

# Network Connectivity Changes through Activity-Dependent Neurite Outgrowth

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**Abstract.** There is experimental evidence that neuronal electrical activity directly influences neurite outgrowth during the development of the nervous system. Using model studies, Van Ooyen and Van Pelt extensively investigated the effect of this phenomenon upon network development and architecture. Their studies are based on the experimental observations that there is an optimal range of electrical activity at which neurite outgrowth takes place. In their model, neurite growth occurs if the activity level of the neuron is below a certain threshold, otherwise the neurite retracts. We extend their results to include a more complete description of the relationship between electrical activity and neurite outgrowth. This takes into account the experimental observation that outgrowth ceases not only when neuronal activity is too high, but also when it is below a certain threshold. The modified model displays a wider range of behaviours during network development. In some cases, for example, growth is only transient and is followed by a total loss of connections in the network. As a consequence of the larger spectrum of possible behaviours, the mechanisms for control of network formation, by the network's internal dynamics as well as by external inputs, are also increased.

## 1. Introduction

Electrical activity plays a pivotal role in the development of neurons into functional neural networks. Besides changes in synaptic strength, many other processes are also activity-dependent, e.g., neurite outgrowth (for a review see [1]). The higher the electrical activity of the neuron the larger is the concentration of intracellular calcium ( $[Ca^{2+}]_{in}$ ), which mediates modifications in outgrowth [2, 3]. The empirical observations are summarized in the 'calcium theory of neurite outgrowth', which states that there is a range of  $[Ca^{2+}]_{in}$ , or level of electrical activity, where outgrowth takes place, while higher or lower concentrations, or electrical activity, cause neurites to retract [2, 4–7].

Simulation models allow us to unravel the possible implications of activity-dependent neurite outgrowth for neuronal morphology and network formation. This has been done extensively for what we will call the 'low calcium hypothesis'. This states that neurite outgrowth or retraction take place when the level of electrical



activity is respectively below or above a certain threshold [8–10]. Here we study the ‘optimal calcium hypothesis’, which states that neurite outgrowth occurs within a range of activity, while above and below this range neurites retract.

## 2. Model

In this section a summary is given of the model used in [8]. The electrical activity of a neuron is governed by the shunting model [11]. For a purely excitatory network of  $N$  neurons, we have:

$$\eta \frac{dx_i}{dt} = -x_i + (A - x_i) \sum_{j=1}^N w_{ij} f(x_j) \quad (1)$$

where  $x_i$  is the membrane potential of the  $i$ th neuron,  $\eta$  is the membrane charging/discharging time constant,  $f$  is the neuron’s transfer function,  $f(x)$  denotes the mean firing rate of a neuron subjected to activation  $x$ ,  $w_{ij}$  is the connection strength between neuron  $i$  and  $j$ , with  $w_{ij} \geq 0$ , and  $A > 0$  is the reversal potential.

The model neurons reside on a two-dimensional surface. They receive no external inputs, but display a low spontaneous background activity (i.e., for small  $x$ ,  $f(x) > 0$ ). Growing neurons are modelled as expanding circular areas, or ‘neuritic fields’, representing axonal and dendritic extensions. When two such fields overlap,  $w$  between the cells is proportional to the area of overlap;  $w$  thus represents axo-dendritic as well as dendro-dendritic interactions. The growth of the radius ( $R$ ) of each field depends on the electrical activity of the neuron through an equation of the form:

$$\frac{dR_i}{dt} = H(x_i) \quad (2)$$

where  $H$  is the growth function for an individual cell.

## 3. Global Description

Provided the variations among the individual cells are small relative to the average values, the global behaviour of the network in terms of average membrane potential  $X$  and average connectivity  $W$  can be described by [8]:

$$\frac{dX}{dT} = -X + (1 - X)WF(X) \quad (3)$$

$$\frac{dW}{dT} = qG(X), \quad (4)$$

where Equation (3) is the transformed shunting Equation [10],  $F(X)$  is the normalized firing rate or neuronal transfer function, and  $q$  a very small parameter



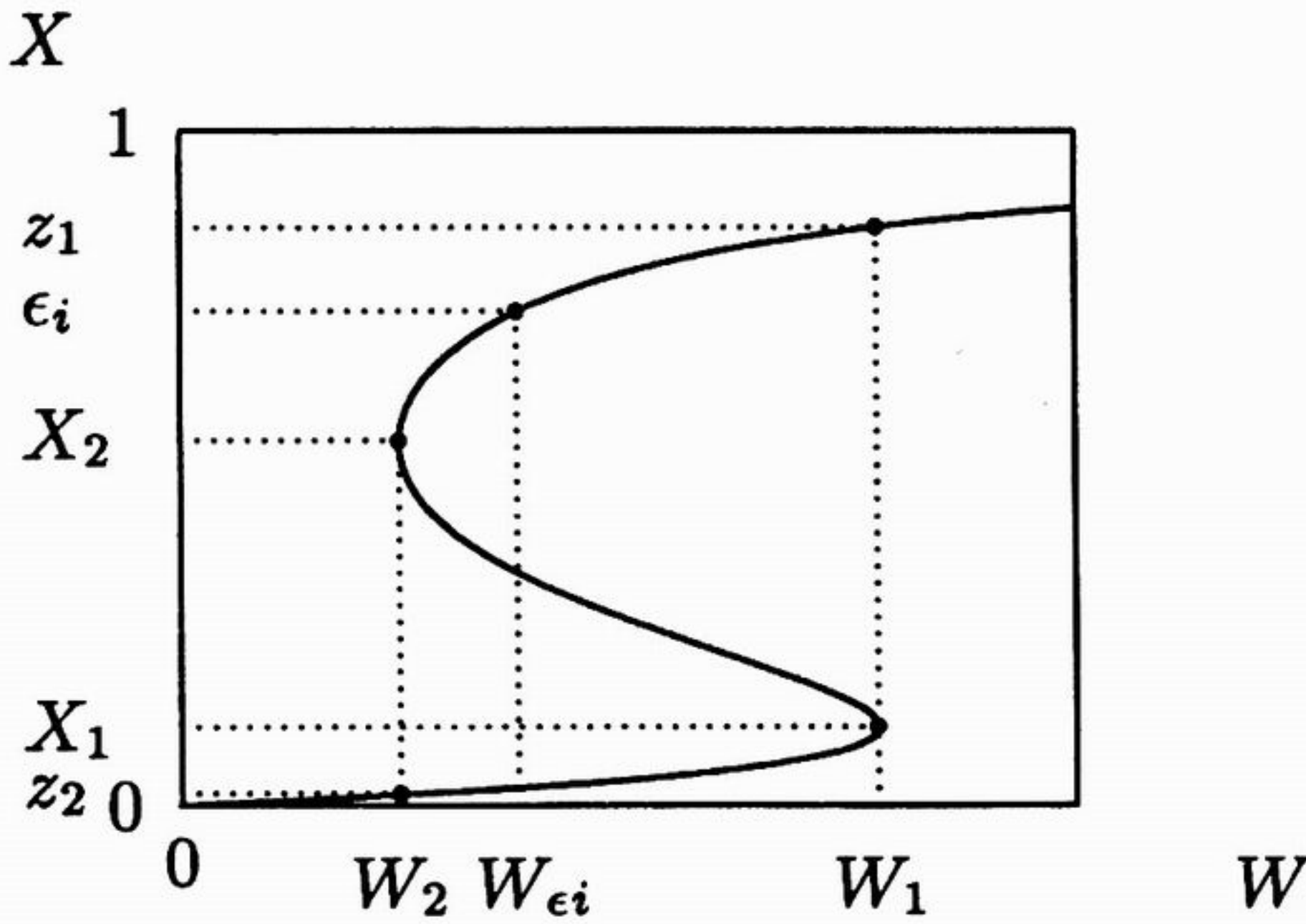


Figure 1. The S-shaped slow manifold with indication of important points.

( $0 < q \ll 1$ ). The function  $G$  has the same essential characteristics as the ‘individual’ growth function  $H$  (Equation (2)), which are described in Section 4.

We consider the extreme case in which  $X$  instantaneously relaxes to its equilibrium value for a given  $W$ , which is a valid approximation considering that outgrowth takes place on the time scale of days and neuronal dynamics on the time scale of seconds. The slow evolution of the system, determined by the dynamics of  $W$ , takes place along the so-called slow manifold. This manifold is defined as the set of points in the  $(W, X)$ -plane where  $dX/dT = 0$  [Equation (3)], thus the set of points  $(S(X), X)$  where  $S$  is the function defined by  $S(X) = X/((1 - X)F(X))$ .

As shown in [8], a hysteresis relationship between  $W$  and  $X$  together with activity-dependent changes in  $W$ , can lead to a transient overproduction with respect to  $W$  during development (‘overshoot’). One way of obtaining a hysteresis relationship is to have an S-shaped slow manifold, i.e., one which has exactly two turning points where  $S'$  changes sign [12].

We assume that  $F(X)$  is such that there exists an S-shaped slow manifold with turning points  $(W_1, X_1)$  and  $(W_2, X_2)$  where  $W_1 = S(X_1)$  and  $W_2 = S(X_2)$  (see Figure 1). This condition is satisfied by sigmoidal transfer functions.

The sign and the zeros of  $G$  are the relevant factors determining the evolution of trajectories of the system (3–4) on the slow manifold. Equilibrium points of this system are zeros of the growth function situated on the slow manifold, i.e., points  $E_i = (W_{\epsilon_i}, \epsilon_i)$  for  $i$  in  $\{1, 2, \dots\}$  with  $G(\epsilon_i) = 0$  and  $W_{\epsilon_i} = S(\epsilon_i)$ .

We further use the following nomenclature to describe points and branches of the S-shaped manifold (Figure 1). The part of the slow manifold connecting  $(0, 0)$  and  $(W_1, X_1)$  is called the lower branch, the part connecting  $(W_1, X_1)$  and  $(W_2, X_2)$  the middle branch, and the part from  $(W_2, X_2)$  to  $(\infty, 1)$  the upper branch. When, starting at  $(W_1, X_1)$ ,  $W$  is made only slightly larger than  $W_1$ , the trajectory jumps to a point on the upper branch. In our approximation this is the point where the vertical line going through  $W_1$  intersects the slow manifold, i.e., point  $(W_1, z_1)$  with  $S(z_1) = W_1$ . Similarly, starting at  $(W_2, X_2)$ , when  $W$  is made



only slightly smaller than  $W_2$ , the trajectory jumps to  $(W_2, z_2)$  on the lower branch with  $S(z_2) = W_2$ .

#### 4. Results

In previous studies [8, 9] it has been assumed that  $G$  has a unique zero  $\epsilon$  with

$$\begin{cases} \text{for } X < \epsilon & G(X) > 0 \\ \text{for } X > \epsilon & G(X) < 0 \\ \text{and} & G'(\epsilon) < 0. \end{cases} \quad (5)$$

In this case, system (3–4) has a unique equilibrium point at  $E = (S(\epsilon), \epsilon)$ , which is unstable when situated on the middle branch ( $X_1 < \epsilon < X_2$ ), and stable when on either the lower ( $\epsilon < X_1$ ) or upper branches ( $X_2 < \epsilon$ ).

We now consider a growth function  $G$  that is assumed to be a smooth function with exactly two zeros,  $\epsilon_1 < \epsilon_2$ , such that  $G'(\epsilon_2) < 0 < G'(\epsilon_1)$ . System (3–4) has now two equilibrium points,  $E_i = (W_{\epsilon_i}, \epsilon_i)$  for  $i$  in  $\{1, 2\}$  with  $S(\epsilon_i) = W_{\epsilon_i}$ . We constrain  $E_1$  to the lower branch of the slow manifold, i.e.,  $\epsilon_1 < X_1$ , where the unstable equilibrium point  $E_1$  is a saddle point. The global behaviour of the system depends on the position of the two equilibria. If  $0 < \epsilon_1 < \epsilon_2 < X_1$  ( $0 < \epsilon_1 < X_1 < X_2 < \epsilon_2 < 1$ , respectively),  $E_2$  is a stable point situated on the lower (respectively upper) branch of the slow manifold. The basin of attraction of  $E_2$  is the set of initial conditions with trajectories converging to  $E_2$ .

The following cases can be distinguished:

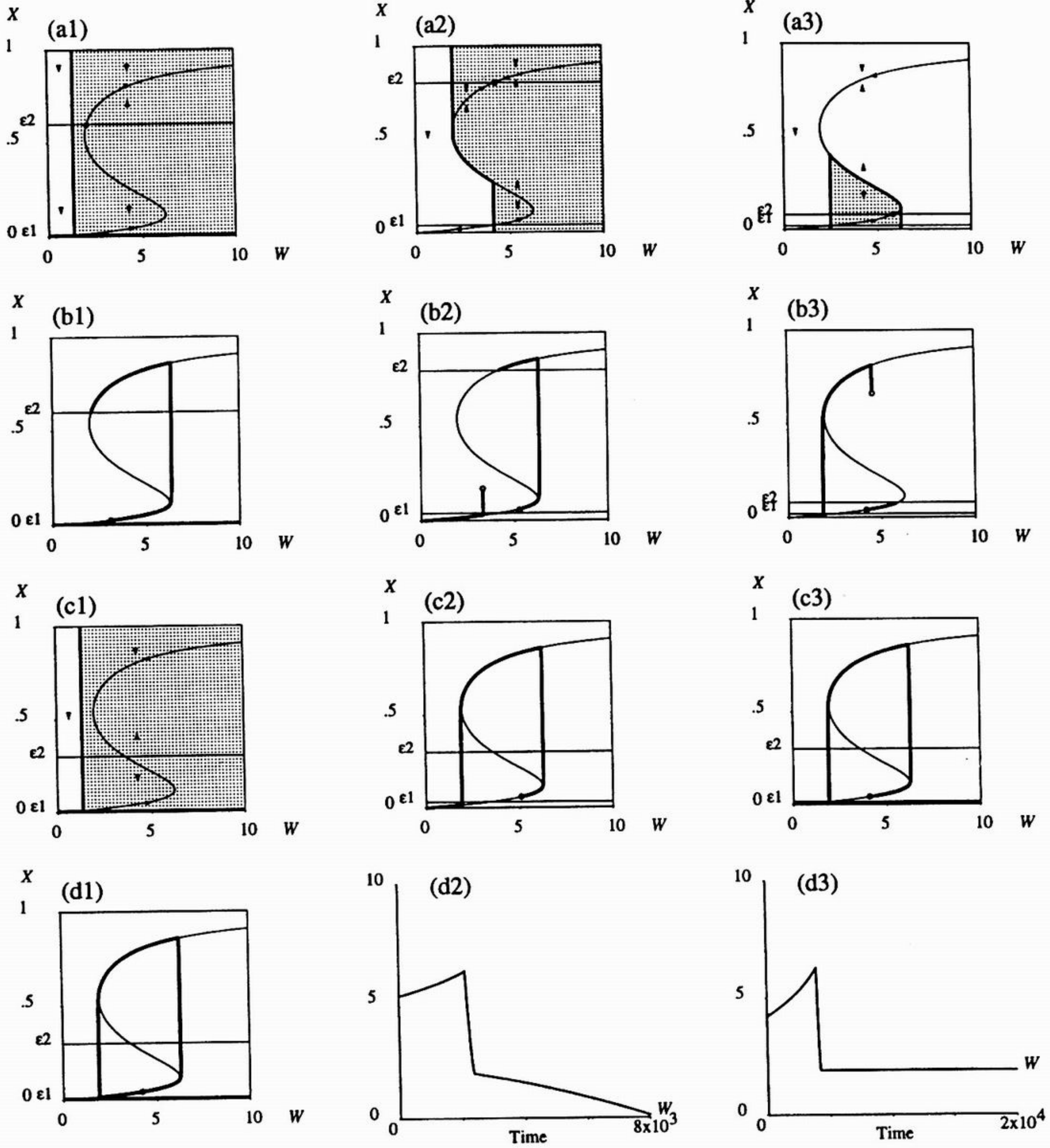
- If  $W_{\epsilon_1} < W_2$ , and  $\epsilon_2$  on the upper or lower branch, the basin boundary is the vertical line going through  $E_1$  (approximately the stable manifold of saddle node  $E_1$ ), and all trajectories with initial conditions  $(W, X)$  with  $W > W_{\epsilon_1}$  will converge to  $E_2$  [Figure 2(a1)].
- If  $W_{\epsilon_1} > W_2$ , and  $\epsilon_2$  is on the upper branch, all trajectories with initial conditions  $(W, X)$  with  $W > W_{\epsilon_1}$  will converge to  $E_2$ , as well as those with  $W_2 < W < W_{\epsilon_1}$  and  $X$  above the middle branch [Figure 2(a2)].
- If  $W_{\epsilon_1} > W_2$ , and  $\epsilon_2$  is on the lower branch, all trajectories with initial conditions  $(W, X)$  with  $W_{\epsilon_1} < W < W_1$  and  $X$  below the middle branch will converge to  $E_2$  [Figure 2(a3)].

Only for  $0 < \epsilon_1 < X_1 < X_2 < \epsilon_2 < z_1$  does the connectivity  $W$  go through a transient overproduction for certain initial conditions [e.g., points on the lower branch of the slow manifold for which  $W > W_{\epsilon_1}$ ; see Figure 2(b1), (b2)].

- At  $\epsilon_2 = X_1$  ( $\epsilon_2 = X_2$ , respectively) there is a Hopf bifurcation, and for  $0 < \epsilon_1 < z_2 < X_1 < \epsilon_2 < X_2$  there is a stable limit cycle with a basin of attraction bounded by the vertical line going through  $E_1$ . All trajectories with initial conditions  $(W, X)$  with  $W > W_{\epsilon_1}$  converge to this attractor [Figure 2(c1)].

In all of the above situations, the unstable point  $E_1$  acts as a threshold below which activity is not effective for growth of connectivity. For points that are ‘below’ this







threshold, the connection weight decreases to zero. If the system is above this threshold, its behaviour is similar to that of a system with a growth function having a single zero at  $\epsilon_2$ .

- For  $\epsilon_1 = z_2 < X_1 < \epsilon_2 < X_2$ , the stable manifold of the saddle node  $E_1$  coalesces with the limit cycle, i.e., a homoclinic orbit, which attracts trajectories of all points enclosed in it [Figure 2(c3)].
- If  $z_2 < \epsilon_1 < X_1 < \epsilon_2 < X_2$ , there will be a transient increase in both  $X$  and  $W$  for some initial conditions (e.g., points on the lower branch of the slow manifold for which  $X > \epsilon_1$ ), but eventually for all trajectories except the equilibria and the set of trajectories tending to  $E_1$  (i.e., the stable manifold of the saddle node),  $W$  will reach zero [Figure 2(c2)].

## 5. Discussion and Conclusion

A transient overproduction with respect to connectivity ('overshoot'), which constitutes an important phenomena during nervous system development, was observed in the model based on the low calcium hypothesis [8]. This behaviour can also be reproduced in the model based on the optimal calcium hypothesis. However, under the latter hypothesis, the neurons need to have a sufficient level of initial activity for growing out in order for the network to display an overshoot in connectivity. As the model shows, a high enough initial activity for growing out is not a sufficient condition to develop a network. In fact, after a transient growth, all the connections in the network might eventually disappear (Figure 2(c2) and (d2)). This situation is not possible in the model based on the low calcium hypothesis, where under the same conditions the connectivity will oscillate.

In this study we have focussed on the global behaviour of the network, using a description where variability among neurons is discarded. The validity of approximating the global behaviour of the network with system (3–4) for small variability among neurons was tested on the complete model consisting of  $N$  neurons. Generally it was found that this approximation is valid under small structural inhomogeneities (positions of the neurons), variability in the parameters of the neuronal transfer function, in the outgrowth rate  $q$ , and within a restricted range in the zeros of the outgrowth function. Numerical investigations showed that also small variations in the initial conditions, with respect to membrane potential and radius of the neuritic field, do not affect the global dynamics.

Large variability among neurons are expected to generate new behaviours not covered by the global description. Preliminary numerical investigations show that large variations in initial connectivity may lead to cluster formation through retraction of neurons that are isolated from others and are not active enough to grow out. Such neurons are not capable of establishing durable connections with other neurons. In other words, they become functionally irrelevant, which may explain the actual neuronal death observed during the development of the nervous system [13], especially when  $[Ca^{2+}]_{in}$  is substantially below resting levels [14]. Due to



neurite retraction in these neurons, the network may become subdivided into clusters within which the neurons are tightly interconnected, and between which there are fewer connections.

External excitatory stimulation during network formation will rise neuronal activity and thus may prevent neurite retraction in weakly connected or inactive neurons. Neurons that without external input did not become part of the network may do so as a result of external stimulation. External excitatory input onto already active neurons, in contrast, may induce retraction. External inhibitory stimulation will have the opposite effects. These mechanisms provide efficient means of external control during network development.

Large variability may also exist in the range of electrical activity for which outgrowth takes place, i.e., neurite outgrowth does not have to occur for the same range of electrical activity for all neurons in the network (i.e., different  $\epsilon_i$  values for different neurons). In this case a selection process may take place during development. Only neurons that have a range of outgrowth appropriate for network parameters, will eventually become connected into the network, while others are effectively deleted, possibly after a transient growth. Thus the neurons with an optimal range for outgrowth become selected during network formation. One may, therefore, start development with neurons that differ with respect to the range of activity where outgrowth takes place.

Concluding, the model based on the optimal calcium hypothesis displays a wider range of behaviours during network development than the one based on the low calcium hypothesis. As a consequence of this, the mechanisms of control of network formation by the network's internal dynamics as well as by external input are also expected to increase. Currently, these expectations are being tested in the complete model consisting of  $N$  neurons.

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