Persistent Na\textsuperscript{+} Current Modifies Burst Discharge By Regulating Conditional Backpropagation of Dendritic Spikes

BRENT DOIRON,\textsuperscript{1} LIZA NOONAN,\textsuperscript{2} NEAL LEMON,\textsuperscript{2} AND RAY W. TURNER\textsuperscript{2}

\textsuperscript{1}Department of Physics, University of Ottawa, Ottawa, Ontario K1N 6N5; \textsuperscript{2}Neuroscience Research Group, Department of Cell Biology and Anatomy, University of Calgary, Calgary, Alberta, T2N 4N1 Canada

Submitted 26 August 2002; accepted in final form 20 September 2002

Doiron, Brent, Liza Noonan, Neal Lemon, and Ray W. Turner. Persistent Na\textsuperscript{+} current modifies burst discharge by regulating conditional backpropagation of dendritic spikes. J Neurophysiol 89: 324–337, 2003; 10.1152/jn.00729.2002. The estimation and detection of stimuli by sensory neurons is affected by factors that govern a transition from tonic to burst mode and the frequency characteristics of burst output. Pyramidal cells in the electrosensory lobe of weakly electric fish generate spike bursts for the purpose of stimulus detection. Spike bursts are generated during repetitive discharge when a frequency-dependent broadening of dendritic spikes increases current flow from dendrite to soma to potentiate a somatic depolarizing afterpotential (DAP). The DAP eventually triggers a somatic spike doublet with an interspike interval that falls inside the dendritic refractory period, blocking spike backpropagation and the DAP. Repetition of this process gives rise to a rhythmic dendritic spike train, termed conditional backpropagation, that converts cell output from tonic to burst discharge. Through in vitro recordings and compartmental modeling we show that burst frequency is regulated by the rate of DAP potentiation during a burst, which determines the time required to discharge the spike doublet that blocks backpropagation. DAP potentiation is magnified through a positive feedback process when an increase in dendritic spike duration activates persistent sodium current (\(I_{\text{NaP}}\)). \(I_{\text{NaP}}\) further promotes a slow depolarization that induces a shift from tonic to burst discharge over time. The results are consistent with a dynamical systems analysis that shows that the threshold separating tonic and burst discharge can be represented as a saddle-node bifurcation. The interaction between dendritic K\textsuperscript{+} current and \(I_{\text{NaP}}\) provides a physiological explanation for a variable time scale of bursting dynamics characteristic of such a bifurcation.

\section*{INTRODUCTION}

The output pattern of central neurons in response to membrane depolarization is a crucial element of signal processing. Two important aspects of spike output with respect to sensory processing are the ability to shift from tonic to burst mode and the regulation of burst frequency. A switch from tonic to burst mode has been proposed to reflect a shift from stimulus estimation to stimulus detection (Sherman 2001), an hypothesis that has experimental support in the electrosensory system (Bastian et al. 2002; Gabbiani et al. 1996). The regulation of burst frequency can influence the ability of neurons to contribute to different behavioral states (Steriade et al. 1990) and in the synchronization of networks (Lisman 1997). Cells discharging spike bursts in the \(\gamma\)-frequency range (40 to >80 Hz) have been reported from the cortical to spinal levels, indicating a role for this output in signal processing at all levels of the CNS (Gray and McCormick 1996; Steriade et al. 1993, 1998; Turner et al. 1994).

Gamma-frequency bursts in pyramidal cells of the electrosensory lateral line lobe (ELL) of weakly electric fish rely on a “conditional backpropagation” of Na\textsuperscript{+} spikes from somatic to dendritic membranes (Doiron et al. 2001, 2002; Lemon and Turner 2000). This mechanism arises when spikes backpropagating from the soma fail in their active conduction near 200 \(\mu\)m from the soma. Spikes thus rapidly increase in duration from \(\leq 1\) ms at the soma to \(\geq 10\) ms as they approach their point of failure in the proximal dendrites. This basic difference in somatic and dendritic spike durations allows current flow associated with dendritic spike discharge to reexcite the soma as a depolarizing afterpotential (DAP). During repetitive discharge, a frequency-dependent broadening of dendritic spikes potentiates the DAP to the point of triggering a somatic spike doublet. The short interspike interval of the doublet falls inside the dendritic refractory period with the result that the second spike of the pair fails to backpropagate. The resulting loss of dendritic depolarization and somatic DAP then allows the cell to repolarize and generate an interburst interval. By repeating this process, pyramidal cells generate a rhythmical series of spike bursts that extend into the \(\gamma\)-frequency range.

The ability for conditional backpropagation to underlie burst discharge reveals that the failure of spike backpropagation from soma to dendrite can exert a direct control over cell output. Compartmental modeling has indicated that conditional backpropagation can be induced at least through a cumulative inactivation of dendritic K\textsuperscript{+} current (Doiron et al. 2001). The present study used experimental analysis and modeling to further examine the somatic and dendritic mechanisms that regulate conditional backpropagation and burst discharge. We show that burst frequency is directly related to the rate of DAP potentiation at the soma, which establishes the time required to generate a spike doublet. The rate of DAP potentiation can be accounted for by a positive feedback process between a cumulative inactivation of dendritic K\textsuperscript{+} current and persistent sodium current (\(I_{\text{NaP}}\)) that amplifies depolarizations underlying conditional backpropagation. A slow activation of \(I_{\text{NaP}}\) further induces a transition from tonic to burst discharge over time. Finally, our results are consistent with a dynamical systems analysis, which predicted that a saddle-node bifurcation separates tonic and burst discharge in pyramidal cells (Doiron et al. 2001).
METHODS

_Apterous leptoerhynthus_ (Brown Ghost Knife fish) were obtained from local importers and maintained at 26–28°C in fresh water aquaria. Anaesthesia prior to dissection was obtained using 0.05% phenoxy-ethanol applied in the tank water and during gill perfusion as accepted by the Canadian Council of Animal Care. The procedures for preparing and maintaining ELL tissue slices have been previously described (Lemon and Turner 2000; Turner et al. 1994). All chemicals were obtained from Sigma (St. Louis, MO) unless otherwise noted. Slices were cut along the transverse or longitudinal axis of the ELL and maintained at room temperature as an interface preparation from Sigma (St. Louis, MO) unless otherwise noted. Slices were cut along the transverse or longitudinal axis of the ELL and maintained at room temperature as an interface preparation.

Intracellular recordings were obtained from pyramidal cell bodies within the pyramidal cell layer (n = 64) and from apical dendrites within 200 μm of the cell body layer (n = 42) in the centromedial segment (CMS) of the ELL. Glass microelectrodes were backfilled with 2 M KAc (pH 7.4; ~90 MΩ resistance). In a random selection of recordings, the input resistance at the soma was 64 ± 21.9 (SD) MΩ (n = 24) and in apical dendrites 59 ± 19.7 MΩ (n = 20). Direct current injection of −0.1 to −0.5 nA was applied when necessary to eliminate spontaneous discharge. Antidromic spikes were evoked by placing a concentric bipolar electrode on pyramidal cell axons in the plexiform layer that courses beneath the pyramidal cell layer. Recordings were digitized (CED, Cambridge, UK) and stored for off-line analysis (Igor Pro, WaveMetrics, Lake Oswega, OR; Corel Draw, Ottawa, ON, Canada). All average values are expressed as means ± SD. Data plots were constructed and regression analyses performed using Microcal Origin (Northampton, MA).

Burst detection

In the majority of recordings, the occurrence and characteristics of burst discharge were extracted using custom software (Igor Pro). We have previously detected spike bursts generated during a slower form of oscillation in pyramidal cells by using interspike interval (ISI) histograms to define a threshold that demarked burst and intraburst ISIs (Turner et al. 1996). However, a shift in ISIs over time during long depolarizations (Fig. 7A) indicates a nonstationarity in the relevant data set that prevents this form of statistical analysis (Gabbiani and Koch 1998). A second approach to identify bursts was to define a minimal sequence of decreasing ISIs in the spike train. This would appear to be highly applicable to the burst discharge studied here given the clear decrease in ISIs that lead up to spike doublet generation at lower intensities of stimulation (Lemon and Turner 2000). However, we found that this method was not effective, as pyramidal cell bursts are composed of only a repeating series of spike doublets at higher intensities (Lemon and Turner 2000; Turner et al. 1994). We were able to define burst discharge using the difference of consecutive ISIs (Holt et al. 1996), although with an unacceptable level of error. Rather, we found that the large burst afterhyperpolarization (AHP) that consistently follows a spike doublet (Lemon and Turner 2000) was the most reliable indicator of the occurrence of burst discharge (Fig. 1, A and B).

We thus used the difference between consecutive AHP amplitudes to detect the occurrence of conditional backpropagation and from this the nature of events during spike bursts. Specifically, we calculated the local difference σ between consecutive AHPs i − 1 and i as σ = (AHPi − AHPi−1)². AHP amplitudes were computed as the trough between two action potentials, and the difference was squared to increase the sensitivity of our measure. Given a spike train of N spikes, this gave a sequence of N − 1 σ values. The σ measured between the AHP within a spike doublet, and the following burst AHP was much larger than the σ measured between other AHPs. We set a threshold value, σthreshold, and marked the ith AHP as a burst AHP if σi−1 and σi satisfied the conditions σi−1 < σthreshold and σi > σthreshold (Fig. 1). The accuracy of burst detection was finally cross-checked by visually inspecting data records to verify that the detection threshold was adequate to define burst AHP occurrence. The ability to use burst AHPs to identify a change in firing mode was indicated by the transition of ISI histogram plots from one of a monophasic to biphasic structure after the onset of burst AHPs (see Fig. 2C). However, the nonstationarity of the data over long depolarizations (see Fig. 7A) allows only qualitative results to be inferred from these histograms, requiring that we use the occurrence of burst AHPs
to demark points for burst analysis. This method proved to be less effective for cases in which burst AHP amplitude approached that of intraburst AHPs, such as found in some dendritic recordings. For this reason, automated burst analysis was restricted to somatic recordings. In a limited number of cases, analysis of burst properties was conducted manually to ensure accuracy if burst AHP amplitudes were not sufficiently large for automated analysis.

In all experiments, the resting potential of the cell was adjusted through slight current injection to remove all spontaneous discharge. When depolarizing current is injected under these conditions, the ISIs progressively decrease toward the generation of a spike doublet and burst AHP (Lemon and Turner 2000). Therefore, all ISIs occurring between consecutive burst AHPs were assumed to represent intraburst intervals. In some cases, burst discharge was temporarily interrupted by a cessation of spike activity after ~2 s of depolarization. Burst analysis in these cells was restricted to only the initial portion of the record.

We estimated the rate of DAP potentiation (defined as Δ; Fig. 2A) as the slope of the net change in potential from the trough of the first AHP (absolute negative peak) to the deflection point of the second spike of the spike doublet. Although this will overestimate the absolute voltage shift associated with DAP potentiation, this approach is validated by our previous work showing that all depolarizing shifts within a burst can be attributed to changes in only the DAP and not AHPs (Lemon and Turner 2000). Because the inflection indicating a DAP could be difficult to detect on the first spike of a burst, we chose to use the more reliable measure of the trough of the first AHP. Control experiments measuring only the deflection of the DAP during a burst for the clearest cases produced comparable results, including all correlations between DAP amplitude and oscillatory discharge. Our stated values of DAP potentiation are thus estimates that were used to compare the relative rate of change under different conditions.

**Compartmental modeling**

We previously developed a compartmental model of an ELL pyramidal cell using the simulation software NEURON (Hines and Carnevale 1997). The compartmentalization (300+ com-

---

**FIG. 2.** Oscillatory spike bursts are triggered through conditional spike backpropagation. A: summary diagram of the factors underlying conditional spike backpropagation and burst discharge (Lemon and Turner 2000). Somatic and dendritic recordings from separate pyramidal cells are aligned to construct a schematic of interactions during repetitive discharge. Each spike initiated at the soma backpropagates over the initial 200 μm of dendrites, leading to a broad dendritic spike that promotes return current flow to re-excite the soma as a DAP (arrows). A frequency-dependent broadening of dendritic spikes increases dendrosomatic current flow until generating a somatic spike doublet that exceeds the dendritic refractory period and blocks backpropagation. A subsequent burst AHP is recorded at the somatic and dendritic level. One oscillation period is defined as the combined duration of a spike burst and subsequent burst AHP, and the rate of DAP potentiation as Δ. B: spike dischagr shifts from tonic to burst output 750 ms after the onset of a 4 s depolarizing current pulse (0.74 nA) initially set subthreshold for burst discharge (top). Arrows denote the occurrence of burst AHPs. The time for each recording is shown on the top left and mean oscillation period below. The variation in spike height results from a low sampling rate. C: a plot of ISI over time for the cell shown in B indicates a dramatic increase in the variability upon the occurrence of burst discharge (top), with the rhythmic downward deflections indicating burst AHP ISIs. ISI histograms calculated below for the tonic and burst phase of spike discharge reveal a clear shift to a bimodal ISI distribution after the occurrence of burst discharge. Nonstationarity of the data set allows only for qualitative inferences from the histograms (unimodal vs. bimodal).
partments) was based on confocal images of a Lucifer-yellow-dye-filled ELL basilar pyramidial cell. The model dynamics were based on 10 ion channels with kinetic properties that were constrained by biophysical and electrophysiological data (Doi- ron et al. 2001). Of specific interest was the modeling of a persistent Na⁺ current (I_{NaP}) that exists over the soma and proximal apical dendrites of pyramidial cells and provides a voltage- and TTX-sensitive boost of EPSPs (Berman et al. 2001). The parameters of I_{NaP} were chosen to reproduce this effect on excitatory postsynaptic potentials (EPSPs), requiring a \( \tau_m \) of activation = 0.2 ms. The current study extends this description to model the time course of I_{NaP} activation in pyramidial cells, which has been shown to generate a depolarization that can last for hundreds of milliseconds following a short train of synaptic input (Berman et al. 2001). To simulate this slow depolarization, we replaced our original treatment of I_{NaP} with I_{NaP,S}, which uses both the original and a slower time scale of activation; I_{NaP,S} was described as

\[
I_{NaP,S} = g_{max,NaP,S} \cdot m \cdot s \cdot (V_m - E_{Na})
\]

Equation 1 gives the I_{NaP} in which \( g_{max,NaP,S} \) represents the NaP channel density (10 mS/cm² in the somatic compartment and 3 mS/cm² in the 1st 10 proximal apical dendritic compartments), \( E_{Na} \) is the reversal potential for Na⁺ (40 mV), and \( m \) (fast activation) and \( s \) (slow activation) are the dynamical gating variables controlling NaP activation. The kinetics and dynamics of \( m \) are described in Doiron et al. (2001). The steady-state kinetics of \( s \) is given by Eq. 2 where \( V_{1/2,s} \) (−58.5 mV) and \( k_s \) (6 mV) were set so that NaP activation is low threshold; these parameters are identical to the steady state of \( m \) \( m_s(V_m) = s_s(V_m) \). The dynamics of \( s \) are given in Eq. 3 with the time constant of activation, \( \tau_s \), set to 1.5 s, as determined by fitting the slope of the linear rise of a slow membrane potential shift in pyramidial cells during 4-s current pulses (2.9 mV/s; see Figs. 6E and 7A). \( g_{max,NaP,S} \) was set larger than \( g_{max,NaP} \) so as to compensate for the new state variable \( s \), yet ensured that the net NaP and NaP.S steady-state currents were nearly equivalent. All model simulations in the current project used the NaP kinetics described in Doiron et al. (2001) until we extend our treatment of NaP to model the slow depolarization described by NaP.S (Figs. 7 and 8).

RESULTS

Conditional backpropagation and burst discharge

Current-evoked depolarizations trigger burst discharge that can be recorded in pyramidial cell somata and apical dendrites (Lemon and Turner 2000). Individual spike bursts are comprised of two to seven spikes with a progressively decreasing ISI that culminates in the generation of a spike doublet and subsequent burst AHP. The burst AHP is largest at the soma and effectively inhibits spike discharge for up to 40 ms, providing a pause between spike bursts. The same pattern of spike burst and burst AHP is recorded at the somatic and dendritic level, although with differences in spike and AHP amplitudes.

The process of conditional backpropagation is summarized in the schematic diagram of Fig. 2A. Pyramidial cells initiate spike discharge at the somatic level, followed by an active Na⁺ spike backpropagation over the initial 200 \( \mu \)m of a 500 to 800 \( \mu \)m dendritic tree. The proximal dendritic spike broadens quickly with respect to the somatic spike, leading to return current flow that generates a DAP at the soma. We have shown that spikes in dendritic membrane exhibit a frequency-dependent broadening during repetitive discharge at ISIs of 3–14 ms (Lemon and Turner 2000). Return current flow to the soma is thus increased during repetitive discharge, potentiating the DAP to the point of triggering a somatic spike doublet. The spike doublet is critical to burst discharge as the short ISI separating the spike pair falls within the dendritic refractory period, abruptly terminating the dendritic depolarization that generates the DAP. The sudden loss of dendritic depolarization from one spike to the next allows a burst AHP to repolarize the cell. Repetition of this process gives rise to oscillatory burst discharge in the \( \gamma \)-frequency range. A recently constructed compartmental model supported this hypothesis by revealing that a cumulative inactivation of dendritic K⁺ current can induce the process of conditional backpropagation through dendritic spike broadening (Doiron et al. 2001). The physiological importance of this mechanism was recently established by the recording of conditional backpropagation at the dendritic level of pyramidial cells during sensory processing in vivo (J. Bastian, personal communication).

Lemon and Turner (2000) reported that oscillatory burst discharge generated in this manner can span a range of at least 100 Hz; an exceptionally wide range of frequencies for a bursting neuron. In other cells a shift in burst frequency results from changes in the burst and/or interburst interval according to such factors as the number or frequency of spikes per burst, which can affect Ca²⁺ influx and a subsequent AHP (Golding et al. 1999; Tegner et al. 1998). However, we have determined that burst discharge in pyramidial cells of the centromedial segment of the ELL is not sensitive to either Cd²⁺ or Ni²⁺ ejections (Noonan and Turner, unpublished observations). This indicates that pyramidial cells rely on different mechanisms to control burst frequency.

A primary objective of this study was to identify the factors within the burst or interburst interval that control burst frequency in pyramidial cells. A second objective was to identify the mechanism by which pyramidial cells can switch from a tonic to burst discharge.

Pyramidal cell output

Pyramidal cells generate a relatively tonic pattern of spike output when depolarized to near spike threshold (Turner et al. 1994). However, over the duration of a 4 s current pulse, 80% of pyramidial cells shifted from a tonic to burst discharge, revealing a time-dependent change in the pattern of spike output (Fig. 2B; \( n = 16/20; 0.2–0.6 \) nA). The transition from a tonic to burst output was evident by the onset of spike doublets and burst AHPs (Fig. 2, B and C) that signified a switch from a monophasic to biphasic structure of ISI histograms (Fig. 2C). The biphasic ISI histogram during burst discharge represents an early peak of high-frequency spike doublets (4–6 ms) and a second peak of ISIs that lead up to spike doublet discharge (7–12 ms) that includes an elongated tail associated with burst AHPs (12–18 ms). At the initial onset
of burst discharge, oscillation period ranged between 63 and 186 ms (mean of 117 ± 43.5 ms; n = 16) but decreased by up to 40 ms (e.g., mean of 21 ± 9.7 ms for the cell shown in Fig. 2B). In the present study, we used this current-evoked decrease in oscillation period over time as a tool to identify the intra- or inter-burst factors that change in association with a shift in oscillation period.

**Shifts in oscillation period are tightly linked to intraburst parameters**

**SPIKE BURSTS.** We found that as oscillation period decreased during current injection there was a prominent and parallel decrease in burst duration (Fig. 3, A and B). There was a further decrease in the number of spikes per burst, eventually leading to a pattern of spike doublets and triplets as burst duration fell to a consistent value (Fig. 3D). In all cells examined, three factors were highly correlated with oscillation period (n = 16): burst duration (r = 0.97 ± 0.02), the number of spikes per burst (r = 0.96 ± 0.03), and the rate of DAP potentiation (r = 0.89 ± 0.07; Fig. 3D), indicating that these burst properties are closely linked to oscillation period. A closer examination of the burst itself revealed that burst duration was also highly correlated to the number of spikes per burst (r = 0.98 ± 0.01; n = 16) and the rate of DAP potentiation (r = 0.91 ± 0.06; n = 16).

**BURST AHP.** Although a change in the duration of the burst AHP would provide the means to shift oscillation period, we found that neither the duration nor amplitude of the burst AHP changed over time (Fig. 3B; n = 16). This finding was supported in all cells by a lack of any correlation between the burst AHP and either oscillation period or burst duration, suggesting no clear link to ionic events during the burst (i.e., Ca\(^{2+}\) entry). Furthermore, burst AHP characteristics were not correlated with any aspect of the subsequent burst as would be predicted in cells controlling burst discharge through an interplay between the hyperpolarization-activated inward currents \(I_h\) and transient Ca\(^{2+}\) current (\(I_F\)) (Huguenard 1996; Pape 1996). Indeed, none of the factors we examined within spike bursts covaried with the burst AHP. We did find that burst AHP duration was reduced in a linear fashion as current intensity was increased (n = 9). However, at any given current level, both the amplitude and duration of the burst AHP were stable throughout the time course of depolarizations that shifted oscillation period. The burst AHP thus plays a role in allowing a recovery from intraburst events but not in the control of oscillation period during long depolarizations.

![Image](https://example.com/image.png)

**FIG. 3.** A shift in oscillation period is associated with specific changes in intraburst properties. A: a plot of oscillation period after the onset of burst discharge (for cell shown in Fig. 2, B and C) reveals that oscillation period decreases from ∼50–60 ms until stabilizing at ∼20–30 ms. B and C: the duration of spike bursts (B) and the number of spikes per burst (C) decrease in concert with oscillation period over time. Note that burst AHP duration is stable as oscillation period is reduced (B). D: the rate of depolarizing afterpotential (DAP) potentiation during a burst is highly correlated to burst duration. E: hypothesis for the mechanism controlling oscillation period in pyramidal cells. Representative traces of single somatic bursts are shown to illustrate the factors that change as oscillation period decreases during long depolarizations. Double arrows above traces signify spike doublets, and spikes are truncated for illustrative purposes. A tonic depolarization reduces oscillation period from 57 ms at the onset of burst discharge (left) to 43 ms 3 s later (right). The DAP first increases at a rate \(\Delta = 0.11\) mV/ms and at the higher rate of \(\Delta = 0.16\) mV/ms at the end of the depolarization (large filled arrow). Note that an increase in the rate of depolarization allows the spike train to reach threshold for a spike doublet in a shorter period of time. As a result, the spike doublet reduces burst duration and the number of spikes per burst and thus oscillation period. In contrast, there is no significant change in burst AHP characteristics. Therefore shifts in oscillation period can be accounted for by the rate of DAP potentiation during a burst, which determines the *time* required to trigger the spike doublet that terminates spike backpropagation.
Control of oscillation period

Our results allow the formulation of an hypothesis of how conditional backpropagation can be modified to produce shifts in oscillation period (Fig. 3E). Because spike bursts are terminated by a spike doublet and burst AHP, burst duration should be highly dependent on the cell reaching threshold for the spike doublet. Therefore, the time required to reach threshold for the spike doublet is the critical determinant controlling burst duration and oscillation period. Importantly, the time to reach threshold for a spike doublet depends on the rate of DAP potentiation during repetitive discharge (Fig. 3E). A shortening of burst duration by the spike doublet also accounts for the number of spikes per burst, as reaching threshold for a spike doublet sooner will decrease the number of spikes discharged. The subsequent burst AHP reliably follows the spike doublet but is essentially uncoupled from other burst factors. The burst AHP is, nevertheless, critical for burst discharge in providing the interburst interval necessary to allow recovery of parameters that change during a burst.

Factors underlying potentiation of the DAP

The working hypothesis presented in the preceding text indicates that burst frequency depends in large part on the factors that control DAP amplitude. Lemon and Turner (2000) already established that changes in the DAP during repetitive discharge do not involve a shift in $E_K$, the properties of AHPs, or recurrent synaptic inputs. Rather, potentiation of the DAP occurs at ISIs of $\sim 3$–14 ms, which closely matches a frequency-dependent broadening of dendritic spikes. By using repetitive antidromic stimulation to induce burst discharge, we identified an ionic contribution in that both the dendritic spike and DAP could be boosted by membrane depolarization (Fig. 4). At the dendritic level, antidromic stimulus trains delivered between 3 and 10 ms ISIs steadily increased the duration of dendritic spikes and the amplitude of an underlying depolarization that was produced as dendritic spikes summed (Fig. 4A; $n = 7$). Membrane depolarizations of 5–10 mV from rest further increased the rate of dendritic spike broadening and temporal summation during a stimulus train (Fig. 4, A and B). At the somatic level, antidromic stimulus trains at ISIs less than $\sim 12$ ms steadily potentiated the DAP (Fig. 4, A and B; $n = 12$). Membrane potential shifts at the soma were more complex in affecting both the DAP and AHPs, such that membrane hyperpolarization increased the relative amplitude of the DAP as the membrane potential approached $E_K$ (Fig. 4A). Nevertheless, slight membrane depolarizations greatly increased the rate of DAP potentiation during repetitive antidromic trains (Fig. 4B).

This voltage-dependent increase in dendritic spike broadening and DAP potentiation can not involve $\text{Ca}^{2+}$ currents as both dendritic and somatic spikes were insensitive to $\text{Cd}^{2+}$ (400 $\mu$M) and $\text{Ni}^{2+}$ ($\leq$1 mM; $n = 12$), and focal $\text{Cd}^{2+}$ ejections only increased DAP potentiation by blocking a somatic slow AHP ($n = 3$; data not shown). However, a TTX-sensitive $I_{\text{NaP}}$ has been shown to boost synaptic depolarizations in ELL pyramidal cells at both the somatic and dendritic level (Berman et al. 1997, 2001; Turner et al. 1994). Previous studies have shown that low concentrations of phenytoin (30–60 $\mu$M) produce a relatively greater block of persistent ($I_{\text{NaP}}$) versus fast inactivating $\text{Na}^+$ currents (Lampl et al. 1998; Segal and Douglas 1997). Focally ejecting phenytoin (75 $\mu$M) hyperpolarized the membrane potential in both somatic and dendritic recordings by 5–15 mV with the greatest effects observed in dendritic locations. Phenytoin further decreased dendritic spike amplitude by $\leq 40\%$ as well as temporal summation of dendritic spikes during antidromic stimulus trains (Fig. 4C; $n = 6$). Similarly, phenytoin ejections at the soma decreased DAP amplitude by $\leq 50\%$ and substantially decreased DAP potentiation during burst discharge (Fig. 4, C and D; $n = 6$).

In a separate set of experiments, we recorded the presence of a slow membrane depolarizing shift in somatic recordings during long current pulses ($n = 9/16$). The depolarization began within a few 100 ms of current pulse onset and continued at a rate of $2.9 \pm 0.83 \text{ mV/s} \,(n = 9)$ to a stable level $4.0 \pm 1.8 \text{ mV} \,(n = 9)$ above the initial membrane potential after $\sim 2$–3 s (Fig. 4E). This slow depolarization was not Ca$^{2+}$ dependent as it was accentuated by focal Cd$^{2+}$ ejections coincident with the reduction of a somatic slow AHP ($n = 3$). However, we found that this slow depolarizing shift was also rapidly blocked by ejections of phenytoin (Fig. 4E; $n = 4$).

Given that burst discharge was still present after phenytoin application, it is apparent that $I_{\text{NaP}}$ is not essential to burst discharge. Rather, $I_{\text{NaP}}$ lowers the threshold for burst discharge by boosting the dendritic spike and DAP and promotes a shift from tonic to burst discharge by generating a long depolarizing membrane potential shift. A relatively selective effect by phenytoin on $I_{\text{NaP}}$ could be argued based on a general reduction of dendritic spike rate of rise, amplitude, and rate of repolarization (Fig. 4C). This result is substantially different from those obtained in response to focal ejections of TTX, which immediately fractionates dendritic spikes into multiple, fast components (Turner et al. 1994). Phenytoin was also able to block substantial portions of both the DAP and slow depolarizing shift without blocking somatic spike discharge. Nevertheless, we could detect a slight (10%) reduction in the amplitude of somatic spikes by the time DAPs were reduced (Fig. 4C) that continued with additional phenytoin ejections. These effects on spike discharge are consistent with previous reports that a sufficient concentration of phenytoin also affects fast inactivating Na$^+$ channels (Lampl et al. 1998; Segal and Douglas 1997). Therefore, to gain a more selective analysis of the role for $I_{\text{NaP}}$, we used a detailed multi-compartmental model of ELL pyramidal cells (see METHODS) (Doiron et al. 2001).

Role for $I_{\text{NaP}}$ in modulating somatic and dendritic spike discharge

The ability for a TTX-sensitive $I_{\text{NaP}}$ to magnify EPSPs in ELL pyramidal cells has been established experimentally (Berman et al. 1997, 2001) and reproduced in a compartmental model (Doiron et al. 2001). By further examining the role of NaP conductance ($g_{\text{NaP}}$) in this model, we found that $g_{\text{NaP}}$ faithfully tracked the time course of both somatic and dendritic spikes (Fig. 5). In the somatic compartment this produced a slight increase in somatic spike amplitude, a depolarization on the falling phase of the spike, and a substantial increase in DAP amplitude (Fig. 5, A and C). At the dendritic level, $I_{\text{NaP}}$ increased both the amplitude and total duration of the dendritic spike (Fig. 5, B and C). In fact, the effects of $I_{\text{NaP}}$ in the
simulations were very similar to those revealed by membrane polarization or phenytoin application (cf. Figs. 4 and 5).

These results are important in indicating that $I_{NaP}$ can boost not only the DAP but also the backpropagating dendritic spike. This characteristic allowed $I_{NaP}$ to magnify the intraburst depolarization at both the somatic and dendritic level. Thus during repetitive discharge at frequencies that led to dendritic spike broadening, $g_{NaP}$ increased the dendritic spike and underlying temporal summation as well as the rate of DAP potentiation (Fig. 6, A and B).

Previous work established that cumulative inactivation of a dendritic delayed rectifier K$^+$ current ($g_{Dr,d}$) that led to dendritic spike broadening was a critical variable for inducing conditional backpropagation (Doiron et al. 2001). The addition of $I_{NaP}$ to account for a boost in synaptic potentials lowered the threshold for burst discharge to within the range encountered in pyramidal cells. The primary role of dendritic K$^+$ current in this process is highlighted by the fact that removing cumulative inactivation of $g_{Dr,d}$ prevented the increase in somatic and dendritic $g_{NaP}$ during a spike burst (Fig. 6, C and D). The inverse relationship between these currents was also apparent in a simultaneous decrease in $g_{Dr,d}$ (through inactivation) and an increase in the baseline $g_{NaP}$ during dendritic spike summation (Fig. 6, E and F). These data indicate that the increase in $g_{NaP}$ during a burst depends upon the initial inactivation of dendritic K$^+$ current. Thus $g_{Dr,d}$ and $g_{NaP}$ act in a synergistic fashion to augment the dendritic spike and rate of DAP potentiation during repetitive discharge.

**FIG. 4.** The rate of dendritic spike broadening and DAP potentiation during a burst are increased by $I_{NaP}$. A: superimposed traces from dendritic and somatic recordings from separate cells in response to antidromic stimulus trains at resting membrane potential (black traces) and during a 7- to 10-mV membrane depolarization (thick gray traces). B: plots of the dendritic spike half-width and degree of DAP potentiation for the records shown in A. C: antidromic stimulus trains recorded in a dendritic and somatic recording indicating a reduction of dendritic spike and DAP amplitude by focal application of 75 µM phenytoin (thick gray traces). Insets: expanded views of spikes evoked by the 1st stimulus of the antidromic train (asterisks). D: focal application of 75 µM phenytoin (gray trace) reduces the degree of DAP potentiation during burst discharge. E: measurement of peak AHP amplitudes during long depolarizing current pulses reveals a slowly rising depolarization that is blocked by 75 µM phenytoin (gray trace). Records in E represent an average of 2 traces, and burst AHP amplitudes are omitted for clarity. Somatic spike amplitudes are truncated in A, C, and D for illustrative purposes.
**I\textsubscript{NaP} underlies the transition from tonic to burst discharge and shifts in oscillation period**

Burst discharge during short current pulses (100 ms) is dependent on the ISI of spike discharge falling between 3 and 14 ms (Lemon and Turner 2000). A transition to burst discharge during long depolarizations might then occur through a progressive decrease in ISI. In agreement with this, we found that cells exhibiting a prolonged initial period of tonic activity switched to burst discharge once the ISIs fell below ~12 ms (n = 6) with all cells discharging bursts at ISIs within 8–16 ms (n = 16). After burst onset, the ISIs remained essentially stable throughout the remainder of the depolarization (not considering burst AHP or spike doublet ISIs) with no clear trends over time despite a reliable decrease in oscillation period (Fig. 7A). We found that cells exhibiting a clear decrease in ISI leading up to burst discharge also presented a well-defined slow depolarizing shift in membrane potential (Fig. 7A). An ISI reduction was most prevalent during the steepest rate of increase in the membrane depolarizing shift. The rate of decrease in ISI then slowed in conjunction with a slower rate of change in the membrane depolarization.

Unlike the results obtained for pyramidal cells, examination of the compartmental model in its original formulation revealed that long-duration current pulses did not invoke a decrease in ISI or a depolarizing membrane potential shift (Fig. 7B). Thus depolarizations set initially to evoke tonic discharge did not shift to burst discharge but simply maintained the initial level of tonic activity (data not shown). If the depolarization began at a level above burst threshold, the model failed to produce any further decrease in oscillation period over time (Fig. 7B).

To simulate a phenytoin-sensitive slow depolarization, we replaced \( I_{NaP} \) with \( I_{NaP,S} \) to introduce a second slower time constant for NaP activation that matched the rate of the slow depolarizing shift in pyramidal cells (termed \( I_{NaP,S} \); \( \tau_c = 1.5 \) s; see METHODS). With the addition of this kinetic parameter, depolarizations initially set to generate tonic spike discharge produced a gradual decrease in ISI to ~8 ms prior to the onset of burst discharge (Fig. 7C). Spike discharge was further accompanied by a slow depolarizing shift that promoted a shift from tonic to burst discharge (Fig. 7C). Once burst discharge was triggered, the oscillation period decreased ~50 ms over time (Fig. 7C); a value within the range expected in pyramidal cells (Fig. 7, A vs. C).

Given the role for \( I_{NaP} \) in augmenting the dendritic spike and DAP (Figs. 5 and 6), we examined whether \( I_{NaP,S} \) could exert additional affects on spike discharge during long depolarizations (Fig. 8). This analysis determined that the transition from tonic to burst discharge was marked by an increase in dendritic spike duration and DAP amplitude due to the increase in \( I_{NaP,S} \) (Fig. 8, B and C). The continued increase in \( I_{NaP,S} \) further affected spike properties during burst discharge by increasing the rate of DAP potentiation from one burst to the next (Fig. 8D). The increase in DAP potentiation had the important effect of triggering a somatic spike doublet in a shorter period of time; thereby reducing burst duration and oscillation period (Fig. 8, B and D; DAP potentiation denoted by dashed lines).

Therefore the addition of \( I_{NaP,S} \) allowed the model to succ-
cessfully reproduce essentially all aspects of spike output in pyramidal cells. This agreement between experimental data and simulations strongly support the hypothesis that the rate of DAP potentiation controls oscillation period by regulating the time required to trigger a spike doublet. The results further indicate a control over conditional backpropagation on two time scales. One is exerted by $I_{NaP}$ within each spike burst as a positive feedback mechanism with respect to the degree of dendritic $K^+$ current inactivation (Fig. 6). The second occurs when a slow activation of $I_{NaP}$ (modeled as $I_{NaP,S}$) modulates the gain of this interaction on a scale of seconds (Fig. 8).

Application of dynamical systems theory to control of burst output

We recently reduced the large compartmental model used in this study to a two-compartmental version composed of six differential equations (Doiron et al. 2002). The advantage in performing this simplification is that it allowed a detailed dynamical systems treatment of conditional backpropagation for comparison to other burst models (Ezhikevich 2000; Rinzel and Ermentrout 1989; for a review of dynamical systems, see Strogatz 1994). The ensuing system, referred to as the Ghostbursting mechanism to ion factors that influence the DAP and spike output within a burst.

A convenient method to illustrate the dynamics of our reduced model is to construct ISI return maps ($ISI_{i+1}$ vs $ISI_i$). Figure 9A shows the somatic voltage of the Ghostburster equations during a single burst evoked by an applied current ($I_{app}$) together with the associated change in $g_{NaP}$ at the soma (C) and dendrite (D). $g_{NaP}$ plots are shown in gray and arrows indicate burst AHPs. Insets (to the right in A and B): expanded and superimposed plots of $V$ and $g_{NaP}$ at the soma and dendrite. Note that $g_{NaP}$ increases through a burst and tracks voltage excursions associated with both the somatic DAP and dendritic spike. C and D: spike bursts and the associated change in $g_{NaP}$ at the soma (C) and dendrite (D) are blocked by removing cumulative inactivation of $g_{Dr,d}$ from the model. E and F: plots of the increase in $g_{NaP}$ at the base of dendritic spikes (E) and cumulative inactivation of dendritic $K^+$ current ($F; g_{Dr,d}$) for the bursts shown in A and B. Plots are normalized to the maximal change from the original baseline in each case.

FIG. 6. $I_{NaP}$ augments the DAP and dendritic spikes during burst discharge. A and B: response of the compartmental model to 0.75 nA applied current with a spike burst ($V$) plotted in conjunction with NaP conductance ($g_{NaP}$) in the soma (A) and proximal dendritic compartments (B). $g_{NaP}$ plots are shown in gray and arrows indicate burst AHPs. Insets (to the right in A and B): expanded and superimposed plots of $V$ and $g_{NaP}$ at the soma and dendrite. Note that $g_{NaP}$ increases through a burst and tracks voltage excursions associated with both the somatic DAP and dendritic spike. C and D: spike bursts and the associated change in $g_{NaP}$ at the soma (C) and dendrite (D) are blocked by removing cumulative inactivation of $g_{Dr,d}$ from the model. E and F: plots of the increase in $g_{NaP}$ at the base of dendritic spikes (E) and cumulative inactivation of dendritic $K^+$ current ($F; g_{Dr,d}$) for the bursts shown in A and B. Plots are normalized to the maximal change from the original baseline in each case.

test some qualitative predictions arising from Doiron et al. (2002) to relate specific aspects of the Ghostbursting mechanism to ion factors that influence the DAP and spike output within a burst.

A convenient method to illustrate the dynamics of our reduced model is to construct ISI return maps ($ISI_{i+1}$ vs $ISI_i$). Figure 9A shows the somatic voltage of the Ghostburster equations during a single burst evoked by an applied current ($I_{app}$) together with the associated change in $g_{NaP}$ at the soma (C) and dendrite (D). $g_{NaP}$ plots are shown in gray and arrows indicate burst AHPs. Insets (to the right in A and B): expanded and superimposed plots of $V$ and $g_{NaP}$ at the soma and dendrite. Note that $g_{NaP}$ increases through a burst and tracks voltage excursions associated with both the somatic DAP and dendritic spike. C and D: spike bursts and the associated change in $g_{NaP}$ at the soma (C) and dendrite (D) are blocked by removing cumulative inactivation of $g_{Dr,d}$ from the model. E and F: plots of the increase in $g_{NaP}$ at the base of dendritic spikes (E) and cumulative inactivation of dendritic $K^+$ current ($F; g_{Dr,d}$) for the bursts shown in A and B. Plots are normalized to the maximal change from the original baseline in each case.

Viewing the burst trajectory with ISI return maps also illustrates two related dynamical systems concepts: saddle-node bifurcation and trapping region. Bifurcations characterize qualitative changes in system dynamics as a parameter, or set of parameters, is varied (see Strogatz 1994). In particular, saddle-node bifurcations occur when a stable fixed point attractor coalesces with an unstable saddle point. After the bifurcation,
The slow component of $I_{\text{NaP}}$ accounts for the transition from tonic to burst discharge and shifts in oscillation period during prolonged depolarizations. A: response of a pyramidal cell somatic recording to a 0.4 nA, 4 s current injection. Cell output begins as tonic spike discharge and then shifts to burst discharge (transition indicated by “-”). During the period of tonic spike discharge the ISI decreases steadily to ~9 ms at the point of burst onset (top). Plotting the membrane potential as the peak negative voltage of AHPs (troughs) reveals a steady depolarization through the course of current injection (middle), followed by a decrease in oscillation period over time (bottom). For illustrative purposes, the values associated with the burst AHP and spike doublets have been excluded, removing the overlying increase in variability of ISI and membrane potential at burst onset (cf. Fig. 2C). B: plots of the output of the compartmental model containing the initial kinetic parameters of $I_{\text{NaP}}$ when activated by a 0.6 nA, 4 s current injection that was set initially above threshold for burst discharge. Note that the model fails to exhibit a shift in ISI (top), a membrane depolarizing shift (middle), or a change in oscillation period over time (bottom). C: the slow depolarizing shift observed in pyramidal cells was simulated by incorporating a 2nd time constant for $I_{\text{NaP}}$, a slow component of $I_{\text{NaP}}$ when activated by a 0.6 nA, 4 s current injection (NaP,S; $\tau = 1.5$ s). This longer $I_{\text{NaP},S}$ permits the model to shift from tonic to burst mode in association with a decrease in ISI (top), a slow membrane depolarization (middle), and a decrease in oscillation period over time (bottom) once bursting is initiated. The segments of regular burst behavior between ~2 and 3 s in C arises from a window of periodic behavior bordered by chaotic dynamics, a characteristic property of chaotic systems (Strogatz 1994).

The system’s trajectory no longer evolves to the stable fixed point but to a new attractor that is often system dependent. We have shown that a saddle-node bifurcation transitions the Ghostburster equation dynamics from a single fixed point attractor reflecting tonic discharge (a single point on the diagonal line $I_{\text{SN},I} = I_{\text{SN},O}$) to a chaotic strange attractor that produces the burst curve shown in Fig. 9A (Doiron et al. 2002). Dynamical systems near saddle-node bifurcations have a trapping region where trajectories have low velocities through phase space (Strogatz 1994). This translates to a finite control of the time scale of the dynamics by choosing the proximity to the bifurcation in parameter space. The trapping region in the Ghostburster system is reflected by the ISI sequence clustering about the diagonal $I_{\text{SN},I} = I_{\text{SN},O}$ (region 1 in Fig. 9A). The sequence must pass through the trapping region before it can finally escape and produce the somatic doublet (2), terminating the burst. The time required to traverse the trapping region (the sum of all the ISIs within the region) is approximately the duration of the burst. Hence, control of burst duration, and equivalently oscillation period, reduces to determining the factors that control ISI clustering in the trapping region.

We now consider how $I_{\text{NaP},S}$ controls oscillation period over time within the framework of our dynamical systems analysis of burst discharge. Because the time scale of $s$ is much larger than the time scale of both spikes and bursts ($\tau_s = 1.5$ s), we can treat $s$ as a quasistatic parameter with respect to the fast bursting dynamics (Rinzel and Ermentrout 1989). The effect of a slow increase in $s$ is then similar to an increasing applied depolarization $I_{\text{app}}$. Thus through analogy to the Ghostburster system, the transition from tonic to burst discharge over time is due to the system passing through a saddle-node bifurcation of limit cycles as the slow activation of $I_{\text{NaP}}$ increases through some critical value $s = s_{\text{SN}}$ (in the quasistatic approximation limit). In addition, the amount of time that the ISI sequence spends in a trapping region reduces as $s$ increases away from the critical value of the saddle-node bifurcation at $s = s_{\text{SN}}$. This prediction is supported by comparing ISI return maps for burst discharge in the full compartmental model and pyramidal cell recordings (Fig. 9, B and C). We specifically compare the return maps at the onset of burst discharge ($s$ is near $s_{\text{SN}}$) to bursts at the end of a long depolarization after the variable $s$ has increased ($s$ is far from $s_{\text{SN}}$). At the onset of burst discharge, the clustering of the ISI sequence near the diagonal in the return map is significant and necessarily the oscillation period of a burst is long. At the end of a long depolarization, the ISI points are further away from the diagonal in the return map and there is significantly less clustering of ISI points. Thus the sequence traverses the trapping region in less time, resulting in

---

FIG. 7. A slow component of $I_{\text{NaP}}$ accounts for the transition from tonic to burst discharge and shifts in oscillation period during prolonged depolarizations. A: response of a pyramidal cell somatic recording to a 0.4 nA, 4 s current injection. Cell output begins as tonic spike discharge and then shifts to burst discharge (transition indicated by “-”). During the period of tonic spike discharge the ISI decreases steadily to ~9 ms at the point of burst onset (top). Plotting the membrane potential as the peak negative voltage of AHPs (toughs) reveals a steady depolarization through the course of current injection (middle), followed by a decrease in oscillation period over time (bottom). For illustrative purposes, the values associated with the burst AHP and spike doublets have been excluded, removing the overlying increase in variability of ISI and membrane potential at burst onset (cf. Fig. 2C). B: plots of the output of the compartmental model containing the initial kinetic parameters of $I_{\text{NaP}}$ when activated by a 0.6 nA, 4 s current injection that was set initially above threshold for burst discharge. Note that the model fails to exhibit a shift in ISI (top), a membrane depolarizing shift (middle), or a change in oscillation period over time (bottom). C: the slow depolarizing shift observed in pyramidal cells was simulated by incorporating a 2nd time constant for $I_{\text{NaP}}$, a slow component of $I_{\text{NaP}}$ when activated by a 0.6 nA, 4 s current injection (NaP,S; $\tau = 1.5$ s). This longer $I_{\text{NaP},S}$ permits the model to shift from tonic to burst mode in association with a decrease in ISI (top), a slow membrane depolarization (middle), and a decrease in oscillation period over time (bottom) once bursting is initiated. The segments of regular burst behavior between ~2 and 3 s in C arises from a window of periodic behavior bordered by chaotic dynamics, a characteristic property of chaotic systems (Strogatz 1994).
shorter oscillation periods compared to those of the earlier bursts.

**DISCUSSION**

This study identifies the mechanisms by which a principle sensory neuron can initiate burst discharge and provide fine control over oscillation period. Both endpoints are achieved by regulating the time required to trigger a spike doublet that periodically blocks spike backpropagation into apical dendrites. Experimental analysis and compartmental modeling identify a key role for \( I_{\text{NaP}} \) in modulating both the dendritic and somatic spikes to generate a DAP at the soma. A similar process is likely to be found in other cells in which backpropagating spikes produce a somatic DAP (Golding et al. 1999; Larkum et al. 1999; Williams and Stuart 1999; Zhang et al. 1993). In ELL pyramidal cells, a steadily decreasing ISI leads to an abrupt loss of spike backpropagation that removes the DAP, generating an interburst interval. By repeating this process of conditional backpropagation, the output pattern is converted from one of tonic discharge to clusters of spikes (bursts) separated by interburst intervals. This periodic activation and loss of excitatory drive is similar to that which produces burst discharge in thalamic neurons, although in this case, the inactivation of \( I_F \) and deactivation of \( I_L \) leads to the interburst interval (Huguenard and Prince 1992; McCormick and Pape 1990). Interestingly, \( \text{Na}^+ \) spikes backpropagate over the initial stem dendrites of thalamocortical relay cells that contain the highest density of \( I_F \) channels (Williams and Stuart 2000). Because backpropagating spikes will almost certainly activate \( I_L \) channels, burst termination by an inactivation of \( I_L \) during a repetitive spike train provides an interesting parallel to the process we have described in ELL pyramidal cells.

**Role of persistent \( \text{Na}^+ \) current**

The molecular identity of \( I_{\text{NaP}} \) has been debated, with evidence that \( I_{\text{NaP}} \) can arise through the same channels that produce fast inactivating \( \text{Na}^+ \) current (Alzheimer et al. 1993; Crill 1996; Taddei and Bean 2002). Evidence that other channel subtypes might contribute to persistent \( \text{Na}^+ \) current(s) come from reports of a larger single-channel conductance for \( I_{\text{NaP}} \) than fast inactivating \( \text{Na}^+ \) channels (Magistretti et al. 1999a,b), the ability to achieve a relatively selective block of

FIG. 8. Oscillation period is controlled over time by the rate of DAP potentiation by \( I_{\text{NaP}} \). A: plot of the onset of burst discharge (---) and shift in oscillation period over time after 0.6 nA current onset in the compartmental model incorporating \( I_{\text{NaP}} \). B: plots of the increase in \( I_{\text{NaP}} \) activation (s) and the rate of DAP potentiation over time. Four time points (1-4) are indicated by arrows to compare voltage and current responses shown in C and D. Note that the rate of DAP potentiation increases over time and changes in concert with oscillation period (compare A and B). C: expanded and superimposed traces of somatic and dendritic spikes (V), \( S_{\text{NaP}} \), and \( D_{\text{Dr,d}} \) at the start of tonic spike discharge (1; black traces) and immediately preceding burst onset at time point 2 (gray traces). Note the increase in DAP amplitude, dendritic spike duration, and \( S_{\text{NaP}} \) by the time of burst onset. D: expanded and superimposed traces of somatic spike bursts at time points 3 (black trace) and 4 (gray trace). Dashed lines denote the rate of DAP potentiation during a spike burst (also plotted in B). Note that the increased rate of DAP potentiation at time point 4 generates a somatic spike doublet in a shorter period of time, resulting in a shorter burst duration and oscillation period.
I_{NaP} pharmacologically (Brumberg et al. 2000; Lampl et al. 1998; Washburn et al. 2000), and the existence of a resurgent Na$^+$ current in some cell types (Raman and Bean 1997). Our work does not attempt to distinguish between these possibilities. Rather we used low concentrations of phenytoin to obtain a relatively selective block of I_{NaP}. Although results from these experiments strongly implicate I_{NaP} in modulating the DAP, additional effects by phenytoin on somatic spike amplitude encouraged us to focus on compartmental modeling to fully examine its role independently of fast inactivating Na$^+$ channels. The close match between experimental data and simulations provides convincing evidence that a persistent component of Na$^+$ conductance augments somatic and dendritic factors underlying burst discharge.

I_{NaP} has been shown to contribute to a wide range of membrane depolarizations, including subthreshold synaptic potentials and oscillations, low-threshold Ca$^{2+}$ spikes, DAPs, and somatic spike bursts (Agrawal et al. 2001; Alonso and Llinas 1989; Azouz et al. 1996; Berman et al. 2001; Brumberg et al. 2000; Mantegazza et al. 1998; Parri and Crunelli 1998; Stuart and Sakmann 1995; Wang 1999; Washburn et al. 2000). I_{NaP} channel activity has also been directly recorded in dendritic regions (Magee and Johnston 1995a,b; Magistretti et al. 1999a; Stuart and Sakmann 1995). However, to our knowledge, the only other work to assess the role for dendritic I_{NaP} in modulating burst discharge was a theoretical study (Wang 1999). We have now shown that I_{NaP} acts to enhance back-propagating dendritic Na$^+$ spikes and the depolarization arising from temporal summation of dendritic spikes during repetitive discharge. The effects of I_{NaP} were linked to the initial cumulative inactivation of dendritic K$^+$ current within a burst and an additional long time constant for activation (I_{NaP,S}). The influence of persistent Na$^+$ current can thus be segregated into an intraburst mechanism that permits I_{NaP} to magnify the key elements underlying conditional backpropagation and a longer activation time (I_{NaP,S}) that modulates the gain of the intraburst mechanism to control burst frequency over time.

I_{NaP} most often shows little or no inactivation over the time frame studied here (Crill 1996). However, there are reports that I_{NaP} in some cells can begin to inactivate during long step commands under voltage clamp (~40% inactivation for a 4-s step command to -40 mV) (Magistretti and Alonso 1999). We are uncertain as to whether this occurs in ELL pyramidal cells. However, if it does, it is apparently not sufficient to prevent the continued activation and growth of a significant phenytoin-sensitive slow depolarizing shift (Fig. 4E). We are unaware of any reports of an additional long time constant for activation of I_{NaP}. We have implemented it here as a means to account for the slow depolarizing shift over time. The biophysical basis for such a process will be important to examine, but is beyond the scope of the present study.

Experimental and model characteristics fit dynamical systems theory

Dynamical systems analysis of a simple two-compartmental model of pyramidal cells predicted that a transition from tonic

---

**FIG. 9.** The interplay between dendritic K$^+$ current and I_{NaP,S} accounts for the time scale of an intermittent escape from the trapping region of a saddle-node bifurcation. A–C, top: single spike bursts from the Ghostbuster model incorporating only I_{NaP,d} (A), the full compartmental model incorporating I_{NaP,d} and I_{NaP,S} (B), and a pyramidal cell recording (C). Numbers above spikes correspond to different sections of the burst (see RESULTS). Oscillation period is denoted by linked arrows below each voltage trace. Illustrated for both the compartmental model and pyramidal cell data is the time course associated with the sections of the bursts indicated in the traces above. Sections 2–4 are qualitatively the same in all ISI maps. However, section 1 of the early bursts in both model and pyramidal cells (B and C) shows much more clustering of ISIs than in the later bursts. We note that the transition through the trapping region for the initial long bursts is smooth for the model (B) and distorted for the data (C). This is to be expected considering the internal noise and fine resolution of the recordings. However, the clustering of ISIs near the diagonal is clear in both model and data.
firing to chaotic bursting is mediated by a saddle-node bifurcation (Doiron et al. 2002). This result prompted a further prediction that the oscillation period of burst discharge could be modulated through fine control of a trapping region born from the bifurcation. The use of ISI return maps establishes that the qualitative predictions arising from the Ghostbuster equations are verified in both the full compartmental model and experimental recordings. Although bifurcations separating tonic and burst discharge and the control of burst frequency have been observed in abstract mathematical models of bursting neurons (Terman 1992; Wang 1993), the present work identifies the ionic mechanisms that underlie these events in a real bursting neuron. The ubiquitous nature of saddle-node bifurcations throughout dynamical systems theory (Strogatz 1994) suggests that the mechanism of burst control delineated here may be applicable to a variety of bursting neurons.

We have several further predictions about this form of burst discharge, namely a scaling law for the oscillation period and that the burst dynamics are chaotic (Doiron et al. 2002). The time that a trajectory spends within a trapping region can be shown theoretically to scale as \( 1/\sqrt{\varepsilon} \), where \( \varepsilon \) is the distance from the bifurcation within parameter space (Pomeau and Manneville 1980; Strogatz 1994). A direct experimental verification of this scaling in ELL pyramidal cell data is problematic. A scaling law has been shown to be dependent upon underlying stochastic processes (Kye and Kim 2000) which are difficult to assess from experimental recordings. Furthermore, the experimental bifurcation parameter is predicted to be the slow Na\(^+\) activation \( s \), which cannot be measured or controlled in a graded manner within experiments. We were thus satisfied that the qualitative nature of the \( 1/\sqrt{\varepsilon} \) scaling law is observed in both the large model and the experimental recordings, i.e. the monotonic decrease of ISI clustering as \( s \) increases past \( s_{\text{SNR}} \). In addition, our theoretical analysis of this burst mechanism predicted a chaotic spike discharge (Doiron et al. 2002). Distinguishing whether deterministic chaos or stochastic processes underlie unpredictability within time series data gained from experiments is often a difficult problem (Eckmann and Ruelle 1992; Theiler et al. 1992). Our small number of spike events in each recording (\( \sim 400 \)) coupled with the nonstationarity of the data sets introduced by the slow activation of Na\(^+\) makes a clear verification of whether this form of burst discharge is intrinsically chaotic quite challenging and was thus not addressed in this study.

**Burst discharge in electrosensory processing**

Spike bursts are recorded in ELL pyramidal cells in vivo and have been shown to detect specific features of sensory input (Gabbiani et al. 1996; Metzner et al. 1998). Depolarizations of the duration used here are expected to be encountered in vivo in response to gradual shifts in electric field strength (Bastian 1999; Bastian and Nguyenkim 2001; Bastian et al. 2002). In fact, global electrical field stimuli simulating electrocommunicative interactions between conspecifics was recently shown to induce burst discharge in vivo through a process of conditional backpropagation (J. Bastian, personal communication). The ability for descending synaptic feedback to activate \( I_{\text{SNAP}} \) in pyramidal cells (Berman et al. 1997, 2001) allows one to predict that synaptic activity will be capable of modifying conditional backpropagation and burst discharge. Should synaptic inputs promote a transition between tonic and burst discharge, it could further induce a switch between stimulus estimation and detection during sensory processing. In this regard, it now appears that pyramidal cells can shift their coding strategy from estimation to detection depending on the spatial distribution of input over pyramidal cell receptive fields (Bastian et al. 2002; Gabbiani et al. 1996). However, the encoding capabilities of pyramidal cells will almost certainly be influenced by the intrinsic (cellular) dynamics exposed in the current study. The details of how conditional backpropagation and network dynamics interact and their summed effects upon spike patterning and stimulus encoding remain to be determined.

We acknowledge the support of Drs. A. Longtin and L. Maler of the University of Ottawa as B. Doiron’s graduate program supervisors. Critical reading of the manuscript by C. Laing, J. Lewis, and L. Maler is greatly appreciated.

This work was supported by a Canadian Institute of Health Research Grant and Alberta Heritage Foundation for Medical Research (AHFMR) senior scholarship to R. W. Turner. L. Noonan was supported by an AHFMR studentship. L. Noonan and B. Doiron by National Science and Engineering Research Council postgraduate fellowships, and N. Lemon by a Medical Research Council studentship.

**REFERENCES**


Steriade M, Curro Dossi R, and Contreras D. Electrophysiological properties of intralaminar thalamocortical cells discharging rhythmic (approximately 40 Hz) spike-bursts at approximately 1000 Hz during waking and rapid eye movement sleep. *Neuroscience* 56: 1–9, 1993.


