ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

Activity-dependent neurite outgrowth in a simple neural network model including excitation and inhibition

C. van Oss and A. van Ooyen

Netherlands Institute for Brain Research,
Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands

Abstract. Empirical studies have demonstrated that electrical activity of the neuron can directly affect neurite outgrowth. In this paper the implications of activity-dependent outgrowth in a simple two-cell model are studied. The results show that the interaction among neurite outgrowth ('slow dynamics'), excitation and inhibition ('fast dynamics') can generate interesting dynamical behaviour, such as bistability, normal and 'bursting' oscillations. These features might be associated with two states of the network: a 'normal' and a 'pathological' one, where the last one shows epileptiform activity patterns.

1. Introduction

Many processes that play a role in shaping the structure of the nervous system are modulated by electrical activity. For example, electrical activity can affect neurite outgrowth: high levels of activity cause neurites to retract, whereas low levels of activity allow further outgrowth [3]. As a result of this and other activity-dependent processes, a reciprocal influence exists between the formation of connectivity ('slow dynamics') and activity ('fast dynamics'). We have made a start at unravelling the implications of activity-dependent neurite outgrowth [4,5]. In this paper, the interactions among outgrowth, excitation and inhibition are studied in more detail in a simple ODE model, which enables us to analyse the complete dynamic behaviour of the model.

2. The Model

The shunting model [2] is used to describe neuronal activity. Here, the dimensionless equations [1,5] are used:

$$\begin{aligned} \frac{dx}{dt} &= -x + (1-x)\, w\, f(x) - (h+x)\, p\, w\, f(y) \\ \frac{dy}{dt} &= -y + (1-y)\, p\, w\, f(x) \end{aligned} \qquad (1)$$

ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

x = membrane potential of the excitatory cell, $x\epsilon[-h, 1]$; y = membrane potential of the inhibitory cell, $y\epsilon[0, 1]$; w = connection strength; p = level of inhibition; $f(u) = \frac{1}{1+e^{(\theta-u)/\alpha}}$.

We exclude self-inhibition and assume that the connection between the excitatory and inhibitory unit is symmetrical. For simplicity, we assume that cell x can adapt its neurites, whereas those of cell y remain constant. The neurite outgrowth of cell x is modelled as follows. We assume that the connection strengths of cell x to itself and to cell y are proportional to the size of its neuritic field. Therefore neurite outgrowth is modelled implicitly by the following equation:

$$\frac{dw}{dt} = q\,(e - b\,w^2 - x) \qquad (2)$$

Thus, high electrical activity $x > (e - b\,w^2)$ causes the neuritic field to decrease, whereas low activity ($x < (e - b w^2)$) allows outgrowth. The dynamics of w is on a much slower timescale than that of x and y and is determined by q. To restrict the size of the cell the saturation term bw^2 is added. Removing the saturation does not influence the qualitative results. The parameter values used are: $\theta = .5; h = .1; q = .005; \alpha = .1; b = .00005$. The parameters e and p vary from 0 to 1, their exact values are denoted in the figures.

3. Results

We are interested in the impact on the dynamical behaviour of parameters e and p; e determines the membrane potential at which the neuron neither grows out nor retracts its neurites; p stands for the level of inhibition in the model. By bifurcation analysis it is possible to construct the parameter space e-p (fig. 1). The space is divided by fold lines and hopf lines into regions with different dynamical behaviour. A fold line consists of points in the parameter space at which a fold bifurcation (=saddle-node bifurcation) occurs. The crossing of a fold line due to a small change in the value of e or p means that two equilibrium points appear or disappear. A hopf line consists of points in the parameter space at which a hopf bifurcation occurs. Crossing a hopf line indicates that the stability of one equilibrium point has changed, and that possibly stable or unstable limit cycles appear or disappear. If all hopf and fold lines in the parameter space are found, the number and stability of equilibria at every point in the parameter space is known. A collection of points bounded by fold or hopf lines is called a parameter region. All points in one parameter region have the same number and stability of equilibria. In this section the parameter regions having the most interesting dynamical behaviour will be described.

The parameter p determines the level of inhibition. At $p < 0.2$, the behaviour of the model is qualitatively the same as that in the model without inhibition. Since $q << 1$, the dynamics of w is much slower than that of x and y. Therefore w can be considered as a slowly varying parameter, and x and y are at quasi steady state at the time scale of w. The trajectories of the system follow the 'slow manifold', which is defined by $dx/dt = 0$, $dy/dt = 0$. The intersection(s) of the slow manifold with the nullcline of w (which is defined by

ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

$dw/dt = 0$) are the equilibrium point(s) of the model. Fig. 2a shows the phase plane of x versus w. The slow manifold is S-shaped (hysteresis curve). There is one equilibrium point.

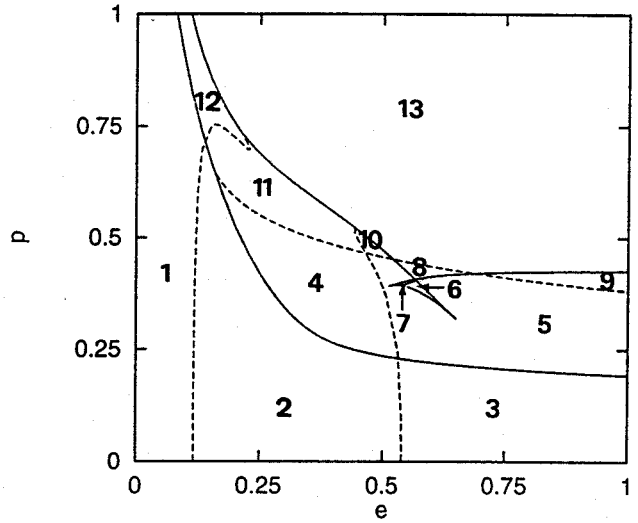

Fig 1: Parameterspace e-p. The bold lines are fold bifurcation lines, the dotted lines are hopf bifurcation lines.

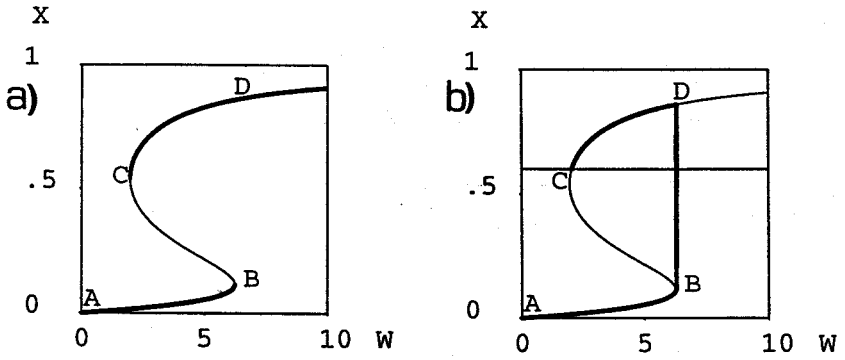

Fig 2(a) The slow manifold in the w-x plane, $p = 0$ (b) The slow manifold and the w-nullcline at e=0.6; $p = 0$, the bold line indicates a trajectory starting at $w = x = y = 0$.

The nullcline of w, and thus the position of the equilibrium point can be shifted vertically by varying the parameter e. This corresponds to a walk through parameter space with constant p and varying e. In parameter region 1 there is one stable equilibrium which is at branch AB of the slow manifold. In region 2 there is one unstable equilibrium at branch BC of the slow manifold and a stable limit cycle. In region 3 there is one stable equilibrium at branch CD. A trajectory starting at w=0 will first follow branch AB, jump to CD and then approach the equilibrium point (fig. 2b, bold line). The trajectory therefore

ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

shows a transient overproduction in w (overshoot).

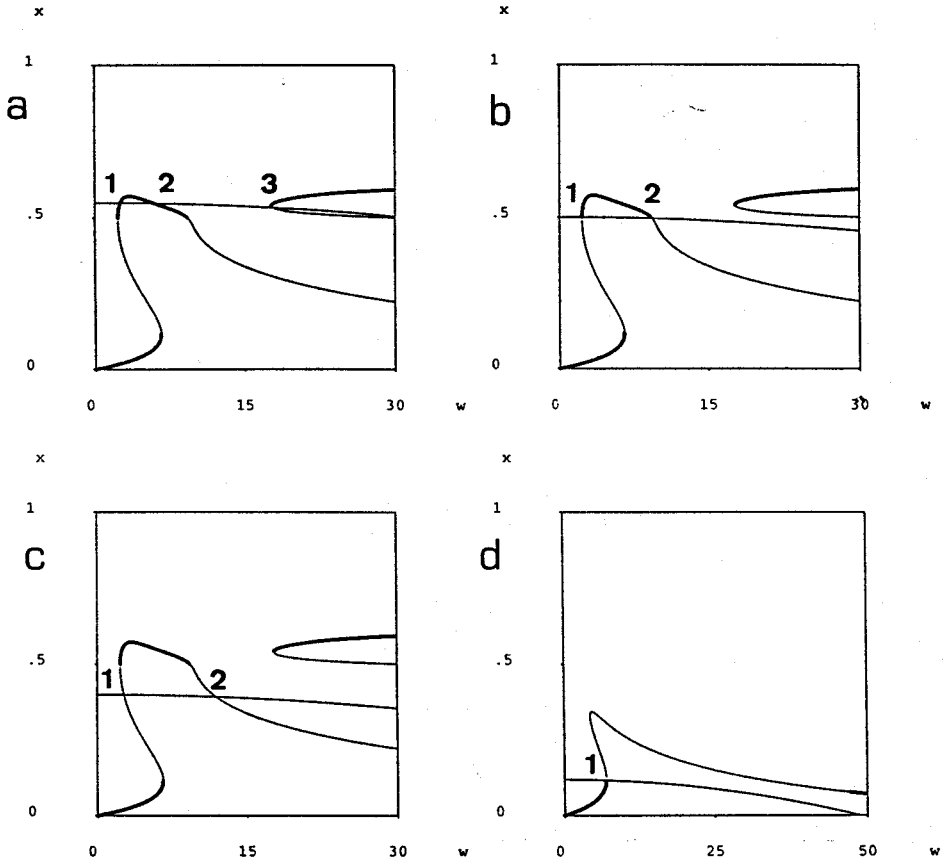

Fig 3: The slow manifold in the w-x plane and the w-nullcline at the following parameter values: (a) p=0.4; e=0.56 (b) p=0.4; e=0.5 (c) p=0.4; e=0.4 (d) p=0.6; e=0.12.

When the value of p is increased, the shape of the slow manifold changes (fig. 3a) due to a cusp bifurcation at $p = 0.394$ and $e = 0.52$ (fig. 1). In parameter region 6 there are five equilibria. Equilibrium points 1 and 3 are stable and 2, 4 and 5 are unstable (equilibria 4 and 5 are not shown). A slight decrease in e causes successively a hopf and a fold bifurcation, thus arriving in region 5. In this region there are 3 equilibrium points, of which one is stable and two are unstable (fig. 3b). Besides the point attractor there is another attractor in the system, namely a stable limit cycle (fig. 4a) The limit cycle can be considered as a switching between two states. Let's for the moment assume w to be a parameter rather than a variable. At $w < 17$, x and y are in an oscillatory regime, whereas at $w > 17$, x and y are stable. At $w \approx 17$ a fold bifurcation occurs, where a saddle and a stable node appear. The limit cycle glues with the stable manifold of the newly appeared saddle node (homoclinic

ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

bifurcation). A very slight increase in w causes the trajectory to move via the unstable manifold of the saddle to the stable node. Now we consider the full system again, where changes in w are dependent on the membrane potential x. If $x < (e - b\,w^2)$, $dw/dt > 0$, whereas w decreases if $x > (e - b\,w^2)$. In the phase plane this means that w increases below the w-nullcline and w decreases above the w-nullcline. At $w < 17$, x and y are in the oscillatory regime and on average $x < (e - b\,w^2)$. Therefore w increases. On the other hand, at $w > 17$, x and y are stable, $x > (e - b\,w^2)$ and thus w decreases. In this way w 'pulls' the system back and forth through the homoclinic bifurcation.

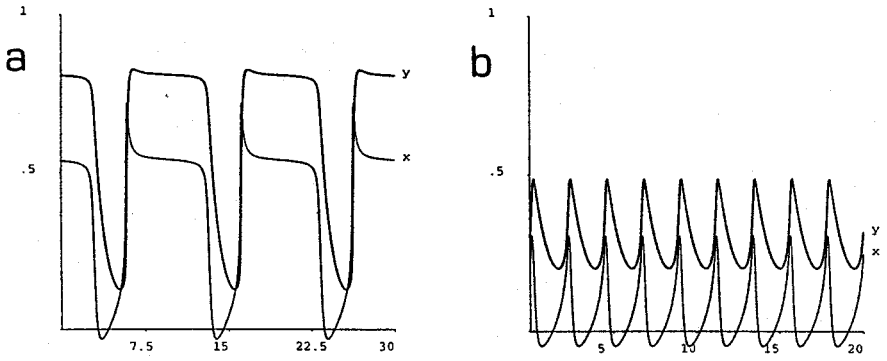

Fig. 4: Timeplots of stable limit cycles. (a) stable limit cycle in parameter region 4 and 5 (b) stable limit cycle in parameter region 1.

This type of oscillations is also known as 'bursting oscillations', and is the second attractor in region 5. Starting at w=0, a trajectory will show overshoot and finally end up in the stable equilibrium point. However, if the network develops without electrical activity w will keep increasing. If the activity is then allowed to return after some time, the system will go to the limit cycle attractor. Thus region 5 shows a 'critical period' for pruning of connections. At larger values of p, even the initial conditions $w = 0$ are in the basin of attraction of the limit cycle attractor. This implies that under high inhibition, even during normal development (electrical activity is not blocked) the system can end up in the limit cycle attractor. For the existence of this limit cycle, it is needed that on average $x < (e - b\,w^2)$ during the oscillations of x and y. This means that if the value of e is too small, the limit cycle will disappear. Another condition for the existence of the limit cycle is an oscillatory state for x and y, which exists only if $0.39 < p < 0.77$. The third condition is the existence of the homoclinic bifurcation, which is caused by a fold bifurcation. Because of these conditions, this limit cycle can exist only in the parameter regions 4, 5, 6 and 7, although the conditions for its existence are not met everywhere in these regions.

Further decreasing e causes a hopf bifurcation in equilibrium 1, arriving in region 4 in which there are three unstable equilibrium points (fig. 3c). The stable limit cycle described previously still exists. At the hopf bifurcation a second stable limit cycle is born that is the same one as that in region 2. The

ESANN'1995 proceedings - European Symposium on Artificial Neural Networks
Brussels (Belgium), 19-20-21 April 1995, D-Facto public., ISBN 2-9600049-3-0, pp. 87-92

two stable limit cycles show different dynamical behaviour. The first oscillates in x and y, alternated by long periods of high steady activity; w is almost constant throughout the process. The second limit cycle causes x, y and w to oscillate very slowly with high amplitude (relaxation oscillations).

As described before, in region 1 there is only one point attractor. However, at some points in this region there exists a second attractor (fig. 3d). This is a stable limit cycle (fig. 4b). Intuitively, we can understand the existence of this limit cycle in the following way. At the present parameter values, x and y are in the oscillatory regime if $w > 7$. On average $x < (e - b\,w^2)$ and w increases. However, at for instance $w = 50$, $x > (e - b\,w^2)$. Somewhere in between, on average x equals $(e - b\,w^2)$, and there is no net increase or decrease in w. Here a stable limit cycle exists that oscillates in x and y with high amplitude and in w with low amplitude. Mathematically, we think that the limit cycle is born at a hopf bifurcation on the hopf line that is the boundary between region 4 and 11.

4. Conclusion

It is demonstrated in this paper that a simple model of activity-dependent outgrowth can generate a great variety in dynamical behaviour, depending on the parameters p and e. For instance, parameter regions 1 and 5 show one stable state at low connectivity level and intermediate values of x and y, together with a stable limit cycle where connectivity is very high and x and y oscillate with large amplitude. The former state could be associated with a normal state of the brain, whereas the latter shows epileptiform activity and could therefore represent a 'pathological' state. As shown in this model, too much inhibition (high p) during early development could result in ending up in the 'pathological' state, whereas at low p this latter state does not exist. Interestingly, the normally inhibitory neurotransmitter GABA works excitatory during early development.

References

[1] Carpenter, G. A. & Grossberg, S. (1983), 'A neural theory of circadian rhythms: the gated pacemaker', *Biol. Cybern.* **48**, 35–59.

[2] Grossberg, S. (1988), 'Nonlinear neural networks: principles, mechanisms and architectures', *Neural Networks* **1**, 17–61.

[3] Kater S.B., Guthrie P.B. and Mills L.R. (1990) 'Integration by the neuronal growth cone: a continuum from neuroplasticity to neuropathology', *Progress in brain research* **86**, 117-128.

[4] Van Ooyen, A. & Van Pelt, J. (1993), 'Activity-dependent outgrowth of neurons and overshoot phenomena in developing neural networks', *J. theor. Biol* .**167**, 27–43.

[5] Van Ooyen, A., Van Pelt, J. & Corner, M. (1995), 'Implications of activity-dependent neurite outgrowth for neuronal morphology and network development', *J. theor. Biol.* **172**, 63–82.