine does not affect myelinated fibres, evokes similar spikes irrespective of the cytoarchitectonic structure of the area, and is followed by a directed propagation of spikes along pathways that course through the white matter. After a few minutes strychnine spikes can be detected in further cortical areas with multi-electrode arrays. The resulting maps of activity show a specific pattern of distribution that varies depending on the stimulated area. The activity maps after local application of strychnine are very similar to the distribution of after-discharges induced with prolonged electrical stimulation or application of penicillin \cite{AN:DusserDeBarenneMcCulloch38}. Extensive use of strychnine

neuronography has yielded comprehensive maps of functional connectivity in the cerebral cortex of cats, macaques, and chimpanzees, for example \cite{AN:Garol42a, AN:Garol42b, AN:MacLeanPribram53, AN:DunsmoreLennox50, AN:McCulloch44, AN:VonBoninBailey47, AN:Baileyetal50}.

2. METHODS

2.1. The connectivity data

Recent publications present accumulated databases of corticocortical connections that were identified by anatomical tracer studies in different species \cite{AN:FellemanVanEssen91,AN:Scannelletal95}. A database of corticocortical connectivity in the cat contains 1139 connections between 65 areas collected from about 75 published studies \cite{AN:Scannelletal95}. The connection strengths in this database were graded from 0 to 3 according to Table 1.

Table 1 about here

The topography of the traced connectivity, the TC connectivity model, was found to differ from simple local connectivity models such as the nearest-neighbor (NN) or nearest-neighbor-or-next-door-but-one (NBO) \cite{AN:Scannelletal95}. In the following the NN, NBO and TC connectivity model will be used in a network model of cortical areas, to investigate the flow of cortical activity on a macroscopical scale.

2.2. The electrophysiological data

The results of our simulations have to be compared with relevant functional imaging data.
Because of the limited amount of PET and fMRT data in the cat we turned to the older but extensive topographic data obtained by functional neuronography \cite{AN:MacLeanPribram53}: Saturated strychnine sulfate was applied to small patches of cortex inducing stable and reproducible patterns of cortical activity recorded with bipolar electrodes in a total of 18 anesthetized cats. The resulting activity was mapped topographically marking active and silent areas. The remainder of the areas had not been explored or showed variable activity.
Detailed studies of the flow of stimulation-evoked cortical activity have been published for interconnected areas in the suprasylvian gyrus of the cat \cite{AmzicaSteriade95}.

2.3. Basic assumptions of the model

Cortical areas have been defined primarily on the basis of singular structural features such as their cellular and fiber architecture \cite{AN:Jones87}. The structural homogeneity of an area implies a degree of functional homogeneity as reflected in the localization of sensory, motor, or speech areas. In the simulations we regard cortical areas as homogeneously activated.
By far the largest contingents of afferents to any cortical area originate from other cortical areas and from thalamic nuclei \cite{AN:White89}. Corticocortical afferents are assumed to be excitatory since long axons originate only from pyramidal neurons. It is known that anesthesia impedes the transfer of activity from the periphery to the cerebral cortex predominantly at the level of the thalamus \cite{AN:Angel1991}. Therefore, cortical stimulation and recordings in anesthetized animals may give an impression of activity flow relying primarily on corticocortical connectivity. Based on these assumptions we wondered whether the activity spread caused by stimulation of small cortical areas in anesthetized cats would be replicated by selective activation of a network of homogeneous units that were linked according to known corticocortical connectivity.

2.4. The network model

Each model unit describes the activity of one cortical area as ``active" or ``silent" by a binary variable. Thus, cortical activity is represented by a binary pattern $x \in \{0,1\}^n$ with the number of areas $n=65$. A connection from area i to area j is denoted with s_{ij}.In the TC model we used the values of interaction strengths $w_{ij} = (s_{ij})^{\gamma}$,where the exponent γ can be used to align the numerical difference between the degrees of connection strength. In the NN and NBO model connections between areas satisfying the corresponding neighbor condition were set to a value of one in a binary connection matrix: $w_{ij}\in\{0,1\}$.

In each of the experiments described by \cite{AN:MacLeanPribram53} the initial pattern $x(0)$ contained a single active component: the strychninized area. It is used in the following parallel iterative update prescription:

x(r+1)_j = H\kle{ \sum_{i=1}^{n}w_{ij} x(r)_i - \Theta } \;\;\; \forall j,

where Θ is the activation threshold of a unit and $H\kle{x}$ is the Heaviside function. For a chosen value a of active units the threshold was aligned so that the network reaches a steady state smoothly, i.e.,

\Theta(r+1) = \mbox{ max}\{ \Theta : \betr{x(r)} < \betr{x(r+1)} \leq a \}.

Following activation of individual units we observed a time-dependent spread of activity. The final activity states (fixed points) reached by (\ref{update}) and (\ref{thresalign}) were compared with the activity maps drawn by \cite{AN:MacLeanPribram53}. Figure~\ref{seq2b} gives an example of a spread of activation sequence obtained by a simulation.

Fig. 1 about here

Possible error types are ``miss'' errors if the simulation results in silent areas that have been reported to be active, and ``add'' errors if activity is found in areas reported to be silent. Areas with unknown or variable activity were disregarded in the error statstics. A fixed set of parameters γ and the auto-interaction $b:=s_{ii} \;\forall i$ were chosen as to produce good agreement between physiological observations and the TC model. In the NN model we used $b=1$. The parameter a was aligned for each initial pattern individually.

3. RESULTS

We investigated the global match between the experimental results from \cite{AN:MacLeanPribram53} with our simulations using the three different connectivity models, NN, NBO and TC. The non-binary connection values in the TC model have been generated with the parameters $\gamma = 2$ and $b=10$. However, variations of these parameters turned out to produce qualitatively similar results: the simulations where not very sensitive on the grading of connection strengths. The error percentages achieved by the three connectivity models is shown in Figure~2. Experiments with frontal, parietal, and occipital stimulation are better reproduced by TC connections, whereas experiments with temporal stimulation are better fit by the NN and NBO connectivity models. With the same overall mean errors of roughly 20 \% the different connectivity models appear to perform equally well.
In order to judge a connectivity model performance, we need to know how much it outperforms models with random connections. We carried out additional simulation experiments using random connections with connection densities taken from the connectivity models. Each curve in Figure~3 displays the average error in an ensemble of 20 random connection configurations. The overall error percentage values for NN-, NBO- and TC-connection density are 35 \%, 37 \% and 41 \% respectively. The most significant difference between random and systematic connections is obtained by the TC model depiced in Figure~4 where the performance of random connections is displayed with mean deviation: Obviously, the probability is very low that random connections can produce similar or better results than really existing connections.

Fig 2, Fig 3 and Fig. 4 about here

There are three basic types of problems causing discrepancies between simulations and experiments: a) the simplifying assumptions in the model design are not correct, b) the electrophysiological data are not appropriately transfered in the model, c) the available anatomical data are incomplete or inaccurate. The stimulated areas located near the Sylvian sulcus and the basal aspect of the brain (corresponding to experiments displayed as the six leftest points in the figures) could not be identified unambiguously from the lateral and medial drawings of the cat brain shown in \cite{AN:MacLeanPribram53}.

In particular for the TC connectivity model this problem of type b) could account for the comparatively high deviations in this range.
With respect to the third type of problems a careful look at the available studies of the cat cortex reveals a more detailed architecture than had been provided in the connectivity database, particularly again for the ventral areas.
Among the problems of type a) are the diversity among cortical areas (we used the same input/output functions), the laminar preferences of corticocortical connections (we did not differentiate between so-called ``forward'' and ``backward'' connections), and the limited selectivity of anesthetic agents (impact on cortical and thalamic firing patterns was ignored). At a first stage, we considered it preferable to keep the model simple rather than to introduce a complexity that would have been hard to evaluate.
In addition to the global results displayed in the figures 2-4 we found a striking correspondence of individual topographic features in the TC model with electrophysiological data. Among the well studied properties of the cerebral cortex of the cat is the massive projection from area 7 to area 5, which is thought to be the anatomical substrate of the short-latency posterior-to-anterior suprasylvian EPSPs described by \cite{AmzicaSteriade95}. Even though the connection strengths in the database of \cite{AN:Scannelletal95} do not reveal a strong asymmetry of the fiber connections between areas 7 and 5 the TC model consistently produced a spread of activity in the suprasylvian gyrus in the posterior-to-anterior direction which can be observed in Figure~\ref{seq2b}) beginning with the 18th time step.
A related feature is the selective spread of activitity in the suprasylvian and posterior ectosylvian gyri (cf. stimulation in areas 36 and 20b). Again, the TC model reproduced this topographic pattern and revealed a low threshold for the activation of areas EPp and 7 in the nomenclature of \cite{AN:Scannelletal95}.
The search for a correlation between structure and function of the brain will be severely supported by recent development of functional imaging techniques, such as PET, fMRT, or MEG, allowing recordings from awake animals with highly enhanced spacial and temporal resolution. Unforunately, for the cat no such experiments have been carried out so far.Recordings of the activation induced by magnetic intragranular stimulation during light anesthesia of the animal with such imaging techniques would be very interesting. The presented method will be applied to anatomical and physiological data of the macaque monkey.

4. SUMMARY

1. The complexity of corticocortical connections requires computer-assisted analysis to reveal its influence on the cortical flow of activity. The present paper examines a straight-foreward approach to this problem: Can the macroscopic activity flow observed in physiological experiments be simulated by network simulations using connectivity models between cortical areas ?

2. The three connectivity models nearest-neighbor (NN), nearest-neighbor-or-next-door-but-one (NBO) and experimentally traced connections (TC) reproduce neuronographic experiments with comparable overall mean errors of approximately 20 \%. The systematic connections performed clearly better than simulations with random connections leading to errors of approximately 40 \%.

3. The most significant performance difference from random connections was obtained with the TC model.

4. The performance of the TC model does not critically depend on the precision of the grading of corticocortical connection strengths from experimental tracer studies.

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