Feed-forward and Reciprocal Inhibition for Gain and Phase Timing Control
in a Computational Model of Repetitive Cough

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Running Heading: Inhibition for Control of Repetitive Cough

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Abstract

We investigated the hypothesis, motivated in part by a coordinated computational cough network model, that second-order neurons in the nucleus tractus solitarius (NTS) act as a filter and shape afferent input to the respiratory network during the production of cough. *In vivo* experiments were conducted on anesthetized spontaneously breathing cats. Cough was elicited by mechanical stimulation of the intrathoracic airways. Electromyograms of the parasternal (inspiratory) and rectus abdominis (expiratory) muscles and esophageal pressure were recorded. *In vivo* data revealed that expiratory motor drive during bouts of repetitive coughs is variable: peak expulsive amplitude increases from the first cough, peaks about the eighth or ninth cough, and then decreases through the remainder of the bout. Model simulations indicated that feed-forward inhibition of a single second-order neuron population is not sufficient to account for this dynamic feature of a repetitive cough bout. When a single second-order population was split into two sub-populations (inspiratory and expiratory), the resultant model produced simulated expiratory motor bursts that were comparable to *in vivo* data. However, expiratory phase durations during these simulations of repetitive coughing had less variance than those *in vivo*. Simulations in which reciprocal inhibitory processes between inspiratory-decrementing and expiratory-augmenting-late neurons were introduced exhibited increased variance in the expiratory phase durations. These results support the prediction that serial and parallel processing of airway afferent signals in the NTS play a role in generation of the motor pattern for cough.
This manuscript proposes a complex inhibitory network of nucleus tractus solitarius (NTS) interneurons for the control of cough. This hypothesis has important implications in disease states, such as cough hyper-responsiveness. This may be largely a function of reduced inhibitory NTS control; thus, reduced cough excitability in part be due to enhanced inhibition. This hypothesis emphasizes that the levels of excitation and inhibition in a network determine sensory gating of afferent input.


Introduction

Chronic cough is a debilitating condition, with broad social and health consequences (1, 17, 19, 21, 22, 26). A subset of patients with acute or chronic cough can experience paroxysmal coughing, defined as intense bouts of uncontrollable repetitive cough (27, 29, 31, 32, 37). Paroxysmal coughing is commonly associated with significant morbidity such as vomiting, headache (17, 19, 21), ruptured abdominal muscles, and broken ribs (17, 19, 21, 26). The success of therapeutic strategies aimed at reducing the morbidity of cough will depend on a greater understanding of the mechanisms of altered excitability across cough bouts.

These bouts or epochs of coughing are evoked by mechanical or chemical stimulation of the larynx (6, 14), pharynx (14, 28, 63), or tracheobronchial tree (14, 61) and are associated with esophageal pressures that can exceed 100 mmHg. Of the most commonly employed animal models of cough, the cat routinely produces intense bouts of repetitive coughing. Spatiotemporal features of coughing in the cat have been reported for large numbers of coughs across a population or within a single animal (45-48, 53, 54, 59, 61). The results of these and other studies (2, 4, 10-12, 49) support the existence of a central control system for cough that regulates the intensities of inspiratory and expiratory motor drive separately. Retrospective inspection of our own data suggested that, within individual intense cough epochs in the cat, the sequential pattern of expiratory motor drive is qualitatively different from inspiratory motor activity. The duration of the passive portion of the expiration phase ($CT_{E2}$) is the primary determinant of the total cough cycle time ($CT_{TOT}$) (61) and can be significantly prolonged to allow the execution of other protective behaviors, such as swallow, that have an airway clearance function. Additionally, our recent work (45) indicated that the duration of the E2 phase has a higher degree of variance during cough than during breathing, and has a reflexive control system property
appropriate for the “interleaving” of different behaviors between successive coughs and
enhanced protection of the airway from intrusion of foreign material. This mechanism allows the
brainstem control system to initiate and complete multiple airway protective behaviors in an
orderly sequence while preserving the mechanical effectiveness of each. We have termed the
coordinated execution of multiple airway protective behaviors a meta-behavioral control system
(45).

The reflexive cough pathway is initiated by mechanoreceptors and/or C-fibers in the
laryngeal and tracheal mucosa (especially the area of the carina) which terminate on second-
order neurons in the NTS (35, 62). These second-order neurons are hypothesized to project to
pontine and medullary respiratory groups (24, 43, 53, 54). Mifflin (38) identified neurons with
monosynaptic (second-order neurons) and polysynaptic responses to electrical stimulation of the
superior laryngeal nerve (SLN); 50% of the second-order and 100% of the polysynaptic-response
neurons exhibited significant frequency-dependent reductions in excitatory post-synaptic
potential amplitude in response to SLN stimulation. Neurons with polysynaptic responses often
exhibited an excitatory–inhibitory post synaptic potential sequence (38). These findings support
the presence of feed-forward inhibitory mechanisms among the NTS second-order interneuronal
population that processes afferent feedback from the larynx. More recently, Canning and
coworkers (15) proposed that the tracheal sensory receptors that induce coughing differ from the
classically defined rapidly adapting receptors (RAR) (57, 62-64). Specific information on the
behavior of intrapulmonary RAR second-order neurons suggests that this population can undergo
altered excitability as a compensatory response to heightened afferent input (52). Haji and
colleagues (24) have provided information in support of the concept that second-order neurons in
the NTS that respond to input from RARs act as filters that shape afferent input to downstream
locations. However, the role of NTS second-order neurons in the processing of tracheobronchial cough receptor feedback and the production of cough is not well understood.

This prior work and gaps in knowledge motivated a computational modeling study of the breathing-cough neural network and in vivo experiments to investigate the mechanisms responsible for timing and modulation of motor drive to spinal respiratory muscle pathways during cough bouts. Our current neuro-mechanical model of the cough-respiratory system has only a single NTS second-order neuronal population that receives tracheobronchial afferent feedback (41, 48). We hypothesized that an enhanced model with additional NTS second-order neuron populations and additional recurrent inhibitory connections among extant VRC populations would confer sensory filtering functions for specific shaping and regulation of the cough motor pattern.

**Methods**

**Computational Modeling Methods**

Neural circuit components of the cough computational model were derived from previously described network models of discrete “integrate and fire” populations after MacGregor (30). These models were developed from in vivo experiments of fictive coughing in the cat as previously described in Rybak et al. (50), Poliacek et al. (48), and O’Connor et al. (41). The network model used herein is further described in the Results. The model published in Poliacek et al. (48) was used as the base model for comparison in this manuscript.

Computational models were implemented using a program package written in C language for the UNIX environment. Simulations were run on a 64-bit Intel multiprocessor-based computer under the Linux operating system. Figure 1 is a visual representation of the final
network model designated Version 2 (see Results for Version 1 and 2 modifications; details in Table 3 and 4). The model is scaled in time with 1 second equivalent to 2,000 integration steps. In Versions 1 and 2 the simulation coughs are approximately twice the rate of in vivo.

In Vivo Methods

Experiments were performed on six spontaneously breathing adult male cats. The protocol was approved by the University of Florida Institutional Animal Care and Use Committee (IACUC). The animals were initially anesthetized with sodium pentobarbital (35-40 mg/kg i.v.), and supplementary doses were administered as needed (1-3 mg/kg i.v.). A dose of atropine sulfate (0.1-0.2 mg/kg, i.v.) was given at the beginning of the experiment to reduce secretions from repeated tracheal stimulation. Cannulas were placed in the femoral artery, femoral vein, and trachea. An esophageal balloon was placed via an oral approach to measure pressure in the mid-thoracic esophagus. Arterial blood pressure and end-tidal CO₂ were continuously monitored. PO₂ was maintained using air mixtures with enriched oxygen (25-60%) to maintain values above 100 mm Hg. Body temperature was monitored and maintained at 37.5 ± 0.5 °C using a heating pad. Arterial blood samples were periodically removed for blood gas analysis.

Electromyograms (EMG) were recorded using bipolar insulated fine wire electrodes. The activities of the parasternal (inspiratory) and the rectus abdominis (expiratory) muscles were used to determine cough. Electrodes were placed in the parasternal muscle at T3. For the rectus abdominis muscle, the electrodes were placed through a small incision in the skin, 7 cm caudal to the xiphoid process and 1 cm lateral to the midline. All electrodes were placed 2-3 mm apart and their positions were confirmed by visual inspection and EMG activity patterns during breathing.
Use of Inhibition in a Computational Model of Cough

Cough was induced by mechanical stimulation of the extra- and intra-thoracic trachea using a thin polyethylene catheter (diameter 0.5 – 1.0 mm). The catheter was continuously rotated along the length of the intra-thoracic trachea for 20 seconds. All EMG signals were amplified, filtered (200-5000 Hz), rectified, and integrated (time constant = 50 ms). EMG amplitude measures were normalized to the peak of the largest signal from each muscle recorded during the stimulus evoked coughs. Parameters from the first 13 coughs that occurred during the 20 second stimulus were measured.

Cough was operationally defined as a burst of activity in the parasternal EMG and rectus abdominis EMG, along with a negative to positive change in esophageal pressure (Figure 2), or a burst in the phrenic followed by lumbar (Figure 3). Cough phase durations were measured using the definitions from Wang et al (61). The inspiratory phase duration (CTI) was defined as the period of time from the onset of inspiratory activity (integrated activity of the parasternal \textit{in vivo}, phrenic in computer simulations) until the maximum inspiratory burst, duration of the first expiratory phase (CTE1) was defined as the maximum inspiratory burst to the end of the expiratory activity (integrated activity of the rectus abdominis \textit{in vivo}, lumbar in computer simulations), and the duration of the second expiratory phase (CTE2) was defined as the end of the expiratory motor burst to the onset of the inspiratory activity for the next cough in the epoch (Figure 2; gray boxes). Total cough cycle duration (CTTOT) was defined as the sum of CTI, CTE1, and CTE2.

Results are expressed as means ± standard error (SE). A pairwise two-sided $t$-test with non-pooled SE was used to assess differences in amplitude of the inspiratory and expiratory activity, and the $p$-values were adjusted for multiple testing (25). A pairwise one-sided $t$-test with non-pooled SE was used to assess whether CTE2 was longer at the end of a cough bout. Each
series was divided into equal halves, unless the epoch was an odd number (the odd cough was included in the second half of the cough epoch). A difference was considered significant if the adjusted $p$-value $\leq 0.05$. Relationships between durations and normalized inspiratory and expiratory burst amplitudes during cough to total cough duration were evaluated by linear regression analysis ($r^2$) (Table 2).

Results

*In vivo*

We conducted eighteen tracheobronchial stimulation trials in six cats (3 per animal). Mechanical stimulation of the tracheobronchial airway elicited $16.7 \pm 1$ coughs per trial with a range of 13-21 coughs. Moving averages of electromyography (EMG) traces for parasternal and abdominal muscles during cough are represented in Figure 2. Means and standard errors (SE) for percent of maximum of the parasternal and abdominal EMGs are presented in Table 1.

The percent of maximum parasternal EMG activity during *in vivo* cough C1 was not significantly different comparing the C1 in the epoch to each subsequent cough (C2 to C13) (Table 1). There was a significant change in the peak amplitude of the abdominal EMG burst, comparing C1 to subsequent coughs in the epoch beginning at C7 to C10 in the series (Table 1).

The average CTI for C1 was $692 \pm 84$ ms, approximately 200 ms longer than any subsequent cough. The C2 through the C13 coughs demonstrated very little variation in CTI, averaging between $416 \pm 42$ ms for C8 to $472 \pm 46$ for C12. $\text{CT}_{E1}$ was stable throughout the cough epoch; average values ranged from $230 \pm 26$ ms for C3 to $268 \pm 26$ ms for C12. Average $\text{CT}_{E2}$ values, however, ranged from $383 \pm 71$ ms for C7 to $618 \pm 155$ ms for C12 (a difference of approximately 62%). Taken with the high correlation between $\text{CT}_{E2}$ and $\text{CT}_{T0T}$ (Table 2), this
suggests, in agreement with previous research (61), that the primary determinant of $C_{\text{TOT}}$ was $C_{\text{E2}}$.

The $C_{\text{E2}}$ over the first half of the cough epoch ($464 \pm 72$ ms) was significantly different than the second half ($652 \pm 99$ ms; $p = 0.03$), and is demonstrated in Figure 2.

**Computational model and simulations**

Five simulated trials were run using each model version. Values (mean $\pm$ SE) for the percent maximum of the phrenic (inspiratory) and lumbar (expiratory) outputs are presented in Table 1. Simulations from *Version 1* resulted in 19 coughs and simulations from *Version 2* resulted in 13 coughs.

Figure 3a shows a simulated motor output from the preliminary version of the model, published in Poliacek, et al (48). *Version 1* of the model (Figure 3b) incorporated an additional second-order circuit for NTS processing of the afferent signal, expanding the number of second-order populations involved with cough from one to two. The added population consisted of a feed-forward inhibitory circuit that received the same excitation as the first second-order cough population and inhibited it. The feed-forward inhibitory circuit accommodated over time, decreasing its suppression of cough excitability over the cough trial (Tables 3 and 4). Early iterations of the model resulted in simulations with irregular and non-physiologic expiratory drive, so the number of terminals from the feed-forward population to the original second-order cough relay population was increased from 100 to 250 to increase spatial and temporal dispersion of the inhibition (Tables 3 and 4).

The NTS circuit was further expanded in *Version 2* by dividing the original second-order population into second-order inspiratory and expiratory populations (Figure 3c). The discharge
identity of these populations was determined by their activities during the inspiratory and expiratory portions of the cough rather than the breathing cycle. The second-order inspiratory population was connected to inspiratory portions of the network through primarily excitatory synapses (I-Aug, I-Dec, and Late-I), and the second-order expiratory population was connected to expiratory portions of the network (E-Aug early, E-Aug late, E-Dec P, and E-Aug BS in the VRC, and E, EI, rostral IE, and caudal IE populations in the pons; see Figure 1 for model population abbreviations), also via excitatory synapses (Tables 3 and 4). Both the inspiratory and expiratory second-order populations received identical inputs from the cough receptor fiber populations and the feed-forward inhibition population. To limit inspiratory amplitude variance, the cough receptor fiber populations were connected to the I-Driver/Plateau population.

The excitability of the I-Dec population is proposed to be an important determinant of the onset of the cough I phase; this group of neurons was inhibited in the base model by the E-Aug late population. To better account for increased variance of the expiratory phase, relative to that during breathing, we added a second E-Aug late population that received many of the same inputs as the extant E-Aug late population and an inhibitory synapse to I-Dec neurons; the I-Dec inhibition by the first E-Aug late population was removed. The number of cells in the added E-Aug late population was doubled and the number of terminals onto the I-Dec population was nearly doubled (55 to 100) with the intent of enhancing temporal dispersion of inhibitory postsynaptic potentials (Tables 3 and 4). In addition, increased inhibition produced a greater post-inhibitory rebound, further affecting timing in the model. The resulting increase in early I-Dec activity would further inhibit the beginning of inspiratory motor activity and contribute to the prolongation of the E2 phase. To achieve modulation of motor drive to inspiratory pathways during the E2 phase, inhibitory synapses from E-Aug late neurons to I-Dec were added. The
resultant simulations of coughing exhibited an inverse relationship between the peak amplitude
of cough expiratory drive and the I-Dec population discharge rate. This connection ultimately
resulted in prolongation of the CTE2 when cough expiratory drive declined, similar to
observations in vivo.

Table 1 includes amplitude measures from Version 1 and 2 of the computational models
for the percent of maximum phrenic and lumbar activity during cough. Similar to in vivo CTE2,
an analysis was performed by splitting the cough epochs into two halves. In Version 1, CTE2 in
the first half of the cough epoch (53 ± 22) was not significantly different from the second half
(78 ± 28; p = 0.09), but in Version 2, CTE2 in the first half of the cough epoch (14 ± 6) was
significantly different from that in the second half (40 ± 9; p = 0.01). Version 2 demonstrated the
prolongation of CTE2 observed in the in vivo results (Figure 3, gray boxes).

Poincaré plots of cough phase durations

For the purpose of visually displaying the variability of cough, Poincaré plots (Figure 4)
were used to compare cough phase durations obtained from the in vivo data, from the base model
simulations, and from simulations created using Versions 1 and 2. The x-axis is the phase
duration during cycle n and the y-axis is the duration of the same phase during cycle n+1,
repeated for each pair of cycles within each cough bout. To normalize the comparisons, in vivo
and simulated phase durations were calculated as a percent of CT_{TOT}. Results of model
simulations exhibited alterations in the variability of cough cycle durations. The model from
Poliacek et al. (48) had limited variability, with each phase in non-physiologic clusters. Version
1 simulations had increased variability in CTE1; however, there were many cycles with a CTE2 of
zero, which is not a feature of cough in vivo. Simulations using Version 2 of the computational
model exhibited variability more closely resembling \textit{in vivo} data in each of the three cough phases.

\textbf{Discussion}

Model simulations of repetitive cough bouts predicted that feed-forward and reciprocal inhibition would produce increased variance in expiratory motor drive. \textit{In vivo} data revealed that expiratory drive during repetitive coughs is not uniform, but increases from the first cough, peaking about the eighth to ninth cough, and then decreases through the remainder of the bout.

The base computational model for cough was first presented by Shannon et al. (53) with the following core hypotheses: a) the NTS is activated by cough receptors and this information is distributed to the core network, and b) medullary neuron drive for breathing and cough arise from, in part, the same neurons. We further hypothesized that behavior excitability is controlled by neurons in the NTS that filter incoming afferent information and initiate an appropriate behavioral response.

The neuronal network for the central pattern of cough has been described by a number of studies (6, 41, 42, 51, 53, 54). This network model has been predictive of the results of \textit{in vivo} studies for modulation of cough by blood pressure (48) and central chemoreceptor effects (42). However, the computational model of repetitive cough presented in Poliacek et al. (48) had limited expiratory drive variability (Figure 3a), with all parameters having a moderate to strong relationship with \(CT_{TOT}\) (Table 2). The second-order population received the “fiber” population input, which was subject to limited perturbation and is represented as an essentially square wave input. However, the current \textit{in vivo} data and results in Wang et al. (61) demonstrate that there is variability in expiratory drive within a cough bout.
To begin to control gain via expiratory excitability, another second-order circuit for NTS processing of the afferent signal was added to the base model to produce Version 1 (Figure 3b). This new feed-forward inhibitory population and all the second-order cough neurons received the same level of excitability. The inhibitory circuit directly inhibited other NTS neurons, but accommodated at a faster rate. The added circuit acted as a sensorimotor gate locally controlling afferent excitability to regulate the motor pattern (13, 16, 38, 40, 44). This process allowed for state-dependent gain control by filtering the afferent signal which resulted in stronger coughs and longer bouts, which is a common feature of repetitive cough (8, 18, 48, 61). The unique advantage conferred by our modeling efforts allowed us to directly investigate the effects of a feed-forward circuit on motor drive in a computational model that has potential predictive value.

Early iterations of Version 1 had irregular and non-physiologic changes in expiratory drive across the cough epoch and even fractionation of the motor burst within a single cough. Based on the work of McGovern et al. (35), there is a large population of NTS interneurons rostral to obex that is labeled subsequent to injection of pseudorabies virus into the trachea in the rat. Even though there is evidence that the rat does not cough, this large population of NTS interneurons may represent a neural substrate for “smoothing” temporal variations in synaptic drive to the downstream elements of the respiratory-related network, as seen in the visual cortex (23), eye movement in the cerebellum (36), and arm movement (33). To simulate this process and minimize variance in motor bursts during the cough-bout model simulations, we increased the convergence to second-order cough population neurons from the feed-forward inhibitory population five-fold. We hypothesized that a large number of neurons and/or connections would be needed within a neural circuit that is responding to rapid shifts in excitability from multiple
afferent populations, such as the process of transition from eupnea to coughing, to affect temporal and spatial dispersion of afferent feedback to stabilize phase transitions.

In Version 2, the second-order population of neurons was split into two discrete populations: one controlling the excitability of the inspiratory core of the network, and a second for regulating the expiratory core. This change allowed “parallel” pathways to independently control excitability of each portion of the cough motor pattern. This circuit arrangement represents a plausible explanation for dynamic changes in expiratory motor drive and relatively little change in inspiratory drive over a cough epoch *in vivo*. Through work on cough suppression induced by pharmacologic agents, Bolser and colleagues (3-6, 9, 11, 12, 45-49, 61) and Mutolo and colleagues (39, 43) have hypothesized that motor drive to the inspiratory and expiratory portions of the network is supplied by distinct interneuronal pathways. More specifically, Bolser et al. (8) demonstrated differential effects of codeine on inspiratory and expiratory motor drive in the cat: administration of codeine resulted in a dose-dependent decline in expiratory motor drive during coughs, whereas inspiratory drive was less affected [Figure 2, (8)]. These effects also have been seen with nociceptin (17-amino acid neuropeptide and endogenous ligand for the nociceptin receptor) (12), a substance P receptor antagonist (11), and more recently with baclofen administration in cats (18). A common feature of each of these studies was the stability of the inspiratory motor drive during the coughing following administration of a cough suppressant drug.

The results from Version 1 revealed an improved model; however, there were additional cycle-by-cycle timing variations in *in vivo* data that were not observed in model simulations. The Poincaré plots (Figure 4) from Version 1 display the abbreviated CT$_{E2}$, and several coughs in the series are missing this phase. Relatively invariant CT$_{E1}$ and significant variations in CT$_{E2}$ were
observed by Wang et al. (61) for tracheobronchial coughing. Computational models of repetitive
cough must account for this temporal regulation of the motor pattern (i.e., a fixed $CT_{E1}$ with a
highly variable $CT_{E2}$). Additionally, Wang et al. (61) demonstrated that $CT_{E2}$ was the only
temporal measurement to correlate with overall cough duration; this observation was confirmed
with the present dataset. This feature of the temporal control of coughing differs significantly
from that of breathing, in which the inspiratory phase is a major determinant of the total
breathing cycle time (20). Table 2 shows regression data including correlations presented in
Wang et al. (61), along with \textit{in vivo} data in this present paper and results from simulations using
\textit{Versions 1 and 2} of the computational model. An additional circuit was added in \textit{Version 2} to
produce an increase in $CT_{E2}$ as the second-order afferent input decreased excitability. A similar
reciprocal inhibitory circuit was used to inhibit the I-Dec population by increased activity in the
additional E-Aug late group. We note that both of these populations of neurons are located in the
ventral respiration column and not the NTS (53, 55). However, the afferent input to this E-Aug
late population did not decrement over time, and thus resulted in extended suppression of the I-Dec
group to delay the onset of the next inspiratory phase of cough.

The impacts of these model revisions are evident in the correlation coefficients (Table 2, \textit{Version 2})
and the Poincaré plots (Figure 4), and illustrate that simulations of \textit{Version 2}
produced the salient \textit{in vivo} relationship between cough phase durations. The relationship
between $CT_{E2}$ and $CT_{TOT}$ is an important feature for the control system of cough, and is integral
for our understanding of how cough interacts with swallow (45). For example, when cough and
swallow occur in sequence, swallow is only present in the E2 phase of cough. These model
enhancements recognize the permissive nature of the E2 phase for appropriate integration of the
behavior of the cough and swallow pattern generators. The balance of inspiratory and expiratory
neuronal synaptic effects in shaping phase transitions from multiple stimuli is manifest by inspection of other parts of the repetitive cough model, and more recently has been examined by Segers et al. (51), who demonstrated the action of expiratory neurons in shaping inspiratory drive in response to peripheral chemoreceptor stimulation. More specifically, reductions in the inhibitory synaptic drive from tonic expiratory neurons can enhance inspiratory drive during breathing and cough (51).

The hypothesis that E-Aug late neurons play an integral role in the timing of the transition from expiration to inspiration is limited by the fact that in vivo studies have not demonstrated a robust frequency of occurrence of this neuron type (53, 54). An alternative hypothesis is that other populations of neurons, with different (perhaps non-respiratory) firing patterns during breathing or the early part of a cough series, change their activity patterns during later coughs in an epoch. Additionally, the extent to which our novel computational model predicts repetitive cough in humans is not known. Smith et al. (56) investigated airflow, volume, and driving pressures in peals (epochs) of coughs in humans. Human cough is characterized by an initial inspiratory effort followed by a cycling of compression and expiration with no intervening inspiratory phases. This laryngeal compression to expiration cycle can be repeated upwards of ten times in adults. Figure 6 in the report by Smith et al. (56) shows changes in volume and pressure for the first cough in the peal, a middle cough, and the last cough. In humans, the expelled volume of air is greatest during the first cough and becomes progressively smaller as the coughing continues. Thoraco-abdominal pressure is a measure of the intensity of cough motor drive and these investigators showed that the first and middle coughs had similar pressures. This sustained expiratory motor drive over the epoch and the ramping of expiratory motor drive in the cat may be a species difference, or a result of differences in the cough stimuli.
As noted above, temporal regulation of the breathing motor pattern differs from that of cough, in particular the importance of inspiratory (breathing) or expiratory (cough) phase duration for controlling total cycle time. The dominant role of $CT_{E2}$ in total cycle time (61) is a critical determinant in how cough and swallow cooperate to maintain pharyngeal, laryngeal, and tracheobronchial airway patency (45). The fundamental temporal differences between cough and breathing appear difficult to reconcile in light of the accepted hypothesis that the core network for breathing is also responsible for phase timing during coughing. Shannon and coworkers (55) envisioned a core network that undergoes a process of “reconfiguration” to produce both behaviors, presenting evidence of functional interaction of multiple neuron populations. Our current modeling efforts suggest several caveats to the reconfiguration hypothesis.

First, the reconfiguration hypothesis does not fully account for the contribution of neurons that have no role in breathing but are important in the neurogenesis of coughing. By definition, 2nd order interneurons in cough receptor pathways are likely quiescent during breathing and are recruited during cough; these interneurons are incorporated in the present modeling efforts. VRC recruitment during cough was incorporated into previous models; however, we believe that the full extent of recruited and/or incorporated populations in the VRC, pons, etc. in cough genesis remains underestimated.

Second, there are profound differences in the sensory regulation of cough and breathing that are grounded in the function of the two behaviors. While the function of breathing is gas exchange, the sole function of cough is airway clearance. As such, the main sensory input that induces cough is located in the airways (larynx, trachea, and bronchi). However, breathing can be produced in the absence of vagal feedback and relies primarily on sensory feedback from the carotid sinus and ventral surface of the brainstem. The model incorporates vagal sensory
feedback for the production of coughing, but does not specifically account for the synaptic input from peripheral and central chemoreceptors. This input is simulated by an excitatory input current to the populations of neurons that participate in the core network. Cough can be produced during hyperventilation below apneic threshold (58). Preliminary simulations have shown that reduction of this input current consistent with hyperventilation will result in apnea and coughing can still be produced by the model. Unlike breathing, there is no relationship between volume and phase timing during coughing (7). Our model retains excitatory pump cells and these neurons excited E-Dec populations and therefore can have a role in cough phase timing. In the absence of specific information regarding the behavior of pump cells during coughing, we have not revised this aspect of the model. However, we acknowledge that neural processing of sensory information related to lung volume during cough is likely to differ significantly from that for breathing.

The proposed presence of a complex inhibitory network of NTS interneurons controlling coughing may have important implications in disease states in which cough excitability is altered. Cough hyper-responsiveness due to airway inflammation may be largely a function of reduced inhibitory control in NTS interneuronal populations. Further, reduced cough excitability could in part be due to enhanced inhibition by the same populations of neurons. The latter hypothesis is really a manifestation of the network scale of organization, in which the balance of excitatory and inhibitory inputs in a system determines function, rather than the presence or absence of highly excitable elements. This idea is effectively the hypothesis of “detailed balance” (60) in which the balance of excitatory and inhibitory activity in a network determines sensory gating of afferent input. In the medial NTS, GABAergic inhibition on vagal 2nd order interneurons is considerably less robust than excitatory glutaminergic neurotransmission (34),
consistent with a distributed network of inhibitory axons that control 2nd order interneuron activity through temporal synchrony. If this mechanism is involved in the regulation of cough, it is likely that our proposed feedforward inhibitory population consists of neurons with highly synchronized activities. As such, central processes that influence synchrony in this population may represent a primary mechanism responsible for the regulation of cough excitability.

Summary/Conclusions

This study demonstrates the variance in pattern of expiratory drive over a cough epoch in the cat. These modulations in timing and gain could not be modeled solely by inclusion of a second-order NTS population with a feed-forward function, but required the addition of separate inspiratory and expiratory second-order populations and a stronger inhibitory synaptic effect from neurons controlling phase transition from expiration to inspiration. These results support the hypothesis that afferent signals and their processing are a significant feature of the motor pattern for cough. Further, our results support the presence of multiple subtypes of NTS neurons that respond to tracheobronchial sensory feedback and have an important role in controlling cough motor bursts on a cycle-by-cycle basis.
Table 1. *In vivo* percent of maximum parasternal and abdominal EMG amplitude, and computational model simulations percent of maximum phrenic (inspiratory) and lumbar (expiratory) activities. The cough number is expressed as C1 to Cn. Values shown are means (± SE) for each cough in an epoch.

<table>
<thead>
<tr>
<th>Cough Number</th>
<th>In vivo Parasternal Mean ± SE</th>
<th>In vivo Abdominal Mean ± SE</th>
<th>Version 1 Phrenic Mean ± SE</th>
<th>Version 1 Lumbar Mean ± SE</th>
<th>Version 2 Phrenic Mean ± SE</th>
<th>Version 2 Lumbar Mean ± SE</th>
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<td>C1</td>
<td>72 ± 7</td>
<td>41 ± 11</td>
<td>58 ± 9</td>
<td>42 ± 6</td>
<td>94 ± 2</td>
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<td>C2</td>
<td>71 ± 7</td>
<td>46 ± 7</td>
<td>76 ± 7</td>
<td>42 ± 6</td>
<td>89 ± 4</td>
<td>55 ± 7</td>
</tr>
<tr>
<td>C3</td>
<td>62 ± 5</td>
<td>44 ± 7</td>
<td>91 ± 4†</td>
<td>60 ± 6</td>
<td>91 ± 3</td>
<td>56 ± 10</td>
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<td>92 ± 3†</td>
<td>64 ± 5</td>
<td>88 ± 2</td>
<td>66 ± 7</td>
</tr>
<tr>
<td>C5</td>
<td>74 ± 5</td>
<td>61 ± 9</td>
<td>94 ± 2†</td>
<td>64 ± 7</td>
<td>86 ± 3</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>C6</td>
<td>76 ± 6</td>
<td>62 ± 5</td>
<td>81 ± 5†</td>
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<td>79 ± 2</td>
<td>75 ± 7</td>
</tr>
<tr>
<td>C7</td>
<td>85 ± 2</td>
<td>69 ± 7†</td>
<td>85 ± 4</td>
<td>69 ± 4</td>
<td>78 ± 3†</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>C8</td>
<td>84 ± 3</td>
<td>69 ± 4†</td>
<td>81 ± 4</td>
<td>81 ± 8</td>
<td>70 ± 2†</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>C9</td>
<td>84 ± 5</td>
<td>72 ± 6†</td>
<td>74 ± 3</td>
<td>87 ± 8*</td>
<td>71 ± 2†</td>
<td>83 ± 4†</td>
</tr>
<tr>
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<td>74 ± 4</td>
<td>82 ± 4†</td>
<td>68 ± 3†</td>
<td>75 ± 5†</td>
</tr>
<tr>
<td>C11</td>
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<td>69 ± 4</td>
<td>68 ± 5</td>
<td>81 ± 8</td>
<td>66 ± 4†</td>
<td>76 ± 2†</td>
</tr>
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<td>76 ± 4</td>
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<td>67 ± 5</td>
<td>88 ± 1†</td>
<td>60 ± 7†</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>C13</td>
<td>82 ± 5</td>
<td>70 ± 9</td>
<td>59 ± 4</td>
<td>83 ± 3†</td>
<td>71 ± 3†</td>
<td>66 ± 2†</td>
</tr>
<tr>
<td>C14</td>
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<td>87 ± 5</td>
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<td></td>
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<td>C15</td>
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<td>85 ± 5</td>
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<tr>
<td>C16</td>
<td></td>
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<td>58 ± 13</td>
<td>80 ± 4</td>
<td></td>
<td></td>
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<tr>
<td>C17</td>
<td></td>
<td></td>
<td>53 ± 6</td>
<td>77 ± 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td></td>
<td></td>
<td>58 ± 9</td>
<td>74 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td></td>
<td></td>
<td>50 ± 3</td>
<td>61 ± 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symbols indicate a significant difference from the corresponding value during C1 (*p* < 0.01; †*p* < 0.05).
Table 2. Correlation coefficients ($r^2$) from each measure with CTTOT for *in vivo* and computational model simulations. *In vivo* data in the first column is from Wang et al. (61) and the base model is from Poliacek et al. (48). Note the strong association between CTTOT and the duration of the second expiratory phase (CTE₂) in the *in vivo* conditions. *Version 2* is the only model which predicted this important *in vivo* interaction and did not predict association of other measures with CTTOT.

<table>
<thead>
<tr>
<th></th>
<th>In vivo (61)</th>
<th>In vivo (present)</th>
<th>Base model (48)</th>
<th>Version 1</th>
<th>Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Amplitude</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>0.50</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>E-Amplitude</td>
<td>0.11</td>
<td>0.01</td>
<td>0.50</td>
<td>&lt;0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>CT₁</td>
<td>0.24</td>
<td>0.10</td>
<td>0.70</td>
<td>0.55</td>
<td>0.14</td>
</tr>
<tr>
<td>CTₑ₁</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>0.60</td>
<td>0.52</td>
<td>0.05</td>
</tr>
<tr>
<td>CTₑ₂</td>
<td><strong>0.89</strong></td>
<td><strong>0.79</strong></td>
<td>0.85</td>
<td><strong>0.68</strong></td>
<td><strong>0.93</strong></td>
</tr>
</tbody>
</table>

**Bold** are moderate and strong associations.

Tables 3 and 4 are attached as a separate document.
**Figure 1.** Schematic representation of *Version 2* of the pontomedullary respiratory network model. Cell populations are represented as rectangles and are labeled with the cells’ respiratory discharge pattern; populations are vertically grouped according to anatomic location. Vertical lines to the right of each group represent the output(s) of each cell population; note that the lines and cell populations have the same names. Cell input is delineated at line intersections marked with dots containing a symbol to indicate the synapse type (excitatory or inhibitory; see Key); the horizontal lines point to the cell population receiving the input. The synapse type (excitatory or inhibitory) is indicated by small circles on cell population (see Key). For example, VRC IE neurons inhibit the VRC I-Dec and I-Aug cells and are excited by, among others, NTS Pump + cells. Nerve outputs are represented by the bottom 4 populations in the VRC column. Sensory receptors are shown at the bottom left; they influence the cell populations via 2nd order populations (left column). Populations and connections present in the base model [as published in Poliacek et al. (48)] that were removed or transformed in *Version 2* are indicated by dashed lines. Added connections and populations are shown in white and highlighted in gray.

**Abbreviations:** NTS, nucleus tractus solitarius; VRC, ventral respiratory column; PRG, pontine respiratory group. Aug and Dec: neurons with augmenting or decrementing activity patterns, respectively, during the indicated phase (I-inspiratory; E-expiratory) of maximum firing rate. ELM, expiratory laryngeal motoneurons; EI, neurons with a peak firing rate during the E-I phase transition; ILM, inspiratory laryngeal motoneurons; Lumbar, lumbar nerve; NBM, non-breathing modulated neurons; Phrenic, phrenic nerve; Pump cells: excitatory or inhibitory neurons excited by pulmonary stretch receptors and most active with lung inflation; BS, bulbospinal; and FF, feedforward.
Figure 2. *In vivo* representative example demonstrating the dynamic expiratory drive over a cough epoch (dotted line) and the change in CTE₂ (gray boxes). Note the change in the CTE₂, with longer E₂ durations occurring at the end of the cough bout.

Figure 3. Evolution of the computational model. A. Base model in Poliacek et al. (48). Note the limited lumbar (expiratory) amplitude variance and the stable CTE₂ during coughing. B. *Version 1* model changes. A feed-forward inhibitory population was added which accommodated over the cough epoch. C. *Version 2* model changes. 1. The second-order population was split into inspiratory and expiratory populations which received identical excitatory and feed-forward inhibitory inputs. 2. A second E-Aug late population was added which increased the expiratory control over the initiation of inspiration, increasing the CTE₂ at the end of the cough epoch (gray boxes). This figure does not indicate anatomical locations for the proposed neuronal populations, although E Aug late neurons are subsets of E Aug neurons located in the Botzinger complex *in vivo* (53, 54). Second-order neurons are located in the NTS (14, 15) and feed-forward populations are also proposed to be located in this area of the dorsal medulla.

Figure 4. Poincaré plots (*n* vs *n*+1; see Methods) of cough phase duration over model evolutions and overlaid on *in vivo* experiments represented by gray symbols. Data for CT₁ is represented as triangles, CTₑ₁ as squares and CTE₂ as circles. The base model from Poliacek et al. (48) is in blue, *Version 1* is in green, and *Version 2* is in red. *Version 1* had instances of CTE₂ equal to zero, which is not seen during *in vivo* repetitive coughing. Note the greater similarity of points generated from *in vivo* data and *Version 2* of the computational model. This and the absence of zero duration E₂ phases suggest an improved model.
References


Use of Inhibition in a Computational Model of Cough


Use of Inhibition in a Computational Model of Cough


Table 1. *In vivo* percent of maximum parasternal and abdominal EMG amplitude, and computational model simulations percent of maximum phrenic (inspiratory) and lumbar (expiratory) activities. The cough number is expressed as C1 to Cn. Values shown are means (± SE) for each cough in an epoch.

<table>
<thead>
<tr>
<th>Cough Number</th>
<th>Parasternal Mean ± SE</th>
<th>Abdominal Mean ± SE</th>
<th>Phrenic Version 1 Mean ± SE</th>
<th>Lumbar Version 1 Mean ± SE</th>
<th>Phrenic Version 2 Mean ± SE</th>
<th>Lumbar Version 2 Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>72 ± 7</td>
<td>41 ± 11</td>
<td>58 ± 9</td>
<td>42 ± 6</td>
<td>94 ± 2</td>
<td>59 ± 2</td>
</tr>
<tr>
<td>C2</td>
<td>71 ± 7</td>
<td>46 ± 7</td>
<td>76 ± 7</td>
<td>42 ± 6</td>
<td>89 ± 4</td>
<td>55 ± 7</td>
</tr>
<tr>
<td>C3</td>
<td>62 ± 5</td>
<td>44 ± 7</td>
<td>91 ± 4†</td>
<td>60 ± 6</td>
<td>91 ± 3</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>C4</td>
<td>64 ± 4</td>
<td>55 ± 10</td>
<td>92 ± 3†</td>
<td>64 ± 5</td>
<td>88 ± 2</td>
<td>66 ± 7</td>
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<tr>
<td>C5</td>
<td>74 ± 5</td>
<td>61 ± 9</td>
<td>94 ± 2†</td>
<td>64 ± 7</td>
<td>86 ± 3</td>
<td>70 ± 9</td>
</tr>
<tr>
<td>C6</td>
<td>76 ± 6</td>
<td>62 ± 5</td>
<td>81 ± 5†</td>
<td>51 ± 10</td>
<td>79 ± 2</td>
<td>75 ± 7</td>
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<td>85 ± 4</td>
<td>69 ± 4</td>
<td>78 ± 3†</td>
<td>81 ± 8</td>
</tr>
<tr>
<td>C8</td>
<td>84 ± 3</td>
<td>69 ± 4†</td>
<td>81 ± 4</td>
<td>81 ± 8</td>
<td>70 ± 2†</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>C9</td>
<td>84 ± 5</td>
<td>72 ± 6†</td>
<td>74 ± 3</td>
<td>87 ± 8*</td>
<td>71 ± 2†</td>
<td>83 ± 4†</td>
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<td>68 ± 5†</td>
<td>74 ± 4</td>
<td>82 ± 4†</td>
<td>68 ± 3†</td>
<td>75 ± 5†</td>
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<td>69 ± 4</td>
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<td>81 ± 8</td>
<td>66 ± 4†</td>
<td>76 ± 2†</td>
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<tr>
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<td>76 ± 4</td>
<td>67 ± 5</td>
<td>67 ± 5</td>
<td>88 ± 1†</td>
<td>60 ± 7†</td>
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<tr>
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<td>70 ± 9</td>
<td>59 ± 4</td>
<td>83 ± 3†</td>
<td>71 ± 3†</td>
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<tr>
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<td>77 ± 4</td>
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<td>58 ± 9</td>
<td>74 ± 5</td>
<td></td>
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<tr>
<td>C19</td>
<td></td>
<td></td>
<td>50 ± 3</td>
<td>61 ± 6</td>
<td></td>
<td></td>
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</tbody>
</table>

Symbols indicate a significant difference from the corresponding value during C1 (*p < 0.01; †p < 0.05).
Table 2. Correlation coefficients \((r^2)\) from each measure with \(CT_{TOT}\) for \textit{in vivo} and computational model simulations. \textit{In vivo} data in the first column is from Wang et al. (61) and the base model is from Poliacek et al. (48). Note the strong association between \(CT_{TOT}\) and the duration of the second expiratory phase (\(CT_{E2}\)) in the \textit{in vivo} conditions. \textit{Version 2} is the only model which predicted this important \textit{in vivo} interaction and did not predict association of other measures with \(CT_{TOT}\).

<table>
<thead>
<tr>
<th>(r^2)</th>
<th>In vivo (61)</th>
<th>In vivo (present)</th>
<th>Base model (48)</th>
<th>Version 1</th>
<th>Version 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Amplitude</td>
<td>0.07</td>
<td>&lt;0.01</td>
<td>0.50</td>
<td>0.05</td>
<td>0.11</td>
</tr>
<tr>
<td>E-Amplitude</td>
<td>0.11</td>
<td>0.01</td>
<td>0.50</td>
<td>&lt;0.01</td>
<td>0.15</td>
</tr>
<tr>
<td>CT(_1)</td>
<td>0.24</td>
<td>0.10</td>
<td>0.70</td>
<td>0.55</td>
<td>0.14</td>
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<tr>
<td>CT(_{E1})</td>
<td>0.09</td>
<td>&lt;0.01</td>
<td>0.60</td>
<td>0.52</td>
<td>0.05</td>
</tr>
<tr>
<td>CT(_{E2})</td>
<td><strong>0.89</strong></td>
<td><strong>0.79</strong></td>
<td><strong>0.85</strong></td>
<td><strong>0.68</strong></td>
<td><strong>0.93</strong></td>
</tr>
</tbody>
</table>

\textbf{Bold} are moderate and strong associations.

Tables 3 and 4 are attached as a separate document.
A. Base model (48)

- \( J_{\text{Phrenic}} \)
- \( J_{\text{Lumbar}} \)

B. Version 1

1. 2nd Order
   - FF INHIB
   - Afferent Input

- \( J_{\text{Phrenic}} \)
- \( J_{\text{Lumbar}} \)
- \( J_{\text{2nd Order}} \)

- Feed-forward Inhibition

C. Version 2

1. INSP EXP
   - FF INHIB
   - Afferent Input

2. E-Aug Late
   - I-Dec

- \( J_{\text{Phrenic}} \)
- \( J_{\text{Lumbar}} \)
- \( J_{\text{2nd Order}} \)

- Feed-forward Inhibition

5 seconds

5 seconds
Overlaid on In Vivo Results (gray)

**Version 2**
(CTE2 duration)  

**Version 1**
(Exp Drive)

**Base Model**  
Poliacek, et al. (48)
Table 3. Population parameters for the 3 computational network models discussed. Symbols in second column indicate neuronal populations added to the Base model from Poliaccek, et al. (48) to create Version 1 (†) and Version 2 (‡) of the model and populations present in the Base model (48) and Version 1 that were removed from Version 2 (o).

<table>
<thead>
<tr>
<th>Population name</th>
<th>Size</th>
<th>Resting threshold (mV)</th>
<th>THO variability (mV)</th>
<th>Membrane time constant</th>
<th>Post-spike increase in $G_{K+}$</th>
<th>Post-spike $G_{K+}$ time constant (ms)</th>
<th>Adaptation threshold increase</th>
<th>Adaptation (ms)</th>
<th>Noise amplitude</th>
<th>DC (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; o  Second-order cough</td>
<td>100</td>
<td>10.0</td>
<td>1.0</td>
<td>9.0</td>
<td>20.0</td>
<td>7.0</td>
<td>0.3</td>
<td>500.0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt; ‡ Second-order cough (insp)</td>
<td>100</td>
<td>10.0</td>
<td>1.0</td>
<td>9.0</td>
<td>20.0</td>
<td>7.0</td>
<td>0.9</td>
<td>600.0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>&gt; ‡ Second-order cough (exp)</td>
<td>250</td>
<td>10.0</td>
<td>1.0</td>
<td>9.0</td>
<td>20.0</td>
<td>7.0</td>
<td>0.9</td>
<td>600.0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>‡ E-AUG-late (#2)</td>
<td>600</td>
<td>10.0</td>
<td>1.0</td>
<td>9.0</td>
<td>27</td>
<td>2.5</td>
<td>0.9</td>
<td>250</td>
<td>0.1</td>
<td>27.0</td>
</tr>
<tr>
<td>&gt; †, ‡ Second-order cough feed-forward inhibition</td>
<td>100</td>
<td>10.0</td>
<td>1.0</td>
<td>9.0</td>
<td>20.0</td>
<td>7.0</td>
<td>0.9</td>
<td>600.0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Variable names used by MacGregor (30) are in italics. All values representing voltages are relative to the resting potential, which is considered equal to zero. $N$ is the number of neurons simulated in each population. THO, the resting threshold, is normally distributed in the population around the value of THO with a standard deviation equal to the “THO variability” value. TMEM is the membrane time constant. B is the amplitude of the post-spike increase in potassium conductance. $T_{GK}$ is the time constant of the potassium conductance decay following an action potential. C and $T_{TH}$ define the change in threshold associated with spike adaptation. C is the ratio of the threshold increase to the membrane potential increase; its value is between 0 and 1. $T_{TH}$ is the time constant of the rise in threshold with spike adaptation. Noise Amplitude: Each cell has an internal noise generator that acts like two synapses, one with an equilibrium potential of 70 mV above resting and the other with –70 mV. Each acts like it has an incoming firing probability of 0.05 per time step, and a synapse time constant of 1.5 ms. This parameter is the conductance that gets added to the synapse conductance on each (virtual) spike. DC: An injected current will raise the membrane potential by an amount that is inversely proportional to the membrane conductance. Instead of being specified directly as a current, this parameter is specified in mV, and it is interpreted as the current that is required to raise the membrane potential by the specified number of mV when the membrane conductance has its resting value. The effect on the membrane potential at other membrane conductances will be inversely proportional to the conductance. Note also that as in other types of IF neuron models, our neuron models do not actually generate action potential-like spikes but only identified moments of spikes, so “spiking” shown in all neuron simulations are represented graphically by assigning vertical spike-like lines at computed times of threshold crossing. (> ) neuron populations that relay perturbations of the network model. A fiber population consisting of 100 fibers, each with 100 excitatory synaptic terminals and a firing probability of 0.07 at each simulation time step, was used to represent cough...
receptor excitation. This fiber population excited the second-order cough and feed-forward inhibitory neuron populations (synaptic strengths = 0.12 and 0.04, respectively) and the I-Driver/Plateau population (synaptic strength = 0.02).
Table 4. Connectivity for the network model. Symbols in the second column indicate connections present in the Base model from Poliacek, et al. (48) and Version 1 that were removed from Version 2 (o) and connections added to the Base model (48) to create Version 1 (†) and Version 2 (‡) of the computational model.

<table>
<thead>
<tr>
<th>Source Population</th>
<th>Target Population</th>
<th>Synaptic Type</th>
<th>Conduction Times</th>
<th>No. of Terminals</th>
<th>Synaptic Strength</th>
<th>Source Population N</th>
<th>Target Population N</th>
<th>Divergence</th>
<th>Mean No. of Terminals</th>
<th>Convergence</th>
</tr>
</thead>
<tbody>
<tr>
<td>‡ E-DEC-P</td>
<td>E-AUG-late (#2)</td>
<td>Inh_1</td>
<td>2 4</td>
<td>150</td>
<td>0.02</td>
<td>300</td>
<td>600</td>
<td>132.51 ± 3.36</td>
<td>1.13</td>
<td>66.26 ± 7.63</td>
</tr>
<tr>
<td>‡ I-DEC</td>
<td>E-AUG-late (#2)</td>
<td>Inh_2</td>
<td>0 5</td>
<td>115</td>
<td>1.0</td>
<td>300</td>
<td>600</td>
<td>104.77 ± 2.71</td>
<td>1.10</td>
<td>52.39 ± 6.40</td>
</tr>
<tr>
<td>‡ E-AUG-early</td>
<td>E-AUG-late (#2)</td>
<td>Inh_1</td>
<td>0 2</td>
<td>50</td>
<td>0.001</td>
<td>300</td>
<td>600</td>
<td>48.01 ± 1.32</td>
<td>1.04</td>
<td>24.00 ± 4.83</td>
</tr>
<tr>
<td>o E-AUG-late (#1)</td>
<td>I-DEC</td>
<td>Inh_1</td>
<td>0 4</td>
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<td>300</td>
<td>50.33 ± 1.87</td>
<td>1.09</td>
<td>50.33 ± 6.68</td>
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<tr>
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<td>I-DEC</td>
<td>Inh_1</td>
<td>0 4</td>
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<td>1.17</td>
<td>170.43 ± 10.33</td>
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<td>VRC IE</td>
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<td>1.17</td>
<td>28.42 ± 5.15</td>
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<td>1.57</td>
<td>63.59 ± 5.84</td>
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<td>0 3</td>
<td>100</td>
<td>0.001</td>
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<td>63.59 ± 3.21</td>
<td>1.57</td>
<td>63.59 ± 5.84</td>
</tr>
<tr>
<td>&gt; o Second order cough</td>
<td>PRG E</td>
<td>Ex_1</td>
<td>0 3</td>
<td>100</td>
<td>0.001</td>
<td>100</td>
<td>100</td>
<td>63.59 ± 3.21</td>
<td>1.57</td>
<td>63.59 ± 5.84</td>
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<tr>
<td>&gt; o Second order cough</td>
<td>PRG El</td>
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<td>0 3</td>
<td>100</td>
<td>0.001</td>
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<td>63.59 ± 3.21</td>
<td>1.57</td>
<td>63.59 ± 5.84</td>
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<td>100</td>
<td>0.038</td>
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<td>1.17</td>
<td>28.42 ± 5.15</td>
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<td>0 3</td>
<td>100</td>
<td>0.02</td>
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<td>85.25 ± 2.83</td>
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<td>28.42 ± 5.15</td>
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<td>63.13 ± 3.05</td>
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<td>63.77 ± 5.20</td>
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<td>Ex_1</td>
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<td>100</td>
<td>0.015</td>
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<td>71.02 ± 9.02</td>
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<td>Ex_1</td>
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<td>71.02 ± 9.02</td>
</tr>
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<td>E-AUG-late (#1)</td>
<td>Ex_1</td>
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<td>100</td>
<td>0.06</td>
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<td>85.28 ± 6.85</td>
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<td>Source Population</td>
<td>Target Population</td>
<td>Synaptic Type</td>
<td>Conduction Times</td>
<td>No. of Terminals</td>
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<tr>
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<td>Pump-</td>
<td>Inh_1</td>
<td>Min.</td>
<td>0</td>
<td>Max.</td>
<td>4</td>
<td>250</td>
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<td>63.42 ± 3.05</td>
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<td>63.42 ± 3.05</td>
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<td>63.42 ± 3.05</td>
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<tr>
<td>➤ Second order cough (exp)</td>
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<td>Max.</td>
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<td>1.58</td>
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<td>1.58</td>
</tr>
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<td>❖ Second order cough feed-forward inhibition</td>
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<td>Inh_1</td>
<td>Min.</td>
<td>0</td>
<td>Max.</td>
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<td>500</td>
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<td>215.94 ± 3.74</td>
<td>2.32</td>
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<td>Max.</td>
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<td>500</td>
<td>100</td>
<td>100</td>
<td>99.33 ± 0.91</td>
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(>) connection relaying a perturbation to the network model. Connections between individual neurons were made according to a sequence of pseudorandom numbers calculated from a unique seed number for each source-to-target connection. Targets were chosen with replacement. This table includes the means ± SD of the number of neurons in each target population innervated by each source neuron in each population. Corresponding values are also shown for source neurons that innervated each target neuron in each population. These data indicate the extent of divergence and convergence, respectively. Most neurons in each source population made a single terminal connection with each target neuron. **Mean No. of Terminals**, the mean number of terminals from each source neuron innervating each target neuron. The efficacy of connections between populations of neurons was influenced by the change in conductance associated with each action potential at a synapse (Synaptic Strength) and the number of terminals for each axon. **Synaptic types** were distinguished by their equilibrium potentials and time constants. The time constant of some synapses was slightly longer than others because troughs in cross-correlograms from which the particular synaptic connections were inferred tended to have longer durations. Six types of synapses were used in the simulation: type 1 excitatory (Ex_1, equilibrium potential of 115.0 mV; time constant, 1.5 ms); type 3 excitatory (Ex_3, equilibrium potential, 115.0 mV; time constant, 5.0 ms); type 1 inhibitory (Inh_1, equilibrium potential, -25.0 mV; time constant, 1.5 ms); type 2 inhibitory (Inh_2, equilibrium potential, -25.0 mV; time constant, 2.0 ms); type 4 inhibitory (Inh_4, equilibrium potential, -25.0 mV; time constant, 5.0 ms); pre-synaptic modulation (Pre, time constant, 1.5 ms). If the value of the pre-synaptic modulatory strength parameter (Synaptic Strength) was <1.0, the strength of the connection it modulates was reduced to the product of the presynaptic Synaptic Strength parameter and target synapse conductance. If the presynaptic Synaptic Strength parameter was >1.0, the amount by which it was greater than 1 is added to its target synapse’s conductance. **Minimum and maximum conduction**
times are expressed in 0.5-ms simulation clock ticks for each source-to-target axon population. No. of Terminals, number of terminals from source neuron.