Tonic-Clonic Transitions in Computer Simulation

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Summary: Network simulations can help identify underlying mechanisms of epileptic activity that are hard to isolate in biologic preparations. To be useful, simulations must be sufficiently realistic to make possible biologic and clinical prediction. This requirement for large networks of sufficiently detailed neurons raises challenges both with regard to computational load and the difficulty of obtaining insights with large numbers of free parameters and the large amounts of generated data. The authors have addressed these problems by simulating computationally manageable networks of moderate size consisting of 1,000 to 3,000 neurons with multiple intrinsic and synaptic properties. Experiments on these simulations demonstrated the presence of epileptiform behavior in the form of repetitive high-intensity population events (clonic behavior) or latch-up with near maximal activity (tonic behavior). Intrinsic neuronal excitability is not always a predictor of network epileptiform activity but may paradoxically produce antiepileptic effects, depending on the settings of other parameters. Several simulations revealed the importance of random coincident inputs to shift a network from a low-activation to a high-activation epileptiform state. Finally, a simulated anticonvulsant acting on excitability tended to preferentially decrease tonic activity.

(*J Clin Neurophysiol* 2007;24: 175–181)

Computer simulation of neural systems can be used to connect micro to macro, explaining behavior at a network or whole neuron level by reference to the underlying proteins that control the dynamics of neurons (voltage- and ligand-sensitive channels) and synapses (receptors) (Lytton, 2002). In the context of epilepsy, these conceptual connections can be used both to explain how a particular pathologic process can produce or provoke seizures (Bush et al., 1999) and to further develop rational pharmacotherapeutic approaches to polypharmacy and syndrome-targeted therapeutics (Drongelen et al., 2005).

A continuing difficulty in neuronal network simulation is the size of the problem, which leads to difficulty both in execution (need for supercomputers; Hereld et al., 2005; Migliore et al., 2006) and difficulty in organizing and interpreting the many thousands of associated parameters (Lytton, 2006; Omurtag et al., 2000). In this article, we use a highly simplified neuron representation that nonetheless preserves the critical dynamics of both neurons and synapses (Lytton and Stewart, 2005, 2006). We use this model to explore large numbers of simulations to evaluate how particular alterations at the cellular or synaptic level lead to epileptiform behavior at the network level. We also use simulated pharmacology to determine possible effects of anticonvulsants on these dynamical patterns.

METHODS

Simulations were done in NEURON using the Artificial Cell mechanism (Lytton and Stewart, 2005,2006). Two different sized networks were used. Each network had three cell types: 1) an excitatory population that was made spontaneously active to play the role of a driver of activity ("drivers"); 2) a larger excitatory population that then expresses epileptiform activity ("expressors"); and 3) an inhibitory population. Network A (NetA) had 10 drivers, 1,000 expressors, and 40 inhibitory cells. Network B (NetB) had 1,000 drivers, 2,000 expressors, and 500 inhibitory cells. In addition to size, a major difference between the two networks was that Network B used feedback to the drivers, which could then have their activity altered by ongoing excitatory and inhibitory activity.

Connectivity was random with the following connection densities listed in Table 1:

Several parameters were explored in these networks. Synaptic parameters were the connectivity weights and time constants for the different connection types (α-amino-3-hydroxy-5-methyl-ioxyzole-4-propionic acid receptor, AMPA; *N*-methyl-d-aspartate receptor, NMDA; γ-aminobutyric acid type-A receptor, $GABA_A$; γ-aminobutyric acid type-B receptor, $GABA_B$). Intrinsic parameters included threshold, intrinsic time constant, refractory period and an afterhyperpolarizing potential (AHP). Synaptic weights were assigned randomly with a normal distribution around the parameter central point within a narrow range of from 5–10% of value. No connection delay was included in these simulations.

A total of 138,240 parameter-exploration simulations were performed using NetA. Due to the large number of simulations, only simulated field potential could be saved for most of these.

Simulations were performed in Linux on various platforms. Multiple simulation runs were performed on an 84-node IBM-1300 Beowulf cluster. Full model definition and a runnable simulation is available for Fig. 4 on ModelDB (http://senselab.med.yale.edu/senselab/ModelDB).

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ISSN: 0736-0258/07/2402-0175

TABLE 1. Connection Densities

NetA: FROM \?\	Driver	Expressor	Inhibitory Cell
TO ↓ driver	—	—	—
Expressor	0.2	0.1	0.4
Inhibitory cell	0.5	0.4	1.0
NetB: FROM \?	**Driver**	**Expressor**	**Inhibitory Cell**
TO ↓ driver	0.1	0.05	0.22
Expressor	0.1	0.05	0.22
Inhibitory cell	0.1	0.1	0.22

RESULTS

Weight matrices were tuned to produce substantial activation in expressors characterized by high-amplitude repetitive population spiking (Fig. 1). Intrinsic and synaptic parameters were subsequently varied. In Fig. 1 the drivers (bottom row) have an average firing rate of 2 Hz. Despite the random nature of the inputs, structure is created in the firing of the expressor cells due to the tendency of random coincident input to produce brief activation chains that involve a large and changing proportion of the expressors. In the current example, the initial population burst involves 60% of the expressor cells while the subsequent population events involve between 20–40% of the population.

Activity Altered by Timing

Despite identical circuitry and parameters, expressor activity patterns could be significantly different due to alterations in the timing of driver activation with no alteration in the total amount of drive. In Fig. 2, the same total number of inputs were applied to identical networks. Time of initial activation of the expressors varied by 200 milliseconds. This can be explained by noting that the proper coincidence of activations are necessary for activating the network to produce ongoing activity. Once the network did begin firing persistently, variability was also seen in the specific pattern of firing. All networks started out with a pattern of population bursting with sets of four or five population spikes. In two cases (top and seventh network in Fig. 2), this pattern persisted throughout the entire 500 milliseconds of simulation. In the other networks, this pattern gave way within 100 to 200 milliseconds to a pattern of faster firing.

Increased Intrinsic Excitability May Have Myriad Effects on Network Behavior

We ran 138,240 parameter variations on NetA with explorations of multiple values of both intrinsic and synaptic parameters. Increasing intrinsic cell excitability by lowering spike threshold (hyperexcitable network) produced a greater number of population spikes and a greater duration of repetitive population spikes activity compared with the low-excitability network (otherwise matched for all parameters and stimulation pattern) in 46% of the assayed simulations (Fig. 3. right-upper quadrant). This meant that a surprising 54% did not show both of these indicators of epileptiform activity. In some cases, this paradox could be readily explained. For example, Fig. 3E demonstrates a single "interictal" spike in the hyperexcitable network (solid line) while showing repetitive spike-wave activity in a low-excitability network that otherwise has the same parameters and stimulation (dashed line). By contrast, Fig. 3G produced a longer but less intense (fewer population spikes) seizure in the hyperexcitable network. Of course, these simple measures are only a gross indication of epileptiform activity. In Figs. 3A and 3B, the hyperexcitable network produces a greater number of population spikes but the low-excitability network shows higher-amplitude population spikes with a clear spike-wave morphology. About 10% of simulation pairs showed very little change in these measures despite the change in cell excitability (Fig. 3D).

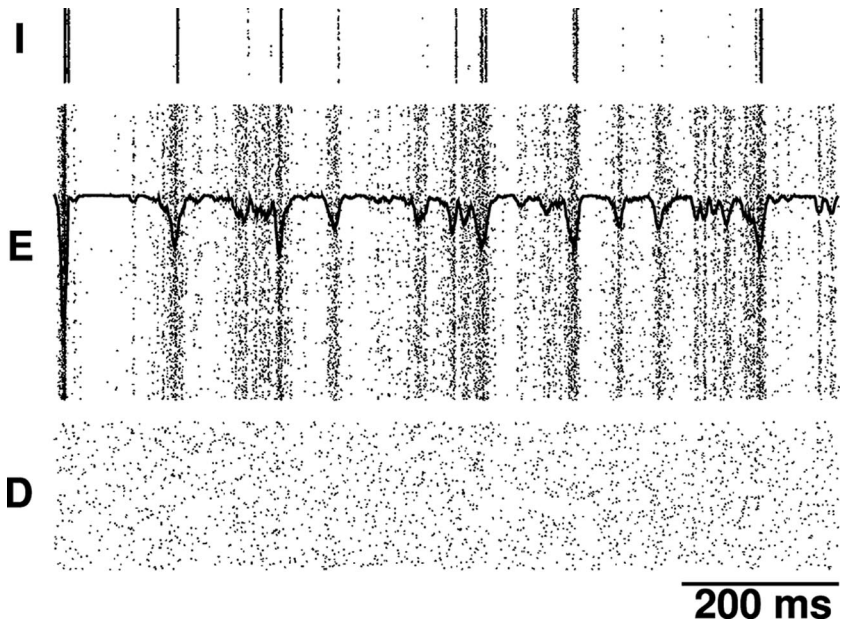

FIGURE 1. Raster plot showing spikes during one second of epileptiform activity in a sample network. Drivers, expressors, and inhibitors are indicated by initial letter. Field potential for expressors is superimposed on the corresponding raster (NetB connectivity).

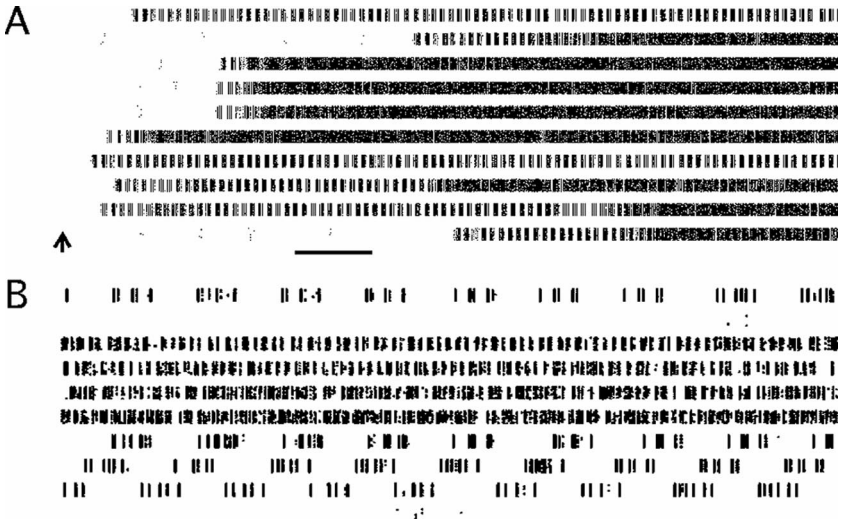

FIGURE 2. Raster plots of expressor cells from 10 runs of NetA with shuffling of driver timing and input targets **(A)**. A 500-millisecond simulation shows different response times and different firing patterns due to reshuffling of input times. Arrow shows time of driver activity onset. **(B)** Expansion of 50 milliseconds of activity from each run (period of bar below **A**).

Due to its larger size, comparable large-scale parameter search of NetB was not feasible. Instead, the effects of individual parameter alterations were explored to assess alterations that either promoted or prevented epileptiform activity. In general, two patterns of activity were seen: recurrent population spikes and prolonged continuous spiking. Recurrent population spiking tended to be less rhythmic than that seen in NetA simulations (Fig. 1).

Simple Networks Prone to Latch-up

In the absence of inhibition, increased excitatory connectivity via AMPA connections could readily produce a temporary latch-up condition with all cells showing tonic spiking at or near the maximum rate allowed by the refractory period (Fig. 4). In the absence of inhibition, intrinsic slow hyperpolarizing mechanisms terminate the latch-up condition. Here the timing of this effect is controlled by the AHP state-variable time-constant. In a compartment simulation or real cell, the timing would represent the combined effects of long-time-constant Ca^{2+}- and voltage-sensitive potassium channels.

Figure 4 shows how a slow-building hyperpolarizing influence will terminate the latch-up condition. By contrast, Fig. 5 illustrates that a slow-building depolarizing influence, that mediated by NMDA, can lead to latch-up. However, whereas the timing of termination of Fig. 4 was predictable directly from the time-course and strength of the afterhyperpolarizing parameters (AHP), the timing of latch-up in Fig. 5 depended not only on NMDA parameters but also on the random near-simultaneous occurrence of inputs (*cf.* Fig. 2). Although intrinsic cellular state-variables are relatively im-

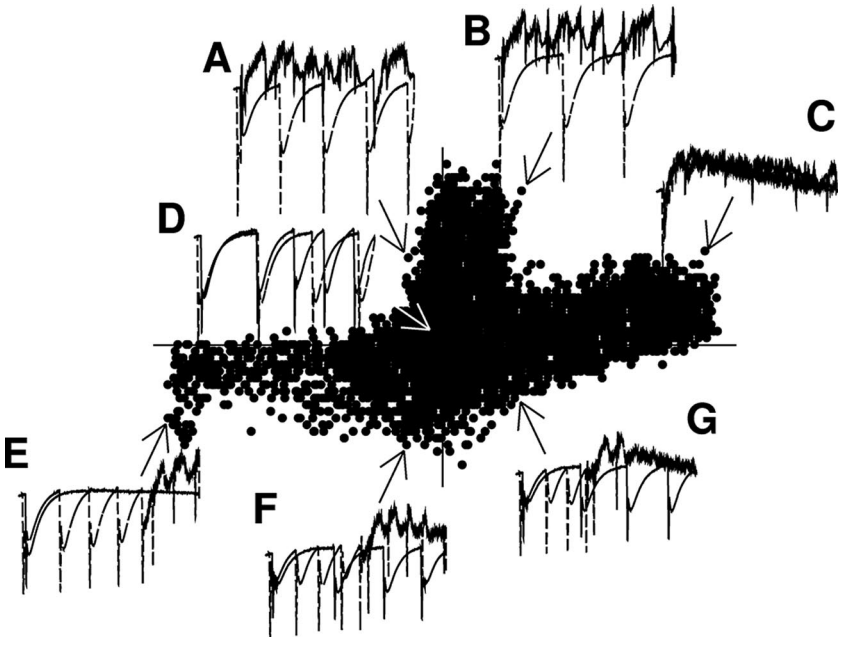

FIGURE 3. Scatter plots of differences in seizure duration (x-axis) and number of population spikes (y-axis) between hyperexcitable and low-excitability versions of NetA. Shown are points for 27,968 out of 138,240 simulations. Simulated field potentials for individual 1-second simulation pairs are shown in **A–G** with arrow indicating location on the scatter plot. Solid-line, hyperexcitable network; dashed-line, low-excitability network.

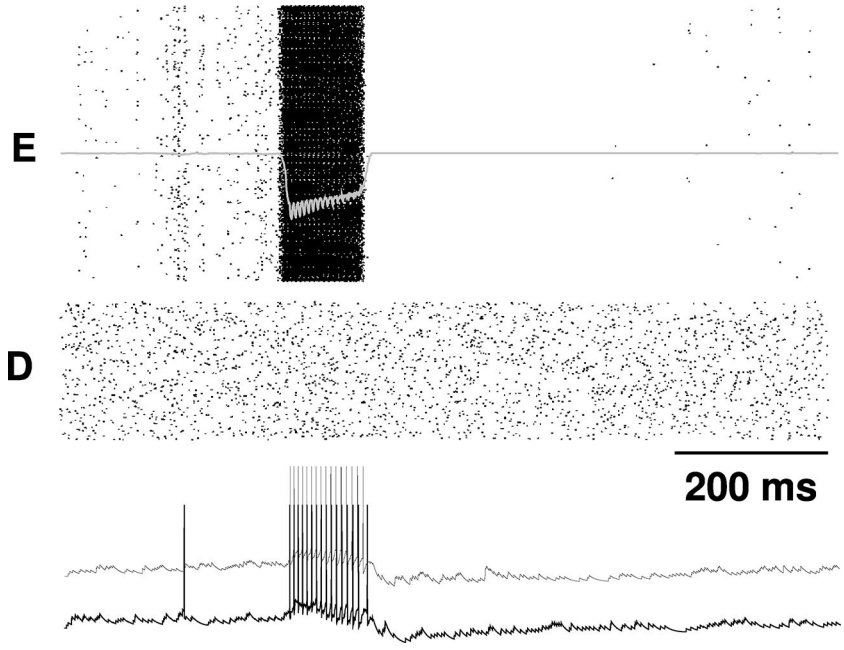

FIGURE 4. Activity in NetB simulation with no inhibition. Field potential for expressors is superimposed on the raster plot. Voltage traces for two expressors are shown at bottom.

mune to random network fluctuations, synaptic state-variables are driven by them and are therefore highly sensitive to random input.

Inhibition in Fig. 5 is dominated by feedforward inhibition from drivers to inhibitors to expressors. Increasing the amount of feedforward inhibition by increasing at either or both intervening synaptic locations reduced activity of the expressors without altering the pattern of firing (not shown). Population firing pattern continued to be dominated by random coincidence patterns of the drivers. By contrast, increasing feedback inhibition did have a significant effect on population firing because feedback carved out periods of inactivation following activation of the expressors (Fig. 6). Interestingly, periods of latch-up could still be seen and were still terminated primarily by the intrinsic AHP.

Burst-Modulating Anticonvulsant Drug Effects

Several of the large variety of current and past anticonvulsants have been found to affect voltage-dependent sodium channels so as to reduce bursting in excitatory cells. This includes older anticonvulsants such as phenytoin and carbamazepine as well as newer agents such as lamotrigine. We modeled our anticonvulsant drug (ACD) simulation effect on that of lamotrigine shown in Fig. 6 of Xie et al. (Fig. 7) (Xie et al., 1995).

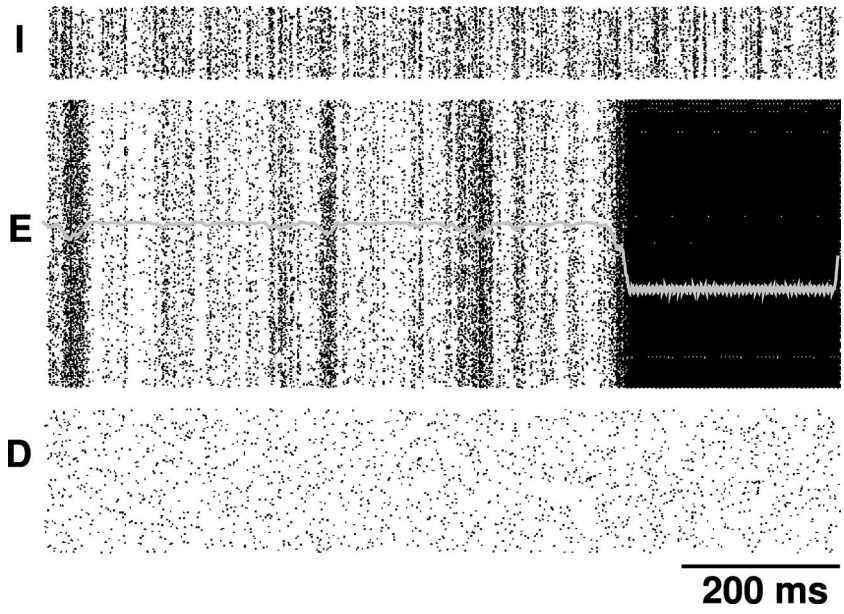

FIGURE 5. Latch-up occurring late in a simulation with augmentation of expressor → expressor NMDA strength.

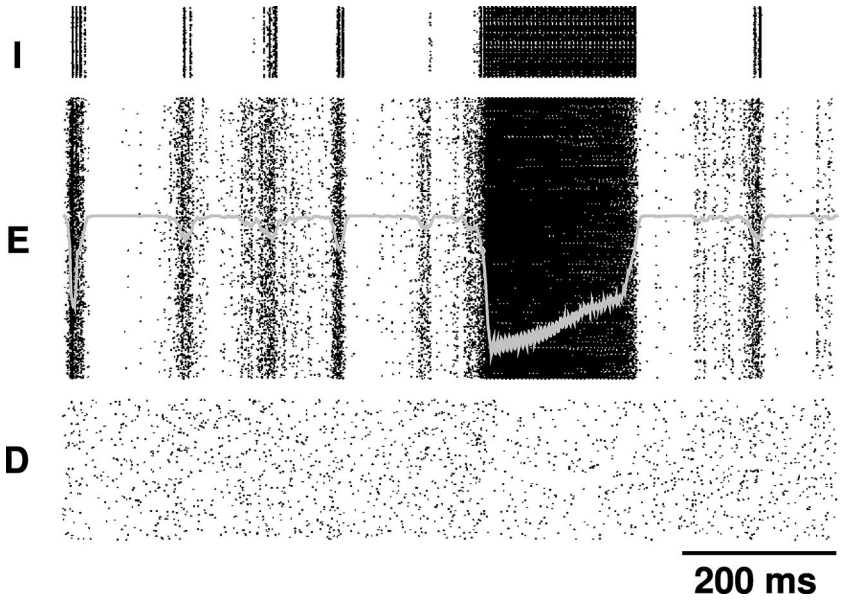

FIGURE 6. Feedback inhibition from expressors → inhibitors → expressors more cleanly carves out episodes of activation.

Application of the ACD effect to the network shown in Fig. 6 reduced the duration of each activation, most notably during the tonic latch-up period (Fig. 8). Despite the elimination of the prolonged latch-up period, the subsequent dynamics appear unchanged (arrow). Cell firing in the ACD simulation occurred at the time of latch-up onset in the control (Fig. 9). Surprisingly, cell firing also occurred near the time of latch-up termination in the control (arrows in Fig. 9; also compare the two field potentials in Fig. 8). This suggests that the random coincident driver firing that initiates such firing played a role in terminating the latch-up firing in the control simulation.

DISCUSSION

Coherent or coordinated firing is a generic property of model networks. Neurons can induce firing in much of the rest of the population as a result of mutual positive synaptic influences and this activation can then be further coordinated in repetitive activity by the modulating effects of inhibition (Lytton and Sejnowski, 1991). These dynamical periods contrast with periods of incoherent firing where minimal correlations exist among the spike times of individual neurons. For relatively simple models, analysis shows that parameter space contains regions that correspond to various forms of coherence, which are separated from regions of incoherence by distinct but complicated boundaries (Sirovich et al., 2006). Due to small changes in intrinsic or synaptic properties, or in the levels of noise, a simple network can switch rapidly among different patterns of firing. Here we have explored more complex networks to determine which biologic parameters are particularly important for these transitions.

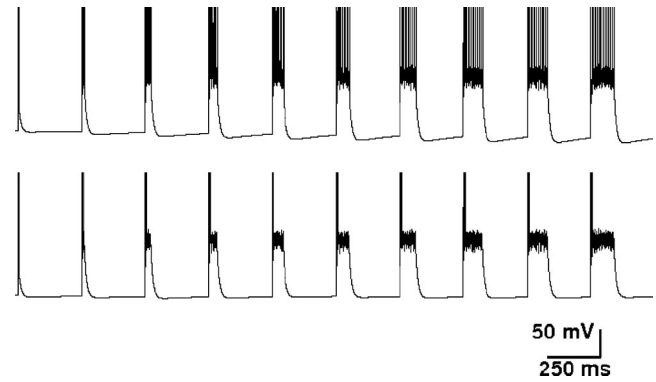

FIGURE 7. Reduction of bursting in ACD simulation with repeated plateau inputs of increasing duration. Top, control; bottom, ACD effect.

In this study, we used the simulation level of artificial cells to permit the running of moderately large networks (thousands of cells) in real time. Although this approach does not include the level of detail permitted by multicompartment modeling, it makes it easier to relate specific parameter changes to network behavior by avoiding the complex parameterizations associated with the single neuron simulation.

The network was designed to be simple and to illustrate an organizational principle that applies to both slice and *in vivo* epileptogenesis: there is typically a subset of cells or a single brain area that provides the activation that then involves a larger number of cells either locally or in different parts of the brain (secondary generalization of a seizure) (Dominguez et al., 2005; Dudek et al., 1999; Meeren et al., 2002; Van Drongelen et al., 2003). Our distinction between drivers and expressors encapsulates this organization principle without specifying whether we are considering local or remote activation.

We regard the dynamics of these simulations as epileptiform due to the relatively large number of expressor cells that spike during population events. The proportion, sometimes upwards of 50%, is likely higher than would be expected in a slice or *in vivo* due to the relatively small size of the simulated network. By contrast, an interictal spike would

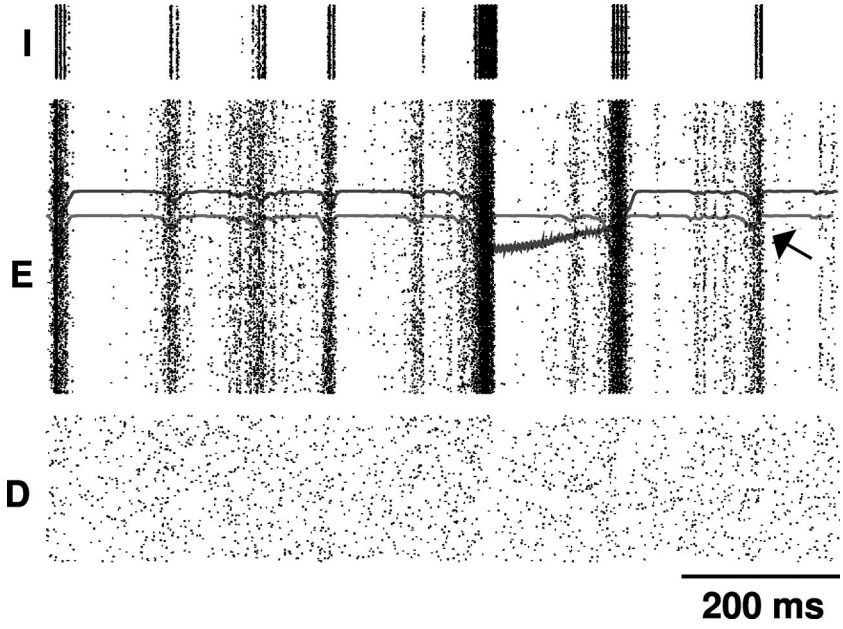

FIGURE 8. Anticonvulsant drug simulation reduces prolonged latch-up period without significantly affecting other dynamics. Field recordings compare control (upper trace from Fig. 6) and ACD simulation (lower trace).

involve a somewhat higher proportion of the network and would exhaust the "consumable" neurons so that activity in the network would cease for some time (Lytton et al., 1998).

Although the time course is compressed, we consider the latch-up phenomenon (Fig. 6) to be suggestive of a tonic epileptic state where near-maximal continuing firing of a large number of neurons would result in constant posturing of corresponding muscle groups. Similarly, we associate repetitive brief activation with clonic activity that would produce rhythmic contractions in associated muscle groups. These activations would also be associated with paroxysmal depolarizing shifts in network cells, as can be seen in Fig. 9.

Our large simulation set (Fig. 3) demonstrated that the many parameters that interact in the dynamics of a neuron network can produce unexpected consequences. In general we expected that increasing the excitability of individual neurons would increase the excitability of the network as a whole, leading to more population spikes. This did occur in a large proportion of cases (upper right quadrant of Fig. 3). However, we also found cases where the increase had almost no effect on network dynamics (Fig. 3D) and other cases where the increase reduced population spiking behavior (Fig. 3F). Some of these latter cases belong to the case alluded to above: overexcitability of neurons will lead to an interictal

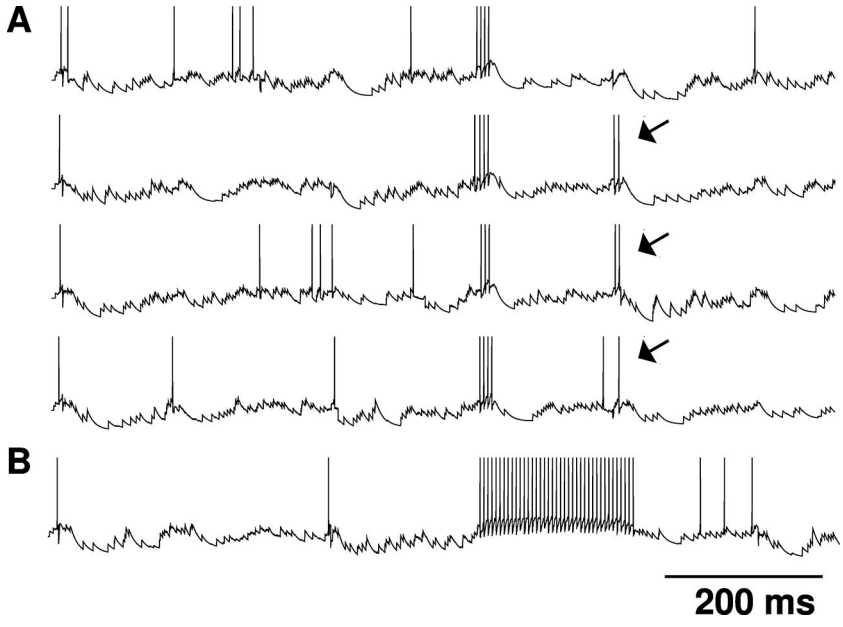

FIGURE 9. Individual neurons in ACD simulation **(A)** tend to fire at times corresponding to beginning and end (arrows) of tonic latch-up periods from control **(B)**, which is important for these transitions.

spike that exhausts firing potential and precludes repetitive population firing (Fig. 3E). The measures that we used (population spike number and period of population spiking) did not always accurately classify the "epileptiform" appearance of a discharge. Some discharges, for example the dashed line in Fig. 3A, would be considered epileptiform based on well-formed spike-and-wave discharges. However, use of other measures also misclassified some patterns and also resulted in scatter across the measurement plane: e.g., the spike-and-wave discharge of Fig. 3A belongs to a low-excitability network.

Several of our simulations suggest the importance of an activity trigger where random activity in the drivers activates enough of the expressors to alter dynamics and initiate clonic or tonic (latch-up) activity. Figure 2 demonstrates that such a trigger may not only produce temporary activation (an interictal spike) but can also move the entire network into a new state producing a prolonged seizure. In Fig. 2, the dynamics appeared to have three states, with the network showing resting behavior (no firing) as well as two patterns of repetitive activity with different characteristic cell firing frequencies. In the networks presented here the triggers were random, but in epilepsy these could in many cases be patterned inputs, whether identifiable (i.e., stimulus-triggered seizures) or occult.

Intrinsic state-variables such as AHP show more reliable effects than do synaptic parameters such as NMDA (here modeled outside the context of long-term potentiation). This is due to the aforementioned randomness of inputs which in these networks pertained not only to the drivers but also to the activation of the expressors by one another due to the random wiring of the network. AHP, acting as an intrinsic inhibitory state-variables, effectively integrates the firing of an individual cell and is not terribly sensitive to precise patterns of activity. Due to its relatively long time-constant and voltage-sensitivity, NMDA provided a set of extrinsic excitatory state-variables that tended to integrate postsynaptic activation (Traub et al., 1994). However, NMDA activation, in tandem with AMPA activation, was sensitive to the precise pattern of presynaptic activity.

Feedback inhibition was more effective in shaping the activity of the network while feedforward inhibition had more of an effect on overall firing level. This appeared to be the case regardless of the time constants of the inhibitory process. Feedback inhibition sculpted activity out of the expressors by limiting firing durations and thereby produced clumps of activity that appeared as patterns in the field potential. Feedforward inhibition produced a more tonic level of firing reduction due to its being driven by the relatively constant random-firing drivers.

Our ACD simulation suggested that anticonvulsants of this class (modulators of sodium channels) might be expected to have a greater effect on extremely fast tonic or latch-up activity than on the briefer activity associated with repetitive clonic activity. However, many ACDs produce effects at multiple receptors and will produce more complex dynamical alterations. We plan to explore such multireceptor effects in the future.

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