MODELING NEURONAL NETWORKS

Spontaneous episodic activity in the developing spinal cord

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BACKGROUND: SPONTANEOUS ACTIVITY IN DEVELOPING NETWORKS

A key problem in neuroscience is to understand the cellular basis of behaviour. In order to discover the principles underlying the activity of neural networks, it may be helpful to understand their history. Neuronal networks are plastic: activity within a network can modify the properties of single cells and the connections between these cells, which in turn leads to changes in the activity of the network. This plasticity is a prominent characteristic of developing networks, that is, these networks can be most profoundly altered by their own activity.

Early in development, neuronal networks of the central nervous system generate spontaneous activity. It is called spontaneous because it is not provoked by sensory inputs or inputs from other parts of the nervous system, but is generated within each of these circuits in isolation. Spontaneous activity has been well characterized in the developing spinal cord, hippocampus, and retina and has also been described in other circuits (O'Donovan, 1999). Although they have widely different architectures, the features of the spontaneous activity are very similar in all these networks (see O'Donovan, 1999). The most characteristic feature of this activity is its episodic nature: most if not all neurons of the network become active together for several seconds to a minute, then the network becomes silent for intervals that can last several minutes, depending on the network (as illustrated in Figure 1).
Because spontaneous activity is so widespread in the developing nervous system and with striking similarities between different circuits, understanding its mechanisms of generation may provide some general principles of neuronal network function. Furthermore, there is evidence that spontaneous activity can drive the refinement of neuronal circuits (Katz & Shatz, 1996; Zhang & Poo, 2001), as this activity usually involves large populations of neurons in a highly correlated fashion (see below) and therefore may lead to strengthening/weakening of synaptic connections through Hebbian mechanisms (Paulsen & Sejnowski, 2000; see Zhang & Poo, 2001 for a discussion of spike-timing dependent potentiation/depression of synapses related to developing circuits). Finally, the temporal pattern of activity may also regulate the electrical properties of the individual neurons (Gu & Spitzer, 1995; Li, Jia, Fields & Nelson, 1995). It is therefore important to understand the mechanisms of generation of spontaneous activity in the developing nervous system. In the following, we focus on the temporal organization of activity through activity-dependent synaptic depression in the developing spinal cord, but suggest that the same features are common to other preparations.

Spontaneous activity was first observed as spontaneous movements in embryos of diverse animals. Embryonic motility was extensively studied in the chicken embryo (Hamburger & Balaban, 1963), as it was easy to observe spontaneous movements through the egg shell, and later to record electrical activity through a small window in the shell. It was shown that these episodic movements were caused by spontaneous electrical activity in the neuronal networks of the spinal cord. More recently, an isolated in vitro preparation of the embryonic chick spinal cord was developed (O'Donovan & Landmesser, 1987), allowing one to record the activity and to manipulate the network (by lesions or pharmacology) at different stages of development.
We can record this activity from a population of motoneurons (the output neurons projecting to the muscles) by suctioning a ventral root (axons from the motoneurons) into an electrode. The activity recorded this way is a combination of two signals. The slow component, illustrated in Figure 1A, represents the depolarization of the motoneurons, propagating passively along the axons. Superimposed on this slow signal is a fast signal (not visible on the figure) caused by the action potentials generated by the motoneurons. The slow signal shown in Figure 1A is a good indicator of the activity in the whole network, as it is due to the synaptic drive onto the motoneurons. The activity is episodic, with episodes lasting up to a minute separated by intervals lasting up to 20 minutes. Within an episode, the activity is rhythmic with a cycle frequency of ~0.2-1.0 Hz, markedly decreasing toward the end of the episode. Each cycle can be seen as a network "spike", representing the depolarization of the whole neuronal population. Although the neurons are activated in synchrony, their action potentials are not synchronized.

How is this activity generated? Several key experimental findings provide a working hypothesis.

The first thing to note is that many developing networks can be considered as purely excitatory circuits. This is because the inhibitory neurotransmitters GABA and glycine have excitatory effects early in development (Ben-Ari, 2002; Cherubini, Gaiarsa, & Ben-Ari, 1991). Indeed, blocking the action of excitatory neurotransmitters acetylcholine and glutamate does not prevent the spinal cord from generating episodic activity (Chub & O'Donovan, 1998). It is therefore easy to understand the presence of spontaneous activity in immature circuits. Any event such as a few
neurons randomly firing can be amplified by positive feedback through the recurrent excitatory projections, leading to massive activity in the whole network. This explains the activity, but not its episodic pattern. How are the episodes terminated?

One possibility is that the network "fatigues" during activity, until it is no longer capable to sustain activity. In other words, there is an activity-dependent process that depresses the excitability of the network. To demonstrate the presence of such activity-dependent depression process, we have stimulated populations of interneurons through sensory or propriospinal afferents and observed the evoked synaptic response on the motoneurons (Fedirchuk, Wenner, Whelan, Ho, Tabak, & O’Donovan, 1999). The synaptic potentials recorded on the motoneurons are decreased after an episode of activity, and progressively increase during the interval between episodes. This suggests that network excitability is depressed by the episodes of activity and that it recovers in the interval between episodes. This depression may be synaptic, that is, activity decreases synaptic efficacy. Another possibility is that this depression acts on the neurons to decrease their excitability, making them less likely to fire action potentials.

Finally, it must be stressed that no particular network structure or cellular properties are thought to underlie the pattern of activity. As mentioned above, spontaneous episodic activity is observed in developing networks with a great variety of structure, and a similar type of activity is observed in dissociated cultures of spinal neurons for which inhibitory transmission has been blocked (Streit, Tschcter, Heuschkel, & Renaud, 2001). In the chick embryo, lesion studies have shown that ventral networks of the spinal cord can generate the activity despite transversal or horizontal sectioning (Ho & O'Donovan, 1993) and pharmacological studies have shown that
episodic activity is still generated when individual neurotransmitters are blocked (Chub & O'Donovan, 1998). In addition, there is no evidence that cellular pacemaker properties underlie the rhythmic activity.

The main hypothesis is therefore that the spontaneous, episodic activity is generated by a purely excitatory network. This activity depresses network excitability and when excitability is too low the activity stops. In the silent period, network excitability can recover until a new episode starts. In order to test this hypothesis, we have built a very idealized model (schematized Figure 2A) based on all these observations. This differential equations model can be analyzed qualitatively using phase plane and dynamical systems concepts, so we can understand its dynamical behavior. It allowed us to explain some experimental results and made some predictions, some of which are presented below.

MODEL OF THE SPONTANEOUS ACTIVITY IN THE EMBRYONIC CHICK SPINAL CORD

According to the experimental findings presented above, we model a purely excitatory network whose detailed structure (connectivity pattern, heterogeneity of cell types) is not known but does not seem to be important. We also assume that the membrane properties of the neurons are not important either and all the neurons are active or inactive together. We therefore use a "mean field" representation of the activity and depression variables, as used by Wilson and Cowan
According to this formulation, the activity $a(t)$ of the network is an average of the firing rate over the population of neurons. Since individual spikes are not modeled (and assumed not to occur synchronously), this firing rate is a temporally coarse-grained representation, that is, averaged over a short period of time. Therefore $a$ can also be related to the synaptic drive (Pinto, Brumberg, Simons, & Ermentrout, 1996). The model consists of 3 equations (Tabak, Senn, O’Donovan, & Rinzel, 2000):

1. $\tau_a \dot{a} + a = a_\infty(n \cdot s \cdot d \cdot a)$
2. $\tau_d \dot{d} + d = d_\infty(a)$
3. $\tau_s \dot{s} + s = s_\infty(a)$ or (3') $\tau_\theta \dot{\theta} + \theta = \theta_\infty(a)$

The first equation describes how activity evolves in a recurrent excitatory network. Basically, $a$ tends to $a_\infty$ with a time constant $\tau_a$. The function $a_\infty$ represents the input-output function of the network. This function depends on the input-output functions of the individual neurons, their distribution across the population, and the dynamics of the synaptic signals. For simplicity we have chosen a sigmoidal function, as illustrated in Figure 2B. For low inputs to the network, there is very little output ($a_\infty \approx 0$), until a threshold ($\theta$) is reached, the output then quickly reaches its maximal value ($a_\infty \approx 1$); $\theta$ can be seen as an average firing threshold in the neuronal population. Note that the activity $a$ is itself the input to the network – modulated by the effective connectivity factor $n \cdot s \cdot d$ – because of the recurrent excitatory connections. The parameter $n$ is the network connectivity, a composite measure of the number of connections per neuron and synaptic strength which determines the maximal gain of the positive feedback loop created by excitatory connections. As described below, the activity defined by this equation is bistable over a wide range of parameters.
The second equation describes the evolution of the synaptic variable \( d \), which represents a fast depression of the effective connectivity – \( \tau_d \approx \tau_a \) is on the order of 100 ms, as in cortical networks (Chance, Nelson, & Abbott, 1998). When \( d = 0 \) all synapses are totally depressed while synapses have full strength when \( d = 1 \); \( d_{\infty} \) is a decreasing function of \( a \), also chosen to be sigmoidal for convenience. The interplay between \( a \) and \( d \) can create oscillations of the activity. Finally, equation 3 describes the variations of the slow (\( \tau_s \gg \tau_a \)) synaptic variable \( s \). This variable also decreases when \( a \) is large and increases for low activity, but on a much slower time scale. A possible biophysical mechanism for this slow (timescale minutes) synaptic depression involves the loss of chloride ions by the neurons during an episode, decreasing the excitatory action of gabaergic and glycinergic connections (Chub & O’Donovan, 2001). Alternatively, the slow depression could be due to a cellular (not synaptic) process increasing the cellular threshold \( \theta \) for high level of activity (equation 3’, \( \theta_{\infty} \) is an increasing function of \( a \)). The slow type of depression, whether synaptic or cellular, is responsible for the episodic nature of the activity (see below).

**Bistability of the excitatory network with fixed synaptic efficacy**

Let us first analyse the properties of the network without depression, that is, we study equation (1) and freeze the depression variables \( (s = d = 1) \). Such a system will reach a steady state \( (\dot{a} = 0) \) for which the activity is defined by \( a = a_{\infty}(n \cdot a) \) (from Equation 1). The steady states can be determined graphically as the intersections of the straight line and the curve of \( a_{\infty}(n \cdot a) \) shown in Figure 3A for any value of \( n \). When \( n \) is too small \((n = 0.3 \text{ in Fig. 3A})\), there is only one intersection
for a low value of $a$. Thus the connectivity is too small to sustain a high level of activity. Even if the network is transiently stimulated, activity will quickly go back to its low level state. On the other hand, for large values of $n$ ($n = 0.9$ in Fig. 3A), there is one intersection but at a high activity level. Connectivity in the network is so high that activity is self-sustained. This is expected from an excitatory network: for very low connectivity the network is inactive, while for high connectivity, the activity is maintained through positive feedback. It is also known that for intermediate connectivity, the low and high activity states can both exist, as described in the following.

For intermediate values of $n$ ($n = 0.5$ in Fig. 3A), we find 3 intersections. There are steady states at low, high and intermediate levels. Note that the middle steady state is unstable. This can be easily seen since the slope of $a_\infty (n \cdot a)$ is greater than 1 at this point, therefore if $a$ is slightly increased (resp. decreased) its derivative $\frac{d}{da} a_\infty (n \cdot a) - a$ will become positive (resp. negative) which will tend to further increase (resp. decrease) $a$. The slightest movement away from this steady state will therefore be amplified. This is illustrated in Figure 3B. If the network activity is perturbed from the low state to just below the middle state level (dashed line), activity will decrease back to its low level (i). On the other hand, if the network is kicked to just above the middle state, activity will jump to the high steady level (ii). The middle steady state is thus a network threshold, separating the low (inactive) and high (active) states.

We can summarize these results by plotting the activity levels (steady states) calculated when $n$ is varied continuously. We obtain the important diagram shown in Figure 3C. The resulting “S-shaped” curve has 3 branches: the lower branch (solid) corresponds to the low activity states, the middle branch (dashed) corresponds to the unstable states and the upper branch (solid)
corresponds to the high activity states. The S-curve defines 2 domains in the \((a – n)\) plane. For any value of \(n\), if the activity is such that the point \((n, a)\) is on the right of the curve, then activity will increase until the system reaches the upper branch (high state). Conversely, if \((n, a)\) is on the left of the S-curve, activity will decrease until it reaches the low state.

We can see that for a range of values of \(n\) (approximately between 0.31 and 0.73) there are two possible stable states. The network is bistable. As we have seen for \(n = 0.5\), a perturbation strong enough to cross the middle branch allows to switch between the two stable states. This bistability is the basis for the oscillatory and episodic behavior described below. Imagine the network is in the high activity state and we slowly decrease the connectivity. The state of the system, defined by a point in the \((a – n)\) plane will be on the upper branch and slowly move to the left, with a minimal decrease of activity. However, when \(n\) passes a critical value around 0.31 where the upper and middle states coincides (the “left knee” of the S-curve) the only remaining state is the low activity state and the network crashes to that state. Now, we slowly increase \(n\), so the state of the system tracks the lower branch, going to the right. Similarly, activity is only going to increase slightly until the “right knee” where middle and lower states coalesces. Once \(n\) is above that point, only the high state remains and the network will jump to its high activity state, terminating the cycle.

*Episodic and rhythmic behavior due to activity-dependent depression of network excitability*
The network could switch spontaneously between the high and low states according to the above mechanism if we add an activity-dependent mechanism to modulate the connectivity. Therefore we now let the slow variable $s$ vary according to equation 3 (for now, the fast depression variable is still frozen: $d = 1$). Because $s_\infty$ is a decreasing function of $a$, the new variable $s$ and therefore the effective connectivity $n \cdot s$ will tend to decrease when the network is in the high state and increase when the network is in the low state. This may lead to slow oscillations between the high and low states as explained in the previous paragraph and illustrated in Figure 4A.

We can explain the oscillatory behavior of the system geometrically as shown in Figure 4B. This treatment is similar to the phase plane analysis of single neuron excitability pioneered by Fitzhugh (Fitzhugh, 1961; Rinzel & Ermentrout, 1998). The variations of the variables $a$ and $s$ (activity and fraction of synapses not affected by slow depression) define a trajectory in the $(a-s)$ plane, called the phase plane. The solid gray S-curve in Figure 4B defines the states of the system for which $\dot{a} = 0$ (cf. Fig 3C) and is called the $a$-nullcline. The dashed curve defines the states of the system for which $\dot{s} = 0$ and is called the $s$-nullcline (it is simply the curve $s = s_\infty(a)$). For any value of $s$, if the activity is below that curve $s$ will be increasing, while $s$ will be decreasing if $a$ is above the $s$-nullcline. The steady states of the system (comprised of equations 1 and 3) are the intersections of the two nullclines. In the case of Figure 4B, there is only one steady state and it is unstable. A necessary condition for the steady state to be unstable is that the intersection occurs on the middle branch of the $a$-nullcline. If there was an intersection on the upper or lower branch, that intersection would define a stable steady state at high or low activity, which would prevent the episodic behavior. This immediately imposes a constraint on the parameters of the model if
episodes are to occur.

Imagine the system is in a state \((s,a)\) on the right of the \(a\)-nullcline. The trajectory will quickly go up as if \(s\) was constant because \(\tau_s \ll \tau_a\), until it reaches the upper branch of the \(a\)-nullcline. Then \(a\) will remain constant, while \(s\) will decrease, since the system is now above the \(s\)-nullcline. The trajectory will thus track the upper branch, going left, until it reaches the left knee of the \(a\)-nullcline. Here, a further decrease of \(s\) forces the system to leave the \(a\)-nullcline and, being on the left of the nullcline, activity decreases so that the trajectory quickly goes down to the lower branch of the \(a\)-nullcline. During this transition, the trajectory crosses the \(s\)-nullcline, so \(s\) increases. The trajectory will thus track the lower branch going right, until it passes the right knee, causing a new transition upward to the upper state.

So far, the combination of the bistability of the activity (equation 1) and the slow, activity-dependent variations of the effective connectivity (equation 3) create slow, spontaneous oscillations between low and high states that mimic the episodic activity observed experimentally. Now, if we allow the fast depression variable, \(d\), to vary (according to equation 2), the system may oscillate quickly during each episode. The system then generates rhythmic episodes as shown in Figure 5.

Finally, note that if we had used equation 3’ instead of equation 3, that is if we had considered a cellular adaptation mechanism instead of a synaptic depression mechanism to drive the episodic behavior, we would obtain a similar dynamical behavior of the system. At this point, we do not see a qualitative distinction between these two mechanisms (cellular or synaptic) of episode
generation. In the next sections, we denote these models $s$-model (synaptic depression) and $\theta$-model (cellular adaptation) and we will show particular parameter variations from which differences in their behaviors will emerge.

**Relationship between episode duration and inter-episode interval**

Can we trigger the network before synaptic strength (or firing threshold if we consider the $\theta$-model) has fully recovered? We can answer this question directly by looking at Figure 4B. At any time during the inter-episode interval (while the system is tracking the lower branch of the S-curve), if we transiently “stimulate” the network so that activity increases above the threshold, the phase point will move to the high state, initiating an episode. However, the episode will start from a lower value of $s$ than a spontaneous episode, therefore the system will track a shorter segment of the upper branch before reaching the left knee and falling back to the low state (whatever the value of $s$ for which we triggered an episode, the critical value of $s$ at which the episode terminates is always the same). Therefore, the triggered episode is shorter than a spontaneous episode. More precisely, the longer we wait to artificially trigger an episode, the longer the episode is, as illustrated in Figure 6A,B.

This model prediction is testable experimentally. Indeed, we have shown that it is possible to trigger episodes by stimulating sensory nerves afferent to the spinal cord, and that the duration of the stimulated episodes increases with the interval between the triggered episode and the end of the previous (spontaneous) episode, as shown in Figure 6C,D (Tabak, Rinzel, & O’Donovan, 2001).
In other words, the longer we let the network excitability recover, the longer the triggered episode is. This suggests that in the experimental preparation, as in the model, there is a critical value of network excitability for which all triggered episodes terminate.

In Figure 6D we have also plotted the durations of spontaneous episodes (gray dots) against the recovery interval that just preceded the episodes. Although their range is different, the relationship is the same as for stimulated episodes, suggesting again that all episodes (spontaneous or triggered) terminate at a fixed level of network excitability. To confirm this finding, we have also looked at the relationship between episode duration and the following interval and found no correlation (Tabak et al., 2001). This lack of correlation suggests that there is no “memory” of the system’s state once an episode is terminated, supporting our finding that all episodes terminate at a fixed level of network excitability.

Figure 6D shows that spontaneous episodes occur after various intervals. Unlike our simple model, episodes therefore can start at various levels of network excitability. Episode initiation is a stochastic event. Although a higher level of excitability means a higher probability of triggering an episode, the network needs a triggering event in order for an episode to start and this is where randomness is introduced. On the other hand, as our data suggest, all episodes terminate at the same value of network excitability; episode termination is a deterministic event. This seems to be a property of many developing or hyperexcitable systems that generate episodic activity, since the same relationships (positive correlation between episode duration and preceding – but not following – interval) was found in the developing retina (Grzywacz & Sernagor, 2000), developing cortical networks (Opitz, De Lima, & Voigt, 2002), hippocampal slices (Staley,
Recovery of the activity after blockade of excitatory connections

One of the most surprising features of the spontaneous activity is its robustness to pharmacological perturbation. When synaptic transmission mediated by the excitatory neurotransmitters glutamate and acetylcholine is blocked using pharmacological agents, the spontaneous activity stops for a long period of time (compared to the inter-episode intervals) but then recovers, as shown in Figure 7A (Barry & O’Donovan, 1987; Chub & O’Donovan, 1998). The activity is then thought to depend exclusively on gabaergic and glycinergic synapses, which have, early in development, an excitatory role. It must be noted that the recovery is not gradual, as the new inter-episode intervals are not gradually decreasing to a new level but remain at a fixed level immediately after the activity has recovered (Fig. 7A, note that after recovery the intervals are larger than in control conditions). We could imagine an additional process, through which the lack of activity is detected and compensated by slowly increasing network excitability until activity reaches its control level. However, this may imply a progressive decrease of inter-episode intervals, unlike the experimental observation.

Surprisingly, the $s$-model can explain this recovery without introducing any additional variable in the model. If we decrease the connectivity parameter ($n$), in order to mimic the blockade of a fraction of the connexions, the $s$-model reacts exactly like the chick spinal cord: activity first stops,
then recovers with a fixed inter-episode interval (Fig. 7B, Tabak et al., 2001). As for the experimental result, the new inter-episode intervals were larger than before the blockade. In addition, episode duration was only slightly affected, also in agreement with the experiments. On the other hand, the θ-model behaved in a different way: activity recovered quickly after the reduction in connectivity and the intervals were then slightly lower than in “control” (Fig. 7B, “θ-model”). In addition, episode duration was markedly reduced for the recovered activity (not shown). This is an important qualitative difference between the s- and θ-models. This difference in how the models react to a decrease in connectivity suggests that the episodic nature of the spontaneous activity in the chick cord is due mostly to synaptic depression, not cellular adaptation.

In order to understand the recovery process, we plotted again the activity generated by the s-model in Figure 8, together with the slow depression variable \( s \) and the effective connectivity \( n \cdot s \). \( s \) and therefore \( n \cdot s \) decrease during the episodes and increase during the inter-episode intervals. When the connectivity \( n \) is suddenly decreased by 25% (from 1.2 to 0.9), this causes a corresponding decrease of \( n \cdot s \), the effective connectivity in the network, i.e. the effective gain of the positive feedback due to excitatory connexions. Activity is therefore blocked until this gain can reach back to its “control” value. This can happen because in the absence of activity, \( s \) keeps increasing towards its maximal value (1). As soon as \( n \cdot s \) reaches its control value, episodes of activity reoccur. The intervals between episodes are somewhat longer than in control, because the exponential increase of \( s \) during the intervals is slower since \( s \) is now closer to its asymptotic value. Therefore, the activity can recover after a moderate decrease of connectivity because the system compensates by decreasing the level of depression (increasing \( s \)).
This predicts that the unblocked synapses see their availability or efficacy increase relative to their control level. To verify this prediction, we have stimulated a pathway (between adjacent ventral roots) that does not contain glutamatergic synapses. Indeed, we have shown that the strength of the response was increased after blockade of glutamatergic connexions and subsequent recovery of the activity (Tabak et al., 2001). The developing spinal circuits are therefore able to approximately maintain their level of activity following the blockade of some of their connexions. This is very important since the temporal pattern of activity may be important in the development of network and cellular properties (Gu & Spitzer, 1995; Stellwagen & Shatz, 2002). During development, some cells and connexions may be lost, while other synapses may see their efficacy increased. Through the very mechanism that regulates its patterned activity (activity-dependent depression), the developing spinal cord is able to compensate for these changes and therefore maintain its activity level within a certain operating range.

**RELEVANCE, APPLICATIONS AND FUTURE WORK**

The model presented in this chapter was developed to understand the spontaneous activity in the developing spinal cord. However it is general enough to apply to spontaneous activity in other developing circuits. Indeed, other modeling and experimental studies have suggested that similar mechanisms can explain the spontaneous episodic activity in developing retinal (Butts, Feller, Shatz, & Rokhsar, 1999; Grzywacz & Sernagor, 2000; Meister, Wong, Baylor, & Shatz, 1991) and cortical networks (Opitz et al., 2002). These mechanisms involve fast positive feedback through
excitatory connections together with a slow activity-dependent depression of network excitability. They may therefore be common to many developing networks. This gives us a framework to study developing and excitatory networks. Can this framework be helpful to the study of mature neural networks?

One critical fact is that with maturation, networks acquire functional inhibitory connections, which stops the episodic activity. Mature networks become segregated into subserving different functions, with a great variety of patterns of activity. Can the concept of recurrent excitatory network still be used to understand mature networks? In the following we review some evidence from experimental and modeling studies suggesting that the “immature” mechanisms of burst generation could be conserved in more mature networks.

First, episodic bursts of activity can be generated in “mature” networks that are disinhibited by pharmacological block of their inhibitory connexions. This was shown in in vitro spinal (Bracci, Ballerini, & Nistri, 1996; Darbon, Scicluna, Tscherter, & Streit, 2002) and hippocampal (Wong & Traub, 1983) networks. Therefore, the immature mechanism is still potentially present in mature networks and can be unmasked. Furthermore, episodic activity can be generated through the same mechanism in some networks with functional inhibitory connexions if inhibition is not too strong or if the networks are rendered more excitable (Latham et al., 2000ab; Staley et al., 1998; Timofeev, Grenier, Bazhenov, Sejnowski, & Steriade 2000; Traub & Dingeredine, 1990; Tscherter, Heuschkel, Renaud, & Streit, 2001; Tsodyks, Uziel, & Markram, 2000). Thus, bursting activity could be evoked in mature networks through neuromodulators that would decrease synaptic inhibition and/or raise cellular excitability.
Although demonstrating that a mechanism of activity can be uncovered does not mean that this mechanism is in fact used during the normal function of a network, there are several examples suggesting such possibility. A model of the spinal circuit for swimming in the lamprey is based on two excitatory subnetworks that generate bursts using a cellular adaptation mechanism. These two units are connected by mutual inhibitory connexions, ensuring that the pattern of rhythmic bursts is in alternation between left and right sides (Hellgren-Kotaleski, Lansner, & Grillner, 1999). Therefore, it is possible that the rhythmic locomotor activity is simply a faster version of the spontaneous activity, with inhibition in the mature network simply allowing the coordination between left and right sides, as well as between flexors and extensors in higher vertebrates. Inhibition would also ensure that the locomotor network is not always “on”, but only activated when necessary. Coupled rhythm generating circuits control many functions like locomotion, respiration, chewing, etc. (Cohen, Rossignol, & Grillner, 1988) and it is therefore important to understand how these circuits generate oscillatory activity.

Another example suggesting that the immature mechanism may play a role in mature networks comes from studies in cortex of anesthetized cat. Timofeev et al. (2000) showed that isolating a small slab of cortex (with truly inhibitory connections) lead to episodic bursts of activity (about 5 bursts per minute), with a mechanism similar to the one presented here. However, when they recorded from a larger network, they observed the 1Hz oscillation that is observed during sleep. This led to the suggestion that the cortical sleep (< 1 Hz) oscillations and the episodic bursts in small slabs could be generated through the same mechanisms.
Finally, an application of this type of activity regarding neural computation was presented by Loebel and Tsodyks (2002). This processing has for its basis the short “population spikes” generated by networks of mostly excitatory neurons with synapses subject to a fast depression (a small fraction of inhibitory cells didn’t disrupt this activity). These populations spikes are generated through a similar mechanism than the episodes described here, but on a much faster time scale. During a population spike, most neurons fire only once, but they become transiently synchronized (Tsodyks et al., 2000). Such synchrony among neuronal populations could play an important role in cortical information processing, and Loebel and Tsodyks have suggested some applications of the transient synchronization allowed by population spikes, by considering whether transient input signals elicited a response (PS) or not from the network. The success in triggering a population spike depends on the level of depression of the synapses in the network at the time of the stimulus. In other words, the response of the network to an input depends on the (short-term) history of network activity (Loebel & Tsodyks, 2002).

On the other hand, it is possible that the episodic activity, which is characteristic of developing networks, is an abnormal mode of activity in mature networks. For example, the episodic activity in cortical slabs mentioned above is due to the much decreased number of synaptic connections once the slab is isolated (Timofeev et al., 2000). It is also thought that epilepsy seizures are due to an impairment of inhibitory synapses, or to an anomalous level of excitation. An example of “epilepsy seizures in vitro” was shown by Staley et al. (1998) who recorded spontaneous, episodic burst of activity in hippocampal slices that were disinhibited or rendered hyper-excitabile. They showed that these bursts were regulated by synaptic depression, as in the $s$-model. Alternatively, a model by Traub and Dingledine (1990) of “epileptic” bursts in hyperexcitable hippocampal
networks proposed that bursts are terminated by a slow hyperpolarizing current, that is, a cellular type of depression.

It is critical to know whether these bursts are terminated by a synaptic or cellular process, if one wants to choose an appropriate pharmacological treatment of seizures. As a thought experiment, suppose that we want to suppress “epileptic bursts” in a hyperexcitable hippocampal network. Should we target cellular excitability or synaptic connections? If, for example, the bursts are terminated by synaptic depression as in Staley et al. (1998) experiments, our results with the $s$-model suggest that we should use a pharmacological agent that blocks excitatory synapses, as this will increase the interval between each burst. Decreasing cellular excitability would also increase the interburst interval, but it would increase burst duration too. Similarly, the effectiveness of a drug potentiating inhibitory synapses in order to stop the bursts would depend on the type of depression mechanism that terminates the bursts and on the effects of the inhibitory connections – phasic or tonic.

Much recent work has been aimed at understanding the role of inhibition in neuronal networks. Although our approach has emphasized excitatory networks in vertebrates, it should be pointed out that circuits of inhibitory neurons may produce oscillations, too (Rinzel, Terman, Wang, & Ermentrout, 1998; Wang & Buzsaki, 1996; Whittington, Traub, & Jefferys, 1995). A great deal of future work should be concerned with adding inhibitory cells in our network models. Because the effects of inhibition will depend on many factors (tonic versus phasic, random versus structured, homogeneous versus heterogeneous populations, etc.) this will certainly require the use of cell based ensemble models (as in Timofeev et al., 2000; Tsodyks et al., 2000), instead of the mean
field type of model presented here.

It will be particularly important to understand how network activity is changed as gabaergic synapses switch from excitatory to inhibitory during development, a transition that may be driven by network activity itself (Ganguly, Schinder, Wong, & Poo, 2001). Our understanding of the spontaneous activity in developing systems will facilitate the study of the role of this activity for network maturation. It will become necessary to identify the long term mechanisms of activity-dependent plasticity operating in developing networks. These “learning rules” will then be added to our models of spontaneous activity, allowing us to study how activity in a network leads to changes in that network, changes which in turn will affect activity.
REFERENCES


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FIGURE LEGENDS

Figure 1
Episodic activity in developing networks. A, Spontaneous activity recorded from the isolated spinal cord of a 7.5 day old chick embryo. The activity is recorded from a ventral root and represents the synchronous activation of a population of motoneurons. It is characterized by rhythmic episodes lasting up to a minute which are separated by silent intervals lasting up to 20 minutes. The high frequency (fast) signal corresponding to motoneuron discharge is not visible because of the scale and the low sampling rate (20 Hz). Modified from Tabak et al (2000). B, Spontaneous activity recorded from the isolated retina of a 9 day old mouse (postnatal). Firing rate averaged over 29 cells. Note the difference in the time scale with the recording in A. Data courtesy of J. Demas, S.J. Eglen and R.O.L. Wong.

Figure 2
A, Schematic representation of the model network. Network output (a) is fed back to the neuron population through recurrent excitatory synapses. The amount of feedback is proportional to the connectivity (n) and can be reduced by fast (d) and/or slow (s) synaptic depression. Network output can also be modulated by slow variations of the average cellular threshold (θ). B, sigmoidal input-output function of the network $a_\infty(i) = 1/(1 + e^{-(i-\theta)/k_\alpha})$, with $\theta = 0.18$ and $k_\alpha = -0.05$. Modified from Tabak et al (2000).
**Figure 3**

A, Graphical solutions of the equation $a = a_s (n \cdot a)$. Depending on the value of $n$, there can be 1 or 3 solutions. B, Time course of network activity for $n = 0.5$. The network receives external inputs at $t = 20$ and $t = 50$ (arbitrary unit normalized to $\tau_a$). The first input (i) brings the activity just below the middle state (network threshold, dashed line) so activity decreases back to the low state. The second input brings activity just above the network threshold, it then jumps up to the high steady state. C, Diagram showing the possible steady state values of activity for all values of $n$ between 0 and 1. The dashed curve (middle branch) indicates unstable states. The steady states determined in A are represented on the curve by filled (stable) or open (unstable) circles. Modified from Tabak et al (2000).

**Figure 4**

Episodic behavior of the network (equations 1 and 3). A, Slow oscillatory variations of activity ($a$, solid curve) and slow depression variable ($s$, dotted curve) with time. Time is in arbitrary units. B, Phase plane representation of the episodic behavior. The trajectory continuously cycles through the high (Episode) and low (Interval) activity states. The transitions between the two activity levels are very fast because they are governed by the small time constant $\tau_a$ while the evolution at either level is slow because governed by the large time constant $\tau_s$. Gray S-shaped curve: $a$-nullcline; Dashed curve: $s$-nullcline.

**Figure 5**

Episodic and rhythmic behavior of the full system (equations 1, 2 and 3). A, Time variations of $a$
and \( s \), showing the episodic behavior with fast oscillations. Note that episodes and intervals between episodes are shorter than in Fig 4A. This is mostly because episodes terminate at a higher value of \( s \) when the fast depression is present. B, Detail of an episode on a faster time scale, showing the fast oscillations of \( a \) and \( d \).

**Figure 6**

Relationship between episode duration and interval preceding the episode. A, Time course of activity generated by the \( s \)-model, for different intervals between a spontaneous episode and a triggered (stim) episode. B, Plot of episode duration against preceding interval for the model; a, b, c correspond to the traces shown in A. C, Time course of activity generated by a spinal cord obtained from a 10 day old chick embryo. Stimulations (stim) were applied at different time intervals after a spontaneous episode. Traces were high pass filtered at 0.01 Hz. D, Plot of episode duration against preceding interval for evoked (black circles) and spontaneous episodes (gray circles); d, e, f correspond to the traces shown in C. Modified from Tabak et al (2001).

**Figure 7**

Recovery of activity after partial block of excitatory connexions. A, results from a 10 day old chick, showing activity (upper trace) and inter-episode intervals in control and after blockade of some glutamatergic connexions (100 \( \mu \text{M} \) APV). B, model results before (“control”) and after \( n \) was decreased from 1.2 to 0.9 (-25%). The upper trace was obtained with the \( s \)-model. On the interval plot, results from both the \( s \)-model (filled diamonds) and \( \theta \)-model (open triangles) are shown.

**Figure 8**

Time course of activity, synaptic strength \((s)\) and effective connectivity \((n \cdot s)\) produced by the s-model before (“control”) and after (“reduced connectivity”) \(n\) was decreased by 25% (from 1.2 to 0.9). Activity stops after \(n\) was decreased, because the effective connectivity becomes too small to support network activity. This allows \(s\) to increase beyond its control level, until \(n \cdot s\) reaches its control level. Activity then reoccurs, although with larger inter-episode intervals. Modified from Tabak et al (2001).