On the relationship between neural density and functional connectivity in the murine cortex

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Abstract

During development, the mammalian brain differentiates into specialized regions with distinct functional abilities. In this work we explore the effect of neuronal density on functional structure. The nonlinear electrical dynamics of living neuronal networks are recorded and used to generate activation graphs using a competitive first response model. The activity patterns are further analyzed using information theory to classify structures according to function. Results demonstrate differences between dense and sparse networks in terms of informational groups, pairwise relationships, and activation graphs. These differences suggest that variations in cell density may result in different functional specialization of nervous system tissue.

Introduction

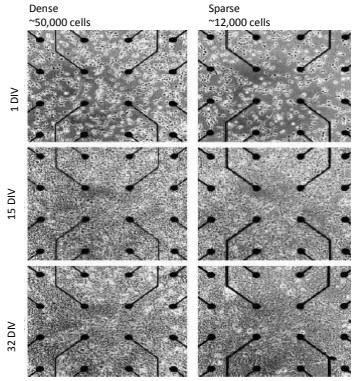
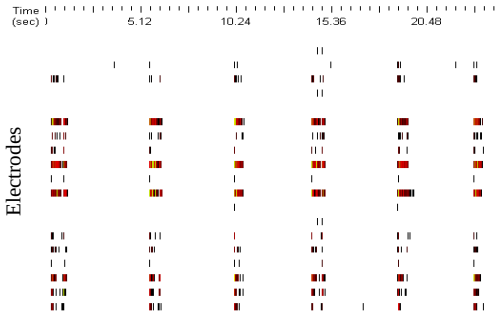


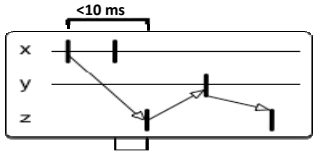
Figure courtesy BMC Neuroscience. From Wagenaar et al., 2006

- Cortical neurons from fetal mice are dissociated, then plated onto microelectrode arrays
- Microelectrode arrays have 60 electrodes, and record electrophysiological signals.
- Networks are allowed to develop and are recorded for half an hour at a time on days ranging from 4-35 days in vitro (DIV). Not every day was recorded
- Four dense (D1-D4) and four sparse (S1-S4) networks were studied in depth

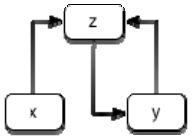


Electrodes record spikes (timestamp) when an electrophysiological threshold is reached. The image above shows an example of spike patterns observed in cultured cortical networks.

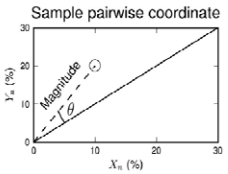
Pairwise Interactions



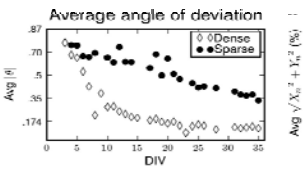
A neuron is said to lead another if the second neuron is the first to respond within a biologically plausible time window (1-10ms)



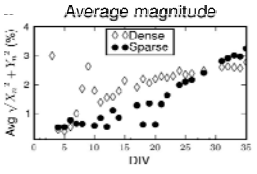
Pairwise connectivity graphs are created to show how neurons lead one another and the strength of that leadership.



For each pair (X,Y) the probability that X leads Y (X_n) and the probability that Y leads X (Y_n) is calculated. Those values are plotted as a coordinate (above) then the coordinates magnitude and deviation from the line $X_n = Y_n$ is calculated



Average angle (radians) of deviation in dense and sparse networks. Throughout maturation, sparse networks show greater deviation than dense. In both cases deviation decreases with age, but deviation in dense networks decreases faster.



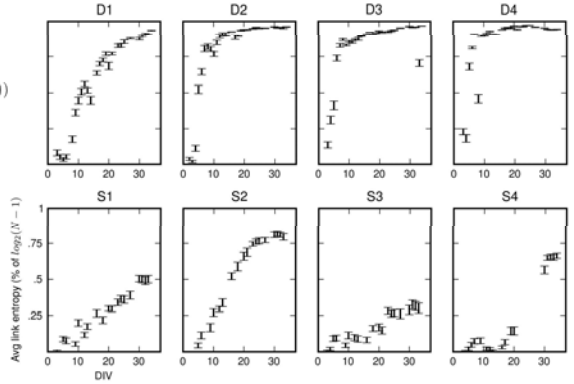
Comparison of average magnitude across all study networks in dense and sparse networks. Magnitude in dense networks increases faster than sparse, but sparse networks exhibit higher vales after 30 DIV.

Link Entropy

- Link Entropy measures the uncertainty that an electrode will lead (activate) another and is given by

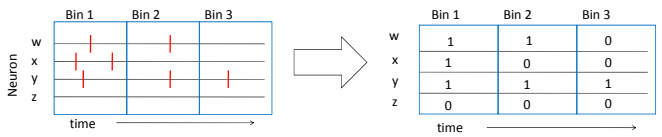
$$H_i = -\sum_{j=1}^{N-1} p(x_{ij}) log_2(p(x_{ij}))$$

- Large values of link entropy indicate that a neuron activates many different follower neurons with nearly uniform probability
- The largest values of link entropy occur when a neuron activates all other neurons with equal probability
- Low link entropy values indicate that a neuron to activates follower neurons with a heavy bias to a small number of them
- Link entropy increased as networks mature



Average daily activation link entropy and standard error in dense (D1-D4) and sparse networks (S1-S4). Averages are plotted as a percent of the maximum link entropy. Average values in dense networks come close to maximal value, indicating that all nodes in the network have nearly equally probable connections with all other nodes. Values plotted are normalized by the maximum possible value, which corresponds to the top of each plot.

Informational Relationships



To create informational relationships, timestamps are first digitized in 10ms bins. If a neuron fires within a bin, the bin gets a value of 1, otherwise it gets a value of 0. This allows the firing probabilities for single neurons *p(x),* pairs of neurons *p(x,y)* and even the neuronal triplets *p(x,y,z)* to be calculated.

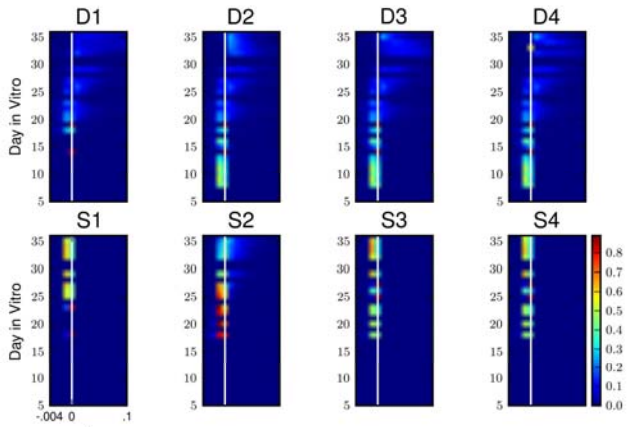
Then mutual information between pairs and triplets (see below) can be calculated.

$$I(X;\{Y,Z\}) = \sum_{x,y,z} p(x,y,z) log_2 \frac{p(x,y,z)}{p(x)p(y,z)}$$

We use the following measure (R) to characterize the functional informational nature of an ensemble (Schneidman et al., 2003).

$$R(X,Y,Z) = I(X;Y) + I(X;Z) - I(X;Y,Z)$$

Groups of three electrodes (triplets), are the smallest (and most abundant) arrangement capable of providing information about functional connectivity in a network (Bettencourt et al., 2008)



Computed R values for all ensembles of 3 electrodes in developing networks. Independent R values (*R=0*) are not depicted. Dense networks (D1-D4) are depicted on the top row and sparse (S1-S4) on the bottom row. Dense networks change from primarily synergetic relationships to primarily redundant at about 18 DIV and by 30 DIV redundant ensembles dominate. At early and late stages of maturation, sparse networks S1, S3 and S4 are dominated by synergetic relationships. Starting around 18 DIV, sparse networks switch between primarily redundant and primarily synergetic until about 25 DIV when they settle on primarily redundant. Note in S2, redundant ensembles that develop around 28 DIV though synergetic relationships do not disappear as in dense networks.

Discussion

- Development of functional connectivity in non linear neural networks is affected by network density
- Link entropy between pairs tend to be biased in sparse networks and nearly equal in dense

  Connections that are nearly equal could allow for fault tolerance in a network

  Biased pathways may help animals make faster decisions

- Due to the similarities between in vivo and in vitro networks, such features may be present in living organisms.

References

Bettencourt L.M.A., Gintautas V., Ham M. I. (2008) Identification of functional information subgraphs in complex networks. Phys Rev Lett 100:238701.

Schneidman E., Bialek W., Berry 2nd M. J. (2003) Synergy, redundancy, and independence in population codes. J Neurosci 23:11539.

Wagenaar D.A., Pine J., Potter S.M. (2006) An extremely rich repertoire of bursting patterns during the development of cortical cultures. BMC Neurosci 7:11.

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