Sensory-evoked perturbations of locomotor activity by sparse sensory input: a computational study

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Bui TV, Brownstone RM. Sensory-evoked perturbations of locomotor activity by sparse sensory input: a computational study. J Neurophysiol 113: 2824–2839, 2015. First published February 11, 2015; doi:10.1152/jn.00866.2014.—Sensory inputs from muscle, cutaneous, and joint afferents project to the spinal cord, where they are able to affect ongoing locomotor activity. Activation of sensory input can initiate or prolong bouts of locomotor activity depending on the identity of the sensory afferent activated and the timing of the activation within the locomotor cycle. However, the mechanisms by which afferent activity modifies locomotor rhythm and the distribution of sensory afferents to the spinal locomotor networks have not been determined. Considering the many sources of sensory inputs to the spinal cord, determining this distribution would provide insights into how sensory inputs are integrated to adjust ongoing locomotor activity. We asked whether a sparsely distributed set of sensory inputs could modify ongoing locomotor activity. To address this question, several computational models of locomotor central pattern generators (CPGs) that were mechanistically diverse and generated locomotor-like rhythmic activity were developed. We show that sensory inputs restricted to a small subset of the network neurons can perturb locomotor activity in the same manner as seen experimentally. Furthermore, we show that an architecture with sparse sensory input improves the capacity to gate sensory information by selectively modulating sensory channels. These data demonstrate that sensory inputs can alter the rhythm of locomotion indicates that sensory afferents can direct or indirect access to spinal locomotor rhythogenic centers; the identity of the neurons comprising these kernels, however, is not known. Understanding the density of the distribution of sensory afferents to these circuits thus serves at least three purposes: 1) to provide fundamental understanding of how sensory information shapes ongoing locomotor activity; 2) to assist in the identification of neurons involved in locomotor rhythogenesis; and 3) to provide some general insight into connectivity densities required to alter microcircuit activity.

In considering afferent input to rhythmogenic circuits, the simplest distribution would be one in which a given sensory input innervates every neuron that comprises a functional subset of the circuit (e.g., rhythm-generating subnetwork; “extensive distribution”; Fig. 1A). Another possibility is that the given sensory input innervates only a small portion of this population of neurons (“sparse distribution”; Fig. 1A). Extensive distribution of sensory inputs would ensure transmission of sensory information (a high safety factor) but in turn would have higher energy demands and would require extensive neural mechanisms to gate sensory transmission. On the other hand, sparse distribution could provide for “sensory channels” through which different sensory inputs (e.g., modalities) are processed by different components of the CPG (and thus lead to “sparse coding” in the circuit; Lin et al. 2014). These sensory channels could be more readily gated; however, the smaller number of sensory inputs might lead to failure of sensory transmission. Thus there are advantages and disadvantages to either extensive or sparse distribution of sensory inputs to motor circuits.

Activation of sensory input during ongoing locomotion can perturb the rhythm in a number of stereotypical manners, the exact nature of which depends on the experimental conditions, the animal preparation studied, the method of evoking loco-
Fig. 1. Sensory perturbation of a spinal central pattern generator (CPG). A: diagram depicting 2 hypothetical distributions of sensory inputs to the CPG of the spinal cord. In the extensive distribution, afferents from multiple sensory modalities (muscle afferents, blue and orange; cutaneous mechanoreceptors, green) project to every single member of the CPG. In the sparse distribution, afferents from multiple sensory modality project to different neurons of the CPG. B: diagram depicting the different types of perturbations evoked by activation of sensory inputs. Red bars depict locomotor bursts. Blue bars depict activation of sensory inputs. Dashed gray vertical bars depict onset of active phase in control situation (without sensory afferent input). i: Initiation: activation of sensory input during the quiescent phase of a locomotor cycle immediately initiates an active phase. ii: Delayed initiation: activation of sensory input during the active phase of a locomotor cycle eventually leads to the initiation of an active phase. iii: Prolongation: activation of sensory input during a quiescent phase of a locomotor cycle prolongs the duration of the active phase compared with control simulations. Note that the timing of the sensory input is such that it is active beyond the duration of the active phase in control simulations.

Motion, the strength of stimulation, and the phase of the locomotor cycle when sensory inputs are activated (Andersson et al. 1978; Conway et al. 1987; Duysens and Pearson 1980; Grillner and Rossignol 1978; Perreault et al. 1999; Quevedo et al. 2005a, 2005b; Schomburg et al. 1998; Stecina et al. 2005). The locomotor cycle is defined here as an active phase followed by a quiescent phase. Sensory-evoked perturbations of ongoing locomotor activity can be classified as initiation of a new locomotor cycle (sensory initiation) or prolongation of an ongoing active phase (sensory prolongation). Sensory initiation of a locomotor cycle is produced by the activation of sensory inputs during a quiescent phase, and it can occur either instantaneously after the stimulus (termed “initiation”; Fig. 1Bi; e.g., Guertin et al. 1995) or with a delay of tens to hundreds of milliseconds (termed “delayed initiation”; Fig. 1Bii; e.g., Guertin et al. 1995, Quevedo et al. 2005a, 2005b). Sensory prolongation is produced when the activation of sensory inputs during an active phase lengthens the duration of that active phase (termed “prolongation”; Fig. 1Biii; e.g., Guertin et al. 1995). When there is initiation or prolongation, the perturbations can be further classified as phase resetting or nonresetting based on whether there is an observed change in the timing of subsequent cycles (Frigon 2012; Rybak et al. 2006; Schomburg et al. 1998; Stecina et al. 2005). Thus sensory stimulation can affect the locomotor cycle in a number of ways.

We used computational modeling to test whether sparsely distributed sensory inputs to spinal CPGs could generate the range of sensory-evoked perturbations that has been experimentally observed. As the structure of locomotor CPGs has not been defined (Brocard et al. 2010; Brownstone and Wilson 2008; Harris-Warrick 2010), we applied sparsely distributed sensory inputs to a diverse set of computational models of locomotor CPGs. In all models tested, sparsely distributed sensory input produced perturbations of locomotor activity similar to those experimentally observed. Having established that sparse sensory inputs could perturb activity within a CPG, we next showed that sparse distribution facilitated the selective gating of sensory inputs to the CPG. The results of this computational study demonstrate that sensory inputs to spinal locomotor networks need only project sparsely to the circuitry involved in generating rhythm. This sparse sensory representation has consequences for the capacity of sensory inputs to affect locomotor activity and may assist in the identification of neurons involved in rhythmogenesis.

METHODS

Models were built and simulated with the NEURON simulation environment.

Single-neuron models. Each neuron was modeled as a multicompartmental model. The soma was modeled as a single cylindrical compartment with a length and diameter of 12.6 μm (surface area = 500 μm²). Each neuron had three unbranched dendrites. Each dendrite was 100 μm long and 1.25 μm in diameter. The axon consisted of an axon hillock (length = 10 μm, diameter = 1.5 μm), an initial segment (length = 10 μm, diameter = 1.0 μm), and an axon that was 200 μm long with a diameter of 0.5 μm. Each compartment was discretized into a number of adjoining compartments, the number of which was determined by NEURON using the d_lambda rule with a value of d_lambda = 0.1.

For all compartments except the axon, the following passive membrane properties were assigned. Axial resistivity was assigned a randomly selected value from a Gaussian distribution with a mean of 100 Ω·cm and a standard deviation of 5 Ω·cm. Specific membrane capacitance was assigned a value of 1 μF/cm². The specific membrane conductance was assigned a randomly selected value from a Gaussian distribution with a mean of 6.6 × 10⁻⁴ S/cm² and a standard deviation of 5.0 × 10⁻⁵ S/cm². For the axon, axial resistivity was assigned a value of 100 Ω·cm, specific membrane capacitance was assigned a value of 0.0001 μF/cm², and the specific membrane conductance was assigned a value of 0.1 μS/cm². For all neurons, resting membrane potential was set at −65 mV.

Calcium diffusion was modeled as described in Booth et al. (1997). Internal calcium concentration is calculated from the following differential equation:

$$\frac{dCa_i}{dt} = P_{free}(-\alpha i_{Ca} - k_{Ca}Ca_i)$$

where $P_{free}$ is the percentage of free calcium to bound calcium and was set to 0.001; $\alpha$ is the total calcium current [in mol/(μm × C)],

$\frac{dCa_{free}}{dt} = \frac{dCa_i}{dt} - \frac{dCa_{bound}}{dt}$

$\frac{dCa_{bound}}{dt} = k_{Ca}Ca_i - \frac{dCa_{free}}{dt}$

$\frac{dCa_{total}}{dt} = \frac{dCa_{free}}{dt} + Ca_{bound}$

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where $Ca_{free}$ is the free calcium concentration, $Ca_{bound}$ is the bound calcium concentration, and $Ca_{total}$ is the total calcium concentration [in mol/(μm × C)].

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$Ca_{free}$ is the free calcium concentration, $Ca_{bound}$ is the bound calcium concentration, and $Ca_{total}$ is the total calcium concentration [in mol/(μm × C)].
where for current $i$, $g_{\text{max},i}$ represented the peak conductance and the variables $m_i$, $h_i$ were the activation and inactivation variables, respectively. $E_{\text{Na}}$, $E_{\text{K}}$, and $E_{\text{Ca}}$ represented the reversal potential for sodium, potassium, and calcium currents, respectively. The $L$-type Ca$^{2+}$ current was only present in a set of simulations testing the selective gating of sensory inputs (see Fig. 7A).

For the strictly voltage-dependent active currents, the activation and inactivation variables, $m$ and $h$, were described by the following differential equations:

$$\tau_m(V) \frac{dm_i}{dt} = m_{\text{max}}(V) - m_i$$

$$\tau_h(V) \frac{dh_i}{dt} = h_{\text{max}}(V) - h_i$$

where for current $i$, $m_{\text{max}}(V)$ and $h_{\text{max}}(V)$ were the voltage dependent steady-state activation and inactivation, respectively, and $\tau_m(V)$ and $\tau_h(V)$ were the time constant of activation and inactivation, respectively. The equations for the activation and inactivation variables and the time constants of activation and inactivation are given in Table 1. The values for the different $g_{\text{max},i}$ in the pacemaker model are given in Table 2.

The tonic NMDA current was modeled as a sum of a calcium and a sodium current whose magnitude depended on a voltage-dependent magnesium block, $mg_{\text{block}}$.

$$I_{\text{NMDA,tonic}}(V) = mg_{\text{block}}(V) \left( 0.7 g_{\text{max,NMDA}}(V - E_{\text{Ca}}) + 0.3 g_{\text{max,NMDA}}(V - E_{\text{Na}}) \right)$$

$$mg_{\text{block}}(V) = \frac{1}{1 + e^{-(V - E_{\text{Mg}})/4}}$$

Tonic-firing neurons. The second class of CPG network that we studied was composed of excitatory neurons that did not fire bursts of action potentials when driven by tonically active glutamatergic synapses. These neurons, named tonic-firing neurons, had a subset of the active currents used to model pacemaker neurons, although the maximal conductances were changed (see Table 2). Oscillatory bursting within this network was driven by synaptic depression and synaptic inhibition between two subnetworks of excitatory tonic-firing neurons. The excitatory synapses in this model included synaptically depressing currents that are described in Network topology.

Sensory afferents. Sensory inputs were modeled as presynaptic fibers that fired at a uniform rate of 100 Hz and were activated for durations of 200 ms.

Network topology. In the pacemaker network, 10 pacemaker neurons were connected in a circular configuration in a wheel-and-spoke arrangement with each pacemaker neuron connected to its clockwise neighbor and the neuron that was diametrically opposite (its fifth-furthest neighbor) such that

$$\{\text{Neuron}_i,\text{output}\} = \{\text{Neuron}_{(i+1) \mod 10}, \text{Neuron}_{(i+5) \mod 10}\}, i = 0 \ldots 9$$

Each postsynaptic neuron receives eight glutamatergic synapses that evoked AMPA and NMDA currents. The eight synapses were uniformly distributed over one dendritic branch of the postsynaptic neuron.

Two glutamatergic sensory afferent fibers connected to this network, targeting $\text{Neuron}_0$ and $\text{Neuron}_c$. Each afferent fiber projected five glutamatergic synapses that evoked AMPA and NMDA currents in the postsynaptic neuron. The five synapses were uniformly distributed over one dendritic branch of the postsynaptic neuron.

Each neuron received a glutamatergic synapse from a tonic source of excitation (“command” neurons), firing at 100 Hz. This synapse was located at the neuron body, and it activated AMPA and NMDA currents.

In the tonic-firing neuron network, two clusters (or “half-centers”) of tonic-firing excitatory neurons were reciprocally connected to each other via two inhibitory neurons. Each cluster consisted of 10 tonic neurons that were connected to 3 other neurons: its clockwise neighbor, the fourth-furthest, and the seventh-furthest neighbor, such that

$$\{\text{Neuron}_i,\text{output}\} = \{\text{Neuron}_{(i+1) \mod 10}, \text{Neuron}_{(i+4) \mod 10}, \text{Neuron}_{(i+7) \mod 10}\}, i = 0 \ldots 9$$

Each postsynaptic neuron received eight glutamatergic synapses that evoked AMPA and NMDA currents. The eight synapses were uniformly distributed over one dendritic branch of the postsynaptic neuron.

There were three glutamatergic afferent fibers connected to the “agonist” cluster of excitatory neurons. They targeted $\text{Neuron}_p$, $\text{Neuron}_o$, and $\text{Neuron}_c$ of the “agonist” half-center. These excitatory synapses activated AMPA and NMDA currents. Each afferent fiber projected five glutamatergic synapses that evoked AMPA and NMDA currents in the postsynaptic neuron. The five synapses were uniformly distributed over one dendritic branch of the postsynaptic neuron.

Each excitatory tonic-firing neuron received one glutamatergic synapse from two tonic sources of excitation (“command” neurons). Unlike for the pacemaker model, each tonic source of excitation was modeled as a Poisson process with mean intervals of 41 ms (mean frequency of 24.4 Hz) and 42 ms (mean frequency of 23.8 Hz), respectively. The interval between spikes consisted of a fixed interval of duration $(1 - 0.25) \times \text{mean interval}$ plus a negative exponential interval of mean duration $0.25 \times \text{mean interval}$. In other words, the probability density function for the tonic source of excitation with mean interval of 41 ms was $0 \times (0.75 \times 41 \text{ ms})$ after the previous spike and $[1/(41 \text{ ms} - 31 \text{ ms})] \exp(- (t - 41 \text{ ms})/41 \text{ ms})$ for $t \geq 31 \text{ ms}$. These synapses were located at the soma, and they activated AMPA and NMDA currents. To facilitate the generation of an alternating rhythm between the two half-centers, the tonic glutamatergic drives to the two half-centers of excitatory neurons were asymmetrically distributed such that the “antagonist” half-center had a 2% smaller current (Brownstone and Wilson 2007; Yakovenko et al. 2005).

Each inhibitory neuron received an excitatory synaptic input located at the soma from one of the tonic-firing neurons of its respective half-center, while targeting every excitatory neuron of the other half-center, thus producing reciprocal inhibition between each cluster. The excitatory synapses activated AMPA and NMDA currents in the inhibitory neurons. The inhibitory neurons activated GABAergic currents on the neuron body.
**Synaptic currents.** Glutamatergic synaptic transmission activated two types of currents: AMPA-type currents and NMDA-type currents. In the pacemaker network models, AMPA-type currents were modeled as the product of the driving force \( (V - 0 \text{ mV}) \), a synaptic weight (see Table 3 for synaptic weights of different models), and an alpha-function-like conductance whose time course is described as

\[
G_{\text{AMPA}}(t) = e^{-\frac{t}{0.5\text{ms}}} - e^{-\frac{t}{3\text{ms}}}
\]  
(13)

This current was implemented as Exp2Syn in the NEURON software. In the tonic-firing neuron network model, AMPA-type currents were modeled as depressing currents \( G_{\text{AMPA,dl}} \) as described by the following equations:

\[
G_{\text{AMPA,dl}}(t) = B - A
\]  
(14)

\[
\frac{dA}{dt} = \frac{A}{\tau_a}
\]  
(15)

\[
\frac{dB}{dt} = \frac{B}{\tau_b}
\]  
(16)

where \( \text{syn}_{w_{ij}} \) is the weight of the synaptic connection from presynaptic axon \( i \) to postsynaptic neuron \( j \), \( \tau_a = 1 \text{ ms} \), and \( \tau_b = 1.05 \text{ ms} \). \( G_{1_{ij}} \) is the fractional change of \( \text{syn}_{w_{ij}} \) at \( t = 0 \) of the simulation. For every incoming synaptic event that occurs within 200 ms of a previous event, \( G_{1_{ij}} \) decayed exponentially according to the equation

\[
G_{1_{ij}}(t) = G_{1_{ij}}(t_{p_{ij}}) - G_{1_{ij}}(t_{p_{ij}})\left(1 - e^{-\frac{t-t_{p_{ij}}}{\tau_{b_{ij}}}}\right)
\]  
(21)

### Table 1. Steady-state activation and inactivation variables and time constants for voltage-dependent currents

<table>
<thead>
<tr>
<th>Ionic Currents</th>
<th>Activation and Inactivation Variables: ( m_{\pm}(V) ) and ( h_{\pm}(V) ), mV</th>
<th>Time Constants: ( \tau_{m_{\pm}}(V) ) and ( \tau_{h_{\pm}}(V) ), ms</th>
</tr>
</thead>
</table>
| \( I_{\text{Ca,L}} \) | \[
m_{\text{Ca,L}} = \frac{1}{1 + e^{\frac{V - (-30)}{6}}}, \quad h_{\text{Ca,L}} = 1 - \frac{C_{B}}{C_{a} + 0.1\mu M}
\]  | \( \tau_{m_{\text{Ca,L}}} = 20 \), \( \tau_{h_{\text{Ca,L}}} = 3,000 \) |
| \( I_{\text{Ca,T}} \) | \[
m_{\text{Ca,T}} = \frac{1}{1 + e^{\frac{V - (-50)}{7.4}}}, \quad h_{\text{Ca,T}} = \frac{1}{1 + e^{\frac{V - (-70)}{5}}}
\]  | \( \tau_{m_{\text{Ca,T}}} = 3 + \frac{1}{e^{\frac{V - (-35)}{10}} + e^{\frac{V - (-100)}{15}}} \), \( \tau_{h_{\text{Ca,T}}} = 85 + \frac{1}{e^{\frac{V - (-40)}{10}} + e^{\frac{V - (-400)}{15}}} \) |
| \( I_{\text{K,DR}} \) | \[
a = 0.032\frac{V - (-40)}{1 - e^{\frac{V - (-40)}{5}}}, \quad b = 0.5e^{-\frac{V - (-40)}{40}}
\]  | \( \tau_{m_{\text{K,DR}}} = 4.7 \frac{a + b}{a} \) |
| \( I_{\text{Na,P}} \) | \[
m_{\text{Na,P}} = \frac{1}{1 + e^{\frac{V - (-54)}{3.1}}}, \quad h_{\text{Na,P}} = \frac{1}{1 + e^{\frac{V - (-25)}{b}}}
\]  | \( \tau_{m_{\text{Na,P}}} = 1 \), \( \tau_{h_{\text{Na,P}}} = \frac{2,000}{\cosh\left(\frac{V - (-45)}{16}\right)} \) |
| \( I_{\text{Na,T}} \) | \[
a = 0.32\frac{V - (-47)}{1 - e^{\frac{V - (-47)}{4}}}, \quad b = 0.28\frac{V - (-10)}{e^{\frac{V - (-10)}{5}} - 1}
\]  | \( \tau_{m_{\text{Na,T}}} = \frac{4.7}{a + b} \), \( \tau_{h_{\text{Na,T}}} = \frac{4.7}{c + d} \) |

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Table 2. Maximal conductances for the different models

<table>
<thead>
<tr>
<th>Network</th>
<th>Neuron</th>
<th>Structure</th>
<th>Maximal Conductance</th>
<th>Value, S/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacemaker network</td>
<td>Pacemaker neuron</td>
<td>Soma</td>
<td>g_{max, Ca,T}</td>
<td>3.0 × 10^{-3}</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>g_{max, K,dr}</td>
<td>3.0 × 10^{-4} ± 2.0 × 10^{-2}</td>
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<td></td>
<td></td>
<td></td>
<td>g_{max, Na,P}</td>
<td>2.0 × 10^{-6}</td>
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<td></td>
<td></td>
<td></td>
<td>g_{max, Na,T}</td>
<td>4.0 × 10^{-7} ± 2.0 × 10^{-2}</td>
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<tr>
<td></td>
<td></td>
<td>Initial segment</td>
<td>g_{max, NM1D tonic}</td>
<td>2.0 × 10^{-2} (S)</td>
</tr>
<tr>
<td>Tonic-firing neuron network</td>
<td>Excitatory neuron</td>
<td>Soma</td>
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<td>3.0 × 10^{-4} ± 2.0 × 10^{-2}</td>
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<td></td>
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<td>4.0 × 10^{-7} ± 2.0 × 10^{-2}</td>
</tr>
<tr>
<td>Gap junction-coupled network</td>
<td>Pacemaker neuron</td>
<td>Soma</td>
<td>g_{max, Ca,T}</td>
<td>1.0 × 10^{-3}</td>
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<td>Initial segment</td>
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<td>Fifty-neuron pacemaker network</td>
<td>Pacemaker neuron</td>
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<td>Initial segment</td>
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<td>2.0 × 10^{-6} (S)</td>
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<tr>
<td>Hybrid pacemaker- tonic neuron network</td>
<td>Pacemaker neuron</td>
<td>Soma</td>
<td>g_{max, Ca,T}</td>
<td>2.0 × 10^{-1}</td>
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<td>g_{max, NM1D tonic}</td>
<td>2.0 × 10^{-1}</td>
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<tr>
<td>Tonic-firing neuron</td>
<td>Soma</td>
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<td>2.0 × 10^{-3}</td>
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\( \tau_{G1,d} = 300 \text{ ms} \) and was the time constant of decay of \( G1_{i,j} \), \( t_{p,j} \) was the time of occurrence of the last synaptic event from presynaptic axon \( i \) to postsynaptic neuron \( j \). For every incoming synaptic event that occurs after at least 200 ms from the previous event, \( G1_{i,j} \) returned back to 1 according to the equation

\[
G1_{i,j}(t) = 1 - e^{-t_{p,j} - t_{G1,d} / \tau_{G1,d}}
\]

(22)

\( \tau_{G1,d} = 6,000 \text{ ms} \) and was the time constant of facilitation of \( G1 \). NMDA currents were taken from a NEURON model (Destexhe et al. 1994) and modified by Migliore and Shepherd (2008).

Similarly to the AMPA currents, GABAergic currents were modeled as double exponential functions that undergo synaptic depression and facilitation (Durstewitz and Seamans 2002).

\[
g_{\text{GABA}}(t) = D - C
\]

(23)

\[
\frac{dD}{dt} = - \frac{D}{\tau_d} \quad (24)
\]

\[
\frac{dC}{dt} = - \frac{C}{\tau_c} \quad (25)
\]

\[
\tau_c = \frac{\tau_c \tau_d}{\tau_d - \tau_c} \quad (26)
\]

With each incoming postsynaptic event, the variables \( C \) and \( D \) were modified according to the following equations:

\[
u_{ij}(t) = 0.3 + 0.7 u_{ij} e^{-t_{p,j} / 800 \text{ ms}} \quad (27)
\]

\[
R_{ij}(t) = 1 + (R_{ij} - 1) e^{-t_{p,j} / 800 \text{ ms}} \quad (28)
\]

\[
y = \text{syn}_n w_{ij} \tau_i R_{ij} H_{ij} \quad (29)
\]

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where \( \text{syn}_{w_{ij}} \) was the weight of the synaptic connection from presynaptic axon \( i \) to postsynaptic neuron \( j \). \( u_{ij} \) and \( R_{ij} \) were the fractional changes of this weight and represented synaptic facilitation and depression, respectively. \( R_{ij} = 1 \) and \( u_{ij} = 0.3 \) at time \( \theta \) of the simulation. \( t_{p_{ij}} \) was the time of occurrence of the last synaptic event from presynaptic axon \( i \) to postsynaptic neuron \( j \).

Gap junctions were modeled as ohmic resistors with values assigned according to a Gaussian distribution with a mean value of \( 2.0 \times 10^3 \ \text{M\Omega} \) and a standard deviation of \( 500 \ \text{M\Omega} \).

Simulation parameters. Each network simulation consisted of 10,000-ms-long simulations unless otherwise noted. The times at which action potentials were fired were collected. To measure the population activity, the numbers of action potentials fired by the clusters of excitatory neurons were binned in 50-ms time bins and summed to produce cumulative sums of action potential firing that can be considered as pseudo-electroneurogram recordings.

RESULTS

Extensive distribution of sensory inputs. To ensure that our networks could reliably produce initiation and prolongation, we first tested the baseline condition of sensory inputs that were extensively distributed across rhythmogenic networks composed of either pacemaker or tonic-firing neurons. In both models, sensory inputs were capable of initiating a new cycle or prolonging an ongoing cycle. In tonic networks a delayed initiation of a new cycle was not observed, whereas in pacemaker networks delayed initiation could be observed (data not shown). Thus our models could successfully emulate experimental findings in this baseline condition.

Pacemaker network. We next asked whether sparsely distributed sensory inputs could generate the various perturbations of ongoing locomotor activity that have been described (Fig. 1). The details of how the spinal cord generates locomotor activity remain in question (Brocard et al. 2010; Brownstone and Wilson 2008; Harris-Warrick 2010). Specifically, it is not known whether the rhythm is generated by neurons that can burst in isolation (pacemaker neurons) or neurons that only burst as a consequence of network connectivity. As such, we first modeled the spinal CPG as a set of recurrently connected excitatory pacemaker neurons (Fig. 2). Ten pacemaker neurons were connected in a wheel-and-spoke configuration (Fig. 2A), with each neuron connected to one immediate neighbor as well as its diametrically opposite neighbor. Each neuron was modeled with multiple compartments with three passive dendrites over which synaptic inputs were distributed and a soma and an axon both with distributed active conductances (Fig. 2B). A persistent riluzole-sensitive sodium current (\( I_{\text{Na,P}} \)) was incorporated into our model (Tazerart et al. 2008; Zhong et al. 2007). The density of \( I_{\text{Na,P}} \) was adjusted such that the neurons could convert a tonically active glutamatergic drive from “command” neurons into rhythmic output in the absence or in the presence of recurrent excitatory connections (Fig. 2C). In this configuration, the cycle period was \( \sim 1,200-1,300 \) ms and the duration of the active phase was in the range of 400–500 ms (Fig.

<table>
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<tr>
<th>Network</th>
<th>Presynaptic Neuron</th>
<th>Postsynaptic Neuron</th>
<th>Synaptic Weight, S</th>
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<tr>
<td>( I_{\text{Na,P}} )-dependent pacemaker network</td>
<td>Pacemaker neuron</td>
<td>Pacemaker neuron</td>
<td>AMPA = ( 1.0 \times 10^{-4} )</td>
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<td>Sensory afferent</td>
<td>Pacemaker neuron</td>
<td>AMPA = ( 2.5 \times 10^{-4} ), ( 3.0 \times 10^{-5} ) (for delayed initiation only)</td>
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<td>NMDA = ( 7.5 \times 10^{-5} ), ( 9.0 \times 10^{-6} ) (for delayed initiation only)</td>
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<td>Tonic-firing neuron network</td>
<td>Tonic-firing neuron</td>
<td>Tonic-firing neuron</td>
<td>AMPA = ( 8.5 \times 10^{-4} )</td>
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<td>NMDA = ( 1.7 \times 10^{-4} )</td>
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<td></td>
<td>Sensory afferent</td>
<td>Tonic-firing neuron</td>
<td>AMPA = ( 4.0 \times 10^{-5} ), ( 5.0 \times 10^{-6} ) (for delayed initiation only)</td>
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<td>NMDA = ( 8.0 \times 10^{-5} ), ( 1.0 \times 10^{-6} ) (for delayed initiation only)</td>
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<td>Tonic excitatory drive</td>
<td>Tonic-firing neuron</td>
<td>AMPA = ( 9.0 \times 10^{-3} )</td>
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<td>NMDA = ( 1.8 \times 10^{-3} )</td>
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<td>Tonic-firing neuron</td>
<td>Inhibitory neuron</td>
<td>AMPA = ( 5.0 \times 10^{-2} )</td>
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<td>NMDA = ( 1.0 \times 10^{-2} )</td>
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<td>Inhibitory neuron</td>
<td>Tonic-firing neuron</td>
<td>GABA = 1.5</td>
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<td>Gap junction-coupled network</td>
<td>Pacemaker neuron</td>
<td>Pacemaker neuron</td>
<td>( R_{\text{gap}} = 2.0 \times 10^3 \pm 500 \ \text{M\Omega} )</td>
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<td></td>
<td>Sensory afferent</td>
<td>Pacemaker neuron</td>
<td>AMPA = ( 2.5 \times 10^{-4} ), ( 5.0 \times 10^{-5} ) (for prolongations)</td>
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<td>NMDA = ( 7.5 \times 10^{-5} ), ( 1.5 \times 10^{-6} ) (for prolongations)</td>
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<td>Fifty-neuron ( I_{\text{Na,P}} )-dependent pacemaker</td>
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<td>AMPA = ( 9.0 \times 10^{-4} )</td>
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<td>Sensory afferent</td>
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<td>NMDA = ( 3.0 \times 10^{-4} ), ( 7.5 \times 10^{-6} ) (for delayed initiation only)</td>
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<td>Hybrid pacemaker-tonic neuron network</td>
<td>Pacemaker neuron</td>
<td>Pacemaker neuron</td>
<td>AMPA = ( 2.0 \times 10^{-3} )</td>
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<td>NMDA = ( 6.6 \times 10^{-4} )</td>
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<td>Pacemaker neuron</td>
<td>Tonic neuron</td>
<td>AMPA = ( 3.6 \times 10^{-4} )</td>
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<td>NMDA = ( 1.2 \times 10^{-4} )</td>
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<td>Pacemaker neuron</td>
<td>Sensory afferent</td>
<td>AMPA = ( 1.0 \times 10^{-4} )</td>
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We then activated two sensory fibers targeting two diametrically opposed neurons at 100 Hz for 200 ms. When the sensory input was activated during a quiescent phase, a new active phase was immediately initiated, resulting in a single shorter cycle period (Fig. 2E). Reducing the synaptic weight of the sensory input could result in the delayed initiation of a new active phase (Fig. 2F). Note that the cycle period returned to the control cycle period, with subsequent active phases being phase advanced. Thus the sensory initiations observed in this model were of the phase-resetting type.

Fig. 2. Sensory perturbations of a CPG composed of pacemaker neurons by sparse sensory input. A: diagram of recurrent network modeled. B: description of ligand-gated receptors and active conductances incorporated in each neuron model. C: firing pattern of a single neuron during simulations where the neuron is isolated from other neurons or connected in a recurrent network. D: raster plot of firing of each neuron during a 10-s run. Bottom left: cumulative sum of the action potentials fired by the 10 neurons in the network. Bin size of 50 ms. Bottom right: cycle period for the cycles depicted. E–G: Sensory-evoked perturbations by sparse sensory input (light blue bar). Left: cumulative sums of the network activity by sensory activity. The pale red trace in E–G depicts the network activity in the absence of sensory activity, which is also depicted in D. Right: cycle period for the cycles depicted. E: initiation. F: delayed initiation. G: prolongation. Length and thickness of light blue bar above cumulative sums indicate time and relative weight of sensory activation.
To estimate the functional strength of the sensory input underlying an immediate initiation of a locomotor cycle versus a delayed initiation, we measured the number of action potentials evoked in synaptically isolated neurons by sensory inputs of different weights. Sensory inputs of weights that evoked zero to four action potentials were incapable of generating any type of initiation of a new locomotor cycle. Weights of sensory input capable of generating a delayed initiation were observed to evoke five or six action potentials. Sensory inputs capable of evoking more than seven action potentials evoked immediate initiation of a new locomotor cycle. We note that by synaptically isolating neurons within this network we are increasing the input resistance of neurons due to an absence of synaptic conductances, so this analysis is done to provide a relative sense of the magnitude of sensory input required for immediate versus delayed initiation.

Activation of sensory inputs during an ongoing active phase as opposed to activation during a quiescent phase led to prolongation of the active phase (Fig. 2G). Subsequent active phases were phase-shifted to occur later than in control simulations (i.e., prolongation with phase-resetting). Activation of sensory inputs could lead to network activity of greater magnitude than those seen during unperturbed locomotor activity, as evidenced by larger peaks during bursts of activity (e.g., Fig. 2E). While this indicates that sensory inputs drove the network to a greater level of activity, this was not a necessary condition for perturbing locomotor activity by sparse sensory inputs (e.g., Fig. 2, F and G). Overall, the above results show that sparsely distributed sensory inputs to a CPG network consisting of pacemaker neurons can affect network activity to initiate a new active phase or prolong an ongoing active phase.

**Rhythmogenic network of tonic excitatory neurons.** We next modeled a network in which synaptically driven events rather than intrinsic pacemaking properties (Del Negro et al. 2010) drove the rhythm and tested the ability of sparsely distributed sensory inputs to perturb ongoing locomotor activity in these systems. Tonically active neurons (tonic neurons) were modeled with no T-type Ca\(^{2+}\) current or tonic NMDA current and very little \(I_{\text{Na,p}}\). In response to two quasi-random glutamatergic inputs from “command” neurons, these neurons fired in a random fashion when all other synaptic inputs were absent (Fig. 3B). Regular rhythmic activity resulted from a network architecture consisting of two half-centers (Brown 1911) composed of recurrently connected excitatory neurons with synthetically depressing glutamatergic synapses and interconnected by reciprocal inhibition (Fig. 3A). The network was driven by the two quasi-random glutamatergic inputs from “command” neurons, and the summation of excitatory postsynaptic potentials (EPSPs) from these two processes could initiate active phases and hence rhythmic activity. Within this network architecture all neurons fired rhythmically in response to the drive from “command” neurons (Fig. 3C). In a 20,000-ms run, the cycle periods ranged from 1,200 ms to 2,300 ms and the burst periods ranged from 300 ms to 1,100 ms. Thus the nonpacemaker model also produced rhythmic activity, although the cycle periods were more variable than those in the pacemaker model.

We next tested the effects of sensory inputs on this rhythm and found that the number of sparse sensory inputs needed to be increased from two to three in order to be able to perturb locomotor activity (Fig. 3, C–F). As was observed in the pacemaker network, immediate initiation of a new locomotor cycle could be generated (Fig. 3D), and reducing the sensory synaptic weight could generate a delayed initiation (Fig. 3E). Whether the sensory input produced immediate or delayed initiation depended on the timing of the action potential produced. If the input produced an immediate action potential in target neurons, then immediate initiation was seen. On the other hand, if a number of sensory-evoked EPSPs summed to produce a delayed action potential, then the subsequent initiation of a new locomotor cycle was also delayed (data not shown). Also, as with the simulations of the pacemaker network, these initiations were accompanied by phase-resetting. In addition, sensory stimuli during an active phase were capable of prolonging that phase (Fig. 3F). These simulation results demonstrate that sparse sensory inputs can also perturb ongoing locomotor activity generated by a recurrent network of excitatory, nonpacemaker neurons.

While initiation and prolongation were seen in both of the above models, for the remaining simulations rhythmic locomotor activity was generated by pacemaker neurons.

**Gap junction-coupled network.** Evidence of gap junctions between spinal interneurons has been reported (Wilson et al. 2007; Zhong et al. 2010). To ensure that our results were not dependent upon the choice of modeling synaptic connections as being chemical in nature, we modified the CPG model of pacemaker neurons by converting all network connections to symmetrical gap junctions (Fig. 4A). The value of the gap junction conductance was adjusted to allow the network to generate rhythmic activity. Sensory inputs continued to be modeled as chemical synapses. We found that activation of sensory inputs to this gap junction-connected network was able to initiate a new cycle or prolong an ongoing locomotor cycle (Fig. 4, B–D). However, while sensory inputs could initiate a new burst when applied during a quiescent phase, the initiation was always immediate. While reducing the synaptic weighting of the sensory input in the two preceding models could generate a delayed initiation (Fig. 2F and Fig. 3E), it could never do so in this gap junction-connected network. This is perhaps due in part to the rapidity of electrical conduction versus chemical transmission.

In this model comprised of neurons connected only through gap junctions, the coupling coefficient between neurons was \(-0.3\), which is somewhat higher than experimental measures of \(-0.1\) (e.g., Haas et al. 2011). We then reduced this coefficient to 0.1 (through a 10-fold increase in the mean resistance of the gap junctions) and found that a concomitant increase in the number of postsynaptic targets of each neuron (from 2 to 3) was required in order for sensory inputs to perturb locomotion. In this modified model sensory input was able to initiate a new cycle or prolong an ongoing locomotor cycle, but, similar to the model with a higher coupling coefficient, delayed initiation was not seen. The peak of the network activity following initiation of a new cycle was at most delayed by 50 ms from onset of sensory input; data not shown.) Therefore, sparse sensory inputs can also modify ongoing locomotor activity driven by an electrically coupled network; however, the perturbations are immediate.

**Fifty-neuron network.** So far, we have shown that in simulations of networks of 10 recurrently connected excitatory neurons sparse (projecting to \(20–30\%\) of excitatory neurons) sensory inputs were able to perturb locomotor activity by either...
initiating or prolonging active phases. To verify that this is not solely a feature of modeling the CPG with a small number of neurons, we modeled the CPG as a network of 50 recurrently connected excitatory neurons. Similar to the above models, each neuron was connected to one neighbor and the neuron diametrically opposed (Fig. 5A). Five sensory inputs projected to this network (i.e., 10% of the population of this CPG). This network was driven by tonically active glutamatergic drive (Fig. 5B). The cycle period ranged from 1,350 to 1,800 ms ($n = 5$ cycles), and the active phase ranged from 400 to 950 ms ($n = 6$ cycles). In this larger network, activation of the sensory inputs produced both initiation and delayed initiation when activated during a quiescent phase and prolongation when activated during an active phase (Fig. 5, C–F). Delayed initiation was not accompanied by phase-resetting. This was the only model in this study in which this did not occur, suggesting that larger networks are less susceptible to phase-resetting and would require a greater change in network activity to sustain a change in phase. Overall these simulations suggest that sparse (10%) sensory inputs can indeed perturb locomotor activity generated by large networks of neurons.

**Hybrid pacemaker-tonic network.** Having considered locomotor networks composed of homogeneous excitatory neurons, we next asked whether sparsely distributed inputs would affect a heterogeneous CPG network (Carroll and Ramirez 2013) differently depending on whether the inputs targeted pacemaker or nonpacemaker neurons. A population of spinal neurons proposed to be involved in spinal rhythmogenesis consists of intrinsic pacemakers and nonpacemakers (Dyck et al. 2012). We tested a network combining two pacemaker
neurons and eight tonically firing neurons. We arranged the neurons in a circular configuration with the two pacemaker neurons diametrically opposite to each other and projecting in a clockwise direction to the four next neurons and the tonic-firing neurons contacting their nearest clockwise neighbor only (Fig. 6A). The synaptic strength of the output of the two pacemaker neurons was three times greater than that of the tonic-firing neurons to allow the pacemaker neurons to have greater driving force on network activity. This network operated under a tonically active glutamatergic drive. The tonic NMDA current that was incorporated in models of pacemaker neurons above was removed such that both pacemaker and tonic neurons received the same glutamatergic drive. As expected, in isolation from other neurons in the network, only the pacemaker neurons fired rhythmically (Fig. 6B). Within the network, both pacemaker neurons and tonic-firing neurons fired rhythmically in the same phases (Fig. 6C). When two sensory inputs of a given strength (see Table 3) projecting to the two pacemaker neurons were activated, a new active phase was initiated if delivered during a quiescent phase and the ongoing active phase was prolonged if delivered during the active phase (Fig. 6, D and E). In contrast, we were unable to evoke initiation of a new locomotor burst or prolongation of an ongoing burst by activation of sensory inputs of that same strength to two nonpacemaker tonic-firing neurons (Fig. 6, D and E). Note that the ability of pacemaker neurons to drive sensory-evoked perturbation is not necessarily due to their threefold greater synaptic strength over that of the tonic-firing neurons but rather to their greater probability of responding to the sensory input because of their more depolarized membrane potential during the quiescent phase (see Fig. 6D, right). While the synaptic weight of the sensory input to tonic neurons in this hybrid model is 100-fold less than for the simulations involving networks consisting of tonic neurons only (Fig. 3, Table 3), in these simulations the strengths of sensory inputs to pacemaker neurons are the same as those to tonic neurons. That only the pacemaker neurons responded to the sensory inputs of this weight suggests that pacemaker neurons are more sensitive to sensory inputs than tonic neurons in rhythmogenic networks. The corollary to this is that if rhythmic activity in spinal CPGs

![Diagram](https://via.placeholder.com/150)

**Fig. 4.** Sensory perturbations of a CPG composed of gap junction-coupled excitatory neurons by sparse sensory input. A: diagram of recurrent network modeled. B, left: cumulative sums of the network activity in the absence of sensory activity (top trace in dark red and pale red trace in C and D). Right: cycle period for the cycles depicted. C and D: sensory-evoked perturbations by sparse sensory input (light blue bar). C: initiation. D: prolongation. Colored bars above cumulative sums indicate time of sensory activation.

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<th>Prolongation</th>
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<td><img src="https://via.placeholder.com/150" alt="Prolongation" /></td>
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Fig. 6. Sensory perturbation of a CPG composed of both pacemaker and tonic-firing excitatory neurons. A: diagram of recurrent network modeled. B: membrane potential of isolated pacemaker and a tonic-firing neuron under a tonic glutamatergic drive. C, left: cumulative sums of the network activity in the absence of sensory activity (top trace in dark red and pale red trace in D and E). Right: membrane potential of a pacemaker neuron (red) and a tonic-firing neuron (gray). D: activation of sensory input during quiet phase. Top: activation of sensory input to the 2 pacemaker neurons (blue bar) leads to initiation. Left: cumulative sums of the network activity. Right: membrane potential of a pacemaker neuron during activation of sensory input. Bottom: activation of sensory input (yellow bar) to tonic-firing neurons 2 and 7 fails to evoke initiation of a locomotor burst. Left: cumulative sums of the network activity. Right: membrane potential of a tonic-firing neuron during activation of sensory input. E: activation of sensory input during active phase. Top: activation of sensory input (blue bar) to pacemaker neurons leads to sensory-evoked prolongation of locomotor burst. Bottom: activation of sensory input (yellow bar) to tonic-firing neurons 2 and 7 fails to prolong locomotor burst. Scale bar is 1 s in C (right) and 500 ms in D (right). Colored bars above cumulative sums indicate time of sensory activation.
is generated by networks composed of pacemaker and non-
pacemaker neurons, pacemaker neurons may preferentially
receive key sensory inputs.

Gating of sparsely distributed sensory inputs. We have
demonstrated, using a number of network architectures with
different types of excitatory neuron firing modes, that sparse
sensory inputs can perturb ongoing locomotor activity. We
next asked whether there is an advantage of having sparse
rather than extensive sensory inputs in terms of the ability to
gate these inputs, i.e., the ability to selectively facilitate or
suppress the influence of particular sensory input relative to
other sensory input.

Selective amplification of sensory inputs that are sparsely
distributed. Neuromodulators such as serotonin can selectively
modulate one sensory afferent over other sensory afferents
(Jankowska et al. 2000; Shay et al. 2005). We considered
whether sparse sensory input would allow selective amplifica-
tion of one source of sensory input over another. To test this,
we connected two sensory inputs to two different pacemaker
neurons in a 10-neuron configuration. One of the two neurons
receiving sensory input was modified through the addition of
L-type \( \text{Ca}^{2+} \) conductance \((2.0 \times 10^{-4} \text{ S/cm}^2) \) to an extra
compartment elongating a dendritic branch \((\text{length} = 50 \mu\text{m},
\text{diameter} = 0.75 \mu\text{m}; \text{Fig. 7A}i) \). This conductance increased the excitability
of this neuron versus the other excitatory neurons. In this
configuration, sensory input to a single neuron without the
increased source of inward current was unable to initiate a new
locomotor burst when applied during the quiet phase of a
locomotor cycle. In contrast, sensory input to the single neuron
with increased excitability was able to initiate a new locomotor
burst. Note that the synaptic weight of each sensory input was
the same \((\text{AMPA weight} = 1.0 \times 10^{-5} \text{ S}, \text{NMDA weight} = 3.0 \times 10^{-6} \text{ S}) \) that converge on a pacemaker
network. We first modeled three pairs of sensory inputs con-
verging on two network neurons and demonstrated that they
summatred such that spurious initiation of a new active phase
was evoked (Fig. 7B). We then separated these inputs such that
the three pairs of sensory inputs projected to three different
pairs of excitatory neurons. In this scenario, activation of the
weak sensory inputs did not result in spurious initiation of a
new phase. Together, these results demonstrate that a sparse
distribution of sensory inputs allows for the separation of
different sources of sensory information, provides a means for
efficient control (suppression or amplification) of sensory input
to the CPG, and prevents sensory perturbations that would
result from the summation of subthreshold sensory events.

**DISCUSSION**

In this computational study, we have shown that sparse
sensory inputs are sufficient to perturb locomotor activity in a
number of different models of locomotor rhythogenesis.
While extensively distributed inputs can produce similar ef-
effects, sparsely connected systems have several advantages: 1
fewer sensory neurons or axons are required, reducing ener-
getic requirements; 2) sensory channels are produced, increas-
ing the computational capacity of the system as a whole \( \text{(for}
\text{example, by specific gating); and 3) this is perhaps a develop-
mentally simpler solution while maintaining key effects on the
motor program. These data also illustrate that connectivity
between networks in general need not be extensive in order for
one circuit to produce impactful changes on another.

The distribution of sensory inputs from sensory neurons to
downstream targets is sparse in several known systems
(Ohshaun and Field 2004). That is, only a small fraction of a
layer of neurons downstream from sensory neurons responds to
the activation of any single sensory stimulus \((\text{Babadi and}
\text{Sompolinsky 2014; Barranca et al. 2014). While it is unknown
whether this is the case in mammalian locomotor networks, there
is evidence of sparse sensory inputs to rhythmic motor
networks in feeding networks of \text{Aplysia californica}, where
sensory inputs are concentrated on a single neuron, B51 (Sa-

Fig. 7. Consequences of sparse sensory inputs for
network activity. A: selective amplification of a
sensory input over another. i: Network diagram
depicting 2 sensory inputs, 1 projecting to a CPG
neuron with no L-type Ca\(^{2+}\) conductance and an-
other sensory input projecting to a neuron with
L-type Ca\(^{2+}\) conductance. Both sensory inputs are
of equal weight. ii: Lack of sensory-evoked initia-
tion following activation of sensory input to CPG
neuron without L-type Ca\(^{2+}\) conductance. iii: Sen-
sory-evoked initiation following activation of sen-
sory input to CPG neuron with L-type Ca\(^{2+}\)
conductance. B: “subthreshold” activation of sensory
inputs converging onto the same CPG neuron leads
to sensory-evoked initiation, whereas separation of the
“subthreshold” sensory inputs onto different
CPG neuron prevents sensory-evoked perturba-
tions. Colored bars above cumulative sums indicate
time of sensory activation.
Sparse inputs have also been shown to disrupt oscillations in the Golgi cell network in the cerebellum (Verhaeke et al. 2010). Thus our computational data fit with experimental observations in mammalian locomotion as well as with evidence of sparse projections in other systems.

Mechanism of sensory perturbations. Several effects on rhythm can be seen with sensory stimulation, including immediate initiation, delayed initiation, and prolongation of the active phase. In this study, several models of spinal cord locomotor rhythm-generating networks were built. Rhythmic activity was characterized by burst firing of all excitatory neurons throughout the active phase and an absence of firing during the quiescent phase. In order for sensory input to initiate a new active phase, it must trigger burst firing in all excitatory neurons of the network. Therefore, when there is sparse sensory input, burst firing must spread from the neurons that receive the sensory innervation to the rest of the network. Thus for sparse sensory input to perturb the network there must be sufficient interconnectivity such that the alteration in the activity of a few neurons can spread to other neurons of the network. If that condition is met, the spread of bursting needs to be very fast for immediate initiation of an active phase. A delayed initiation could be caused by the need for sensory-evoked EPSPs to temporally summate to evoke an action potential in the targeted cell, or it could be caused by a gradual spread of firing throughout the network following sensory activation (Guerthin et al. 1995; Quevedo et al. 2005a, 2005b). We observed the former in the tonic network. In the pacemaker network, only sensory inputs capable of evoking five or six action potentials in synaptically isolated neurons were able to initiate an active phase with a delay, suggesting that delayed initiation was caused by a slower gradual spread of network activity following sensory activation.

To prolong an ongoing active phase, sensory inputs must maintain the bursting of network neurons despite the intrinsic cellular mechanisms that lead to their termination. We found that sparse sensory input could be sufficiently potent to maintain an active phase past its expected duration. This prolongation of ongoing active activity by sparse sensory input was not limited to those neurons receiving sensory inputs. That is, the effects of sensory activation were reverberated through the networks by recurrent connections. The positive feedback from recurrent connectivity therefore led to prolongation of the burst, which then terminated because of the actions of neural mechanisms such as the inactivation of sustained inward currents like $I_{Na,P}$ or NMDA (pacemaker network) or synaptic depression (tonic network). Thus sparse sensory input is sufficient to adjust rhythmogenesis in the variety of models we tested and in the variety of ways that sensory input can affect locomotor activity.

Sparse sensory input: implications for gating of sensory inputs. Given that sensory inputs convey multiple sensory modalities (e.g., proprioception, mechanoreception, nociception) and submodalities (e.g., mechanoreception involves light touch, skin stretch, vibration among others; Abraira and Ginty 2013), central mechanisms are necessary to select relevant sensory information. There is ample evidence of gating through selective facilitation or suppression of sensory inputs to motor networks (Burke et al. 2001; Duyssens and Loeb 1980; Duyssens and Pearson 1980; Forssberg et al. 1977; Jankowska et al. 2000; McCrea et al. 1995; Perreault et al. 1999; Quevedo et al. 2005a, 2005b; Seki et al. 2003; Seki and Fetz 2012; Shay et al. 2005; Van Wezel et al. 1997). Such selection may be dependent on the motor task or even on the phase of a given motor behavior. For example, group I ankle extensor afferents can initiate a new extensor phase in locomotion (Gossard et al. 1994), yet these afferents do not perturb scratch (Frigon and Gossard 2010). On the other hand, sartorius group II afferents affect both forms of rhythmic motor activity (Frigon and Gossard 2010). Sparse distribution of sensory inputs to a central motor network would readily enable central sensory selection mechanisms. To enable selective sensory gating in the presence of an extensive distribution of sensory inputs to neurons of the spinal locomotor network, a greater distribution for the gating mechanism, e.g., presynaptic inhibition, would be required. Furthermore, given that we have shown that sensory neurons need only to synapse on a few neurons in motor rhythm-generating networks for the rhythm to be affected, if there were extensive distribution almost all of the inputs would need to be gated in order to deselect those inputs. That is, sparse distribution of sensory inputs is not only sufficient but is likely necessary in order to affect rhythm generation appropriately.

This distribution creates sensory channels, which support the concept of labeled lines for sensory inputs (Hyvärinen et al. 1968; Ma 2012; Prescott and Ratté 2012). We have shown that with this distribution amplification of sensory input requires only a sparsely distributed mechanism of amplification. We used facilitation of L-type Ca$^{2+}$ channels in one rhythmic neuron as a means of amplifying one sensory input over others; however, other means of amplification could include postsynaptic excitation or neuromodulation of a neuron receiving a specific sensory input. While we focused on amplification, suppression of select sensory inputs would be similarly effected by sparsely distributed mechanisms of sensory inhibition, whether presynaptic or postsynaptic. Thus, as a whole, sparsely distributed sensory input would lead to the benefit of sensory channels that are efficiently gated via suppression or facilitation through sparsely distributed mechanisms.

Sparse sensory input: implications for separation of functionally unrelated sensory inputs. In addition to the many different sensory modalities present, sensorimotor pathways can be functionally synergistic or opposed based upon the location of the sensory input and/or the sensory modality conveyed (e.g., cutaneous afferents from skin overlying knee extensor vs. cutaneous afferents from skin overlying knee flexors; Hagbarth 1952). Thus functionally related sensory inputs are more likely to summate, whereas functionally unrelated sensory inputs are less likely to summate or may even negate each other (Brink et al. 1983; LaBella and McCrea 1990; Perrier et al. 2000; Rudomin 2009). With a sparse distribution of sensory input, there are more “channels” available for different afferent information, and thus more possibilities for summation or negation. We have shown that a sparse distribution of sensory inputs creates a mechanism that can prevent the perturbation to ongoing locomotor activity by activation of weak functionally unrelated inputs.

Spinal locomotor CPGs as sparsely encoding networks. We have shown here that sparsely distributed primary sensory afferents can affect locomotor rhythmic networks. This may form the basis of a sparsely encoding network, in which each input modality targets only a few neurons and each
network neuron receives only a few inputs (Lin et al. 2014). This type of organization has been seen in a number of different systems (Kumar et al. 2010; Lin et al. 2014; Olshausen and Field 2004; Vondrachen and Chacron 2011) and has been suggested to provide circuits with several advantages. For example, sensory processing can be efficient, minimizing energy requirements. In addition, as has been shown in the Drosophila olfactory system, there is a direct relationship between the sparseness of afferent input and the specificity of stimulus discrimination (Lin et al. 2014). To ensure information transmission, however, the strength of input must increase as the density of connectivity decreases (Kumar et al. 2010). There must therefore be an optimal range (the “Goldilocks zone”) in which the degree and strength of connectivity are such that the advantages of sparse connectivity are maintained while still allowing for appropriate information transmission.

Composition of CPG. The term “central pattern generator” has been used to describe neural networks that produce rhythmic alternation (Grillner 2006; Hägglund et al. 2013; Wilson and Wyman 1965). The composition and structure of locomotor CPGs have not been fully described. A number of neuronal populations, defined by anatomical, physiological, or genetic characteristics, have been identified as key components of spinal locomotor networks (reviewed by Arber 2012; Grillner and Jessell 2009; Grossmann et al. 2010; Kiehn 2011). Part of the difficulty of describing the CPG is that no population of neurons has been found to be critical to rhythm generation (Crone et al. 2008; Gosgnach et al. 2006; Kwan et al. 2009; Lanuza et al. 2004; Zhang et al. 2008). Thus the search for sources of rhythmogenesis in spinal locomotor CPGs has concentrated on cells exhibiting rhythmogenic or pacemaker characteristics (Dyck et al. 2012; Wilson et al. 2005). Whether pacemaker neurons are essential has been discussed (Brocard et al. 2010; Brownstone and Wilson 2008; Harris-Warrick 2010). Our study used models consisting of pacemaker and/or tonic nonpacemaker neurons, and in all cases sparse sensory inputs were able to perturb rhythmic activity. Therefore, we provide no evidence to favor either of these possibilities. As shown by experimental demonstrations of phase-resetting, neurons of the rhythmogenic kernel must receive some sensory inputs (Brownstone and Wilson 2008), but given the findings presented here we suggest that only a subpopulation of neurons involved in rhythmogenesis need be targeted by sensory inputs. Our simulations of a heterogeneous network composed of pacemaker and tonic neurons (Carroll and Ramirez 2013) do suggest that, because of subthreshold membrane potential oscillations in pacemaker neurons during the quiescent phases of the locomotor cycle, sensory perturbations are more readily caused by sensory inputs to pacemaker neurons than to tonic neurons. Therefore, if rhythmic activity in spinal CPGs is generated by networks composed of pacemaker and nonpacemaker neurons, we would predict that pacemaker neurons preferentially receive key sensory inputs.

Implications of sparsely distributed sensory input to the dynamics of spinal CPGs. The rhythmic activity of the spinal CPG that underlies locomotion can be considered to be produced by a dynamical system (Izhikevich 2007; Shenoy et al. 2013). In other words, the neurons of the spinal CPG form a system such that their collective behavior operates around a limit cycle that generates the steady rhythm characteristic of locomotion. The evolution of the firing rate, \( r(t) \), of spinal CPG neurons over time can be described by the equation

\[
\dot{r}(t) = h(r(t)) + u(t)
\]

where \( r \) is a vector denoting the firing rate of all neurons of the rhythm-generating network, \( \dot{r} \) is the derivative of the firing rate with respect to time, \( \tau \) is the time constant of the network dynamics, and \( h \) is a mapping that drives the evolution of firing rate and consists of limit cycles. Function \( h \) is determined by a combination of the intrinsic properties of individual neurons and the connectivity of the network. External inputs to the system, \( u(t) \), modify the state of the system, and accordingly its dynamical behavior. The specific distribution of sensory afferents over the spinal CPG would influence the structure of \( u(t) \) and thus shape the response of the system to sensory input. Thus determining whether sensory inputs are extensively or sparsely distributed will provide insight into which elements of the locomotor network drive its dynamics (i.e., shape \( h \)) and how sensory inputs can shape these dynamics. This will provide insight into the structure of the CPG, and thus assist in the identification of neurons involved in locomotor rhythmogenesis.

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