Intracortical connectivity of pyramidal and stellate cells: estimates of synaptic densities and coupling symmetry

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Abstract. A method is outlined for estimating the the average number of synapses forming between cortical neurons as a function of their intercellular separation and the geometry of their dendritic and axonal arborization. Consideration is confined to the formation of local intracortical connections and to the case where the distribution of axonal and dendritic fibres has spherical symmetry. Parameters are deduced from quantitative anatomical studies in murine cortex. It is demonstrated that the majority of local connections forming within a given volume of isotropic cortex can be accounted for on the assumption that local connections between neurons form randomly.

From these computations the symmetry of connection between neurons, the likely position for synapse formation on the dendritic tree and the relative synaptic densities attributable to long- and short-range interaction between excitatory and inhibitory neural subsets is determined. Local intracortical couplings appear to be highly asymmetric, and account for about 3200 synapses forming on pyramidal and stellate cells.

1. Introduction

For the purposes of simulating cortical neural networks, it would be desirable to have general analytical relationships describing the density of interaction of neurocellular components at the different scales found in the cerebral cortex. Defining this anatomical interaction has implications for the magnitudes of feedforward and feedback gains in both lumped and discrete models of cortical electro-rhythmogenesis (see following paper [21]) and also specifies the spatial transformation of activity to be expected in discrete cellular models.

The neocortex is complex. Areal variations exist in the cortex, both in terms of vertical (the familiar laminae of heterotypical cortex) and horizontal (e.g. Brodmann’s areas) organization. However, if we are prepared to make a number of simplifying assumptions, progress can be made towards defining some sort of regularity and order. While upwards of 30 morphologically distinct neuronal subtypes have been identified [16, 22], it is possible to divide the cortical neuronal population broadly into two groups based on the geometry and distribution of axonal and dendritic ramification. These are the pyramidal and stellate cells. This morphological classification also corresponds to their functionality: pyramidal cells are thought to be exclusively excitatory and the stellate cells inhibitory [4].

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Interaction between neurons occurs at a number of different spatial scales: short range (local intracortical interactions), medium range (the surface-parallel conduction fibres in layer I) and long range (the anisotropic and isotropic cortico-cortical efferents and afferents).

Anatomical data suggests that lawful relationships can be found to describe the geometric organization of branching in pyramidal and stellate cells in the visual and motor cortices of the cat [14]. Regrettably there is a deficit of similar data for axonal ramification, in part because of technical difficulties imposed by the narrow diameter of axons and, in the case of pyramidal cells, their wide area of distribution. This has necessitated our attempt to describe axonal branching using very schematized models of axonal growth that ignore many features of development.

For the purposes of this paper we confine ourselves to the investigation of local intracortical connectivity between pyramidal and stellate cells, developing a simple 'stochastic' method for determining the expected number of synapses between two cells separated by a distance \( r \). This method was motivated by the work of Uttley [19].

However, Uttley's treatment never dealt with the more general cases, had a fatal theoretical error and, due to the paucity of anatomical data at the time, was never applied to estimating total synaptic numbers or coupling symmetry.

2. A method for calculating connectivity

2.1. Basic assumptions

The following assumptions apply throughout. Other specific assumptions and simplifications are introduced as needed.

- The basal dendritic system of a neuron has approximately spherical symmetry. This implies that the expected distribution of axonal and dendritic branches crossing any arbitrary concentric sphere about the cell body is uniform.
- The apical dendritic tree can be ignored for calculation of intracortical connectivity as it usually ramifies in the uppermost layers and is believed not to be a significant recipient of local intracortical axons.
- Only axo-dendritic connections need be accounted for.
- As the volume of axonal and dendritic branching per cell is small compared with the volume in which the fibres distribute themselves the probability of a synapse forming between any two cells, at any particular point in the field of their overlap, is small.
- Systematic variations in dendritic radius and horizontal and vertical anisotropies in cortical organization can be ignored for the purposes of simplicity.
- Axonal fibre density for all neurons can be described by a radially homogenous exponential distribution of the form \( a_{ax} e^{-r/r_a} \), where \( r_a \) is the axonal space constant, and \( a_{ax} \) is the 'density' of the axonal tree at \( r = 0 \).

Our approach uses certain established quantitative anatomical measurements as primary to our calculations. Their specific values are introduced as needed, while both primary and derived statistics are presented in tabular form (table 1).

2.2. Formulation

We choose to treat each fibre tree as composed of small straight segments. These segments may correspond physically to the sections between bifurcations or fibre deviations. Because the growth of the dendritic and axonal trees is complex, we ignore correlations between the
Table 1. Tabular outline of all the empirical data used to calculate derived estimates of cortical connectivity. Also shown, for comparison, is the correspondence between quantities which can be estimated both empirically and theoretically.

<table>
<thead>
<tr>
<th>Quantity Description</th>
<th>Empirical value</th>
<th>Derived value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(^a)</td>
<td>Reference</td>
</tr>
<tr>
<td>(r_{ax}) radius of an axonal fibre (µm)</td>
<td>0.15 ([3])</td>
<td></td>
</tr>
<tr>
<td>(r_{d}) radius of a dendritic fibre (µm)</td>
<td>0.45 ([3])</td>
<td></td>
</tr>
<tr>
<td>(\rho) cell density (mm(^{-3}))</td>
<td>9 (\times) 10(^4) ([3])</td>
<td></td>
</tr>
<tr>
<td>(\rho_{ax}) relative pyramidal cell density</td>
<td>0.85 ([3])</td>
<td></td>
</tr>
<tr>
<td>(\rho_{d}) relative stellate cell density</td>
<td>0.15 ([3])</td>
<td></td>
</tr>
<tr>
<td>(L_{D}) stellate cell dendrite length (mm)</td>
<td>2.16 ([3])</td>
<td></td>
</tr>
<tr>
<td>(L_{p}) total pyramidal cell dendrite length (mm)</td>
<td>3.08 ([3])</td>
<td></td>
</tr>
<tr>
<td>(L_{A}) stellate cell axon length (mm)</td>
<td>20 ([3])</td>
<td></td>
</tr>
<tr>
<td>(L_{p}) total local pyramidal axonal length (mm)</td>
<td>20 ([3])</td>
<td></td>
</tr>
<tr>
<td>(a, r_0) parameters describing branching of pyramidal basal and stellate dendrite (µm(^{-2}), µm)</td>
<td>0.0028, 31.25 ([13,14,15])</td>
<td></td>
</tr>
<tr>
<td>(a, r_0) parameters describing branching of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>local pyramidal cell axon</td>
<td>- -</td>
<td>0.8, 3.17</td>
</tr>
<tr>
<td>stellate cell axon ((r_0^{-2}, r_0))</td>
<td>- -</td>
<td>2.73, 2.12</td>
</tr>
<tr>
<td>(d_{Ax}) stellate axonal intersynapse spacing (µm)</td>
<td>1.25–5.0 ([3])</td>
<td>4.45 ([13,14,24])</td>
</tr>
<tr>
<td>(d_{Ax}) pyramidal axonal intersynapse spacing (µm)</td>
<td>1.25–5.0 ([3])</td>
<td>6.81 ([13,14,24])</td>
</tr>
<tr>
<td>(d_{d}) stellate dendritic intersynapse spacing (µm)</td>
<td>0.33 ([3])</td>
<td>0.68 ([13,14,24])</td>
</tr>
<tr>
<td>(d_{d}) pyramidal dendritic intersynapse spacing (µm)</td>
<td>0.4 ([3])</td>
<td>0.68 ([13,14,24])</td>
</tr>
<tr>
<td>(N_{t_{st},l}) total number of synapses per stellate cell dendrite</td>
<td>6545 ([3])</td>
<td>3169 ([24])</td>
</tr>
<tr>
<td>(N_{t_{py},l}) total number of synapses per pyramidal cell basal dendrite</td>
<td>6545 ([3])</td>
<td>3169 ([24])</td>
</tr>
<tr>
<td>(N_{t_{st},a}) total number of synapses per stellate cell axon</td>
<td>4000–16 000 ([3])</td>
<td>4496 ([24])</td>
</tr>
<tr>
<td>(N_{t_{py},a}) total number of synapses per pyramidal cell local axon</td>
<td>4000–16 000 ([3])</td>
<td>2935 ([24])</td>
</tr>
</tbody>
</table>

\(^a\) Mean of all cortical areas of the mouse for all quantities except \(a\) and \(r_0\) measured in visual cortex of the cat.

Positions and orientations of these segments. Therefore we are considering a large number of small straight axonal and dendritic segments, distributed randomly, but not necessarily uniformly, over space, orientation and length.

Further, we assume that these segments are so short that the probability that a given axonal segment will intersect the same dendritic tree more than once is negligible. Additionally we require that the orientations of the fibres are uniformly distributed over the unit sphere, and that location, orientation and length are independent random variables.

Let each segment of the axonal or dendritic tree be described by the location in space of its centre, \(r\), its length \(l\) and its orientation \((\theta, \phi)\) (the familiar polar angles). Therefore the number of segments (axonal \((A)\) or dendritic \((D)\)) within \(d^3r\) about \(r\), with length between \(l\) and \(l + dl\) and orientation in \((\theta, \phi + d\theta) \times (\phi, \phi + d\phi)\) is given by

\[
dN_k = \rho_k(r) f_k(l) \frac{\sin \theta}{4\pi} \, d^3r \, dl \, d\theta \, d\phi
\]

where \(\rho_k(r)\) (length\(^{-3}\)) and \(f_k(l)\) (length\(^{-1}\)) are the ‘distribution’ functions for segment position and length, respectively.

An axon segment with orientation \((\theta, \phi)\) and length \(l_A\), will intersect a dendritic segment with centre at \(r_D\), orientation \((\eta, \psi)\) and length \(l_D\), if its centre, \(r_A\), lies in a parallelepiped about \(r_D\) (see figure 1). When this happens a synapse is said to have formed.
Here we have assumed that the diameters of the fibres are small compared with the linear dimensions of the region. We have also ignored the detailed shape of the sides of the region. The volume of this region is seen to be

\[ V_{\text{int}}(l_A, l_D, \theta, \phi, \eta, \psi) = 2\epsilon l_A l_D \sin \gamma(\theta, \phi, \eta, \psi) \]  

(2)

where \( \epsilon = r_{ax} + r_d \) (\( r_{ax}, r_d \) are the average axonal and dendritic radii respectively) and \( \sin \gamma(\theta, \phi, \eta, \psi) \) is the angle between an axonal and dendritic segment. If this region is small enough for the axonal segment density function to be regarded as constant within it, then the number of intersections of axons of this orientation and length with the dendritic segment is

\[ N(\epsilon) = \int \int 2\epsilon l_A l_D \sin \gamma(\theta, \phi, \eta, \psi) \rho_A(\tau_A) \rho_D(\tau_D) f_A(l_A) f_D(l_D) \]  

(3)

For the more general case, the total number of synapses forming, \( N_s \), is

\[ N_s = \int \int 2\epsilon l_A l_D \sin \gamma(\theta, \phi, \eta, \psi) \rho_A(\tau_A) \rho_D(\tau_D) f_A(l_A) f_D(l_D) \]  

\[ \times \frac{\sin \theta \sin \eta}{4\pi} d^3 r_A d^3 r_D \]  

(4)

Defining

\[ \tilde{l}_k = \int l f_k(l) dl \]  

for \( k = A, D \)  

(5)

we are able to define the length of axonal or dendritic fibre per unit volume as

\[ l_A(\tau_A) = \tilde{l}_A \rho_A(\tau) \quad l_D(\tau_D) = \tilde{l}_D \rho_D(\tau). \]  

(6)

Thus, using equations (5) and (6) equation (4), the expected number of synapses forming between a presynaptic cell \( i \) and a postsynaptic cell \( j \), can be written, after partial integration, as

\[ N_{ij} = \frac{\pi \epsilon}{2} \int_{\mathcal{V}} l_A(\tau) D_j(\tau) d^3 r. \]  

(7)

If we define either the axonal or dendritic fibre density function relative to the position of the respective cell body, then (7) can be rewritten as the convolution

\[ N_{ij}(s) = \frac{\pi \epsilon}{2} \int_{\mathcal{V}} l_A(\tau) D_j(\tau - s) d^3 r. \]  

(8)
Cortical connectivity of pyramidal and stellate cells

where $s$ is the distance separating the pre- and postsynaptic cells.

The probability that a single axonal segment selected at random will intersect a dendrite somewhere in the region of co-arborization will be small. The number of such axonal segments will probably be large. Therefore the distribution of such connections or synapses will be reasonably well described by a Poisson distribution [7]. Hence the probability that a postsynaptic neuron will receive $q$ connections from a presynaptic neuron is

\[
p(q, r) = \frac{\exp[-N_{ij}(r)] N_{ij}(r)^q}{q!}.
\]

(9)

2.3. Specifying the axonal and dendritic fibre densities

2.3.1. The dendritic tree. For the case of a spherically symmetrical dendritic tree the dendritic fibre density at a distance $r$ from the soma, $D$, can be determined from anatomical data as [14]

\[
D = \frac{n}{(4\pi r^2 \cos \theta)}.
\]

(10)

This is shown in figure 2.

Assuming that all dendritic fibres intersect this imaginary sphere at right angles $\cos \theta = 1$ (i.e. all fibres in a unit volume can be considered to be parallel to each other) then the length of fibre per unit volume is equal to the number of fibres crossing a unit area multiplied by a unit distance.

Sholl [14] has measured the number of dendrites crossing concentric spheres of radius $r$ centred on the perikaryon for the dendritic systems of stellate and pyramidal neurons in the striate and motor areas of the cat. Spherical symmetry holds approximately for the basal dendritic system, and Sholl [14] has shown that $D$ falls off exponentially with $r$. Thus $D$ is given empirically as

\[
D = ae^{-r/r_0}.
\]

(11)
The values of \( a \) and \( r_0 \) vary little between the dendritic systems of stellate and pyramidal cells. Thus we have chosen, from Sholl [14] average regression estimates of \( a \) and \( r_0 \) as 0.0028 \( \mu \text{m}^{-2} \) and 31.25 \( \mu \text{m} \). If we measure all distances in units of \( r_0 \), the treatment becomes dimensionless making computation easier. Taking this step

\[
D = ae^{-r} \tag{12}
\]

where

\[
a = 2.73 r_0^{-2}. \tag{13}
\]

Measurements of the radius of dendrites and axons can similarly be modified. Electron micrographs suggest [4] that \( r_d \) is of the order of 0.45 \( \mu \text{m} \) and \( r_{ax} \) is of the order of 0.15 \( \mu \text{m} \).

\[
r_d = 0.014r_0 \quad r_{ax} = 0.0048r_0. \tag{14}
\]

2.3.2. The axonal tree. Statistical descriptions of axonal systems analogous to those for dendrites appear not to exist. For what follows we assume that axonal fibre density for all neurons can be described by a radially homogenous exponential distribution of the form

\[
A = a_{ax}e^{-r/a}. \tag{15}
\]

Using anatomical information we can make a tentative attempt to estimate \( r_a \) and \( a_{ax} \) for pyramidal and stellate cells. These two parameters can be estimated by observing that:

- cell diameter \( 2r_c \approx 20 \mu \text{m} \):
- only one axon emanates from the soma for pyramidal cells and \( a_{ax} \) is estimated as

\[
a_{ax} = \frac{1}{4\pi r_c^2}. \tag{16}
\]

The pattern of axonal ramification for stellate cells is highly variable with dense branching near the cell body [4, 15]. Thus in the absence of contrary evidence, we assume that the axonal and dendritic branching near the soma resemble each other. This being the case, we take \( a_{ax} \) for stellate cells to be 2.73 \( r_0^{-2} \).

For both stellate and pyramidal cells we have taken the total length of local axon to be 20 mm (or 640 \( r_0^{-1} \)) based on anatomical values obtained from murine cerebral cortex [4]. These values appear to represent upper bounds.

Thus, as \( a_{ax} \) is known, we can calculate \( r_a \) by integrating (15) for a radially symmetric ‘exponential’ tree,

\[
r_a = \left( \frac{L}{8\pi a_{ax}} \right)^{1/3} \tag{17}
\]

where \( L \) is the total length of local intracortical axon. Solving equation (17) we obtain \( r_a = 3.17 \) for pyramidal cells and \( r_a = 2.12 \) for stellate cells.

2.4. Calculation of the number of synapses given or received

The fibre density distributions of the axonal and basal dendritic trees are approximated by equations (11) and (15). Equation (8), exploiting the symmetry inherent in the problem, can then be written as

\[
N_{lf}(r) = \pi^2 e a_{ax} a \int_0^\infty \int_{-\infty}^{\infty} y \exp \left( -\left( \frac{(x-r/2)^2 + y^2}{r_a} \right)^{1/2} - \left( \frac{(x+r/2)^2 + y^2}{r_a} \right)^{1/2} \right) \, dx \, dy. \tag{18}
\]
This can be integrated, by changing to elliptic coordinates, to yield

\[ N_{ij}(r) = 2\pi^2 (r_d + r_{ax}) a_{ax} Q_{ij}(r) \]  \hspace{1cm} (19)

where

\[ Q_{ij}(r) = \frac{1}{rf^3 d^3} \left[ e^{-r/a} \{ f^2 (fr - 2) + f^2 (dr + 2) \} + e^{-r} \{ f^2 (fr + 2) - f^2 (dr + 2) \} \right] \]  \hspace{1cm} (20)

and

\[ N_{ij}(0) = \frac{4\pi^2 (r_d + r_{ax}) a_{ax}}{d^3} \]  \hspace{1cm} (21)

\[ f = \frac{(r_a - 1)}{r_a} \]  \hspace{1cm} (22)

\[ d = \frac{(r_a + 1)}{r_a}. \]  \hspace{1cm} (23)

Figure 3 shows the connectivity profile for two pyramidal cells obtained by substituting (19) with the parameter values obtained in section 2.3. Figure 4 shows the connectivity profile for a presynaptic stellate cell and a postsynaptic pyramidal cell.

Figure 3. The probability \((p)\) of \(n\) synapses forming between two pyramidal cells separated by a radial distance \(r\) (in units of \(r_0\)).

Figure 4. The probability \((p)\) of \(n\) synapses forming between a presynaptic stellate cell and a postsynaptic pyramidal cell separated by a radial distance \(r\) (in units of \(r_0\)).
3. Some consequences for cortical connectivity

We can now estimate:

- the total number of synapses a stellate cell is likely to give and receive;
- the number of local intracortical synapses a pyramidal cell will receive and project;
- the likely distribution of synapses within the dendritic tree;
- coupling symmetry.

3.1. Total synaptic number

The total number of synapses given by a presynaptic cell of type $k$ located at $r_0$, $N_{\text{total},k}^A(r_0)$, is

$$N_{\text{total},k}^A(r_0) = \sum_l \int_R d^3r \ N_{kl}^A(r) \rho_l(r)$$

(24)

where $N_{kl}^A(r)$ is the 'connectivity' function for the $k$th presynaptic cell type and the $l$th postsynaptic cell type, $\rho_l(r)$ is the $l$th cell density for the postsynaptic cell of the pair. A similar expression exists for $N_{\text{total},l}^A$.

The estimators for the mean and variance of the total number of synapses, are, assuming constant cell density,

$$\mu_k = \bar{N}_{\text{total},k}^A$$

(25)

$$\sigma_k^2 = \sum_l \rho_l \bar{N}_{\text{total},kl}^A$$

(26)

where $\bar{N}_{\text{total},kl}^A$ is the total number of synapses forming between a presynaptic cell of type $k$ and all other postsynaptic cells of type $l$.

When (19) is substituted into (24), all parameters to calculate $\bar{N}_{\text{total},k}^A$ are available. For constant cell density, $9 \times 10^4$ mm$^{-3}$ [4], over the region of integration,

$$\bar{N}_{\text{total},kl}^A = 16\pi^3 r_a a_{ax} a (r_a + r_{ax}) Q$$

(27)

where

$$Q = \frac{r_a^6}{(r_a - 1)^2(r_a + 1)}$$

(28)

Table 1 summarizes values of $\bar{N}_{\text{total}}$ for derived axonal space constants for stellate and pyramidal cells on the assumption that 85% of neurons are pyramidal and 15% stellate and that cells are mixed randomly [4].

3.2. The likely position for synapse formation

Equations (8) and (11) also allow us to predict the radial distance from the soma of a postsynaptic neuron at which a synapse from a given presynaptic cell is most likely to form. The mean radial position of a synapse is

$$\langle |s| \rangle_r = \frac{\pi \varepsilon}{2N(r)} \int_s |s| A(s) D(r - s) d^3s$$

(29)

Figure 5 shows $\langle |s| \rangle_r$ as a function of intercellular distance and axonal space constant.
3.3. Estimates of coupling symmetry

Figures 6 and 7 show a number of estimates of the symmetry of connection between neurons, based on

\[ P_{ij}(n, r_{ij}) = p_{ij}(n, r_{ij}) p_{ji}(n, r_{ji}) \]  

(30)

where \( P_{ij} \) is the probability that two cells \( i \) and \( j \), separated by an intercellular distance \( r_{ij} \), will give each other exactly \( n \) synapses. \( p_{ij} \) and \( p_{ji} \) are calculated from equations (8) and (9).

We define two measures of symmetry. The first we shall call 'strong' symmetry. By this we mean that two cells will give each other exactly \( n \) synapses. The second measure we shall call 'weak' symmetry; this is the probability that two cells sharing a total of \( n \) presynaptic contacts will have these synapses distributed as \( n - m \) to one cell and \( m \) to the other, where \( 0 < m < n \).

The expression for strong symmetry is a function of intercellular separation and is given by

\[ P_{ij}^s(r_{ij}) = \sum_{n=1}^{\infty} p_{ij}(n, r_{ij}) p_{ji}(n, r_{ji}). \]  

(31)

For the case of weak symmetry we have the discrete convolution

\[ P_{ij}^w(r_{ij}) = \sum_{n=2}^{\infty} \sum_{m=1}^{n-1} p_{ij}(m, r_{ij}) p_{ji}(n - m, r_{ji}). \]  

(32)
Combining these measures of symmetry defines a quantity called the 'expected symmetry' on the range [0,1] (0 being the case where no connections are shared, 1 being the case when all connections are reciprocal), which varies with intercellular separation

$$\Phi_{ij}(r_{ij}) = 1 - E\left(\frac{m-n}{m+n}\right) = \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} \left(1 - \frac{m-n}{m+n}\right) p_{ij}(m, r_{ij}) p_{ji}(n, r_{ji}).$$  \hspace{1cm} (33)

Figures 8 and 9 show $\Phi_{ij}(r_{ij})$, $P_{ij}^w(r_{ij})$ and $P_{ij}^p(r_{ij})$ for a pair of pyramidal cells and a stellate and pyramidal cell.

3.4. A general schema for connectivity in homotypical cortex

Figure 10 shows derived estimates for axo-synaptic couplings in an arbitrary volume of homotypical cortex. We define the axo-synaptic coupling density between the various cell groups to be the fraction of the total number of synapses per unit volume involved in this interaction. The figures were derived on the following assumptions.

- The basal dendritic tree and the dendritic tree of the stellate cell are of approximately the same length and the variation of this dendritic fibre density with respect to the distance
Cortical connectivity of pyramidal and stellate cells

Figure 9. Derived estimates of coupling symmetry $P^m$, $P^n$ and $\phi$ for a pyramidal and stellate cell as a function of intercellular separation $r$ (in units of $r_0$).

from the cell body is described by the same relationship (viz equation (11)) [4, 16].

- Termination of cortico-cortical afferents is assumed to be distributed uniformly over all layers. This has been demonstrated to be so for prefrontal cortico-cortical efferents in rhesus monkeys [9]. There is, however, great variability and specificity in the laminar distribution of such efferents as well as anisotropy of connectivity of ipsi- and contra-lateral cortico-cortical projections [11].

- For a given volume of cortical tissue the number density of incoming cortico-cortical fibres equals the number of outgoing cortico-cortical fibres [2, 16].

- Non-specific subcortical efferents and afferents have been conservatively calculated at 1% of the total number of cortical efferents and afferents [2].

Under these assumptions the fraction of the total number of synapses per unit volume involved in the local intracortical interaction between the $i$th presynaptic cell group and the $j$th postsynaptic cell group is

$$\beta_{ij} = \frac{\rho_k \rho_l \int d^3r \; N_{kl}}{N_{\text{total}}}$$

where $N_{kl}$ is defined by equation (19), $\rho_k$, $\rho_l$ are the respective cell densities and the $\beta_{kl}$ are the local intracortical anatomical coupling coefficients between the given neuronal groups.

$N_{\text{total}}$ is the total number of synapses per unit volume of cortex and is given by

$$N_{\text{total}} = \sum_k \rho_k (N_{\text{total},k}^{D} + N_{\text{total},k}^{g} + N_{\text{total},k}^{l})$$

where the addends on the right side of (35) are the number of synapses on dendrites due to local, cortico-cortical and subcortical interactions respectively.

Similarly the fraction of the total number of synapses involved in long-range interactions between excitatory cells and between excitatory and inhibitory cells is

$$\alpha_{ee} = \frac{\rho_e N_{\text{total},e}^{g}}{N_{\text{total}}} \quad \alpha_{ei} = \frac{\rho_i N_{\text{total},i}^{g}}{N_{\text{total}}}$$

where $\rho_e$, $\rho_i$ are the densities of pyramidal and stellate cells respectively, and $N_{\text{total},e}^{g}$, $N_{\text{total},i}^{g}$ are the number of synapses per excitatory cell and inhibitory cell, respectively, that are due to long-range afferents. Because stellate cells are not believed to give rise to long-range projections $\alpha_{ie}$ and $\alpha_{ii}$ are necessarily zero.
The $\mu_k$, the relative synaptic densities attributable to subcortical fibres, are determined in a similar manner to the anatomical coupling coefficients in equation (36). $N^\alpha_{\text{total,e}}$ and $N^\mu_{\text{total,i}}$ can be estimated by noting that

$$N^\alpha_{\text{total,e}} + N^\mu_{\text{total,e}} = \frac{L^D}{d^D} - N^D_{\text{total,e}},$$

(37)

$$N^\alpha_{\text{total,i}} + N^\mu_{\text{total,i}} = \frac{L^D}{d^D} - N^D_{\text{total,i}},$$

where $L^D$ is the total length of pyramidal cell dendrite, $L^D_s$ is the total length of stellate cell dendrite and $d^D, d^D_s$ are the anatomically determined intersynapse spacing on pyramidal and stellate cell dendrite respectively, and where

$$N^\mu_{\text{total,e}} = \sum_v N^\mu_{\text{total,e}v} \quad N^\mu_{\text{total,i}} = \sum_v N^\mu_{\text{total,iv}}$$

(38)

where the sums are over all afferent subcortical fibre systems, $v$.

If the isotropic cortico-cortical and subcortical fibre systems can be assumed to contribute cortical synapses in direct proportion to the relative numbers of each fibre type entering an arbitrary volume of cortex we can make progress towards defining values for the quantities on the left-hand side of (37). Anatomical evidence suggests that the numbers of fibres entering cortex from subcortical and distant cortical areas are in the ratio 1:100 [2, 3, 12]. Denoting this ratio by $\kappa$, from (37) we have

$$N^\mu_{\text{total,e}} = \kappa N^\alpha_{\text{total,e}} \quad N^\mu_{\text{total,i}} = \kappa N^\alpha_{\text{total,i}}$$

(39)

and

$$N^\alpha_{\text{total,e}} = \frac{1}{\kappa + 1} \left( \frac{L^D}{d^D} - N^D_{\text{total,e}} \right),$$

$$N^\alpha_{\text{total,i}} = \frac{1}{\kappa + 1} \left( \frac{L^D_s}{d^D_s} - N^D_{\text{total,i}} \right).$$

A putative estimate of the magnitude of the anatomical coupling coefficients in homotypical murine neocortex is shown in figure 10.

4. Conclusions

This model is an a posteriori model. No attempt has been made to incorporate the effects of growth and development. Nonetheless, this simple formulation is able to account for the observed pre- and postsynaptic synaptic densities seen in adult murine cortex, within the limits of experimental uncertainty. We have calculated the mean total number of synapses (from local fibre distribution only) for the basal dendritic tree of a pyramidal cell and the dendritic tree of the stellate cell to be $\sim 3200$. From this we deduced that the expected number of synapses on a pyramidal cell, due to long-range isotropic cortico-cortical fibres and subcortical fibres, is of the order of 4500. Thus the total number of synapses a pyramidal cell receives is about 7700. From this we conclude that the total number of synapses per mm$^3$ is $7.4 \times 10^8$. Braitenberg and Schuz [4] have measured, using detailed electron-micrographs, a mean value of $7-9 \times 10^8$ synapses per mm$^3$. Based on this they estimate that, on average, a pyramidal cell in the murine cortex would expect to form about 8000 synapses. Table 1 summarizes all the empirical data used to determine the theoretical values outlined above, together with estimates of these values.
In section 3.4, we showed that, in terms of the numbers of synapses contributed from 'non-local' and local fibre systems, the effect of short-range pyramidal axons is about half as strong as that due to long-range afferents, in the case of the mouse.

In our calculations the ratio of thalamo-cortical to cortico-cortical afferents ($\kappa$ in equation (39)) has been treated very conservatively. Thalamo-cortical afferents in the mouse may be as much as 10-fold greater than the 1% figure cited for the human work, but no clear estimates for the mouse are presently available. Larger values of $\kappa$ would lower the estimates for the cortico-cortical connectivity determined by our method.

This formulation can be generalized to take into account any arbitrary distribution of axonal or dendritic fibre density. For instance, the distribution of pyramidal cell axons may be better described by a functional form other than a radially homogenous exponential axonal field.

In this treatment we have not accounted for the axo-somatic synapses formed exclusively by stellate cells on pyramidal cells [4]. For a stochastic mechanism to describe the formation of these synapses, it would require axonal growth and synaptogenesis in stellate cells to precede axonal and dendritic development in pyramidal cells. Alternatively, or in addition, chemo-affinic mechanisms may need to be considered [10].

It has been assumed that a synapse forms only when an axonal fibre and a dendritic fibre are in direct physical contact. However, the effect, as yet incompletely verified, of soluble trophic metabolic gradients in initiating and facilitating synapse formation has not been included. The effect of this may be to modify $\epsilon$ such that two fibres do not need to be in physical apposition for a synapse to form. In principle such a mechanism can be easily incorporated in our formulation, as can areal variations in cell density and branching.

We have ignored, for the present, the role spines may have in promoting and modifying connectivity. Spines are thought to have a role in increasing the surface area of a dendrite such that a greater number of synaptic contacts can be accommodated [5]. The latter assertion is difficult to demonstrate due to the difficulty in obtaining quantitative anatomical evidence. Despite this, certain general conclusions can be arrived at. If the number of synapses per unit length of smooth dendrite is compared with the number of synapses per unit length of spiny dendrite, the figures are essentially equivalent – about 3 synapses/$\mu$m [4]. Also, it is rare to find a case in which a spine does not have an associated synapse.
simple calculation, which we shall omit, shows that if spine development preceded synapse formation, then for the case of adult murine cortex, one would expect only 13% of all spines in the cortex to have an associated synapse. Thus, the role of spines in facilitating the formation of connections in the cortex remains doubtful. For these and other anatomical reasons [13] we have ignored their effect.

Autoexcitatory and autoinhibitory synapse formation appears to be significant, in contrast to some expectation [8]. Autoinhibitory synapses are more likely as the stellate cell axon arborizes within the volume of distribution of dendritic ramification. Referring to figure 4 at $r = 0$, and as the branching of the pyramidal cell basal dendritic tree is approximately the same as that of the dendritic tree of the stellate cell, we see that 1 to 3 autoinhibitory synapses per stellate cell are likely to form.

One important aspect of our conclusions is the high asymmetry of cortical neuronal connections which our calculations imply. We discuss this in more detail elsewhere [20]. Amit [1] has investigated the case for networks in which asymmetry has been introduced into a symmetric network having $N^2$ synapses, by deleting a fraction $\gamma$ (typically defined on $0 < \gamma \leq 1$) of $\frac{1}{2}N^2$ synapses. For the case of 100% dilution this implies that every pair of neurons has probability 0.25 of being reciprocally connected (i.e. $\gamma^2/4 - \gamma + 1$). Although the analogy with our calculations of asymmetry is incomplete, from our estimates, for strong asymmetry, the likelihood of reciprocally connected pyramidal cells is 0.16, for weak asymmetry this rises to 0.44 (for two pyramidal cells separated by one dendritic space constant). Thus a real neural network, by analogy with a spin glass, is 120% diluted for the case of strong symmetry and 67% diluted for the case of weak symmetry. At 100% asymmetric dilution spin glass effects are totally absent. However, Derrida et al [6] have shown, for the case of extreme asymmetric dilution, that such networks may perform as well as their symmetric counterparts. In fact, the storage capacity per synapse is higher than that for a fully connected network. At this extreme dilution almost all feedback loops are eliminated, i.e. the network forms a branched graph.

Additional tests of the plausibility of this model of cortical connectivity might be found in experiments in which spike-triggered averaging of postsynaptic potentials is used to identify local circuit connections between neurons [17, 18].

As a partial test of the approximate validity of these results – in particular the schema for connectivity in homotypical connectivity – the following paper [21] introduces our calculations of relative synaptic density into a model of the origin of the electrocorticogram, in the form of coupling coefficients among lumped aggregates of excitatory and inhibitory cells.

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