Control of the Firing Patterns of Vibrissa Motoneurons by Modulatory and Phasic Synaptic Inputs: A Modeling Study

Omri Harish and David Golomb

Department of Physiology and Neurobiology and Zlotowski Center for Neuroscience, Ben-Gurion University, Be’er-Sheva, Israel

Submitted 19 November 2009; accepted in final form 1 March 2010

Harish O, Golomb D. Control of the firing patterns of vibrissa motoneurons by modulatory and phasic synaptic inputs: a modeling study. J Neurophysiol 103: 2684–2699, 2010. First published March 3, 2010; doi:10.1152/jn.01016.2009. Vibrissa motoneurons (vMNs) generate rhythmic firing that controls whisker movements, even without cortical, cerebellar, or sensory inputs. vMNs receive serotonergic modulation from brain stem areas, which mainly increases their persistent sodium conductance ($g_{NaP}$) and, possibly, phasic input from a putative central pattern generator (CPG). In response to serotonergic modulation or just-suprathreshold current steps, vMNs fire at low rates, below the firing frequency of exploratory whisking. In response to periodic inputs, vMNs exhibit nonlinear suprathreshold resonance in frequency ranges of exploratory whisking. To determine how firing patterns of vMNs are determined by their 1) intrinsic ionic conductances and 2) responses to periodic input from a putative CPG and to serotonergic modulation, we construct and analyze a single-compartment, conductance-based model of vMNs. Low firing rates are supported in extended regimes by adaptation currents and the minimal firing rate decreases with $g_{NaP}$ and increases with M-potassium and h-cation conductances. Suprathreshold resonance results from the locking properties of vMN firing to stimuli and from reduction of firing rates at low frequencies by slow M and afterhyperpolarization potassium conductances. h conductance only slightly affects the suprathreshold resonance. When a vMN is subjected to a small periodic CPG input, serotonergically induced $g_{NaP}$ elevation may transfer the system from quiescence to a firing state that is highly locked to the CPG input. Thus we conclude that for vMNs, the CPG controls firing frequency and phase and enables bursting, whereas serotonergic modulation controls transitions from quiescence to firing unless the CPG input is sufficiently strong.

INTRODUCTION

Rats explore their immediate environment primarily by sweeping their mystacial vibrissae (Diamond et al. 2008; Kleinfeld et al. 1999, 2006), projecting them outward and forward from their snout. The frequency of this exploratory whisking is 5–15 Hz (Berg and Kleinfeld 2003). Vibrissa motoneurons (vMNs) in the facial nucleus innervate the intrinsic and extrinsic muscles that move the vibrissa and are the final common path for vibrissa motor control (Dörfl 1982). Despite extensive research efforts, what causes vMNs to fire is unclear. Rhythmic whisking does not rely on cortical inputs (Gao et al. 2003; Sembra and Komisaruk 1984), cerebellar inputs (Lovic 1972), or sensory feedback (Welker 1964). Facial motoneurons are not chemically coupled because they do not have axon collaterals (Courville 1966) and no interneurons were found in the facial nucleus (Fanardjian et al. 1983).

Like other rhythmic motor acts (e.g., locomotion, respiration, chewing, and sucking), whisking is hypothesized to be regulated by a central pattern generator (CPG) (Brecht et al. 2006; Hattox et al. 2003). In agreement with this, vMNs exhibit selective sensitivity to input within the frequency range of exploratory whisking, expressed in a suprathreshold resonance response to periodic input currents (Nguyen et al. 2004). However, a specific premotor nucleus that functions as a CPG for vMNs has never been found. Keller and colleagues (Cramer et al. 2007; Hattox et al. 2003) raised an alternative hypothesis: rhythmic firing is induced in vMNs by application of serotonin from a premotor nucleus, presumably in the lateral paragangiocellularis nucleus (LPGi) in the brain stem. In fact, they found that application of 5-hydroxytryptamine (5-HT, serotonin) in vitro causes motoneurons to fire, primarily by increasing the conductance of the persistent Na$^+$ current ($g_{NaP}$). For most serotonin concentrations, the firing rate of vMNs is low (below or around the lower range of exploratory whisking frequencies) and can be as low as 1–2 Hz (Cramer et al. 2007). Similar frequency ranges were obtained in response to applied current injection just above the firing threshold (Nguyen et al. 2004), showing that rat vMNs, in contrast to mouse spinal motoneurons (Manuel et al. 2009), have intrinsic properties that allow them to fire at such low rates in a robust manner. However, it is still unclear how serotonergic control of vMN activity can coordinate firing of several vMNs, cause vMNs to fire more than one spike per cycle (Cramer and Keller 2006), or enable rapid motor control in response to changing external conditions.

Herein, we use computational and theoretical approaches to examine how the firing properties of vMNs are determined by their intrinsic ionic properties, by their response to synaptic inputs, and by serotonergic modulation. Specifically, we examine the entrainment properties of vMNs to periodic CPG inputs that enable different vMNs to fire in a coordinated manner. Such an analysis is crucial for understanding active touch properties of the vibrissa system. These issues are addressed by constructing and analyzing a single-compartment, conductance-based model of the vMN.

METHODS

vMN model

A single-compartment model for a vMN is represented by coupled differential equations according to the Hodgkin–Huxley-type scheme. The model includes active ionic currents that exist in motoneurons and are necessary to generate the experimentally observed firing patterns. The transient Na$^+$ current ($I_{Na}$) and the delayed rectifier K$^+$ current ($I_{Kdr}$) generate spikes. The slowly activating potassium afterhyperpolarization (AHP) current ($I_{AHP}$) and potassium M current ($I_{M}$)
generate the strong AHP observed in motoneurons (Meunier and Borejsza, 2005; Zhang and Krmjevic, 1987). The persistent sodium current $I_{NaP}$ affects the excitability of the neurons and is a major target of serotonergic modulation (Cramer et al. 2007; Hattoo et al. 2003). The h-current was related to subthreshold resonant behavior (Nguyen et al. 2004; Richardson et al. 2003). The current balance equation (Booth et al. 1997) is

$$C \frac{dV}{dt} = -g_L(V - V_L) - I_{Na} - I_{NaP} - I_{Kdr} - I_{AHP}$$

$$- I_M - I_h + I_{noise} = I_{CPG} + I_{app}(t) \quad (I)$$

where $V$ is the membrane potential of the neuron, $C = 1 \mu F/cm^2$ is the membrane capacitance of the neuron, and the parameters of the leak current are $g_L = 0.12 mS/cm^2$ and $V_L = -70$ mV. The external current injected into the neuron is denoted by $I_{app}(t)$, which we consider to be

$$I_{app}(t) = I_0 + I_1 \cos (2 \pi ft) \quad (2)$$

where $I_0$, $I_1$, and $f$ are constants. This form of $I_{app}(t)$ enables us to compare results obtained with our model with those obtained from experiments in which step currents (Hattoo et al. 2003; Nguyen et al. 2004) and sinusoidal currents (Nguyen et al. 2004) were injected into the neuron.

The Na$^+$ current $I_{Na}$ is given by

$$I_{Na}(V, h) = g_{Na} m_a(V)(h(V - V_{Na})) \quad (3)$$

where $g_{Na} = 100 mS/cm^2$

$m_a(V) = \{1 + \exp[-(V - \theta_a)/\sigma_a]\}^{-1} \quad (4)$

and the gating variable $h$ follows

$$\frac{dh}{dt} = [h_a(V) - h]/\tau_h(V) \quad (5)$$

$$h_a(V) = \{1 + \exp[-(V - \theta_a)/\sigma_a]\}^{-1} \quad (6)$$

$$\tau_h(V) = 30 \left[\exp \left(\frac{V + 50}{15}\right) + \exp \left(-\frac{V + 50}{16}\right)\right]^{-1} \quad (7)$$

The parameters $V_{Na} = 55 mV$, $\theta_a = -28 mV$, $\sigma_a = 7.8 mV$, $\theta_h = -50 mV$, and $\sigma_h = -7 mV$ were modified from Lape and Nistri (2001). The time constant $\tau_a(V)$ is taken from Booth et al. (1997).

The delayed rectifier K$^+$ current $I_{Kdr}$ is given by

$$I_{Kdr}(V, n) = g_{Kdr} n(V - V_k) \quad (8)$$

where $g_{Kdr} = 20 mS/cm^2$

$$\frac{dn}{dt} = [n_a(V) - n]/\tau_n(V) \quad (9)$$

$$n_a(V) = \{1 + \exp[-(V - \theta_a)/\sigma_a]\}^{-1} \quad (10)$$

$$\tau_n(V) = 7 \left[\exp \left(\frac{V + 40}{40}\right) + \exp \left(-\frac{V + 40}{50}\right)\right]^{-1} \quad (11)$$

The parameters $V_k = -80 mV$, $\theta_a = -23 mV$, and $\sigma_a = 15 mV$ were modified from Lape and Nistri (1999). The time constant $\tau_n(V)$ is taken from Booth et al. (1997).

The persistent Na$^+$ current $I_{NaP}$ is given by

$$I_{NaP}(V, p) = g_{NaP} p_a(V)(V - V_{Na}) \quad (12)$$

$$p_a(V) = \{1 + \exp[-(V - \theta_a)/\sigma_a]\}^{-1} \quad (13)$$

where $\theta_a = -53 mV$ and $\sigma_a = 5 mV$ (Enomoto et al. 2007; Tazerart et al. 2007). The effect of serotonin application on the vMN is modeled as an increase in the conductance $g_{NaP}$ (Cramer et al. 2007). The reference parameter value (in the absence of serotonin application) is $g_{NaP} = 0.04 mS/cm^2$.

The AHP current is a Ca$^{2+}$-dependent K$^+$ current that is activated slowly following intracellular accumulation of Ca$^{2+}$, which occurs as a result of vMN depolarization during spikes. This activation affects the firing patterns of facial (Magarinos-Ascone et al. 1999) and other (Meunier and Borejsza 2005) motoneurons. Based on the work of Prescott and Sejnowski (2008), this activation current is modeled as a voltage-dependent activation with half-maximum potential above threshold. In this form, spikes are needed to activate the AHP channels. The current is given by

$$I_{AHP}(V, u) = g_{AHP} u(V - V_K) \quad (14)$$

$$\frac{du}{dt} = \left[u_a(V) - u\right]/\tau_a \quad (15)$$

where $g_{AHP} = 10 mS/cm^2$, $\theta_a = -25 mV$ was chosen to be above the firing threshold, and $\sigma_a = 3 mV$. The time constant $\tau_a = 75 ms$ was modified from Lape and Nistri (2000).

The M current is another slow K$^+$ current that was observed in motoneurons, at least those of turtles (Alaburda et al. 2002). The M current is activated by membrane depolarization. Unlike the AHP current, it is partially activated even when the membrane potential is lower than the firing threshold (Ermelout et al. 2001; Golomb et al. 2006a,b; Gutkin et al. 2005; Halliwell and Adams 1982; Prescott and Sejnowski 2008). The current is given by

$$I_{M}(V, z) = g_M (V - V_K) \quad (16)$$

$$\frac{dz}{dt} = \left[z_a(V) - z\right]/\tau_z \quad (17)$$

$$z_a(V) = \{1 + \exp[-(V - \theta_z)/\sigma_z]\}^{-1} \quad (18)$$

where $g_M = 1 mS/cm^2$, $\theta_z = -45 mV$ was chosen to be below the firing threshold, and $\sigma_z = -4.25 mV$. We choose the time constant of the M current to be $\tau_z = 75 ms$ (i.e., equal to the time constant of the AHP current), to emphasize that the difference between the dynamic effects of the two currents stems from differences in the voltage thresholds for activation, not from different kinetics.

The hyperpolarization-activated h-current $I_h$ is given by

$$I_h(V, r) = g_h (V - V_h) \quad (19)$$

$$\frac{dr}{dt} = \left[r_a(V) - r\right]/\tau_r(V) \quad (20)$$

$$r_a(V) = \{1 + \exp[-(V - \theta_r)/\sigma_r]\}^{-1} \quad (21)$$

where the parameters $V_h = -27.4 mV$, $\theta_r = -83.9 mV$, and $\sigma_r = -7.4 mV$ (Sirois et al. 2002) and the function

$$\tau_r(V) = 6,000 \left[\exp \left(\frac{V + 140}{21.6}\right) + \exp \left(-\frac{V + 40}{22.7}\right)\right]^{-1} \quad (22)$$

are based on Aponte et al. (2006) and $\theta_h = 0.05 ms/cm^2$.

The effect of noise on the firing patterns of vMNs is studied by adding an additional external input, $I_{noise}$ of the form (Golomb et al. 2007)

$$I_{noise}(t) = \sigma \xi(t) \quad (23)$$

where $\xi(t)$ is a Gaussian white noise: $(\xi(t)) = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta(t - t')$; $(\cdot)$ means average over trials and $\delta$ is the Dirac function (see Golomb 1998). The units of $\sigma$ are $\mu A \times ms^{1/2}/cm^2$. We use the value of $\sigma = 0$ unless stated otherwise.

Basic experimental information about the CPG that drives the vMN is lacking. In the model, we assume that the vMN receives periodic excitatory input from the CPG, representing synaptic contributions from many CPG neurons projecting on that neuron that are not fully synchronized. For simplicity, we consider only the first Fourier component of this input, expressed as

$$I_{noise}(t) = \sigma \xi(t) \quad (23)$$
where \( g_{\text{CPG}} \) and \( f \) are the amplitude and the frequency of the CPG input, respectively, and \( V_{\text{syn}} = 0 \) is the reversal potential of excitation.

Simulations are carried out with the above-described “reference parameter set” unless otherwise stated. In Figs. 2, 3, 5, 6, and C1, results from simulations with this parameter set are denoted by thick solid black lines.

Average firing rate, locking measure, and impedance

The average firing rate of the neuron is defined as

\[
I_R = \frac{N_t}{T_{\text{integ}}}
\]

where \( N_t \) is the number of spikes the neuron fires during the integration time \( T_{\text{integ}} \) and \( T_{\text{integ}} \) is large. If the neuron responds to periodic input with a frequency \( f \), we take \( T_{\text{integ}} \) to be an integer product of the time period \( 1/f \).

The locking of the neuronal spiking pattern to the CPG stimulus (Eq. 24) is quantified by using the locking measure \( L \), where

\[
L = \frac{1}{N_t} \sum_k \exp(2\pi i f t_k)
\]

Time \( t_k \) is time of the \( k \)th spike the neuron fires during the integration time \( T_{\text{integ}} \) and \( k \) is a running spike index. In auditory literature, this type of measure is known as a synchronization or a phase-locking measure (Goldberg and Brown 1969). The measure \( L \) equals 1 if the neuron always fires at the same phase with respect to the CPG input. If the neuron fires at random times, \( L \) converges to 0 with \( T_{\text{integ}} \) like \((T_{\text{integ}})^{-1/2}\). If \( N_t = 0 \), \( L \) is defined to be 0. Calculation of \( I_R \) and \( L \) is carried out by averaging over \( T_{\text{integ}} \) between 100 and 1,000 s.

Based on the work of Nguyen et al. (2004), we use the membrane impedance \( Z \) to characterize a subthreshold response of vMNs to a small-amplitude sinusoidal current injection (Eq. 2 with \( I_0 = 0 \) and \( I_1 \) small). This current evokes membrane potential oscillations of the form \( V(t) = V_{\text{rest}} + V_1(f) \cos(2\pi ft + \phi) \). The impedance \( IZ/f \) is defined as

\[
|Z(f)| = \frac{V_1(f)}{I_1}
\]

The function \( V_1(f) \) is calculated from simulations by computing the difference between the maximal and the minimal values of \( V(t) \) and dividing by 2.

Numerical methods

Simulations of differential equations without noise were performed using the fourth-order Runge–Kutta method with a time step of 0.01 ms implemented as a C program or within the software package XPPAUT (Ermentrout 2002). Simulations of stochastic differential equations were performed using the Euler method with the same time step. Simulations with a smaller time step (0.001 ms) did not reveal any observable differences. Bifurcation diagrams were computed using XPPAUT.

RESULTS

In this work we explore the intrinsic mechanisms responsible for vMN responses to combinations of constant, modulatory, and periodic inputs. We ask the following.

1. How are the responses of vMNs to applied step currents controlled by the slow conductances: the two adaptation conductances and the h conductance?

2. What are the effects of serotonergic modulation, resulting in \( g_{\text{NaP}} \) increase, on the firing pattern of vMNs?

3. What is the mechanism responsible for suprathreshold resonance properties of vMNs? Note that subthreshold resonance properties are addressed only in comparison with corresponding suprathreshold properties.

4. How do suprathreshold resonance properties of vMNs depend on intrinsic ionic conductances and the external input?

5. How does a vMN respond to the combination of periodic synaptic conductance from a putative CPG and elevation of the persistent sodium current \( g_{\text{NaP}} \)?

To answer these questions we examine the responses of our vMN model (without and with the slow intrinsic conductances) to applied step currents, investigate the response of the model to periodic applied currents, and eventually analyze a model subjected to both a CPG periodic input and \( g_{\text{NaP}} \) modulation.

Firing patterns of vMNs in response to applied step currents and their control by slow ionic conductances

We use our model to characterize the intrinsic firing patterns of vMNs, with an emphasis on transitions from rest to firing and the ability of a neuron to fire at low rates. Naturally, the slow ionic conductances, \( g_{\text{AHP}}, g_M, \) and \( g_h \) are expected to play a role in enabling vMNs to fire at low rates in response to wide input ranges. Therefore we examine how neuronal firing patterns are affected by those slow ionic conductances, starting with a model subjected only to constant input currents.

To evaluate the role of slow ionic currents in the firing properties of vMNs, we first consider a model with all slow currents blocked: \( g_{\text{AHP}} = g_M = g_h = 0 \). Under these conditions, the model neuron fires tonically when the baseline input current \( I_0 \) is above a minimal current \( I_{0\text{,min}} \) (Fig. 1A). The gain of the neuron is large and, for \( I_0 \) slightly above \( I_{0\text{,min}} \), the neuron fires at firing rates of \( \approx 20 \) Hz. Increasing the AHP conductance \( g_{\text{AHP}} \) does not affect \( I_{0\text{,min}} \) because the AHP current is activated only during spikes (Fig. 1A). Increasing \( g_{\text{AHP}} \) decreases the gain, i.e., the slope of the \( I_R-I_0 \) curve, and makes it look linear, except for a narrow \( I_0 \) range just above \( I_{0\text{,min}} \). For an extended \( I_0 \) interval, the neuron fires at rates within, or below, those of exploratory whisking (5–15 Hz). Arbitrarily low frequencies can still be obtained. The effect of the AHP current on the response of the vMN model to step currents is similar to its effect on other neuron models, such as those proposed by Ermentrout (1998) and Prescott and Sejnowski (2008).

Increasing the h-conductance \( g_h \) while maintaining the reference value for \( g_{\text{AHP}} \), has only a minor effect on the neuron gain (the slope of the \( f_R-I_{\text{app}} \) curve) (Fig. 1B). Increasing \( g_h \) increases the firing rate for each value of \( I_0 \) and therefore shifts the \( f_R-I_{\text{app}} \) toward lower \( I_0 \) values. For larger \( g_h \) values, the minimal firing rate becomes greater than zero and the class of firing shifts from “class I” to “class II” (Hodgkin 1948), as explained in APPENDIX A using bifurcation theory. The minimal firing frequency over all \( I_0 \) values is denoted by \( f_{R\text{,min}} \). Above
\( g_{\text{h}} \), a critical value of \( g_{\text{h}} \), the frequency \( f_{R,\text{min}} \) increases continuously from 0 (Fig. 1C). For an extended \( g_{\text{h}} \) region, \( f_{R,\text{min}} \) remains at values of order 1 Hz.

In vMNs, the slow potassium conductances, \( g_{\text{AHP}} \) and \( g_{\text{M}} \), cause adaptation in response to step currents. Therefore we use the model to examine how \( g_{\text{AHP}} \) causes adaptation. Traces of the membrane potential in response to a step current show that the model neuron responds to the injection of a current step substantially above \( I_{t,\text{min}} \) by firing two spikes with a relatively small interspike interval (ISI), followed by a train of spikes with larger ISIs that are almost constant in time (Fig. 2A). For just suprathreshold currents, adaptation effects are barely observed. Similar behavior was observed experimentally (see Fig. 2 in Nguyen et al. 2004). Generally, as \( I_{0} \) increases, both the first ISI (\( T_{1} \)) and steady-state ISI (\( T \)) decrease (Fig. 2B), but \( T_{1} \) decreases more than \( T \), which makes the adaptation ratio \( T_{1}/T \)

\[ T_{1}/T = \frac{g_{\text{h}}}{g_{\text{AHP}}} \]

FIG. 1. Effects of the afterhyperpolarization (AHP) and hyperpolarization-activated (h) currents on the steady-state firing frequency of the model neuron; \( M \)-potassium conductance \( (g_{\text{M}}) = 0 \). A: firing rate–baseline input current \( (f_{R}-I_{0}) \) curve for AHP conductance \( (g_{\text{AHP}}) = 0 \) (dashed line) and 10 mS/cm\(^2\) (solid line); h-cation conductance \( (g_{\text{h}}) = 0 \). Arrow indicates value of the minimal current \( (I_{t,\text{min}}) \). B: firing rate–baseline input current \( (f_{R}-I_{0}) \) curve for \( g_{\text{h}} = 0 \) (solid line), 0.05 (dashed line), and 0.3 (dotted line) mS/cm\(^2\); \( g_{\text{AHP}} = 10 \) mS/cm\(^2\). Open circles denote patterns shown in Fig. 2A. C: minimal firing frequency \( f_{R,\text{min}} \) as a function of \( g_{\text{h}} \); \( g_{\text{AHP}} = 10 \) mS/cm\(^2\). Arrow indicates the value of \( g_{h,\text{min}} \).

FIG. 2. Adaptation in the vibrissa motoneuron (vMN) model. A: voltage traces in response to step currents with \( I_{0} = 1 \) µA/cm\(^2\) (middle trace) and 2.5 µA/cm\(^2\) (top trace); \( g_{\text{M}} = 0 \). \( g_{\text{h}} = 0.05 \) mS/cm\(^2\). For just suprathreshold currents, adaptation effects are barely observed. B: the initial interspike interval (ISI; \( T_{1} \)) (solid lines) and the steady-state ISI (\( T \)) (dashed lines) as functions of \( I_{0} \) for \( g_{\text{h}} = 0 \) (red); \( g_{\text{h}} = 0.05 \) mS/cm\(^2\); \( g_{\text{M}} = 0 \) (green); \( g_{\text{h}} = 0.05 \) mS/cm\(^2\); \( g_{\text{M}} = 1 \) mS/cm\(^2\) (reference parameters, black). C: the ratio \( T_{1}/T \) as a function of \( I_{0} \). Parameters and color code are the same as those in B. Arrows indicate values of \( I_{0} \) used in A.
smaller and the adaptation effect more pronounced (Fig. 2C). Blocking \(g_Na\) increases both \(T_1\) and \(T\), especially for just suprathreshold values of \(I_0\), leaving the ratio \(T_1/T\) almost constant (Fig. 2, B and C).

Similar to the AHP conductance, the M conductance \(g_M\) also generates spike-frequency adaptation (Prescott and Sejnowski 2008). Introduction of \(g_M\) into the model increases the current threshold for spiking because the M current is partially activated in the voltage threshold range and may prevent spiking. When spiking occurs, the M current increases both \(T_1\) and \(T\) (Fig. 2B). Since the resulting increase of \(T_1\) is greater than the increase in \(T\), introduction of \(g_M\) increases the \(T_1/T\) ratio (Fig. 2C). Thus despite being capable of endowing a neuron with the adaptation property, the M current may reduce adaptation (increase the ratio \(T_1/T\)) when adaptation has already been generated by the AHP current.

**Firing patterns under serotonergic modulation (\(g_{NaP}\) increase)**

In this modeling work, we explore how enhancing persistent sodium conductance \(g_{NaP}\) affects the firing patterns of vMNs, since Keller and colleagues observed that the main effect of serotonin on vMNs is to enhance \(g_{NaP}\) (Cramer et al. 2007). Increasing \(g_{NaP}\) enhances neuron excitability and thus shifts the \(f_R-I_0\) toward lower \(I_0\) values (Fig. 3A). When \(g_{NaP}\) is sufficiently large, the neuron fires even for \(I_0 = 0\). Furthermore, \(g_{NaP}\) decreases the minimal firing rate of the vMN during the tonic, periodic state. The mechanism for this reduction, which is related to the enhancement of the total \(Na^+\) current at steady state, is explained by Golomb et al. (2007) and Prescott et al. (2008). However, in the present vMN model, there is an exception, since the neuron exhibits a “mixed-mode oscillations” state (Rubin and Wechselberger 2007) in a narrow range of \(g_{NaP}\) and \(I_0\). In this state, the membrane potential oscillates several times between consecutive spikes (Fig. 3B) and the minimal firing frequency is smaller than the minimal frequency for larger values of \(g_{NaP}\) outside this region (Fig. 3A, thin solid line). This state, which is observed experimentally in vMNs (Hattox et al. 2003; Nguyen et al. 2004) and spinal motoneurons (Manuel et al. 2009), exists only if \(g_M\) is sufficiently strong.

Without injecting any \(I_{app}\), increasing \(g_{NaP}\) causes the neuron to fire (Fig. 3C). For the set of reference parameters, the minimal firing rate is 2.6 Hz. The minimal firing rate is reduced if either \(g_M\) or \(g_h\) decreases, although for an extensive range of these parameters it can be on the order of a few Hertz. For \(g_{NaP} = g_h = 0\), the firing rate can go to zero. Based on these results, we conclude that when \(g_{NaP}\) is enhanced, the vMN model can exhibit tonic firing with a firing rate of the order of a few Hertz. Similar behavior, with a minimal firing rate around 2 Hz, was observed experimentally in vMNs upon an application of serotonin that increases \(g_{NaP}\) (Cramer et al. 2007).

**Suprathreshold resonance responses of vMNs to periodic currents are related to locking properties of spike firing**

External periodic input may entrain a vMN to fire at frequencies that correspond to those of exploratory whisking. However, the resulting neuronal responses will depend on the intrinsic ionic conductances of the neuron. Therefore we examine whether certain conductances enable the vMN to respond at higher rates \(f_R\), specifically to input currents \(I_{app}(t) = I_c \cos(2\pi ft)\), with frequencies \(f\) within the range of exploratory whisking (Nguyen et al. 2004). Responses of the model neuron to periodic input with the reference parameter set are depicted in Fig. 4A. The neuron fires three spikes per cycle for \(f = 1\) Hz, one spike per cycle for \(f = 9\) Hz, one spike every two cycles for \(f = 15\) Hz, and one spike every three cycles for \(f = 20\) Hz. The average number of spikes per cycles \(N_c\) is shown as a function of \(f\) in Fig. 4B. For low \(f\), the neuron fires an integer number of spikes per cycle. Generally, \(N_c\) decreases as \(f\) increases, but there are regions where \(N_c\) can fluctuate between an integer and that integer minus 1. For example, for 0.5 Hz < \(f < 0.8\) Hz, \(N_c\) varies between 4 and 3. The number \(N_c\) is 1 for moderate values (2–10 Hz) of \(f\). For extended ranges of \(f > 10\) Hz, \(N_c\) is a rational fraction (1/2, 1/3, 2/3, etc.). Between those ranges, \(N_c\) varies between those fractions. Therefore the dependence of \(N_c\) on \(f\) has a “devil’s staircase” shape (Pikovsky and Rosenblum 2007). Eventually, for sufficiently large \(f\) (~25

![FIG. 3. Effect of persistent sodium conductance (\(g_{NaP}\)) on the vMN model. A: \(f_R-I_0\) curve for several \(g_{NaP}\) values (in mS/cm\(^2\)): 0.034 (dotted-dashed line), 0.04 (solid line, reference value), 0.06 (dashed line), and 0.08 (dotted line). The thin line for \(g_{NaP} = 0.04\) mS/cm\(^2\) represents the \(f_R\) during the mixed-mode oscillations state. B: voltage trace showing mixed-mode oscillations for \(I_0 = 1.74\) \(\mu\)A/cm\(^2\). C: firing rate \(f_R\) as a function of \(g_{NaP}\) for \(I_0 = 0\) and several sets of \(g_M\) and \(g_h\) (both in mS/cm\(^2\)): \(0.0, 0.0\) (dashed line), \(0.0, 0.05\) (dotted-dashed line), \(0.4, 0.05\) (dotted line), and \(1.0, 0.05\) (solid line).](http://jn.physiology.org/doi/10.1152/jn.00211.2007)
Although the suprathreshold resonance effect is strongly related to locking, it is not a direct consequence of it. Resonance is obtained only if: 1) for \( f < f_{\text{max}} \), \( N_c \) decreases more weakly than \( 1/f \) as \( f \) increases; and 2) for \( f > f_{\text{max}} \), \( N_c \) decreases more strongly than \( 1/f \) as \( f \) increases. The latter condition occurs if the neuron does not fire without external input, since \( f_{R,c} = 0 \) for \( f > f_0 \). For very low \( f, f_{R,c} \) is independent of \( f \), as shown analytically in APPENDIX B. Therefore to get a suprathreshold resonance, there should be a value of \( f \) for which \( f_{R,c}(f) > f_0 \). Such a value of \( f \) is likely to exist because \( f_0 \) for moderate \( f \) values is expected to be larger than \( f_0 \) for very low \( f \), due to the biophysics of the sodium current. Specifically, hyperpolarization followed by depolarization within an appropriate timeframe enhances spiking (Izhikevich 2007) because hyperpolarization increases the inactivation variable \( h \) (Eqs. 3, 5, and 6). The maximal value of \( f \) for which the neuron spikes once every cycle, \( f_{\text{max}} \), is a candidate for that global maximum. In fact, for all the cases we explore (Figs. 5 and 6), a global maximum is obtained for \( f = f_{\text{max}} \). However, not only the ratio between the values of \( f_{R,c} \) and \( f_0 \), but also the shape of the resonance curve depend strongly on the intrinsic ionic conductance of the neuron (see the following text).

The suprathreshold resonance behavior exhibited by our vMN model is also exhibited experimentally by vMNs of young rats with a peak firing rate, \( f_{R} = f_{R,\text{max}} \), of about 12 Hz at a stimulus frequency, \( f_{\text{max}} \), about 10–20 Hz (see Fig. 7 in Nguyen et al. 2004), which is within the frequency range of exploratory whisking. The firing rate \( f_{R} \) decreased to low values (3 Hz) with very low input frequencies and decreased further, approaching 0, for high \( f \). Whereas secondary peaks in the \( f_{R} = f_{\text{max}} \) curve occur in all our simulations (Figs. 5 and 6), they were not observed experimentally (Nguyen et al. 2004) for the following reasons. The experimental results reported by Nguyen et al. (2004) were averaged over several neurons. Heterogeneity in neuronal properties causes different neurons to have secondary peaks at different frequencies and thus secondary peaks are smeared by averaging. Furthermore, frequency sampling in experiments might not be sufficiently dense for identification of secondary peaks.

**Dependence of suprathreshold resonance on intrinsic ionic conductances and external input**

 Dependence of suprathreshold resonance properties on \( g_{\text{NaP}} \), \( g_{\text{AHP}} \), \( g_{\text{h}} \), \( g_{\text{AHP}} \), and \( g_{\text{M}} \), stimulus amplitudes \( (I_0 \) and \( I_1) \), and noise level are examined using our vMN model. For all stimulus frequencies \( f \) the firing rate \( f_{R} \) decreases with \( g_{\text{AHP}} \) (Fig. 5A). This effect is strong when \( g_{\text{AHP}} \) decreases from a reference value of 10 mS/cm\(^2\) to 0, but is less pronounced as \( g_{\text{AHP}} \) increases above the reference value. This behavior occurs because when the firing rate is already low, the activation variable \( u \) (Eqs. 13–15) decays almost completely between spikes and the AHP conductance \( g_{\text{AHP}} \) exerts only a residual effect. As \( g_{\text{AHP}} \) decreases, the resonance structure is maintained, but the frequency \( f_{\text{max}} \) for which the global maximum is obtained increases because the neuron can fire in every stimulus cycle (1:1 mode) at higher values of \( f \). The frequency \( f_0 \) does not vary with \( g_{\text{AHP}} \) because this conductance does not affect subthreshold behavior.

When \( g_{\text{M}} \) is blocked (Fig. 5B), the increase of \( f_{R} \) caused by \( g_{\text{AHP}} \) is more pronounced. Furthermore, the small-\( f \) limit of \( f_{R} \)
is obtained at about $f = 1$ Hz, instead of values of $f$ one order of magnitude smaller for which this limit is obtained when $g_M$ is not blocked (Fig. 5A). This occurs because when $g_M = 0$, the only slow conductance capable of strongly influencing neuron firing is $g_{AHP}$ ($g_h$ does not substantially affect firing; see the following text). The activation variable of the AHP conductance $u$ decays in the quiescent period between consecutive cycles and this period is on the order of $1/f$. The AHP activation time constant $\tau_u$ is on the order of 100 ms. Therefore if $f$ is on the order of 1 Hz, the effect on $u$ of firing during one cycle will have already vanished by the beginning of the next cycle. For such values of $f$, the instantaneous firing rate is determined approximately by the instantaneous value of $I_{app}$ (see APPENDIX B) and $f_R$ is almost independent of $f$. The activation variable of the M conductance $z$, in contrast to that of the AHP conductance $u$, is activated below firing threshold when the membrane potential of the neuron $V$ is around the half-maximum potential, $\theta_z = -45$ mV. The value of $z$ is determined by the part of the cycle during which $V$ is around $\theta_z$, whereas $I_{app}(t)$ increases. This part of the cycle is considerably smaller than the cycle period $1/f$. Therefore for $g_M$ intact, the small-$f$ limit for which $f_R$ is independent of $f$ is achieved only when this part of the cycle is large compared with the time constant of the M current $\tau_c$ (in this case 75 ms), i.e., when $f$ is on the order of $\leq 0.1$ Hz.

When the conductance $g_M$ decreases, the firing rate $f_R$ increases for all $f$ values (Fig. 5C). Since the M conductance is effective even if $V$ is below voltage threshold, decreasing $g_M$ increases $f_0$ and thus the neuron can also fire for larger input frequencies. For sufficiently large $g_AHP$, such as 2 mS/cm$^2$, the neuron is quiescent at low frequencies and fires only in a restricted range of $f$. Similar effects occur when $g_{AHP} = 0$ (Fig. 5D).

Increasing the depolarizing conductance $g_h$ causes not only an increase in $f_R$ for all $f$ values, but also an increase in the frequency $f_0$ above which the neuron is quiescent (Fig. 6A). The increase in $f_R$ is quite small compared with the effects of varying $g_{AHP}$ and $g_M$ (Fig. 5). This small increase in $f_R$ as $g_h$ varies is due to $r$, the activation variable of $I_R$ (Eqs. 19–22), being deactivated by depolarization during the rising phase of the periodic input and thus not substantially affecting the prespike dynamics. Interestingly, varying $g_h$ in the range of 0 to 0.1 mS/cm$^2$ has a considerable effect on firing properties in response to step currents (Fig. 1), on sag responses to hyperpolarizing current steps, and on subthreshold impedances $I_z(f)$ (Fig. C1A in APPENDIX C).

The effect of $g_{Nap}$ on the $f_R$ curve is more pronounced than that of $g_AHP$ (Fig. 6B). Reducing $g_{Nap}$ decreases $f_R$, reduces $f_{max}$, and may also prevent firing at low firing rates because the neuron is not excitable enough. Enhancing $g_{Nap}$ beyond a critical value causes the neuron to fire without any input (see Fig. 3). For such $g_{Nap}$ values, the neuron also fires for large $f$. In the limit of very large $f$, the firing rate with the periodic input is equal to the firing rate without any input (denoted by the arrow in Fig. 6B; $g_{Nap} = 0.08$ mS/cm$^2$) because the fast oscillatory input is averaged out by the neuron. In contrast to the substantial effect on suprathreshold resonance of blocking $g_{Nap}$, the same blockade only moderately affects on the subthreshold resonance properties of vMNs (Fig. C1B in APPENDIX C).

The effect of elevating the baseline input current $I_0$ on the suprathreshold resonance curve is similar to the effect of elevating $g_{Nap}$ (Fig. 6C). Both $f_{max}$ and $f_R$ increase with $I_0$. For sufficiently large $I_0$, the neuron fires even for large $f$ values.

The most prominent properties of the suprathreshold resonance curve such as the global maximum at $f_{max}$, the existence of local maxima (Fig. 6C), and the dependence on adaptation conductances (not shown) also characterize the dynamics for which $I_0 = I_1$. Therefore they are expected to characterize the neuronal response to periodic, excitatory CPG inputs (Eq. 24).
The firing rate $f_R$ increases with the amplitude $I_1$ of the periodic stimulus (Fig. 6D), as do the frequencies $f_{\text{max}}$ and $f_0$. For sufficiently small $I_1$, the neuron does not fire at low $f$. Increasing the noise level $\sigma$ smooths the $f_R$-$f$ and also enables the neuron to fire for $f$ values for which the neuron is quiescent in the absence of noise (Fig. 6E). However, secondary maxima still exist, even for a relatively large noise level, such as $\sigma = 1 \ \mu$A $\times$ ms$^{1/2}$/cm$^2$ (Fig. 6E) (Golomb et al. 2007).

**FIG. 6.** Effects of $h$ and NaP conductances, the input amplitudes ($I_0$ and $I_1$), and the noise level ($\sigma$) on the suprathreshold resonance response to sinusoidal input currents. Averaged firing rates $f_R$ are plotted as functions of the input frequency $f$. The input amplitude $I_1$ is 2.5 $\mu$A/cm$^2$ in A, B, C, and E. The noise level $\sigma$ is 0 in A–D. The baseline input amplitude $I_0$ is 0 except in C. In all panels, the solid line denotes the $f_R$-$f$ curve for the reference parameter set. All conductance values are written in units of mS/cm$^2$. A: $g_h = 0$ (dotted-dashed line), 0.05 (solid line), and 0.1 (dashed line). B: $g_{\text{NaP}} = 0.02$ (dotted-dashed line), 0.04 (solid line), 0.06 (dotted line), and 0.08 (dashed line). The arrows on the right denote $f_R$ for $g_{\text{NaP}} = 0.08$ mS/cm$^2$ and $I_1 = 0$. C: the baseline amplitude $I_0$ (in $\mu$A/cm$^2$) is: 0 (solid line), 0.5 $I_1$ (dashed line), and $I_1$ (dotted line). D: the input amplitude $I_1$ (in $\mu$A/cm$^2$) is: 1.5 (dotted line), 2.5 (solid line), and 5 (dashed line). E: the noise level $\sigma$ (in $\mu$A $\times$ ms$^{1/2}$/cm$^2$) is: 0 (solid line), 0.15 (dashed line), and 1 (dotted line). Results are averaged over 10 realizations of the noise.
Response of the model neuron to periodic synaptic currents from an external CPG and $g_{NaP}$

Two types of stimulations were suggested for innervations of vMN: periodic input from a CPG (Brecht et al. 2006) and serotonergic modulation, which mainly strengthens $g_{NaP}$ (Cramer et al. 2007; Hattox et al. 2003). The response of our vMN model to various levels of CPG input (Eq. 24) and $g_{NaP}$ conductance is examined while subjecting the neuron to a moderate level of noise ($\sigma = 0.15 \mu A \times m^{1/2}/cm^2$). The resulting response is quantified by the average firing rate $f_R$ and the locking measure $IL$ (Eqs. 25 and 26). In the $g_{CPG}-g_{NaP}$ plane, regimes are observed in which the neuronal spiking is locked to the periodic stimulus and the locking number is either an integer (1:1, 2:1, etc.) or half-integer (1:2, 3:2, etc.). Regimes in which the locking number is a fraction with a denominator that is $\geq 3$ (e.g., 1:3, 2:3, 4:3...) are either narrow or nonexistent and are not computed here.

The dependences of $f_R$ and $IL$ on $g_{CPG}$ and on $g_{NaP}$ for $f = 10$ Hz, a typical whisking frequency (Berg and Kleinfeld 2003), are shown in Fig. 7A. When $g_{CPG} > g_q$ (0.068 mS/cm$^2$ in this instance), the neuron fires for all $g_{NaP}$ values. For $g_{CPG} < g_q$, the neuron is quiescent if $g_{NaP}$ is below a threshold value, $g_{NaP, th}$, that decreases as $g_{CPG}$ increases (Fig. 7B). When the parameters of the neuron are within the quiescent regime and either $g_{CPG}$ or $g_{NaP}$ is increased, the neuron starts to fire and the firing rate increases along with increases in these two parameters. Locking behaviors above threshold for low ($<0.15g_q$) and for moderate (0.15$g_q < g_{CPG} < g_q$) $g_{CPG}$ values differ. There is a smooth crossover, rather than a sharp transition, in both firing frequency and locking properties between the two regimes ($g_{CPG} < 0.15g_q$ and $0.15g_q < g_{CPG} < g_q$).

**Fig. 7.** Response of the vMN model to periodic input conductance from an external central pattern generator (CPG, Eq. 24) with $f = 10$ Hz and amplitude $g_{CPG}$, and to the persistent sodium conductance $g_{NaP}$. A: firing frequency ($f_R$, top) and locking measure ($IL$, bottom) are plotted as functions of $g_{CPG}$ and $g_{NaP}$. The quiescent regime is denoted by dark blue areas. Arrow indicates $g_q$. B: phase diagram of the vMN model in the $g_{CPG}-g_{NaP}$ plane. The quiescent regime is denoted by the dark gray area and the locking regimes from the n:1 and n:2 types (n is an integer) are denoted by (and labeled in) the light gray areas. C: firing frequency ($f_R$, top) and locking measure ($IL$, bottom) as functions of $g_{NaP}$ for several values of $g_{CPG}$ (in mS/cm$^2$): 0 (blue), $5 \times 10^{-4}$ (red), $2 \times 10^{-3}$ (green), 0.01 (black), 0.02 (yellow), and 0.05 (orange). Note the peaks in IL value when $g_{CPG}$ is either $5 \times 10^{-4}$ or $2 \times 10^{-3}$ mS/cm$^2$. Green arrows denote $g_{NaP}$ values used in D. For $g_{CPG} = 0$, the peaks in IL are spurious and decrease with the integration time $T_{integ}$ like $(T_{integ})^{-1/2}$. D: voltage time traces for $g_{CPG} = 2 \times 10^{-3}$ mS/cm$^2$ and $g_{NaP} = 0.09$ (top, thick line) or 0.065 mS/cm$^2$ (middle, thin line). Bottom: input synaptic conductance $g_{CPG}(t) = (g_{CPG}/2)(1 + \cos(2\pi ft))$. Spike times are indicated by $*$ for $g_{NaP} = 0.09$ mS/cm$^2$ and by $\circ$ for $g_{NaP} = 0.065$ mS/cm$^2$. 

\[ f = 10 \text{ Hz} \]
Nevertheless, the qualitative behavior in these regimes will be described separately (see the following text).

Even for low $g_{\text{CPG}}$ values, except zero or extremely small ones, the value of $I_L$ just above threshold is of order $1$. For example, $|I_L|$ can attain values of 0.7 for $g_{\text{CPG}}$ more than an order of magnitude smaller than $g_q$ (Fig. 7C, green line; $g_{\text{CPG}} = 2 \times 10^{-3}$ mS/cm$^2$) and even 0.3 for $g_{\text{CPG}} < 10^{-2} g_q$ (Fig. 7C, red line; $g_{\text{CPG}} = 5 \times 10^{-4}$ mS/cm$^2$). The firing rate $f_R$ is small for those just-suprathreshold values of $g_{\text{NaP}}$, with the neuron firing sporadically once every several cycles and in a phase-locked manner to the stimulus (Fig. 7).

For moderate $g_{\text{CPG}}$ values, $|I_L|$ jumps to 1 at threshold and remains at that value for a widespread range of $g_{NaP}$, with the neuron firing sporadically once every several cycles and in a phase-locked manner to the stimulus (Fig. 7D, thin green line; $g_{\text{CPG}} = 5 \times 10^{-4}$ mS/cm$^2$). The measure $|I_L|$ peaks again when $f_R = 5$ Hz and the neuron fires every second cycle (Fig. 7, B and D, thick green line). As $g_{\text{NaP}}$ increases further, $|I_L|$ decreases to low values, whereas $f_R$ gradually increases.

For moderate $g_{\text{CPG}}$ values, $|I_L|$ jumps to 1 at threshold and remains at that value for a widespread range of $g_{\text{NaP}}$ (see Fig. 7C; black, yellow, and orange curves). In most of this range, the firing rate is locked in the 1:2 mode (Fig. 7B). As $g_{\text{NaP}}$ further increases, $|I_L|$ decreases to $<1$, but remains relatively high (mostly $>0.9$) until firing locks again to the stimulus in a 1:1 mode. For larger $g_{\text{NaP}}$ values, the firing mode switches to a 3:2 mode, with more complicated firing patterns between the 1:1 and 3:2 regimes, although the locking measure remains high. Firing patterns with more spikes per cycle, which correspond to bursting firing patterns, are observed for moderate $g_{\text{CPG}}$ values only for very large $g_{\text{NaP}}$. Such large values of $g_{\text{NaP}}$ are beyond the scale in Fig. 7, and are probably not physiological and cannot be obtained by just applying serotonin. Since bursting behavior can be obtained when $g_{\text{CPG}}$ is sufficiently large (e.g., firing at 2:1, 3:1... modes), we conclude that enhancing the CPG input considerably beyond $g_q$ is necessary for generating bursting firing patterns.

For all parameters examined, if the neuron fires once every one (1:1 mode) or two cycles (1:2 mode), the firing phase is also locked to the stimulus and thus $|I_L| = 1$. For higher integer locking modes, with $n$ spikes per cycle (2:1, 3:1, etc.), the timing of the $i$th spike ($1 \leq i \leq n$) with respect to the phase of the periodic input repeats itself every cycle, after transients have decayed.

If $g_{\text{CPG}}$ is not small, the effects of increasing $g_{\text{CPG}}$ and increasing $g_{\text{NaP}}$ on the vMN firing patterns are similar. This is not valid, however, if $g_{\text{CPG}}$ is small. For example, it is possible to obtain the 1:1 locked state only within a very restricted parameter regime for small $g_{\text{CPG}}$ values, but it is easy to obtain it for small (or even 0) $g_{\text{NaP}}$ values. Our simulations are carried out with a moderate level of noise to show that such a noise level does not destroy the locking properties. Results of simulations without noise are not significantly different.

Decreasing the input frequency to 5 Hz only slightly affects the firing frequency (compare Figs. 7A and 8A) and the sharp transitions from quiescent to a highly locked state as either $g_{\text{NaP}}$ or $g_{\text{CPG}}$ increases (Fig. 8B). However, for $f = 5$ Hz and $f = 10$ Hz, we observe several differences in the firing and locking properties of the neuron. For $f = 5$ Hz, the quiescent regime is more extended for low $g_{\text{NaP}}$ ($g_q = 0.088$ mS/cm$^2$ in Fig. 8B) because the input current oscillates at lower frequency and the sodium current is less deinactivated as a result of the trough in $g_{\text{CPG}}$. Also, the 1:2 locking regime does not exist for $f = 5$ Hz, since the adaptation currents generated by the firing of one spike decay after two cycles (400 ms) and cannot cause spike locking.

Another difference is that the 1:1 locking regime does not extend beyond moderate ($>0.1$ mS/cm$^2$) values of $g_{\text{NaP}}$, since for $g_{\text{CPG}} = 0$, the neuron fires at 5 Hz for $g_{\text{NaP}} = 0.096$ mS/cm$^2$. The input conductance cannot prevent the neuron from firing when $g_{\text{CPG}} = 0$.
from firing at higher rates for larger \( g_{\text{NaP}} \) values and thus cannot maintain 1:1 entrainment to the CPG input.

Yet another difference is that regimes of half-integer locking mode are narrower for 5 Hz than those for 10 Hz and the \( n:1 \) locking regimes occupy larger regions in the phase diagram. To understand the basis of this difference we examine the dynamics of the AHP conductance. The time courses of \( V(t) \) and \( u(t) \) (the AHP activation variable) for \( g_{\text{NaP}} = 0.096 \text{ mS/cm}^2 \) and two values of \( g_{\text{CPG}} \) are plotted in Fig. 8C. For \( g_{\text{CPG}} = 0.1 \text{ mS/cm}^2 \), the neuron fires three spikes per cycle, all before the CPG input reaches its peak. The activation variable \( u \) decays until the input conductance increases again and is about halfway toward its peak when the neuron fires three more spikes. For \( g_{\text{CPG}} = 0.07 \text{ mS/cm}^2 \), the neuron alternately fires three and two spikes. When three spikes are fired, the last one is fired well after the stimulus peak and, as the new cycle of excitation arrives, \( u \) is sufficiently strong to postpone the next spike. The next spike (first in its cycle) is eventually fired later in the cycle, when the synaptic input and \( u \) are larger than those at the onset of the first spike in the previous cycle. The second spike of this cycle is also fired at a later time and, for larger \( u \), than those of the second spike in the previous cycle. As a result, the neuron has neither the time nor the ability to overcome the AHP current and to fire a third spike. Therefore a cycle-to-cycle “memory” effect, via the adaptation currents, is needed to obtain noninteger locking patterns. This memory effect is stronger for higher \( f \) because adaptation currents have less time to decay and thus noninteger locking patterns are more abundant as \( f \) increases.

The contribution of AHP current is reexamined by computing the firing rate (Fig. 9A) and the locking modes (Fig. 9B) as functions of \( g_{\text{CPG}} \) and \( g_{\text{NaP}} \) when the AHP conductance is blocked. As expected, the quiescent regime is not affected by the AHP block, and, in the regimes where the neuron fires, the firing rate increases considerably. Under these conditions, noninteger locking patterns do not occur because there is no AHP conductance to generate a cycle-to-cycle “memory” effect and the reference value of \( g_{\text{M}} \) is not large enough to support it. However, elevation of \( g_{\text{M}} \) to a value such as 4 mS/cm\(^2\) restores the noninteger locking regimes (data not shown).

**DISCUSSION**

**Theoretical results obtained with our vMN model**

Vibrissa motoneurons are the final common path for vibrissa motor control and receive synaptic and modulatory inputs, such as serotonin, that enhance the persistent sodium conductance \( g_{\text{NaP}} \) (Cramer et al. 2007; Hattox et al. 2002, 2003). Herein, we evaluate how interplay between constant or slowly varying inputs, phasic inputs, and intrinsic neuronal properties shapes neuronal firing patterns. This is achieved by using a single-compartment, conductance-based model of vMNs. Adaptation currents are shown to enable vMNs to fire at low rates, below those of exploratory whisking, for a wide range of inputs (currents and serotonin modulation). The minimal firing rate of a vMN can be either zero or on the order of a few Hertz (Figs. 1 and 3); it increases continuously with \( g_b \) and \( g_M \) and decreases with

\[ f=10\text{Hz}, g_{\text{AHP}}=0 \]

---

**FIG. 9.** Response of the vMN model to periodic input conductance from an external CPG (Eq. 24) with \( f = 10 \text{ Hz} \) and amplitude \( g_{\text{CPG}} \), and to the persistent sodium conductance \( g_{\text{NaP}} \); \( g_{\text{AHP}} = 0 \). A: firing frequency \( (f_b) \) plotted as a function of \( g_{\text{CPG}} \) and \( g_{\text{NaP}} \). Arrow indicates \( g_{\text{NaP}} \). B: phase diagram of the model neuron in the \( g_{\text{CPG}}-g_{\text{NaP}} \) plane. Notation as in Fig. 7B.

\( g_{\text{NaP}} \): For exploratory whisking frequencies, vMN tuning for firing at maximal rates (Berg and Kleinfeld 2003; Nguyen et al. 2004) is generated by adaptation conductances, especially \( g_{\text{M}} \), whereas the role of \( g_b \) in shaping the suprathreshold resonance is minor (Figs. 1 and 6). The suprathreshold resonance is closely related to the locking properties of the neuronal response; these properties result in a “devil’s staircase” structure (Brumberg and Gutkin 2007) of the number of spikes per cycle as a function of frequency (Fig. 4). When a vMN is subjected to a small CPG input, increasing \( g_{\text{NaP}} \) by serotonergic modulation results in the firing of the neuron in a highly correlated manner with the periodic input (Fig. 7), even if the firing rate is low. The combined effects of a periodic, excitatory input from a CPG and \( g_{\text{NaP}} \) elevation result under most conditions in vMNs firing at \( n:1 \) or \( n:2 \) locking (Figs. 7 and 8), where noninteger locking patterns are generated by the adaptation conductances (Fig. 9). Large CPG amplitudes are needed for generating bursting response.
The main results of this study are qualitatively generic for vMN models and are not dependent on the particular choice of a parameter set. The generation of suprathreshold resonance by locking properties and adaptation currents can also be obtained using an integrate-and-fire with adaptation model (Meunier and Borejsza 2005) (not shown). The particular choice of parameters, however, determines the shape of the resonance curve and the value of input frequency $f_{\text{max}}$ for which the maximal firing rate $f_{\text{R}}$ is obtained. We thus show that vMNs are tuned to respond at maximal rate in the frequency range of exploratory whisking. The dependence of the minimal firing rate in response to step currents on intrinsic conductances ($g$, in particular) and the high locking of the firing pattern to the periodic input just above threshold are also qualitatively general properties of conductance-based neurons.

Role of $I_{\text{AHP}}$ and $I_{\text{M}}$ in slow firing dynamics of vMNs

In contrast to rat vMNs, mouse spinal motoneurons can fire tonically only at high frequencies (>60 Hz) (Manuel et al. 2009). The fast activity of these spinal motoneurons is related to their fast passive time constant and fast AHP decay time compared with other motoneurons (Manuel et al. 2009). In agreement, we show that the slow potassium currents, $I_{\text{AHP}}$ and $I_{\text{M}}$, with decay rates on the order of 0.1 s, shape the rat vMNs’ efficient responsiveness to periodic input frequencies on the order of 10 Hz and enable low firing rates (<5–10 Hz) in response to constant inputs over considerable parameter ranges (Fig. 1).

The AHP current linearizes the $f_{\text{R}}$–$I_{0}$ curve and reduces its gain (Fig. 1) (see Ermentrout 1998; Prescott and Sejnowski 2008). Previously, the M, but not the AHP, current, was shown to transfer the neuronal firing class from I to II (Hodgkin 1948) and increase the minimal firing rate (Ermentrout et al. 2001; Prescott et al. 2008). Here, we describe the same behavior in response to $g_{\text{NaP}}$ elevation instead of current injection (Fig. 3C). An M current, active below the spiking threshold, elevates the current threshold and increases both the first and the steady-state interspike intervals $T_1$ and $T$ (Fig. 2). However, with strong $I_{\text{AHP}}$, the adaptation ratio $T_1/T$ may paradoxically increase with enhancing $g_{\text{NaP}}$.

In response to sinusoidal inputs, both adaptation currents generate the suprathreshold resonance effect by reducing the firing rate $f_{\text{R}}$ at low input frequencies $f$, more than for intermediate $f$ values, around 10–20 Hz (Fig. 5). The M, but not the AHP, current can suppress firing at low $f$ and decrease the maximal $f$ value for which the neuron can spike. When the neuron fires at low $f$, the M current can cause $f_{\text{R}}$ to increase with $f$ for $f$ values of 0.1–1 Hz. Both the AHP and M currents can support half-integer mode locking in response to CPG inputs in the frequency range of exploratory whisking (5–15 Hz, Figs. 7–9).

Serotonergic modulation and $g_{\text{NaP}}$ enhancement

vMNs receive serotonergic modulation from premotoneurons located in the LPGi in rat brain stem (Hattox et al. 2003). Serotonin enhances the persistent sodium conductance $g_{\text{NaP}}$ in vMNs (Cramer et al. 2007) and other motoneurons (Hsiao et al. 1997). Thus we focus on the effect of $g_{\text{NaP}}$ on neuronal firing patterns. With our model, we demonstrated that upon elevation of $g_{\text{NaP}}$, the $f_{\text{R}}$–$I_{0}$ curve shifts leftward, the minimal firing frequency decreases, and the gain at tonic firing onset increases. These results are consistent with previous experimental observations on guinea pig trigeminal motoneurons under serotonergic modulation (compare our Fig. 3A with Fig. 2F in Hsiao et al. 1997). In the absence of external current, increasing $g_{\text{NaP}}$ leads to tonic firing with a minimal firing rate of a few Hertz (Fig. 3C), which is consistent with the experimentally observed effects of the application of 5-HT$_2$ receptor agonist (Cramer et al. 2007). According to our model, enhancing $g_{\text{NaP}}$ increases the frequency of the peak of the suprathreshold resonance curve $f_{\text{max}}$ and enables firing at very high $f$ (Fig. 6B).

In guinea pig trigeminal and rat facial motoneurons, serotonin depolarizes the membrane potential and increases input resistance by reducing the potassium leak conductance, decreases the amplitude of medium afterhyperpolarization, decreases spike threshold, and enhances $I_{\text{h}}$ by depolarizing $\theta_1$ (Hsiao et al. 1997; Larkman and Kelly 1992). The resemblance between our modeling results and the experimental observations of Cramer et al. (2007) regarding vMN dynamics under serotonin application is consistent with the hypothesis that the main effect of serotonin on vMNs is $g_{\text{NaP}}$ enhancement. Whether serotonin affects other conductances in vMNs remains to be tested experimentally. In any case, experimentally observed serotonergic modulations of ionic conductances usually increase neuronal excitability and are thus expected to enhance the effects of $g_{\text{NaP}}$ elevation on the activities of vMNs.

vMN control by CPG and serotonin

Keller and colleagues (Cramer et al. 2007; Hattox et al. 2003) suggested that serotonin is both necessary and sufficient to generate rhythmic whisker movement, with additional input from an external CPG still being possible. We suggest a scheme that combines serotonergic modulation with small or moderate CPG input (Figs. 7–9). In this scheme, the CPG dictates the frequency and phase of whisking, whereas serotonin controls the long-time state (quiescent or active) of the system. Furthermore, the whisking amplitude, governed by the number of spikes per cycle, is controlled by both the CPG input and the serotonin level.

Our scheme resolves several questions posed by the hypothesis that vMNs fire in response only to serotonergic modulation.

1) What causes not only the unilateral and bilateral coordination of firing of vMNs that activate intrinsic muscles, but also the three-phase rhythm of contractions of extrinsic and intrinsic muscles (Hill et al. 2008)? According to the scheme, the CPG input, even if it is small, can coordinate the frequency and phase of vMN firing (Fig. 7C).

2) How can serotonergic modulation, which varies on a timescale of minutes (Fig. 1B in Cramer et al. 2007), control whisking on the timescale of 100 ms (Berg and Kleinfeld 2003)? This can be explained by fast switching between whisking modes as a result of fast modification of the CPG frequency $f$.

3) Why is the transition period from whisking to quiescence not characterized by low-rate (1–2 Hz) whisking? According to
the scheme, even with small CPG input, there is an abrupt transition from CPG-coordinated firing to a quiescent state.

4) How can a motoneuron burst (Cramer and Keller 2006)? The neuron can fire several spikes per input cycle. However, the CPG input should be strong and g_{NaP} should be sufficiently large (Figs. 7–9).

Our scheme can be compared with the experimental results of Cramer et al. (2007) and Hattox et al. (2003)) who revealed that infusion of serotonin receptor antagonists into the facial nucleus in vivo reduces the amplitude of voluntary whisking, but not its frequency. Furthermore, rhythmic whisking evoked by intracortical microstimulation of the rhythmic protraction region of motor cortex was suppressed by serotonin receptor antagonists. These results are consistent with our modeling result that increasing g_{NaP} switches the neuron from quiescence to firing (Figs. 7–9). Whisker movements evoked by stimulation of serotonergic premotor neurons in the LPGI were small and not rhythmic (Hattox et al. 2003). Based on our model, this would be expected upon elevating g_{NaP} in a population of heterogeneous motoneurons, each firing at its own frequency. In vitro, serotonin drives vMNs to fire at or below whisking frequency, as we found with our model (Fig. 3). Finally, the tonic activity of putative serotonergic premotoneurons recorded in vivo correlates positively with the frequency of whisking evoked by cortical microstimulation. In contrast, serotonin level controls the whisking amplitude in the model, whereas frequency is controlled by the CPG. This apparent contradiction can be resolved by assuming either that the CPG frequency is also modulated by the serotonergic level or that cortical output can modulate both CPG frequency and amplitude.

Predictions from the model

Our modeling work yields predictions that can be examined using whole cell recordings in brain stem slices that include the facial nucleus. We suggest that suprathreshold resonance curves have secondary peaks in addition to the global maximum. We predict that those peaks will be found in in vitro experiments on vMNs if the input frequencies are sampled in a sufficiently dense manner (e.g., with the ZAP input current; van Brederode and Berger 2008) and if the results of each resonance graph are computed from recording carried out on only a single neuron. Spike-firing resonance curves taken from hypoglossal neurons are consistent with this prediction (van Brederode and Berger 2008).

According to our result, suprathreshold resonance behavior is generated by adaptation currents. This prediction can be tested by blocking the M current (say, by linopirdine or XE991; Golomb et al. 2006b; Yue and Yaari 2004) and by blocking the AHP current using calcium chelators such as BAPTA. Blocking the M current, but not the AHP current, is expected to increase f_0, the input frequency above which the neuron is quiescent. In response to step currents, blocking the M current is expected to increase adaptation by reducing the ratio T_f/T. We also predict that the h-current does not have any significant effect on the suprathreshold resonance. This can be tested by blocking this current using cesium, ZD-7288 (Nguyen et al. 2004), or zatebradine (Pape 1994). In those experiments, it will also be possible to examine whether the minimal firing rate of vMNs in response to constant currents indeed increases with g_h.

Our computational work shows that the peak of the suprathreshold resonance curve f_{max} is shifted to the right by enhancing g_{NaP}. If g_{NaP} is partially blocked, we expect to obtain no firing for small or large input frequency f and firing only in an intermediate range of f. We suggest testing these predictions either by blocking g_{NaP} (e.g., by riluzole; Golomb et al. 2006b; or phenytoin; Su et al. 2001) or by enhancing it using dynamic clamp (Sharp et al. 1993). Our model yields another prediction related to g_{NaP}: in response to periodic input conductance, when g_{NaP} is increased just above firing threshold, the neuron fires in a locked manner to the periodic input even if its firing rate is small. This prediction can also be tested using dynamic clamp. In particular, it will be interesting to confirm that locking can occur in cases when the neuron fires near the troughs of the periodic input (Fig. 7D). Similar experiments can be carried out with the application of serotonergic agonists instead of increasing g_{NaP}.

A shift of the peak of the suprathreshold resonance curve to the right is also expected to occur when the baseline input I_0 or the modulation amplitude I_1 are enhanced. These experiments can be carried out by varying those input parameters.

A major conclusion of this study is that the firing frequency of the motoneuron population is determined by the external CPG. It will be possible to test this prediction in vivo in the future if the CPG is located, by recording from CPG neurons and relating the firing patterns of those neurons with the motion of the whiskers. Assuming that the CPG input turns out to be glutamatergic, it will be possible to block it partially to test the prediction that even weak CPG input controls the global firing frequency of the motoneuron population. It may also be possible to record from CPG neurons and from serotonergic premotor neuron and verify that their firing pattern is correlated, as expected from the outcome of both our modeling results and the experimental observation of Cramer et al. (2007). Moreover, it will be possible to examine whether CPG neurons are affected by serotonergic modulations using antagonists of serotonergic receptors (Hattox et al. 2003).

Our model predicts that intermittent behavior is possible for g_{NaP} values just above threshold (Fig. 7, C and D). In rats, M neurons innervate intrinsic muscles of a macrovibrissa, where M = 50–100 (Herfst and Brecht 2008; Klein and Rhoades 1985). If vMNs fire intermittently at 1:n mode, M/n neurons on average fire and stimulate muscle cells during each cycle and the ratio between the SD and the mean of the number of spiking neurons is (n/M)^{1/2}, which is 0.2 for n = 4 and M = 100. This ratio is comparable with the level of fluctuations of the protraction amplitudes and durations during certain whisking tasks (e.g., Gao et al. 2001). The possibility of intermittent firing during whisking can be tested by recording from vMNs of awake, head-fixed rats.

**APPENDIX A: BIFURCATION ANALYSIS OF THE EFFECT OF g_h ON EXCITABILITY CLASS**

The minimal firing rate f_{h,min} of our vMN model 0 is for g_h = 0 and is positive and increases with g_h for g_h > g_{h,min}. We explain this behavior
CONTROL OF VIBRISSA MOTONEURON FIRING

\[ f_R = -\frac{1}{2\pi} \int_{-\varepsilon}^{\varepsilon} \frac{f_{\text{inst}}(I_0)}{\sqrt{A^2 - I_0^2}} \, dI_0 + \frac{1}{2\pi} \int_{-\varepsilon}^{\varepsilon} \frac{f_{\text{inst}}(I_0)}{\sqrt{A^2 - I_0^2}} \, dI_0 \quad (B2) \]

where the first term in Eq. B2 relates to the decreasing half cycle of the input and the second term relates to the increasing half cycle of the input. According to Eq. B2, \( f_R \) is independent of \( f \). The same calculation can be extended to the case for which the instantaneous \( f_{\text{RC}} - I_0 \) is from class II and there is a regime of \( I_0 \) for which the neuron can either be quiescent or fire. In that case, the calculation of the first integral in Eq. B2 over the bistable \( I_0 \) interval is carried out for the firing branch of the \( f_{\text{RC}} - I_0 \) curve and the calculation of the second integral over the bistable interval is carried out for the quiescent branch of the \( f_{\text{RC}} - I_0 \) curve.

APPENDIX C: SUBTHRESHOLD RESONANCE

We compute the subthreshold resonance response of our vMN model to injection of low-amplitude sinusoidal current, quantified by the impedance \( |Z(f)| \) (Eq. 27) (Nguyen et al. 2004). A resonance with a peak at \( f_{\text{max}} = 5 \) Hz is shown (Fig. C1A). Blocking the \( h \) conductance, which eliminates the sag response to hyperpolarizing step currents (Fig. C1A, inset), considerably reduces the peak of the subthreshold resonance (Richardson et al. 2003). Additional blockade of the \( M \) current completely eliminates the resonance. Similarly, decreasing \( g_{\text{NaP}} \) (from its reference value) reduces the amplitude of the resonant peak (Fig. C1B). However, the effect of blocking \( g_{\text{NaP}} \) is

APPENDIX B: \( f_R \) IS CONSTANT FOR SMALL \( f \)

We suppose that the \( I_{\text{app}} = I_0 \cos(2\pi ft) \) and that the input frequency \( f \) is very small, such that for a time interval \( df \ll 1/f \), the firing frequency of the neuron is determined by the instantaneous \( f_{\text{RC}} - I_0 \) with a constant \( I_0 \). We denote the instantaneous value of \( f_{\text{RC}} \) for a fixed \( I_0 \) by \( f_{\text{inst}} \). We also assume that \( f_{\text{inst}} \) is uniquely determined by \( I_0 \), i.e., the neuron is from class I (Hodgkin 1948). The time-averaged firing rate \( f_R \), over the entire cycle, is given by

\[ f_R = \frac{1}{2\pi} \int_{-\varepsilon}^{\varepsilon} f_{\text{inst}}(I_0(t)) \, dt \quad (B1) \]

By changing variables, we obtain

\[ f_R = \frac{1}{2\pi} \int_{-\varepsilon}^{\varepsilon} f_{\text{inst}}(I_0) \, dI_0 \quad (B2) \]

FIG. C1. Effects of \( g_{\text{NaP}}, g_M \), and \( g_{\text{NaP}} \) on subthreshold resonance. A: subthreshold membrane impedance \(|Z(f)|\) (Eq. 27) normalized to \(|Z(0.1 \text{ Hz})|\) for: \( g_{\text{NaP}} = 0.05 \text{ mS/cm}^2 \), \( g_M = 1 \text{ mS/cm}^2 \), \( g_{\text{NaP}} = 0 \text{ mS/cm}^2 \), \( g_{\text{NaP}} = 0 \text{ (dashed line)} \). Inset: membrane potential response to an injection of a hyperpolarizing (1 mS/cm) step current. “Sag” response observed for \( g_{\text{NaP}} = 0.05 \text{ mS/cm}^2 \), but not \( g_{\text{NaP}} = 0 \text{ (blue line)} \). Impedance calculation made with an oscillatory current amplitude of \( I_1 = 0.01 \mu\text{A/cm}^2 \). B: subthreshold membrane impedance \(|Z(f)|\) normalized to \(|Z(0.1 \text{ Hz})|\) for \( g_{\text{NaP}} = 0 \text{ (dashed), 0.02 (dotted), and 0.04 (solid) mS/cm}^2 \).
less pronounced than that of blocking the h current. Our modeling results are consistent with the in vitro experiments of Nguyen et al. (2004), in which the vMNs exhibited subthreshold resonance with a maximal |Z(f)| around f_{res} = 5 Hz. As in our model, blocking the h current almost abolished the resonance experimentally.

Our work demonstrates that the subthreshold and suprathreshold resonances in response to strong periodic currents may be governed by different dynamic and ionic mechanisms. The h current substantially enhances the subthreshold resonance (Fig. C1B; Nguyen et al. 2004; Richardson et al. 2003), but modifies the suprathreshold resonance curve only weakly (Fig. 6A). Blocking $\text{Na}_P$ decreases the subthreshold resonance only moderately, but substantially narrows the suprathreshold resonance curve (Fig. 6B) because it prevents the neuron from firing at low $f$. However, this does not mean that ionic conductances may not exert similar effects on subthreshold and suprathreshold activity. For example, in the crayfish pyloric CPG, the membrane resonance of pacemaker neurons can correlate strongly with the CPG oscillation frequency (Takahashi and Nadim 2009).

For $I_s$ values near firing onset, the relationship between subthreshold and suprathreshold resonances may depend on the class of the neuron. For class II neurons without adaptation currents, suprathreshold resonance was found to be related to the subthreshold resonance (Izhikevich et al. 2003). Neurons from class I appear to have a resonance of their firing frequency that is set by the DC current $I_{\text{app}}$ (Brunberg and Gutkin 2007; Gutkin and Ermentrout 1998; Hunter et al. 1998; Laing and Longtin 2003). The current $I_{\text{app}}$ modulates both resonance behavior and reliability of spike timing (Schreiber et al. 2004).

Acknowledgments

We thank E. Ahissar and E. Simony for helpful discussions and C. Meunier and B. Schick for careful reading of the manuscript.

Grants

The research was supported by European Union Biomimetic Technology for Vibrissal Active Touch (BIOTACT) Grant ICT-215910, United States-Israel Binational Science Foundation Grant 2007121, and Israeli Science Foundation Grant 311/04.

Disclosures

No conflicts of interest are declared by the authors.

References


